The Clinical, Therapeutic and Radiological Spectrum of SUNCT, SUNA and Trigeminal Neuralgia

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I, Giorgio Lambru, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Dr Giorgio Lambru

Abstract

This thesis examines and compares the demographics, clinical phenotype, radiological findings and response to medical and surgical treatments of SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) and SUNA (short-lasting unilateral neuralgiform headache attacks with autonomic symptoms). Given the similarities between SUNCT, SUNA and trigeminal neuralgia (TN), the demographics and clinical phenotype of these disorders were also compared.

In the first study (Chapter 2) a cohort of 133 patients (SUNA=63 and SUNCT=70) was phenotyped and the clinical characteristics of SUNA compared to those of SUNCT. Statistically significant predictors for SUNCT rather than SUNA were only found for ipsilateral ptosis [OR: 3.37 (95% CI: 1.50, 7.66), p<0.0001] and rhinorrhoea [OR: 2.42 (95% CI: 1.09, 5.41), p=0.034]. Furthermore, a significantly higher proportion of SUNCT patients (n=56, 80.0%) reported marked lacrimation compared to SUNA patients (n=20, 46.5%) (*P*<0.001).

In the second study (Chapter 3) 45 SUNCT and 34 SUNA patients had high-resolution cisternal imaging MRI scans to asses the presence of trigeminal neurovascular conflict. The prevalence of neurovascular contact on the symptomatic trigeminal nerves was higher (57.3%) than on the asymptomatic trigeminal nerves (25%) (P≤0.001). Severe neurovascular contacts were considerably more prevalent on the symptomatic side (47.6%), compared to the asymptomatic side (11.8%) (P≤0.001). There was no statistically significant difference in the proportion of neurovascular contacts on the symptomatic nerves between SUNCT (61.7%) and SUNA (57.1%) (P=0.67). The presence of a vascular contact and its location at the root entry zone were strong predictors for the nerve to be symptomatic rather than asymptomatic.

In the third study (Chapter 4) the response to treatments of 161 SUNCT and SUNA patients was analysed. Our findings suggest that lamotrigine was the most effective treatment (responders: SUNCT= 53.5%, SUNA= 57.9%) followed by oxcarbazepine (responders: SUNCT= 44.8%, SUNA= 47.0%); duloxetine and topiramate were more effective in SUNCT rather than SUNA (duloxetine responders: SUNCT= 45.0%, SUNA: 11.8%; p= 0.027; topiramate responders: SUNCT= 33.3%, SUNA= 10.7%; p=

0.028). Amongst transitional treatments intravenous lidocaine led to a significant headache improvement in 83.3% SUNCT (n=25) and in 76.5% SUNA (n=13) patients (p=0.73). A greater occipital nerve block was beneficial in 27.3% (n=21) of patients for a median of 21 days (IQR: 53 days; range: 1 to 150 days), without any significant difference between SUNCT (24.4%; n=11) and SUNA (37.0%; n=10) patients (p=0.42). We found intravenous dihidroergotamine able to worsen or even to precipitate a de novo SUNCT/SUNA when administered to manage a different primary headache disorder.

In the fourth study (Chapter 5) occipital nerve stimulation (ONS) was tried in nine and trigeminal microvascular decompression was tried in ten refractory, chronic SUNCT and SUNA patients. At a median follow-up of 38 months (range 24-55 months) ONS led to a marked headache improvement in eight of the nine patients (89%). One patient did not report any benefit from the stimulator at 24 months' follow-up and opted to have the ONS explanted. At a mean follow-up fo 19.6 months (range: 12-36 months) after trigeminal microvascular decompression surgery, seven patients (70%) became headache-free after the operation. Five of the seven patients (71.4%) remained headache-free at the last follow-up. The remaining two patients were headache-free respectively for 9 and 12 months before the headache relapsed. There were no major surgical and post-surgical complications.

A comparison of the clinical phenotype of SUNA (n=133) and TN (n=79) was undertaken in the last study (Chapter 6). Several similarities between SUNA and TN were found. Furthermore, some clinical features, namely pain location in V1 (OR: 11.29 95%CI: 3.92, 35.50, p<0.001), spontaneous only attacks (OR: 44.40, 95%CI: 4.50, 437.83, p=0.001) and a chronic pain pattern (OR: 13.19, 95%CI: 4.04, 43.08, p<0.001) predicted the diagnosis of SUNA rather than TN. Similarly duration of the attacks <1 minute (OR: 7.95, 95%CI: 2.30, 27.57, p=0.001) and the presence of a refractory period in between triggered attacks (OR: 0.06; 95%CI: 0.02, 0.28, p-value <0.001) were predictors for TN rather than SUNA.

In summary our novel findings advance the clinical understanding of SUNCT and SUNA and suggest that their relationship with TN may represent` a clinical continuum between disorders. This view will hopefully open novel research directions towards a better understanding of these complex clinical entities.

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Publications

The publications marked with an asterisk (*) are derived from work presented in the thesis. The remaining publications describe other collaborative work undertaken during the period of PhD study:

Journals

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Abu Bakar N, Tanprawate S, Lambru G, Torkamani M, Jahanshahi M, Matharu M. Quality of life in primary headache disorders: A review. Cephalalgia. 2016. 36(1):67-91

Torkamani M, Ernst L, Cheung LS, Lambru G, Matharu M, Jahanshahi M.
The neuropsychology of cluster headache: cognition, mood, disability and quality of life with chronic and episodic cluster headache. Headache. 2015;55(2):287-300

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Book Chapters

Lambru G and Matharu MS. Cluster headache and other trigeminal autonomic cephalalgias. In: Ishaq Abu-Arafeh editor. Childhood Headache. Cambridge University Press.

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List of abbreviations

CH: cluster headache

CM: chronic migraine

DHE: dihydroergotamine

fMRI: functional magnetic resonance imaging

HC: hemicrania continua

ICHD: International classification of headache disorders

IHS: International Headache Society

IPG: implanted power generator

IV: intravenous

MRI: Magnetic resonance imaging

NHS: National Health Service

ONS: occipital nerve stimulation

PH: paroxysmal hemicrania

RCT: randomised control trial

SC: subcutaneous

SUNCT: Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

SUNA: Short-lasting unilateral neuralgiform headache attacks with autonomic symptoms

TACs: Trigeminal autonomic cephalalgias

TN: trigeminal neuralgia

Chapter 1. SUNCT, SUNA and Trigeminal Neuralgia: focus on demographic, clinical characteristics, management strategies and pathophysiological hypotheses

1.1. Introduction

The International Headache Society (IHS) classifies headaches and facial pain conditions in three broad chapters. The primary headaches chapter recognises four groups of headaches: migraine, tension-type headache, trigeminal autonomic cephalalgias (TACs) and other primary headache disorders, which encompasses a heterogeneous group of poorly understood headache disorders. These conditions are considered primary, because the headache and associated symptomatology represents the symptom and no identifiable underlying pathological process can be found. The secondary headaches chapter encompasses headaches, which have an underlying pathology that can be established with appropriate investigations. The third chapter includes a miscellaneous group of painful cranial neuropathies and less prevalent forms of headache and facial pain (Headache Classification Subcommittee of The International Headache, 2013).

A primary headache disorder called SUNCT (Short-lasting Unilateral Neuralgiform Headache attacks with Conjunctival injection and Tearing) has recently been validated and included in the International Classification of Headache Disorders (ICHD-2) (Headache Classification Subcommittee of The International Headache Society., 2004; Headache Classification Subcommittee of The International Headache, 2013). SUNCT is currently classified within the TACs group along with cluster headache (CH), paroxysmal hemicrania (PH) and hemicrania continua (HC) in view of laterality and trigeminal distribution of pain that occurs in association with ipsilateral cranial autonomic features. In particular, to fulfill the IHS diagnostic criteria for SUNCT both conjunctival injection and tearing should accompany the pain. Clinical data though suggests that this is not invariably the case, since patients with very similar phenotypes can report only one of the two cranial autonomic symptoms or some of the other cranial autonomic signs and symptoms that invariably accompany the TACs. For this reason, the IHS has proposed the term short-lasting unilateral neuralgiform headache attacks

with cranial autonomic symptoms (SUNA), where only one cranial autonomic signs or symptoms would be sufficient to make the diagnosis. However, since this terminology proposal, only a few cases of SUNA have been published, hence no systematic clinical comparison between SUNCT and SUNA has been undertaken. It has therefore been difficult to formally establish whether SUNCT and SUNA are the same clinical entity or two distinct conditions. This paucity of clinical data is partly due to the low prevalence of SUNCT and SUNA, which are considered very rare in the general population. Additionally, the diagnosis of SUNCT and SUNA is often challenging in view of their clinical overlap with some of the TACs and mostly with other trigeminal neuralgiform paroxysmal disorders, such as classical trigeminal neuralgia (TN), purely paroxysmal and classical TN with concomitant persistent facial pain. SUNCT and SUNA share striking clinical similarities with TN. This clinical overlap between the three conditions has raised the question whether they are different entities or whether they constitute a clinical continuum (Sesso, 2001). At present the recent revision of the ICHD has kept SUNCT and SUNA as separate entities within the grouping of the TACs and TN within the group of painful cranial neuropathies and other headaches and facial pains (Headache Classification Subcommittee of The International Headache, 2013). The limited research on the phenotype of these disorders has prevented any progress in the understanding of the neurobiological basis for SUNCT and SUNA, and in turn has limited the development of effective medical and surgical treatments, leaving sufferers in severe disability.

The aims of this thesis were to:

1) Assess whether SUNCT and SUNA are the same or whether they are different clinical entities and to formulate new diagnostic criteria accordingly.
2) To assess the prevalence of trigeminal neurovascular conflict on trigeminal MRI sequences in SUNCT and SUNA patients.
3) To assess the outcome of medical and surgical treatments of SUNCT and SUNA.
4) To assess any clinical similarities and differences between large series of SUNCT, SUNA and TN aiming to ultimately shed light on the nosological position of these disorders within the IHS classification.

This thesis encompasses seven Chapters:

Chapter 1 provides an overview of demographic, clinical characteristics, aetiology, management and pathophysiological hypotheses for the trigeminal autonomic cephalalgias group, with a focus on SUNCT and SUNA syndromes. It also provides an overview of demographic, clinical characteristics, aetiology, management and pathophysiological hypotheses for TN, detailing the research questions that are ongoing matter of debate in the headache literature on SUNCT, SUNA and TN. The aims of this study are also outlined.

Chapters 2 provides the description of the SUNCT and SUNA phenotyping study, including the clinical comparison between the two conditions and the proposed diagnostic criteria.

Chapters 3 provides the description of the structural MRI study in SUNCT and SUNA.

Chapter 4 provides a description of the efficacy of a variety of pharmacological treatments in the cohorts of SUNCT and SUNA patients.

Chapter 5 provides a description of the efficacy of some surgical approaches in a subgroup of SUNCT and SUNA patients refractory to pharmacological treatments.

Chapter 6 provides the comparison between the series of SUNCT, SUNA and a large series of TN patients.

Chapter 7 outlines the summary of the main findings and conclusions of the thesis.

1.2. Trigeminal Autonomic Cephalalgias

The trigeminal autonomic cephalalgias (TACs) are a group of primary headache disorders that are characterised by strictly unilateral trigeminal distribution pain occurring in association with ipsilateral cranial autonomic symptoms. This group includes cluster headache (CH), paroxysmal hemicrania (PH), short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms

(SUNA) and hemicrania continua (HC). CH, PH, SUNCT, SUNA and HC are currently grouped into section three of the IHS classification (Headache Classification Subcommittee of The International Headache, 2013). The TACs seems to constitute a clinical spectrum that differs in attack duration and frequency as well as response to therapy. Cluster headache has the longest attack duration and relatively low attack frequency. PH has intermediate duration and intermediate attack frequency. SUNCT and SUNA have the shortest attack duration and the highest attack frequency. HC is characterised by a unilateral continuous headache with superimposed moderate/severe exacerbations of the headache accompanied by ipsilateral cranial autonomic features. The importance of recognizing these syndromes resides in their excellent, but highly selective, response to treatment.

1.2.1. Cluster Headache

1.2.1.1. Introduction and background

CH is a strictly unilateral headache that occurs in association with cranial autonomic features and, in most patients, has a striking circannual and circadian periodicity. It is an excruciating headache syndrome and is probably one of the most painful conditions known to mankind.

1.2.1.2. Epidemiology

The prevalence of CH is estimated to be 0.1% (D'Alessandro, et al., 1986), although a recent study suggests that the prevalence of CH may be as high as two per 1000 (Torelli, et al., 2005). The male: female ratio is 2.5:1 (Bahra, et al., 2002). It can begin at any age, though the most common age of onset is the third or fourth decade of life.

1.2.1.3. Clinical features

Cluster attacks are excruciatingly severe, strictly unilateral, episodes of headache, which are located mainly around the orbital and temporal regions, although any part of the head can be affected. The headache episodes usually last 45–90 minutes, but can range from 15 minutes to three hours. It has an abrupt onset and cessation, and attacks are accompanied by cranial autonomic symptoms. The cluster attacks occur from one every other day to eight daily. To fulfil the IHS diagnostic criteria (Headache Classification Subcommittee of The International Headache, 2013) the cluster headache pain needs to be accompanied by at least one of the cranial autonomic signs and symptoms, ipsilaterally to the side of the pain, namely: conjunctival injection, lacrimation, miosis, ptosis, eyelid oedema, rhinorrhoea, nasal blockage and forehead or facial sweating, forehead and facial flushing, aural fullness, or restlessness or agitation (see Table 1). Symptoms normally seen in migraine, such as nausea, vomiting, photophobia and phonophobia, are reported by a significant proportions of cluster patients (Bahra, et al., 2002; Schurks, et al., 2006) and aura has also been reported (Rozen, 2011). The vast majority of CH patients report restlessness or even aggressiveness during the attacks (Bahra, et al., 2002) and, therefore, this feature has been incorporated into the ICHD-II and ICHD-IIIβ diagnostic criteria (Headache Classification Subcommittee of The International Headache Society., 2004; Headache Classification Subcommittee of The International Headache, 2013).

The principal precipitants for CH attacks include: alcohol, nitroglycerine and elevated bodily or environmental temperature. Alcohol induces acute attacks, usually within one hour of intake, in the vast majority of cluster headache sufferers, which contrasts with migraine sufferers who generally have headache some hours after alcohol intake. Alcohol triggers attacks during a cluster bout, but not in a remission (Schurks, et al., 2006).

CH is classified according to the duration of the bout. About 80-90% of patients have episodic cluster headache (ECH), which is diagnosed when they experience recurrent bouts, each lasting for more than a week and separated by remissions lasting more than four weeks. The attacks follow a striking circadian rhythmicity, with some patients reporting that the attacks occur at the same time each day. The majority of patients with

ECH have one or two bouts per annum, lasting between one and two months. Often, a striking circannual periodicity is seen in ECH sufferers, with bouts occurring in the same month of the year. The remaining 10-20% of patients have chronic cluster headache (CCH) in which either no remission occurs within one year or the remissions last less than one month (Headache Classification Subcommittee of The International Headache, 2013).

Table 1. International Headache Society diagnostic criteria for cluster headache

A. At least 5 attacks fulfilling criteria B-D

B. Severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes (when untreated).

C. Either or both of the following:

1. At least one of the following symptoms or signs, ipsilateral to the headache:

a) Conjunctival injection and/or lacrimation.

b) Nasal congestion and/or rhinorrhoea

c) Eyelid oedema

d) Forehead and facial sweating

e) Forehead and facial flushing

f) Sensation of fullness in the ear

g) Miosis and/or ptosis

2. A sense of restlessness or agitation

D. Attacks have a frequency of one every other day and eight per day for more than half of the time when the disorder is active.

Adapted from The International Headache Society Classification Committee of (2013)

1.2.1.4. Differential diagnosis

The major differential diagnostic considerations for CH are the TACs characterised by paroxysmal short-lasting headache attacks with no inter paroxysmal background continuous pain (Table 2) and secondary causes of CH. The vast majority of CH patients have a primary headache syndrome, with symptomatic causes only being identified in a very small minority. However, the true prevalence of symptomatic causes of CH is unknown as there are no prospective population-based neuroimaging studies. A review of retrospective case reports published in the medical literature suggests that the TACs may be associated with pituitary tumors, although this most likely reflects a considerable element of publication bias (Cittadini, et al., 2009). Similarly, an observational study of headache disorders in patients with pituitary tumors reported that

CH occurred in 4% and SUNCT in 5%, but the study was conducted in a tertiary referral neurosurgical centre and, therefore, does not give a meaningful indication of the prevalence of these headaches in patients with pituitary disorders (Levy, et al., 2005). It remains unclear whether every TAC patient requires neuroimaging, although, if it is considered, then magnetic resonance imaging (MRI) is the preferred modality. Some authors suggest that all patients with TACs should have dedicated pituitary imaging. However, approximately one in 10 of the general population has an incidental pituitary microadenoma (<1 cm diameter) on routine MRI, and up to one in 500 will have a macroadenoma (Ezzat, et al., 2004). This approach is therefore likely to identify a significant number of incidental lesions, which could then be erroneously considered to be the cause of the TAC syndrome. One way of addressing this clinical dilemma could be that all TAC patients should be carefully assessed for pituitary disease-related symptoms and that further investigations with MRI of the pituitary gland should be undertaken in patients with atypical features, abnormal examination or those resistant to the appropriate medical treatments.

Table 2. Clinical features of the Trigeminal Autonomic Cephalalgias

	Cluster headache	**Paroxysmal hemicrania**	**SUNCT/SUNA**
Sex F:M	1:2.5-7.2	1:1	1:1.5
Pain:			
Type	Sharp, Throbbing	Sharp, Throbbing	Stabbing, Burning
Severity	Very severe	Very severe	Very severe
Site	Orbit, temple	Orbit, temple	Orbit, temple
Attack frequency	1/alternate day – 8/day	>5/day when disorder is active	≥1/day when disorder is active
Duration of attack	15-180mins	2-30mins	1-600secs
Circadian periodicity	70%	45%	Absent
Autonomic features	Yes	Yes	Yes†
Restless or agitated	90%	80%	65%
Migrainous features	Yes	Yes	Rare
Triggers:			
Alcohol	++	+	-
Cutaneous	-	-	++
Indometacin effect	- (rarely +)	Absolute response	-
Abortive treatment	Sumatriptan injection Sumatriptan or Zolmitriptan nasal spray Oxygen	Nil	Nil
Prophylactic treatment	Verapamil Methysergide Lithium Topiramate	Indometacin	Lamotrigine Topiramate Gabapentin
Transitional treatment	Corticosteroids GONB	GONB	GONB IV lidocaine

†SUNCT: prominent conjunctival injection and lacrimation by definition.

†SUNA: only one or neither of conjunctival injection and lacrimation by definition [1].

F, female; GONB Greater occipital nerve block; IV, intravenous; M, male; SUNA, Short-lasting Unilateral Neuralgiform headache attacks with autonomic symptoms; SUNCT, Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing

1.2.1.5. Treatment

The European Federation of Neurological Societies (EFNS) (May, et al., 2006) and the American Academy of Neurology (AAN) (Francis, et al., 2010) have published an overview of the recommendations for CH abortive and preventive treatments. The AHS provided a recent update on the AAN guidelines (Robbins, et al., 2016).

Abortive agents

Subcutaneous sumatriptan

Sumatriptan 6 mg subcutaneous (SC) injection is the drug of choice as abortive treatment of a cluster attack (Ekbom, et al., 1992; The Sumatriptan Cluster Headache Study, 1991). In CH, unlike in migraine, subcutaneous sumatriptan can be prescribed at a frequency of twice daily, on a long-term basis if necessary, without risk of tachyphylaxis or rebound (Ekbom, et al., 1995; Gobel, et al., 1998). Level of evidence: Class I.

Oxygen

Inhalation of 100% oxygen, at 7–12 L/min is rapidly effective in relieving pain in the majority of sufferers (Kudrow, 1981; Fogan, 1985; Cohen, et al., 2009). It should be inhaled continuously for 15–30 min via a non-rebreathing facial mask. However, up to 25% of the patients note that oxygen simply delays the attack for minutes to hours rather than completely aborting it (Kudrow, 1981). Level of evidence: Class I.

Intranasal triptans

Sumatriptan nasal spray (20 mg) and zolmitriptan nasal spray (5 mg and 10 mg) are both more effective than placebo (Van Vliet, et al., 2003; Cittadini, et al., 2006; Rapoport, et al., 2007). Given the efficacy of both zolmitriptan 5 mg and 10 mg doses,

it has been advised that 10 mg might be the optimal initial dose for those with very severe attacks occurring only once per day or every other day, while 5 mg should be the initial dose for those with more frequent attacks or poor tolerability. Level of evidence: Class I.

Sphenopalatine ganglion stimulation

The American Headache Society (AHS) has granted Class I evidence to a recent randomised-controlled study evaluating the safety and efficacy of sphenopalatine ganglion (SPG) stimulation, using a wireless microstimulator implanted in the pterygopalatine fossa Autonomic Technologies, Inc. [ATI] Neurostimulator) (Schoenen, et al., 2013). This treatment will be more extensively discussed in the paragraph on preventive treatments for CH.

Topical lidocaine

Lidocaine solution, given as nasal drops (10% lidocaine solution) or a spray deep in the nostril on the painful side has been studied in an open-label study and in a small double-blind placebo-controlled study. Both studies reported a mild to moderate relief in patients during a CH attack, although only a few patients obtain complete pain relief (Robbins, 1995; Costa, et al., 2000). Level of evidence: Class II. Therefore, intranasal lidocaine may serve as a useful adjunct to other abortive treatments but is rarely adequate on its own.

Subcutaneous octreotide

Subcutaneous octreotide 100 μg, a somatostatin analog, was found to be an effective abortive treatment in CH in a randomized, double-blind, two-attacks, crossover study versus placebo. The primary outcome measure of the trial was a reduction in headache from moderate, severe, or very severe to nil or mild within 30 minutes from the injection (Matharu, et al., 2004). Level of evidence: Class I.

Dihydroergotamine nasal spray

Dihydroergotamine (DHE) nasal spray 1 mg has been studied in a double-blind, placebo-controlled, crossover trial (Anderson, et al., 1986). There was no difference in the headache frequency or duration, but the pain intensity was significantly reduced with DHE compared with placebo. The dosage used (1 mg) was rather low; therefore, DHE nasal spray at a dose of 2 mg or 4 mg may be more effective than 1 mg, although this needs to be studied in a controlled fashion.

Indometacin

CH is generally considered a disorder unresponsive to indometacin. Nevertheless, in the literature, there are a few case reports/series of CH responsive to indometacin in some cases with long term follow-ups. Very large doses of indometacin (up to 300 mg/day) were needed in the majority of patients reported to obtain a complete response. Indometacin has also been tried as an abortive CH attack treatment. Intravenous (IV) and intramuscular (IM) indometacin treatments have been reported to be able to successfully treat CH attacks in some patients (Prakash, et al., 2010). However, there are no placebo-controlled studies of indometacin in cluster headache and these reports of "indometacin-responsive cluster headache" may simply represent placebo responders.

The complete and consistent response to indometacin given as preventive treatment in patients with a CH phenotype may enforce the concept of a continuum between the TACs with overlapping clinical characteristics and response to certain medications. An alternative potential explanation would be that all patients with the phenotype of cluster head and paroxysmal hemicrania who respond to indomethacin are likely to have the same pathophysiology as paroxysmal hemicrania; hence, "indometacin-responsive cluster headache" may be best categorised as paroxysmal hemicrania for now. This is a controversial issue and often debated in headache circles.

In clinical practice, indometacin may be used in those forms of established primary CH with atypical features, such as short-lasting attacks, high attack frequency or lack of response to sumatriptan injections and high flow oxygen, to rule out PH. In some cases,

indometacin could be used as an abortive treatment in CH, if the main treatments are ineffective or poorly tolerated.

Transitional treatments

There can be a lag of several days to a few weeks before the efficacy of preventive treatments becomes apparent. Transitional treatments, which produce a rapid suppression of the attacks for a limited period of time or cannot be used for prolonged periods, can be used when waiting for the beneficial effect of a preventive treatment to become evident. Transitional treatments can be also be used in patients with ECH to treat relatively short bouts (≤1 month), without the need to start a preventive drug.

Corticosteroids

Several investigators have reported the beneficial effect of oral or parenteral corticosteroid regimens in the treatment of CH (Couch, et al., 1978; Kudrow, 1980). The methodological quality of these studies is low, with uncontrolled and inconclusive studies being the norm (Level of evidence: Class IV). However, these studies have nearly uniformly reported positive treatment effects, and this is consistent with the clinical experiences of most physicians caring for CH patients (Shapiro, 2005). Caution has to be exercised in their use because of the potential for serious side effects. Thus, a tapering course of prednisone or prednisolone for 3 weeks is prudent. Unfortunately, relapse almost invariably occurs as the dose is tapered. For this reason, steroids are used as an initial therapy in conjunction with preventives, until the latter are effective. A shared protocol used in clinical practice suggests starting patients on oral prednisone 1 mg/kg, to a maximum of 60 mg daily, for five days and thereafter decrease the dose by 10 mg every three days.

Greater occipital nerve block

A double blind, placebo-controlled study of suboccipital injection with a mixture of rapid- and long-acting betamethasone have been performed in CH (Ambrosini, et al., 2005). The authors studied 16 ECH and seven CCH patients. Eleven of 13 (85%) CH patients treated with betamethasone suboccipital injection became pain-free within one week compared with none of the ten patients treated with placebo. This effect was maintained for at least four weeks in the majority of the patients. Given the relatively good evidence of efficacy, suboccipital steroid injection has been recommended in the treatment of CH (Francis, et al., 2010). A Class I randomised, double-blind, placebo-controlled study, 43 CH patients received either cortivazol 3.75 mg ipsilateral to the CH attack or normal saline. Injections were performed three times, each 48-72 h apart with the view to achieving short-term prophylaxis of CH attacks. The group treated with cortivazol experienced a statistically significant reduction in number of attacks up to 15 days post-treatment, suggesting a rapid short-lasting therapeutic effect of suboccipitally delivered corticosteroid in CH (Leroux, et al., 2011). A recent open-label prospective study tested the efficacy and consistency of response of greater occipital nerve blocks (GONB) in 83 CCH patients. A positive response was observed in 57% of patients, lasting a median of 21 days. The overall rate and average duration of response remained consistent after the second (n = 37, 31 responders: 84%; median duration: 21 days), third (n = 28, 20 responders: 71%; median duration: 25 days), and fourth (n = 14, 10 responders: 71%; median duration: 23 days) injections, suggesting that, performed three monthly, GONB may have a useful role also in the management of CCH (Lambru, et al., 2014). GONB is generally a well tolerated procedure. No serious adverse events have been reported in the RCTs and in the open label trials. Side effects reported across the studies include: tenderness in the injection site, neck stifness, dizziness post-procedure.

Level of evidence in ECH: Class I. Level of evidence in CCH: Class II.

Intravenous dihydroergotamine

Repetitive intravenous DHE administered to inpatients over a period of 3 days was reported to be very useful in some cases of both ECH and CCH. In a study of 54 patients with intractable CH (23 episodic, 31 chronic), the open-label use of repetitive intravenous DHE rendered all patients, headache free (Mather, et al., 1991). At 12-

month follow-up, 83% and 39% of the patients with ECH and CCH, respectively, remained free of headache. A retrospective analysis evaluated the efficacy and safety of intravenous DHE for the treatment of refractory CH in 70 patients, and showed a complete resolution of the pain at one month after treatment in 62% of the cases, partial improvement in 14% and failure in 24%. Side effects were transient and well tolerated in most patients (Magnoux, et al., 2004). More recently a retrospective audit was conducted in 34 CCH and four ECH patients who were treated with IV DHE given for five consecutive days to prevent the attacks. Thirty-two out of 38 patients (84.2%) were rendered headache-free during treatment with DHE. The mean time for attacks to return was 17 days. At the time of discharge 45% of the treated patients were started on a CH preventive treatment, making the assessment of time to return to the pre-DHE attacks frequency difficult to ascertain accurately (Nagy, et al., 2011). A range of adverse events have been reported with the use of IV DHE. Nausea is the most commonly reported, followed by leg cramps, chest tightness, shortness of breath, insomnia, diarrhoea and paresthesia. No side effects were life-threatening in the above-mentioned studies. Level of evidence: Class IV.

Preventive treatments

The preventive agents used include verapamil, lithium, topiramate, methysergide, gabapentin, melatonin and valproate. Verapamil is the first-line agent of choice. Second-line agents include lithium and topiramate, while methysergide is a reasonable choice for a third-line agent.

Verapamil

Verapamil is the preventative drug of choice in both episodic and chronic CH (Bussone, et al., 1990; Leone, et al., 2000). Dosages commonly employed range from 240 mg to 960 mg in divided doses (two or three times a day). Verapamil can cause heart block by slowing conduction in the atrioventricular node. Observing for PR interval prolongation on electrocardiogram (ECG) can monitor potential development of heart block. There is only one formal guideline in the literature for the titration of the verapamil dose (Cohen, et al., 2007). After performing a baseline ECG, patients are usually started on 80 mg tds and, thereafter, the total daily dose is increased in

increments of 80 mg every 10-14 days. An ECG is performed prior to each increment. The dose is increased until the cluster attacks are suppressed, side effects intervene, or the maximum dose of 960 mg daily is achieved. ECG monitoring should be performed periodically in patients on long-term verapamil. Level of evidence: Class II.

Lithium

Lithium is an effective agent for CH prophylaxis, although the response is less robust in ECH than in CCH (Ekbom, 1981; Bussone, et al., 1990). Most patients will benefit from dosages between 600 mg and 1200 mg daily or at plasma concentrations comprised between 0.8 mEq/L and 1.0 mEq/L. Renal and thyroid function tests are performed prior to and during treatment in view of the long-term risk of hypothyroidism and nephrogenic diabetes insipidus. Level of evidence: Class III.

Topiramate

Five open-label studies have reported the efficacy of topiramate in the preventive treatment of CH (Wheeler, et al., 1999; Förderreuther, et al., 2002; Mathew, et al., 2002; Lainez, et al., 2003; Leone, et al., 2003). The dose of topiramate used in these studies ranged from 25 mg to 250 mg daily. The side-effect profile of this agent, including cognitive slowing and depression, often limits its use. Level of evidence: Class III.

Methysergide

Methysergide has long been used for the treatment of CH (Kudrow, 1980; Dodick, et al., 2001). It is an ideal choice in patients with short cluster bouts, which last less than 4–5 months. Doses up to 12 mg daily can be used, if tolerated. Prolonged treatment has been associated with fibrotic reactions (retroperitoneal, pulmonary, pleural and cardiac). For this reason, a 1-month holiday every six months of therapy and check for evidence of pulmonary, cardiac, renal or abdominal pathology yearly is normally advised if repetitive courses of treatment are required over a prolonged period. In view

of the possible serious fibrotic reactions, this medication was discontinued in the UK in 2013, so it is no longer in use. Level of evidence: Class IV.

Other preventive treatments

In a double-blind, placebo-controlled trial of melatonin 10 mg, five of ten subjects randomized to melatonin were rendered pain free within five days, while none of the ten subjects taking placebo derived any benefit (Leone, et al., 1996). Recently, Peres and Rozen reported two chronic CH patients inadequately managed on verapamil 640 mg daily who were rendered pain free with add-on therapy with melatonin 9 mg daily. The authors concluded that melatonin could be a useful adjunctive treatment for CH prophylaxis (Perez, et al., 2001). Level of evidence: Class II.

Gabapentin was tried at the dose of 900 mg/day in an open-label fashion in eight ECH and four CCH patients (Leandri, et al., 2001). All patients were rendered pain free within eight days of initiating therapy. Patients with ECH discontinued gabapentin after 60 days of treatment without recurrence of the attacks. The four CCH patients remained pain free at follow-up of four months. This high response rate needs to be reproduced in controlled trials. Level of evidence: Class IV.

New randomised, double-blind controlled trials have been recently published on warfarin, frovatriptan, candesartan and cimetidine, a histamine H2 receptor antagonist (Siow, et al., 2004; Trovnik, et al., 2013; Anthony, et al., 1978). The preventive effect of warfarin was evaluated in a Class II crossover study of 34 patients with CCH. Warfarin was administered in order to keep an International Normalized Ratio (INR) range of 1.5 to 1.9 over a 12-week treatment period. Subsequently after a wash out period of two weeks, patients were crossed over from one treatment to the other. The primary outcome was the occurrence of remission lasting at least four weeks. In the intention to treat analysis, 50% underwent remission for 4 weeks during the warfarin period compared with 11.8% patients during the placebo period (P = .004). The number needed to treat was 2.6 (95% CI 1.7-5.5). No serious adverse events were reported (Hakim, 2011).

A Class III multi-center, placebo-controlled, randomised, double-blind study was designed to assess the efficacy of Frovatriptan 5 mg/day as a short preventive strategy

in CH. The study was discontinued prematurely due to slow recruitment and major protocol violations (Pageler, et al., 2011).

A Class II parallel group study evaluated candesartan 16 mg daily for one week followed by 32 mg daily for two weeks was conducted in ECH prophylaxis. Thirty-two patients were enrolled (candesartan=19 patients; placebo=13 patients). The primary efficacy variable was the number of attacks per week. The study failed to meet the primary endpoint, compared to placebo. The difference in attack numbers between week 1 and 3 was not statistically significant ($p = 0.38$). However, the Authors noticed a progressive reduction of the attacks frequency during week 3 of the study in both groups, though the proportion of patients with reduced attacks was higher in the candesartan group (61%) as opposed to the placebo group (38%)., suggesting that larger studies may be needed to explore the role of this medication in the prevention of CH (Trovnik, et al., 2013).

Surgery

Surgical approaches are alternative options in patients with headache-related poor quality of life. These treatments should be considered in patients refractory to medical management because of inefficacy and/or poor tolerability. Historically, destructive procedures, like trigeminal sensory rhizotomy and radiofrequency trigeminal ganglio-rhizolysis, have been tried in CH (Mathew, et al., 1988; Jarrar, et al., 2003). However, they are associated with considerable morbidity and therefore have been largely abandoned. Neurostimulation therapies that entail peripheral or central nervous system targets are emerging as very promising approaches (Figure 1). Candidates for peripheral and central neurostimulation therapies should be medically refractory according to shared guidelines. Recently, the members of the European Headache Federation have published a consensus statement on the definition of refractory CCH for clinical and research use. The diagnostic criteria require the presence of at least three severe CH attacks per week that impact patients' quality of life. Patients have to fail prophylactic trials with at least three established treatments such as verapamil, lithium, oral or intravenous steroids, greater occipital nerve infiltration, topiramate, methysergide, ergots, civamide and long acting triptans, at the maximum tolerated dose over a

sufficient period of time. Secondary CH has to be ruled out by appropriate investigations (Mitsikostas, et al., 2014).

Ventral tegmental area deep brain stimulation

Based on the functional neuroimaging finding of ipsilateral posterior inferior hypothalamic activation in CH (May, et al., 1998), various headache centers have treated intractable CCH patients by electrode implantation and stimulation of this region (Leone, et al., 2001; Leone, et al., 2008; Schoenen, et al., 2005). The vast majority of the studies were conducted in an open label fashion. To date only one multicentre, randomized, double blind, crossover study using hypothalamic deep brain stimulation (DBS) for the management of refractory CCH has been published. The study enrolled 12 patients, with only 11 undergoing surgery. The randomised phase compared active and sham stimulation during a 1-month period. The primary study outcome was change in weekly CH attacks. Results were not encouraging in the blinded crossover phase. However, the very short crossover assignment was criticised. Such a short period may not have allowed the treatment to exert its effect in full since it is thought that central and peripheral neuromodulation therapies in primary headache may require months to display their full effectiveness. Indeed, in the same study, during the open phase, six of 11 patients became responders, suggesting that a longer randomised phase may have led to different results (Fontaine , et al., 2010). Sixty-four drug-resistant CCH patients treated with DBS of the posterior hypothalamic region have been reported in the literature so far (Magis, et al., 2012). Of these, 42% became pain free and 22% experienced a ≥50% improvement in headache frequency and/or intensity, supporting the utility of this procedure in this sub-group of patients.

Although studies on DBS claim that the posterior hypothalamic region was stimulated, subsequent anatomical studies have established that in fact the precise localization of the stimulation was the ventral tegmental area (VTA) rather then the posterior hypothalamus, posing challenging issues regarding the precision of the neuroanatomical target used in DBS studies (Matharu, et al., 2010). Recently an open-label prospective study reported favourable outcomes of VTA DBS in a cohort of 21 medically refractory CCH patients. At a median follow-up of 18 months, 60% of the patients reported a 60% improvement of the headache frequency and 30% of the

headache severity. This improvement was reflected in the reduction of abortive treatments and improvement in the disability and mood scales employed, providing class IV evidence of efficacy of DBS targeting the VTA (Akram , et al., 2016).

VTA DBS is not a risk-free procedure. One patient died from an intracerebral haemorrhage along the electrode track a few hours after microelectrode-guided implantation (Schoenen, et al., 2005).

Occipital nerve stimulation

In 1999, Weiner and Reed used occipital nerve stimulation to successfully treat what was thought to be drug-resistant occipital neuralgia (Weiner, et al., 1999). This work opened the way for observational studies of this moderately invasive method of neurostimulation in various chronic primary headache disorders.

Studies conducted in small cohorts of medically intractable CCH patients have shown occipital nerve stimulation (ONS) to be a promising therapy. Magis and colleagues treated eight patients with medically intractable CCH using unilateral ipsilateral to the side of the pain ONS. After a mean follow-up of 15 months, two patients were pain free; three patients had a 90% reduction in attack frequency while two patients had improvement of around 40%. Interruption of ONS was followed within days by recurrence and increase of attacks in all improved patients (Magis, et al., 2007). Burns and colleagues treated 14 patients with medically intractable CCH using bilateral ONS. At a median follow-up of 17.5 months, ten of the 14 patients reported improvement that was sufficiently meaningful for them. Subjective self-reporting of improvement was 90% or more in three patients, 40–60% in three patients and 20–30% in four patients. Benefit from stimulation was not immediate, with maximal effect noted after several months (Burns, et al., 2009). In a recently published review, out of 91 CCH patients treated with ONS, 61 (67%) experienced a significant improvement in terms of reduction of headache frequency and intensity (Magis, et al., 2012). The most common device-related adverse events include: lead migration, infection in the battery site and lead breakage. A recent open-label study confirmed the very long-term efficacy (median of six years) of this neurostimulation treatment in about two-third of refractory

CCH patients (Leone, et al., 2017). At present ONS and SPG stimulation are considered the surgical treatments of choice for CCH (Martelletti , et al., 2013).

Sphenopalatine ganglion stimulation

The rationale for targeting the sphenopalatine ganglion (SPG) is based on the close relation between headache and autonomic activation in the TACs. The parasympathetic autonomic symptomatology of the TACs is mediated by crosstalk between trigeminal nociceptive afferents and cranial parasympathetic efferent fibres that arise from the superior salivary nucleus. The SPG receives preganglionic parasympathetic fibres from the superior salivatory nucleus in the brain stem via the greater petrosal nerve, which forms the Vidian nerve. Postganglionic parasympathetic fibres innervate the lacrimal gland, the nasopharyngeal mucous membranes and meningeal vessels (Figure 2) (Ruskell , 2003). When activated, these fibres release neurotransmitters and vasodilators that activate sensory trigeminal fibres causing further activation of the trigeminal pain pathway which, in turn, causes further parasympathetic outflow, referred to as the trigeminal-autonomic reflex (Goadsby, et al., 1997). A non-destructive approach using acute percutaneous SPG stimulation with a removable electrode was initially examined in five patients with CH. This proof of concept study showed complete pain relief in 11/18 (61.1 %) of the attacks, partial resolution (50 % VAS reduction) in 3/18 attacks (16.7 %) and minimal to no relief in 4/18 attacks (22.2 %). Stimulation also resolved the associated autonomic features of CH (Ansarinia , et al., 2010). Based on these preliminary findings, a new implantable microstimulator was developed. This device is positioned in the pterygopalatine fossa (PPF), powered and controlled transcutaneously by radio frequency waves generated by an external remote controller (Autonomic Technologies Inc., Redwood City, CA, USA). A multicentre randomised double blind and sham-controlled trial has been conducted to examine the efficacy of acute SPG stimulation in refractory CCH (Schoenen, et al., 2013). In this study, 32 CCH patients experiencing a minimum of four attacks per week were included. The design of the study consisted of a 4-week baseline period followed by a post-implant stabilisation and therapy titration period. The experimental period lasted until 30 CH attacks were treated or, if attack frequency was not high enough, for a maximum of 8 weeks. During this period, patients were

instructed to use the stimulator to treat each attack for 15 min. The primary endpoint of pain relief after 15 min of stimulation was achieved in 67.1 % of full stimulation-treated attacks compared to 7.4 % of sham stimulation-treated attacks. Fourteen out of 28 patients (50%) experienced an acute response for at least 50% of the attacks treated. Moreover, some patients did not manage to treat 30 attacks during the study period, because they experienced an attack frequency reduction of 50% from baseline, suggesting that a proportion of CH patients treating the attacks acutely may experience a preventive effect. Five device or procedure-related side effects occurred. There were three lead revisions and two neurostimulators were explanted. Sensory disturbances occurred in 81 % of patients with complete resolution in the majority of patients. Two patients experienced infections, though in both cases they were resolved with antibiotic therapy.

SPG stimulation offers several major advantages as opposed to the traditional neurostimulation approaches. It has shown, for the first time in the headache neuromodulation field, the ability to provide abortive therapy. The device delivers a ‘‘on demand’’ treatment for the management of the acute attacks, as opposed to the continuous stimulation of the traditional ONS. This allows patients to apply it multiple times per day without any limitation due to cardiovascular risks, as are associated with the use of sumatriptan injections. As far as the SPG stimulation device is concerned, the wireless stimulation avoids those hardware-related complications that are routinely reported by patients treated with ONS. Moreover, since the microstimulator is fixed with two or three bone screws to the zygomatic process of the maxillary bone, the chance of electrode migration or breakage is unlikely, as opposed to the significantly high lead migration rate that has been reported using traditional ONS (Dodick, et al., 2015). SPG stimulation using this advanced wireless on demand technology certainly constitutes a step forward in the management of refractory CH. Nonetheless, long-term data on SPG stimulation efficacy is required and better designed randomised controlled studies with more reliable sham stimulation should be performed to confirm the preliminary findings of the Pathway CH-1 study. Moreover, despite the use of wireless technology, the device remains expensive and access to the therapy can be difficult. This aspect paired with the lower efficacy compared to sumatriptan injection, limits the SPG therapy to a small proportion of CH patients.

Figure 1 From left to right: Ventral tegmental area deep brain stimulation, occipital nerve stimulation and sphenopalatine ganglion stimulation

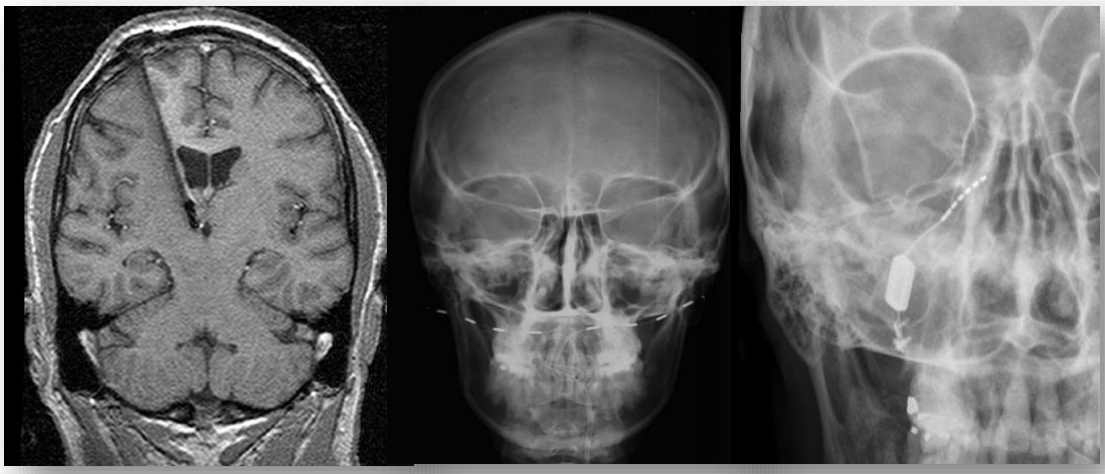
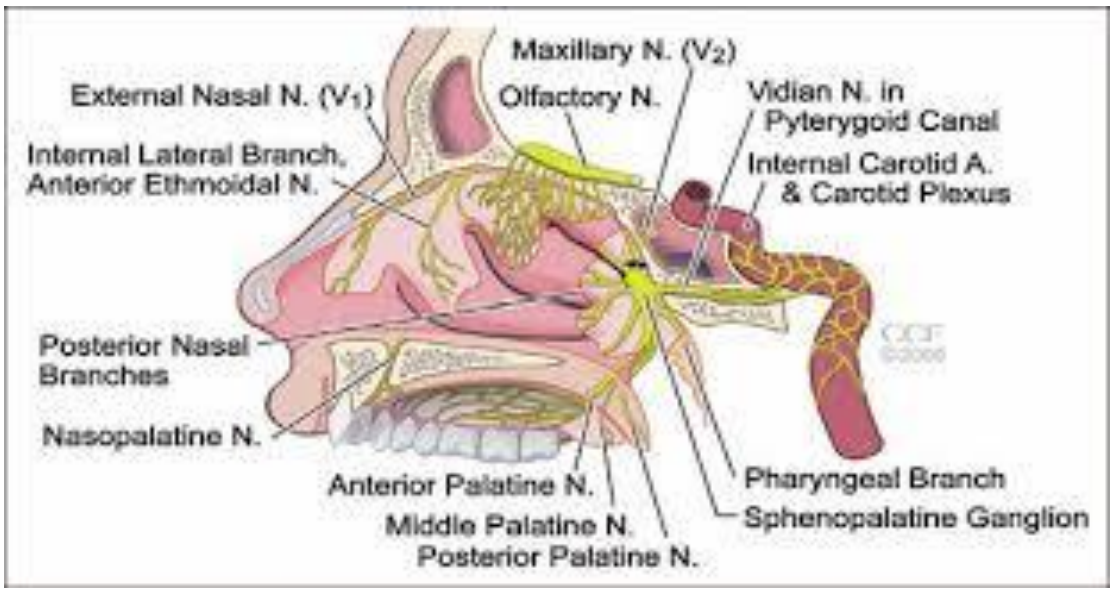


Figure 2. Anatomy of the sphenopalatine ganglion.



Vagus nerve stimulation

Vagus nerve stimulation (VNS) is a well-established treatment for intractable epilepsy and depression. Initial positive data on the efficacy of VNS in migraine was gathered from retrospective analysis of patients implanted for the treatment of epilepsy. A positive effect of VNS was reported in two CCH patients who also suffered from severe depression (Mauskop, 2005). Invasive VNS consists of a subcutaneous pulse generator (Cyberonics) typically implanted in the left chest wall connected by a wire to the bipolar lead wrapped around the left cervical vagus nerve. The stimulation consisted of electrical pulses, 30 s in duration at intervals of 5 min.

The rationale of using non-invasive VNS for headache management derives from initial animal studies showing that VNS alleviates trigeminal allodynia and pain in rats after only two minutes of stimulation, without the need for an implantable device. Moreover, microdialysis experiments demonstrate that non-invasive VNS stimulation suppresses the increase in extracellular glutamate in allodynic rats after glycerin trinitrate (GTN) treatment. The suppression of the increased glutamate levels seems to take place in the trigeminal nucleus caudalis (TNC), which is a key structure involved in the pathophysiology of primary headaches (Oshinsky , et al., 2014).

A non-invasive, portable transcutaneous VNS device (gammaCore) has recently been tested in the acute and preventive treatment of primary headaches, including the TACs. Non-invasive VNS was audited in 25 patients with episodic or chronic CH over a 12-month period in an open label fashion. The treatment was given acutely (three consecutive doses) to treat an attack or in a preventive fashion (two to three consecutive doses) twice daily. Patients were trained to deliver the stimulation on the side of the neck ipsilateral to the majority of the cluster attacks. The outcomes were collected from patients' subjective opinion. Nineteen out of 25 patients were included in the final analysis. Fifteen out of 19 patients (79%) reported a reduction of approximately 50 % in CH attack frequency during the treatment period. Four patients did not report any improvement. In addition to a prophylactic effect, some patients also obtained a favourable abortive effect in approximately 11 min. The treatment was generally well tolerated (Nesbitt , et al., 2015). This initial experience was corroborated by a prospective open-label study that randomised CCH patients on standard of care alone and patients on standard of care plus nVNS. During the randomised phase, the group

treated with nVNS showed a greater reduction in number of CH attacks/week vs controls (-5.9 vs -2.1) and about 40% of patients treated with nVNS experienced at least 50% reduction in mean number of attacks/week compared to 8.3% of the controls (Gaul , et al., 2016). This initial evidence may suggest a useful role of nVNS in CH patients before consideration for invasive neurostimulation therapies.

1.2.2. Paroxysmal Hemicrania

1.2.2.1. Introduction and background

Paroxysmal hemicrania (PH), like CH, is characterized by strictly unilateral, brief, excruciating headaches that occur in association with cranial autonomic features. PH differs from CH mainly in the higher frequency and shorter duration of individual attacks, although there is a considerable overlap in these characteristics. However, unlike CH, PH responds completely to indometacin (Headache Classification Subcommittee of The International Headache, 2013), thereby underlining the importance of distinguishing it from CH.

1.2.2.2. Epidemiology

PH is a rare syndrome. However, with increasing awareness, it is being recognized more frequently. The prevalence of PH is not known and seems to occur equally in females and males (Cittadini , et al., 2008). It can begin at any age, although the most common age of onset is the second or third decade of life (Boes , et al., 2002).

1.2.2.3. Clinical features

The attack profile of PH is highly characteristic (Antonaci , et al.). The headache is strictly unilateral. The maximum pain is most often centred on the ocular, temporal, maxillary or frontal regions; less often, the pain is centred on the neck, occiput or the retro-orbital regions. The pain is typically excruciating in severity and described as a

throbbing, aching or boring sensation. The headache usually lasts 10–30 minutes but can range from 2 minutes to 45 minutes. It has an abrupt onset and cessation. Interictal discomfort or pain is present in up to 60% of the patients (Cittadini , et al., 2008).

Attacks of PH invariably occur in association with ipsilateral cranial autonomic features. The IHS classification criteria for chronic paroxysmal hemicrania require the attacks to be accompanied by at least one of the following, which have to be present on the pain side: conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, ptosis or eyelid oedema (Headache Classification Subcommittee of The International Headache, 2013). Photophobia and nausea may accompany some attacks, although vomiting and phonophobia are rare. During episodes of pain, approximately 50–80% of the sufferers are agitated and restless, and one-quarter are described as being aggressive during the pain. In PH, the attacks occur at a high frequency. Typically, patients have more than five attacks daily, although the frequency of attacks shows a considerable fluctuation, ranging between one and 40 daily. The attacks occur regularly throughout the 24-h period, without a preponderance of nocturnal attacks as in CH. While the majority of attacks are spontaneous, approximately 10% of the attacks may be precipitated mechanically, either by bending or by rotating the head. Attacks may also be provoked by external pressure against the transverse processes of C4-5 and C2 root or the greater occipital nerve. Alcohol ingestion triggers headaches in only 7% of the patients (Antonaci , et al.).

1.2.2.4. Classification

PH is classified depending on the presence of a remission period (Headache Classification Subcommittee of The International Headache, 2013). About 35% of the patients have episodic paroxysmal hemicrania (EPH), which is diagnosed when there are clear remission periods between bouts of attacks. The remaining 65% of the patients have chronic paroxysmal hemicrania (CPH), which is diagnosed when patients have either no remission within one year or the remissions last less than one month (Cittadini , et al., 2008).

Table 3. International Headache Society diagnostic criteria for Paroxysmal hemicrania

A. At least 20 attacks fulfilling criteria B-D

B. Severe unilateral orbital, supraorbital and/or temporal pain lasting 2-30 minutes

C. At least one of the following symptoms of signs, ipsilateral to the pain:

1) Conjunctival injection and/or lacrimation.
2) Nasal congestion and/or rhinorrhoea
3) Eyelid oedema
4) Forehead and facial sweating
5) Forehead and facial flushing
6) Sensation of fullness in the ear
7) Miosis and/or ptosis

D. Attacks have a frequency above five per day for more than half of the time.

E. Attacks are prevented absolutely by therapeutic doses of indomethacin

F. Not better accounted for by another ICHD-3 diagnosis

Adapted from The International Headache Society Classification Committee of (2013)

1.2.2.5. Differential diagnosis

The differential diagnoses that need to be considered are: secondary causes of PH and other TACs. PH can be differentiated from CH and SUNCT, with a trial of indometacin. No cases of SUNCT responding completely to indometacin have been reported. Conversely, cases of CH responsive to indometacin have been rarely described. Although these cases should instigate new research studies aiming to understand the mechianisms of action of indometacin, in clinical practice, indometacin-responsive CH, if needed, should be treated with medications known to be effective in both CH and PH, namely: topiramate, verapamil and GONB. HC is a strictly unilateral headache that is continuous and associated with ipsilateral cranial autonomic symptoms. Both PH and HC are exquisitely responsive to indometacin and have to be differentiated on the basis of the clinical phenotype (Matharu , et al., 2003).

A large number of secondary cases of PH have been described, although a causal relationship is difficult to ascertain in most of these cases (Cittadini, et al., 2009). An

MRI brain scan is a reasonable screening test in all patients with PH. As with CH, an association with pituitary tumors has been reported, suggesting that all TAC patients should be carefully assessed for pituitary disease-related symptoms, but further investigations with MRI of the pituitary gland should only be undertaken in patients with atypical features, abnormal examination or those resistant to the appropriate medical treatments.

1.2.2.6. Treatment

Indometacin

The treatment of PH is prophylactic. Indometacin is the treatment of choice and, in fact, has been deemed the *sine qua non* for establishing the diagnosis (Headache Classification Subcommittee of The International Headache, 2013). Complete resolution of the headache is prompt, usually occurring within 1–2 days of initiating the effective dose. The typical maintenance dose ranges from 25 mg to 100 mg daily, but doses up to 300 mg daily are occasionally required (Cittadini , et al., 2008). In patients with EPH, indometacin should be given for slightly longer than the typical headache bout and then gradually tapered. In patients with CPH, long-term treatment is usually necessary, although drug withdrawal should be advised at least once every 6 months. Gastro-protective agents should always be considered for patients who require long-term treatment.

To circumvent some of the problems with oral indometacin administration (i.e., difficulties with achieving adequate dose due to side-effects), an intramuscular trial of indometacin, the "Indotest," has been shown to be a rapid and useful test for PH and HC (Antonaci , et al., 1998), although the role of a placebo response is not defined. Therefore, a modified indotest (placebo-controlled intramuscular indometacin 100 mg) has been proposed and validated in a small cohort of patients with HC (Matharu , et al., 2004). The modified indotest has been shown to be a useful alternative to oral indometacin also in a series of PH patients (Cittadini , et al., 2008).

Other medications

There has been some limited success in the treatment of PH with cyclooxygenase-2 (COX-2) inhibitors, rofecoxib (Lisotto , et al., 2003; Chakravarty , et al., 2004; Siow , 2004) and celecoxib (Siow , 2004; Mathew , et al., 2000). However, prolonged use of both of these agents has recently been linked with an increased risk of myocardial infarctions and strokes, and this culminated in the withdrawal of rofecoxib from the market worldwide (Lenzer , 2005). In view of this, the available COX-2 inhibitors should be prescribed only with great caution in PH. Topiramate has been found to be effective in three cases of PH (Cohen , et al., 2009; Camarda , et al., 2008). GONB has been described as helpful in this condition (Afridi , et al., 2006; Rossi , et al., 2005) and can, therefore, be tried, especially in view of its relatively safe adverse effect profile. Further data are necessary in order to clarify the consistency of its effect in PH.

1.2.3. Hemicrania Continua

1.2.3.1. Introduction and Background

Hemicrania continua (HC) unlike PH and CH, is a continuous strictly unilateral headache with superimposed exacerbations. The headache is associated with facial autonomic symptomatology and restlessness. HC is an indometacin-responsive headache and, similarly to PH, it responds absolutely to therapeutic doses of indometacin.

1.2.3.2. Epidemiology

The mean age of onset of HC is in the thirties, but the condition can begin at any age. The condition has a slight female preponderance with a sex ratio of 1.6:1 (Cittadini , et al., 2010; Peres , et al., 2001).

1.2.3.3. Clinical Features

HC is characterised by a unilateral, continuous headache of mild to moderate intensity, centred over the temporal, orbital, retrorbital and frontal regions (Cittadini , et al., 2010). Exacerbations of moderate or severe headache can occur daily to weekly, though

in a minority of patients the severe attacks can occur on a monthly basis and they can last few hours to several days. The constant background pain or the more severe exacerbations are associated with at least one of the common cranial autonomic symptoms and restlessness seems to occur in about 70% of patients (Cittadini , et al., 2010). The vast majority of HC patients report at least one migraine feature with the headache, especially photophobia, phonophobia and nausea. The presence of a migraine biology (that is personal and/or family history of migraine) in HC patients is remarkably high (Kuhn , et al., 2005; Palmieri , et al., 2004; Peres , et al., 2002; Cittadini , et al., 2010).

The latest version of the IHS classification proposed that HC is subclassified as HC, remitting subtype, where the headache is interrupted by remission periods of at least one day and HC unremitting subtype, where the headache is continuous for at least one year without any remissions (Headache Classification Subcommittee of The International Headache, 2013). Most patients with HC display the chronic unremitting form.

A complete response to indometacin is a prerequisite for diagnosis according to the IHS classification criteria (Headache Classification Subcommittee of The International Headache, 2013) (Table 4).

Table 4. International Headache Society diagnostic criteria for Hemicrania continua

A. Unilateral headache fulfilling criteria B-D
B. Present for > 3 months, with exacerbations of moderate or greater intensity
C. Either or both of the following:
    1. At least one of the following symptoms or signs, ipsilateral to the headache:
        a) Conjunctival injection and/or lacrimation.
        b) Nasal congestion and/or rhinorrhoea
        c) Eyelid oedema
        d) Forehead and facial sweating
        e) Forehead and facial flushing
        f) Sensation of fullness in the ear
        g) Miosis and/or ptosis
        f) A sense of restlessness or agitation, or aggravation of the pain by movement
D. Responds absolutely to therapeutic doses of indomethacin
E. Not better accounted for by another ICHD-3 diagnosis

Adapted from The International Headache Society Classification Committee of (2013)

Medical and Surgical management

By definition, HC must show a complete response to indometacin. Alternatives to indometacin have been studies in case series only, hence their level of evidence is low. They include: selective COX-2 inhibitors (celecoxib, rofecoxib), which have been shown to be effective for the treatment of HC, but due to cardiovascular side effects, particularly at higher doses, caution should be used with this class of medication. Topiramate (Matharu , et al., 2006; Brighina , et al., 2007; Camarda , et al., 2008), Gabapentin (Spears , 2009; Moura , et al., 2012) and melatonin (Rozen , 2006; Spears , 2006) have also shown to be beneficial in patients with HC. Other antiepileptic drugs such as valproic acid (Lambru , et al., 2008) or pregabalin (Coşkun , et al., 2014) have been used with variable response for HC. Cases of HC responsive to verapamil have also been reported (Rajabally , et al., 2005; Rozen, 2006). Interestingly high flow oxygen and injectable or oral sumatriptan seem not to exert any abortive effect during the severe HC exacerbations (Cittadini , et al., 2010).

Trigeminal and occipital nerve blocks in HC have been used in the management of HC with success. Guerrero and colleagues tested the outcome of at least one anaesthetic block of the GON (greater occipital nerve) or SON (supraorbital nerve), or an injection of corticosteroids in the trochlear area in nine patients with HC who did not tolerate indometacin. All these patients experienced total or partial improvement lasting from two to 10 months. Moreover, it seemed that in those patients where the blocks were repeated, the response duration increased (Guerrero , et al., 2012).

ONS has shown promising evidence in some small open-label studies of patients with refractory HC. Schwedt and colleagues reported two patients with HC who were treated successfully with ONS (Schwedt , et al., 2006). Subsequently, Burns and colleagues used a BION microstimulator in six people with HC. At a follow-up of 6–21 months, four patients had pain reduction of 80–90%, suggesting the efficacy of this therapy also in this condition (Burns , et al., 2008).

1.2.4. Short-Lasting Unilateral Neuralgiform headache with Conjunctival injection and Tearing (SUNCT) and Short-Lasting Unilateral Neuralgiform headache with autonomic symptoms (SUNA)

1.2.4.1. Introduction and background

Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) is a recently-described headache disorder characterised by short-lasting unilateral headache attacks accompanied by ipsilateral lacrimation and conjunctival injection. In recognition of the possibility that all patients with generically the same condition might not have both conjunctival injection and tearing, the IHS Classification Committee considered that SUNCT syndrome may be a subset of a broader entity called short-lasting unilateral neuralgiform headache attacks with autonomic symptoms (SUNA). In SUNA only one cranial autonomic feature is sufficient to fulfil the diagnostic criteria (Headache Classification Subcommittee of The International Headache, 2013).

1.2.4.2. Epidemiology

SUNCT is relatively rare, with a recent study showing a prevalence of 6.6/100,000 and an incidence of 1.2/100,000 (Williams , et al., 2008). The disorder has a male preponderance, with a gender ratio of 2:1. In a small case series of nine SUNA patients, the disorder seemed to display a female preponderance with a gender ration of 2:1. The typical age of onset is between 40 and 70 years, with a mean age of onset at 48 years (Cohen , et al., 2006).

1.2.4.3. Clinical features

SUNCT is a primary headache disorder first described in 1978 (Sjaastad, et al., 1978). The full description of the syndrome stems from 1989 (Sjaastad , et al., 1989). The first case series of 21 patients with SUNCT was published six years after the first description (Pareja , et al., 1997). The Authors found a robust male preponderance (male: 17, female: 4), similarly to CH. However, unlike CH, the mean age at onset of the condition was 51 years old. Attacks were strictly unilateral, most frequently centred over the orbital/periorbital area, with an erratic temporal pattern characterized by bouts of pain and remissions period where the condition would go quiescent. The attacks were burning, electrical, or stabbing in character and moderate to severe in intensity. Conjunctival injection and lacrimation were both constant and prominent accompaniments of an attack. Rhinorrhea or nasal obstruction were also frequent, although not invariably present and possibly less marked. In 18 patients, conjunctival injection, lacrimation, and rhinorrhea or nasal stuffiness were all present. Some patients also reported eyelid oedema, ptosis, facial redness, nausea and photophobia during the attacks. The onset of pain was invariably abrupt, and the maximum intensity was usually reached within a few seconds. The attack duration varied between patients, ranging between 5-300 seconds. The attacks could follow different patterns: "plateau-like," "repetitive," saw-tooth-like," and "plateau-like plus exacerbations". The attack frequency also varied broadly amongst patients, ranging from less than one attack/day to 30 attacks/hour. Attacks could occur at any time of the day. Nocturnal attacks were also reported. In 18 out of 21 patients (86%) attacks could be precipitated by several

stimulations in the trigeminal territory ipsilaterally to the side of the pain, seldom in the extratrigeminal territory (neck rotation). The reported triggers included: mastication (61.1%), neck movement (50%), touching forehead (44.4%), touching ala nasi (33.3%), touching hair (16.7%), touching eyelids (22.2%), rapid eye movements (27.8%), blowing nose (27.8%), neck rotation towards symptomatic side (27.8%), washing face (22.2%), eating (22.2%), coughing (22.2%), brushing teeth (22.2%), swallowing (22.2%), talking (16.7%), squeezing eyelids (16.7%), pressing tongue against palate (16.7%), sneezing (11.1%), yawning (11.1%), eating ice cream (11.1%), bright light (11.1%), eye strain, touching face (11.1%), touching upper lip (11.1%), neck extension (11.1%), touching cheek (5.5%), drying face (5.5%), shaving, tasting spicy foods (5.5%), tongue movements (5.5%), neck flexion (5.5%), bending forward (5.5%) cold air (5.5%) and loud noise (5.5%). The majority of patients presented with both triggered and spontaneous attacks. Only two patients had exclusively spontaneous attacks. There seem not to be any refractory period following a triggered attack in all but one patient.

Subsequently, Matharu and colleagues reviewed the epidemiology, clinical features, aetiology and management of the SUNCT patients published until 2003 (Matharu , et al., 2003). This study confirmed most of the clinical findings reported in the first series. SUNCT was confirmed to be a condition with male preponderance. However, compared to the initial cases description, there was a trend towards increasing female preponderance (gender ratio of 1.3:1). In terms of clinical phenotype, it emerged that very rarely the pain in SUNCT can alternate sides or even occur on both sides of the head simultaneously. Unlike the first series of patients described in the literature, where the severity of the cranial autonomic symptomatology was more pronounce that the severity of the headache, it emerged that the pain in SUNCT was more often severe, rather than mild or moderate. The short-lasting duration of the SUNCT attacks was confirmed in this study. However, several case reports suggested that attacks could last longer than thought (600 seconds to 120 minutes). SUNCT was thought not to be associated with a background inter-paroxysmal pain. However, six out of 50 patients reviewed (12%), described the occurrence of a dull interictal ipsilateral mild pain over the same site that could be continuous (four cases) or intermittent (two cases). In terms of periodicity, the initial descriptions of SUNCT suggested that the condition occurred with an episodic periodicity, similar to CH. However, in Matharu's review, 11 patients displayed a chronic form of SUNCT, mainly chronic from onset.

In terms of aetiology of SUNCT, most cases described in the literature at that time were primary, though secondary cases were reported. The most frequent pathologies causing SUNCT-like symptoms were posterior fossa abnormalities and pituitary tumors. Seven case reports of SUNCT secondary to a posterior fossa abnormality were described at that time. They included: cerebellopontine angle arteriovenous malformations in two patients (Bussone, et al., 1991; Morales , et al., 1994); a brainstem cavernous hemangioma (De Benedittis , 1996); a posterior fossa lesion in a patient with HIV/AIDS (Goadsby, et al., 1997); severe basilar impression causing pontomedullary compression in a patient with osteogenesis imperfecta (ter Berg , et al., 2001); craniosynostosis resulting in a foreshortened posterior fossa (Morís , et al., 2001); and ischemic brainstem infarction (Penart , et al., 2001). MRI evidence of neurovascular conflict with the ipsilateral trigeminal nerve by the superior cerebellar artery was also identified in a SUNCT patient (Zidverc-Trajkovic , et al., 2005). Pituitary adenomas began to be associated with SUNCT. Two of the patients with SUNCT-like phenotype had a microprolactinoma and two had a macroprolactinoma with cavernous sinus invasion (Massiou , et al., 2002).

The largest series of SUNCT along with the first, albeit small, series of SUNA patients was described by Cohen and colleagues in 2006. They prospectively studied the clinical and epidemiological characteristics of 43 patients with SUNCT and nine patients with SUNA (Cohen , et al., 2006).

As far as the defining clinical features of SUNCT and SUNA syndromes are concerned, the study confirmed the preponderance of the painful attacks on the right-hand side (42%) as opposed to the left (38%). Nine patients had unilateral, side-alternating attacks and one SUNCT patient had bilateral attacks. Although 78% of the patients had pain in peri-orbital, retro-orbital and temporal regions, 33% of SUNCT and SUNA patients had pain in the V2 trigeminal territory and 33% of the SUNA patients had pain in V3 trigeminal territory. By definition, all of the SUNCT patients had both ipsilateral conjunctival injection and lacrimation associated with the attacks. Almost half of the patients also reported eyelid oedema and ptosis during the pain; 40% had nasal blockage and 53% of the patients had ipsilateral rhinorrhoea associated with their attacks. Nine percent of the SUNCT patients had facial flushing, two of which were unilateral and two bilateral. Seven percent of patients had facial sweating, two of which

were unilateral and two bilateral. Nine percent had other cranial autonomic symptoms. The vast majority of patients rated their attacks as very severe and occurring following three patterns: single stabs, group of stabs or saw-tooth pattern of stabs. The single stabs pattern was more often associated with shorted-lived attacks as opposed to the groups of stabs and the saw-tooth profiles, which were associated with longer lasting episodes. The number of daily attacks was quantifiable in most patients ranging from two to 600/day, though there were some patients in whom the attacks were so numerous that they could not be accurately quantified. The vast majority of SUNCT patients had both triggered and spontaneous attacks. One patient had triggered attacks only and six patients had entirely spontaneous attacks. The vast majority of SUNCT patients (79%) could trigger their attacks by various cutaneous stimulations. Touching the face ipsilaterally to the side of the pain, chewing, eating, wind blowing on the face, washing the face and brushing teeth were the most prevalent types of triggers. Alcohol was not a trigger. Given the presence of cutaneous and intraoral triggers, the concept of refractory period, which has traditionally been described in the trigeminal neuralgia (TN) literature, has also been applied in SUNCT. A refractory period is the lack of the ability of triggering an attack immediately after the cessation of the previous one by continuining with the triggering action. All except two SUNCT patients denied the presence of a refractory period.

As far as the non-defining clinical criteria were concerned, the study confirmed a male preponderance in SUNCT as well as the mean age of onset, which was in the late forties-early fifties (48 years, range: 19–75 years). In terms of other features associated with the pain, 25 out of 40 SUNCT patients felt agitated during an attack and approximately one third of SUNCT patients reported a combination of nausea, photophobia and phonophobia during the SUNCT attacks. Interestingly 47% of SUNCT patients experienced a background interictal pain, with a negative indometacin test.

In terms of pattern of occurrence, this study confirmed the initial trend noticed in Matharu and colleagues review (Matharu , et al., 2003). Indeed, 70% of SUNCT patients had a chronic form and 30% an episodic form, which is in contrast to the pattern described by Pareja and Sjaastad, where most patients reported an episodic pattern (Pareja , et al., 1997).

1.2.4.4. SUNA: initial clinical description

SUNA was introduced in the Appendix of the ICHD-2 and its diagnostic criteria proposed mainly for research purposes, aiming to unravel the definite phenotype of the condition and to clarify whether SUNA and SUNCT should be kept separate or considered one clinical entity (Headache Classification Subcommittee of The International Headache Society., 2004).

The clinical description of the first, although small, series of SUNA patients suggested that the SUNA clinical phenotype may be similar to that of SUNCT in terms of the length, frequency and severity of attacks; the character of the pain; the triggerability of the attacks, the lack of refractory period between attacks, and the nocturnal occurrence of the pain. Unlike SUNCT, all of SUNA patients seem to display a chronic pattern. Although in SUNA the pain was mainly centred in V1, the temple and V3 territories were involved more often than in SUNCT. Light touch of the face ipsilaterally to the side of the pain was not reported to be a trigger in the nine SUNA patients, unlike SUNCT where about two thirds of SUNCT patients reported touching the face as a precipitating factor. Cranial autonomic symptoms were more varied and less pronounced in SUNA, where the combination of conjunctival injection and lacrimation was not allowed. Despite this initial description, the SUNA phenotype has not been fully detailed and comparison with SUNCT has not been possible. For this reason, SUNCT and SUNA have been kept separate in the latest revision of the IHS classification (Headache Classification Subcommittee of The International Headache, 2013).

1.2.4.5. Nosological status

In 1997, Goadsby and Lipton (Goadsby, et al., 1997) proposed the first set of diagnostic criteria for SUNCT. They proposed that SUNCT should be characterized by headache attacks of unilateral moderately severe orbital or temporal stabbing or pulsating pain lasting from 15-120 seconds and occurring 3 to 100 times/day. Pain needed to be associated with at least one of conjunctival injection, lacrimation, nasal congestion, rhinorrhea, ptosis and eyelid oedema. Conjunctival injection needed to be most often

present and very prominent. In view of the combination of pain in the trigeminal territories associated with ipsilateral cranial autonomic symptoms, they proposed to classify SUNCT together with CH and PH under the TACs.

After validating its phenotype in 50 patients, SUNCT syndrome was included in the second edition of the ICHD (Table 5), whereas SUNA was included in the Appendix of the classification and its diagnostic criteria were proposed (Table 6), hoping for further research in the field to clarify whether SUNCT and SUNA were two sides of the same coin or two separate entities (Headache Classification Subcommittee of The International Headache Society., 2004). The proposed criteria for SUNA differed to the one of SUNCT for the number of cranial autonomic symptoms required, with at least one in the former and two in the latter condition; in terms of attack duration, which was extended up to 10 minutes for SUNA; attack frequency, which was generically set at ≥1/day for more than half of the time. The IHS classification Committee also acknowledged the high proportion of attacks triggered by trigeminal cutaneous stimulation and added the concept of absence of a refractory period following a triggered attack. Of note, the array of cranial autonomic signs and symptoms that normally accompany the pain in the other TACs was shrunk to only a few (Table 6).

Table 5. International Headache Society diagnostic criteria for SUNCT

A. At least 20 attacks fulfilling the following criteria B-D:
B. Attacks of unilateral orbital, supraorbital, or temporal, stabbing or pulsating pain lasting from 5-240 seconds
C. Attack frequency from 3 to 200/day
D. Pain is accompanied by ipsilateral conjunctival injection and lacrimation
E. Not attributed to another disorder

Adapted from Headache Classification Committee of The International Headache Society (2004)

Table 6. International Headache Society diagnostic criteria for SUNA (Appendix)

A. At least 20 attacks fulfilling the following criteria B-E:
B. Attacks of unilateral orbital, supraorbital, or temporal, stabbing or pulsating pain lasting from 2 seconds to 10 minutes
C. Pain is accompanied by one of:
1. Conjunctival injection and/or lacrimation
2. Nasal congestion and/or rhinorrhoea
3. Eyelid oedema
D. Attacks occur with a frequency of ≥ 1 per day for more than half of the time
E. No refractory period follows attacks triggered from triggers areas
F. Not attributed to another disorder

Adapted from Headache Classification Committee of The International Headache Society (2004)

In the revised beta version of the IHS classification recently published, SUNCT and SUNA were grouped together under the umbrella term "Short-lasting unilateral neuralgiform headache attacks" within the TACs group. SUNCT and SUNA were still classified as two different subtypes and were kept separated from each other, in view of the lack of further studies after Cohen and colleagues work (Cohen , et al., 2006). In the new proposed set of diagnostic criteria, the criterion of lack of refractory period following attacks triggered from triggers areas was removed. Similarly, to the other TACs, SUNCT and SUNA were sub-classified into the episodic form, with attacks occurring in periods lasting from seven days to one year, separated by pain-free periods lasting at least one month; or the chronic form, with attacks occurring for more than one year without remission, or with remission periods lasting less than one month (Headache Classification Subcommittee of The International Headache, 2013).

Table 7. International Headache Society diagnostic criteria for Short-lasting unilateral neuralgiform headache attacks

A. At least 20 attacks fulfilling the following criteria B-D:

B. Moderate or severe unilateral head pain, with orbital, supraorbital, or temporal and/or other trigeminal distribution, lasting for 1-600 seconds and occurring as single stabs, series of stabs or in a saw-tooth pattern.

C. At least one of the following cranial autonomic symptoms or signs, ipsilateral to the pain:

1. Conjunctival injection and/or lacrimation
2. Nasal congestion and/or rhinorrhoea
3. Eyelid oedema
4. Forehead and facial sweating
5. Forehead and facial flushing
6. Sensation of fullness in the ear
7. Miosis and/or ptosis

D. Attacks have a frequency of at least one a day for more than half of the time when the disorder is active

E. No better accounted for by another ICHD-3 diagnosis

Adapted from Headache Classification Committee of The International Headache Society (2013)

1.2.4.6. Differential diagnosis

The vast majority of SUNCT and SUNA are primary, though ruling out secondary forms of SUNCT is mandatory in view of the potential life-threatening nature of some underlying brain pathologies. Within the primary forms of SUNCT, the differential diagnosis encompasses a broad group of conditions characterised by unilateral short-lasting neuralgiform headache and facial pain attacks. This group includes: the other TACs, trigeminal neuralgia purely paroxysmal, trigeminal neuralgia with concomitant persistent facial pain and primary stabbing headache. Table 8 outlines the main clinical differences between SUNCT and SUNA and the other TACs. Since a significant proportion of SUNCT and SUNA patients may experience a continuous background

pain on the same side and site of the paroxysmal attacks, an indometacin trial may be required to differentiate them from HC.

Table 8. Differentiating features between SUNCT/SUNA and the other TACs (HC excluded)

	Cluster headache	**Paroxysmal hemicrania**	**SUNCT/SUNA**
Pain:			
Type	Sharp, Throbbing	Sharp, Throbbing	Stabbing, Burning
Severity	Very severe	Very severe	Very severe
Site	Orbit, temple	Orbit, temple	Orbit, temple
Attack frequency	1/alternate day – 8/day	>5/day for more than half the time	≥1 day for more than half the time
Duration of attack	15-180mins	2-30mins	1-600secs
Circadian periodicity	70%	45%	Absent
Autonomic features	Yes	Yes	Yes
Restless or agitated	90%	80%	65%
Migrainous features	Yes	Yes	Rare
Triggers:			
Alcohol	++	+	-
cutaneous	-	-	++
Indometacin effect	- (rarely +)	++	-

HC: hemicrania continua. SUNA: short-lasting neuralgiform headache attacks with autonomic symptoms. SUNCT: short-lasting neuralgiform headache attacks with conjunctival injection and tearing; TACs: trigeminal autonomic cephalalgias.

Differentiating SUNCT from trigeminal neuralgia (TN) can be challenging, as there is a considerable overlap in the clinical phenotypes of the two syndromes; indeed, some authors postulated that SUNCT may be a TN variant (Sesso, 2001). Some clinical

features can aid in differentiating these disorders. These features are outlined in Table 9. In SUNCT the pain is most frequently centred over the V1 trigeminal territory, whereas in TN in mainly centred in V2-V3. The length of each attack is normally longer in SUNCT compared to TN. One of the signature features of SUNCT, which should not occur in TN is the presence of prominent cranial autonomic signs and symptoms ipsilaterally to the side of the pain. Additionally, those SUNCT patients with attacks triggered by trigeminal stimulation usually report that they can trigger an attack immediately after the termination of the previous one without any breaks (absence of refractory period), unlike in TN.

Primary stabbing headache (PSH) is characterized by short-lived episodes of stabbing pain centred over the V1 trigeminal territory, occurring in single stabs or cluster of stabs. The attacks normally last a few seconds up to a minute and can occur on a daily or weekly basis. One of the cornerstone clinical features of PSH is that the stabbing attacks tend to change site of occurrence within the trigeminal distribution, normally sparing the face. Since the majority of the attacks are spontaneous and there are no associated cranial autonomic features, PSH can usually be distinguishable from SUNCT and SUNA (Pareja , et al., 1999).

SUNCT-like phenotypes are typically caused by pathologies of the posterior fossa or pituitary gland lesions. An observational study that defined the headache characteristics in pituitary tumor patients reported SUNCT-like phenotype in 5% of these patients, although the patient population studied was not representative of pituitary tumor patients as the study was performed in a tertiary referral neurosurgical setting (Levy, et al., 2005). In view of the remarkable clinical similarities between SUNCT, SUNA and TN, Williams and Broadley systematically looked for trigeminal neurovascular conflict with dedicated trigeminal MRI scans. In their small cohort of SUNCT and SUNA patients they found a high proportion of ipsilateral vascular loops in contact with the trigeminal nerve (88%) (Williams , et al., 2008). Therefore, a full diagnostic work-up for SUNCT/SUNA should include a brain MRI scan with dedicated trigeminal and pituitary fossa views and a trial of indometacin to exclude indometacin-responsive headaches, if appropriate.

Table 9. Differentiating features of SUNCT and trigeminal neuralgia

Feature	SUNCT	Trigeminal Neuralgia
Gender ratio (male: female)	1.5:1	1:2
Site of pain	V1	V2/3
Severity of pain	Moderate to severe	Very severe
Duration (seconds)	1-600	<1-120
Autonomic features	Prominent	None
Refractory period	Absent	Present
Response to carbamazepine	Partial	Complete

SUNCT: short-lasting neuralgiform headache attacks with conjunctival injection and tearing

1.2.4.7. Natural History

The natural history of SUNCT is poorly understood yet and longitudinal studies are needed to clarify the natural history of this disorder.

1.2.4.8. Medical management

The management of SUNCT syndrome has historically been considered extremely challenging. Some reports have pointed towards the possible efficacy of certain classes of drugs. However, due to the rarity of these disorders, the series published so far have included very small numbers of patients and have produced data on a very limited number of medications. No RCTs have been published so far. In addition, in most studies, efficacy measures are not described adequately. As far as SUNA is concerned, it is still unclear whether medications effective in SUNCT are also effective in SUNA.

Abortive treatments

Since the attacks are very short lasting, abortive therapy strategies are not a useful concept in SUNCT/SUNA.

Preventive treatments

Lamotrigine

Before the use of lamotrigine, SUNCT was considered to be highly refractory to medical treatments. Lamotrigine acts mainly by blockade of voltage-dependent sodium channel conductance, although antifolate, antiglutamate, and antiaspartate actions have been suggested (Zona, et al., 1997; Lees, et al., 1993). The first report of possible effectiveness of this medication was the case of a 66-year-old woman with a seven-month history of SUNCT. The attacks were characterized by a short lasting (5 to 10 seconds) severe throbbing or stabbing pain centred over the left retro-orbital region and accompanied by ipsilateral prominent tearing, conjunctival injection, and nasal obstruction. The attacks were all occurring spontaneously with a daily frequency of ten to 15 per day. The attacks did not respond to indometacin and carbamazepine, but lamotrigine at the dose of 150 mg/day rendered the patient pain free (D'Andrea , et al., 1999). Since then several case reports and small case series have shown the efficacy of lamotrigine in SUNCT (Table 10). Lamotrigine at the dose of 200 mg/day was highly effective in a patient with atypical SUNCT due to a microprolactinoma. The headache was characterized by bilateral multiple daily attacks centred over the first and second trigeminal divisions. The headache did not respond to amitriptyline, sodium valproate, carbamazepine, gabapentin, sumatriptan subcutaneous injections and high flow oxygen (Zidverc-Trajkovic , et al., 2009). This case suggests that appropriate investigations should be arranged even in cases responding to medications, if the phenotype is atypical.

Table 10. SUNCT cases responding to lamotrigine

	Number of patients	Dose achieving improvement	Dose achieving pain-freedom	Side effects
D'Andrea et al (1999)	Patient 1	50 mg/day	150 mg/day	None
Leone et al (2000)	Patient 1: Patient 2:	75 mg/day -	125 mg/day 100 mg/day	None None
D'Andrea et al (2001)	Patient 1: Patient 2: Patient 3: Patient 4: Patient 5:	75 mg/day 50 mg/day 75 mg/day - 100 mg/day	125 mg/day 150 mg/day 125 mg/day 150 mg/day 200 mg/day	None None None None None
Gutierrez-Garcia (2002)	Patient 1	150 mg/day	200 mg/day	None
Malik et al (2002)	Patient 1	25 mg/day	400 mg/day	None
Chakravarty (2003)	Patient 1	-	200 mg/day	None
Piovesan et al (2003)	Patient 1	100 mg/day	300 mg/day	None

SUNCT: short-lasting neuralgiform headache attacks with conjunctival injection and tearing

Cohen described the outcome of 25 SUNCT and four SUNA patients treated with lamotrigine up to a dose of 400 mg/day. Seventeen out of 25 SUNCT patients (68%) obtained a meaningful therapeutic effect from the medication. Of the four SUNA patients, one (25%) reported some benefit (Cohen, 2007). A subsequent Australian series of 24 SUNCT (17 SUNCT, five SUNA and two patients with both SUNCT/SUNA phenotypes) of which six were chronic and 11 episodic SUNCT, three were chronic and two episodic SUNA and of those with both phenotypes, one had an episodic and the other had a chronic pattern. Lamotrigine was used up to the dose of 600 mg/day. The response to lamotrigine depended on the subtype of SUNCT; lamotrigine was reported to produce an excellent response in eight out of the 11 episodic SUNCT patients, but a poor response in those with the chronic form. Only one episodic SUNA patient reported a meaningful benefit with lamotrigine. Side effects during lamotrigine trials included skin rash, drowsiness and fatigue (Williams , et al.,

2008). In another series of 15 SUNCT patients, lamotrigine was tried in 13 out of 15 patients at a dose ranging from 75 to 150 mg/day. Of these patients 61.5% were considered responders. On the basis of the current evidence and although no randomised-controlled trials have been published, lamotrigine is at present considered the drug of choice for the preventive treatment of SUNCT (May, et al., 2006).

Topiramate

Topiramate has multiple mechanisms of action. It exerts its action through blockade of the voltage-gated sodium channels, enhancing GABA-mediated chloride influx involving GABA-A receptor and antagonism of the glutamate kainate/AMPA receptor (Schneiderman , 1998). Topiramate was reported to be effective in five SUNCT patients at doses up to 300 mg daily (Matharu , et al., 2002; Rossi , et al., 2003). Subsequently, 11 of 21 SUNCT patients (52%) benefited from topiramate given up to a dose of 400 mg/day in an open-label study whereas the only SUNA patient treated with topiramate did not notice any benefit (Cohen, 2007). One out of 15 SUNCT cases described recently benefited from topiramate 100 mg/day (Cação , et al., 2016). Topiramate has been shown to be effective in atypical cases of SUNCT. Kuhn and colleagues described the case of a young man who reported bilateral short lasting (30-120 seconds) multiple daily (20-30/day) painful headache attacks centred over the retro-orbital and temporal regions. The attacks were accompanied by bilateral tearing and conjunctival injection. Topiramate 200 mg/day improved the condition by reducing the frequency of occurrence of the attacks (Kuhn , et al., 2005). Another case of SUNCT-like symptoms triggered by orgasm and associated with persistent focal neurological signs and symptoms with normal detailed imaging of the neuroaxis has been reported to respond to high doses of topiramate (800 mg/day) (Khalil , et al., 2014).

Zonisamide

Zonisamide, which has got similar mechanisms of action to topiramate, has been tried in a SUNCT patient who did not tolerate carbamazepine with excellent results on long-term follow-up (Ikawa , et al., 2011).

Gabapentin

SUNCT has been shown to respond to gabapentin, with complete suppression of attacks in three of nine patients treated with 800 to 2700 mg daily (Graff-Radford , 2000; Hunt ,

et al., 2002; Porta-Etessam , et al., 2002). When tried in an open label fashion in 22 SUNCT and five SUNA patients at up to 3600 mg daily, it was reported to be effective in 60% of SUNA but only 45% of SUNCT patients (Cohen, 2007).

Carbamazepine

Carbamazepine acts by blockade of use- and frequency-dependent sodium channels, although a blockade of the N-methyl-D-aspartate receptor-activated sodium and calcium influx and effects on the purine, monoamine, and acetylcholine receptors also have been proposed (Macdonald, et al., 1993). The therapeutic response to carbamazepine has been reported in 33 SUNCT cases. In 22 of 33 patients (67%), there was no beneficial response with the sole use of carbamazepine. Among the 11 patients with a favourable response, eight of the 33 patients had a partial response and three had a complete or almost complete response (Matharu , et al., 2003). In a recent open label series of 36 SUNCT and five SUNA patients treated with carbamazepine, 40% of SUNCT and 20% of SUNA patients reported a favourable response (Cohen, 2007).

Oxcarbazepine

There is a case report of SUNCT responding to oxcarbazepine 600 mg daily (Dora , 2006). Another SUNCT patient was treated successfully using a combination of oxcarbazepine (600 mg daily) and gabapentin (400 mg daily) (Marziniak , et al., 2009).

Botulinum toxin A

OnabotulinumtoxinA infiltrated at four points around the orbit, injecting 10 U at each site, was reported to be consistently effective in a SUNCT patient refractory to oral treatments after 2.5 years of follow-up (Zabalza , 2012).

Other drugs

Several other medications, alone or in combination, have been employed to treat SUNCT and SUNA, including clomiphene (Rozen , et al., 2005; Rozen, 2014), and verapamil (Narbone , et al., 2005). Given the sparse data available on these drugs, it is difficult to comment on their efficacy.

Transitional treatments

There can be a lag of several days to a few weeks before the efficacy of preventive treatments becomes apparent. Transitional treatments, which produce a rapid suppression of the attacks for a limited period of time, can be used when waiting for the beneficial effect of a preventive treatment to become evident.

Intravenous lidocaine

Lidocaine is thought to mediate its antineuropathic pain effect through blockade of sodium channels (Mao, et al., 2000). The administration of intravenous (IV) lidocaine at a rate of 1.3 to 3.3 mg/kg/h suppressed the headaches in four patients with SUNCT syndrome (Matharu , et al., 2004). Subsequently 11 SUNCT and four SUNA patients reported a favourable outcome during administration of IV lidocaine at the dose of 1.5–3.5 mg/kg/h. Seven SUNCT patients were pain free for times varying between the duration of the infusion to six months. Three SUNCT patients had reduced attack frequency or severity, and one was lost to follow-up. All SUNA patients were pain free for two days to 12 weeks (Cohen, 2007). Given the quick and dramatic, but often short-lasting effect in most of SUNCT and SUNA patients, it is advisable to use IV lidocaine as a short-term treatment in patients who present in a so called "SUNCT status" (Pareja , et al., 1996) and also in order to avoid breakthrough attacks while switching from one preventive drug to another in patients with high load of attacks. Twenty-four hours ECG monitoring is mandatory during the infusion to monitor the occurrence of cardiac arrhythmias. Common IV lidocaine side effects include: cognitive impairment, dizziness, nausea, diarrhoea and paranoid ideation.

Greater occipital nerve blocks

A sub-occipital injection of a combination of lidocaine and a steroid was beneficial in five out of eight SUNCT patients (Cohen, 2007). Greater occipital nerve injections may render the patient pain free for weeks or months, allowing the introduction and dose escalation of preventive medications.

Corticosteroids

The response to corticosteroids has been reported in 21 SUNCT patients. Eleven patients were administered prednisone and six of the 11 patients taking prednisone reported a beneficial response; two reported a partial effect, one reported a complete response, and one, who was tried on prednisone in combination with valproate and

nortriptyline, improved transiently (Matharu , et al., 2003). Two patients, one with idiopathic SUNCT and one with SUNCT secondary to a prolactinoma were rendered pain free with oral prednisone 40 mg daily within 24-48 hours (de Lourdes Figuerola , et al., 2009). There can be a recrudescence of pain on either lowering the dose or discontinuing the corticosteroids.

Six of eight patients taking prednisolone or methylprednisolone reported a favourable effect (Matharu , et al., 2003). One patient treated with prednisolone and carbamazepine reported a complete response and the other treated with intravenous methylprednisolone, in combination with carbamazepine and followed by oral prednisolone, was seemingly rendered pain-free on three occasions for a variable period of time (Raimondi , et al., 1998). Oral administration of methylprednisolone for three to six weeks at the daily doses of ≤ 1 mg/kg was efficacious in suppressing bouts of SUNCT attacks in three patients with the episodic form of the disorder (Trauninger , et al., 2010). Intravenous methylprednisolone administered at the dose of 1 gram for three days completely suppressed attacks in a patient with a six-month history of SUNCT (Maihöfner , et al., 2013).

Surgical management

Some patients with the chronic form of SUNCT and SUNA are refractory to the available medical treatments, although the extent of this problem is unknown. This group of patients are left with severe disability. For these patients, surgical approaches have been tried. The approaches attempted can be subdivided into three main groups: ablative procedures of the trigeminal nerve, microvascular decompression of the trigeminal nerve and neurostimulation techniques. Table 11 summarize the *status quo* of the surgical management in SUNCT and SUNA syndromes.

Table 11. Surgical treatments for SUNCT and SUNA syndromes

	Age (years) /Sex	**Type**	**Headache duration (years)**	**Follow-up (months)**	**Outcome**	**Complications**
Trigeminal microvascular decompression (19 patients)	Range: 28-73 -14/M - 5/F	- 14 SUNCT - 5 SUNA	- Range: 1 month- 26 years	-Median (range): 14 (0.5-32)	12/19 patients: pain free	-5 patients: infection, vertigo, jaw pain) -2 patients: hearing loss, ataxia
VTA deep brain stimulation (11 patients)	- 50 (26-67) - 6 M and 5 F	- 8 SUNCT - 3 SUNA	9 (range: 4-20)	Median (range): 29 (7-63)	82% of patients had ≥50% benefit	- 1 system removed - 1 IPG repositioned - 7 biological events
Glycerol rhizotomy (4 patients)	- 80/M - 72/F - 52/M - 38/M	- SUNCT - SUNCT -SUNCT - SUNCT	- 25 - 10 - 8 - 2	- 87 - 90 - 7 - 5	- >50% benefit - >50% benefit - Pain free - Ineffective	- Facial sensory loss - Facial sensory loss - Missing data - Hypoesthesia
Gamma knife radiosurgery (5 patients)	- 82/M - 39/M - 28/M - 50/M - 83/F	- SUNCT - SUNCT - SUNCT - SUNCT - SUNCT	- 6 - 2 - 10 - 1 - 3	- 39 - 5 - 2 - 4 - 16	- Pain free - Mild benefit - Ineffective - Pain free - Pain free	- None - Anaesthesia dolorosa - Missing data - None - None
Gasserian ganglion balloon compression (2 patients)	- 66/F - 68/F	- SUNCT - SUNCT	- 0.1 - 17	- 120 - 18	- Pain free - >50% benefit	- None - None
Radiofrequency thermocoagulation (2 patients)	- 45/M - 60/F	- SUNCT - SUNCT	- 5 - 5	- 24 - 36	- Pain-free - Pain-free	- None - Trigeminal hypoesthesia

F: female; IPG: implanted pulse generator; M: male; SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

Ablative procedures of the trigeminal nerve

Data on ablative procedures on the trigeminal nerve are limited to isolated cases reports, and there is considerable potential for bias due to under reporting of unsuccessful cases or those with adverse outcomes. Additionally, these procedures may have irreversible complications, such as residual hypoesthesia, anesthesia dolorosa and keratitis. The most feared of these complications is anesthesia dolorosa, but in studies of rhizotomy for TN, this outcome is extremely rare (Harries , et al., 2011). Procedures that have been tried in SUNCT syndrome include: retrogasserian glycerol rhizolysis, percutaneous trigeminal ganglion compression, trigeminal ganglion thermocoagulation and gamma knife surgery.

Glycerol rhizolysis

Three of the four patients (three SUNCT and one SUNA) who underwent glycerol rhizolysis achieved complete pain relief lasting from seven months to four years. Two of them were successfully treated twice. Another SUNCT patient underwent glycerol rhizolysis with only two weeks of pain reduction (Hannerz , et al., 2002; Black , et al., 2002).

Radiofrequency thermocoagulation

Two SUNCT patients showed an apparent benefit following radiofrequency thermocoagulation of the trigeminal nerve that lasted for two and three years, respectively (Piovesan , et al., 2003; Matharu , et al., 2004).

Percutaneous trigeminal ganglion balloon compression

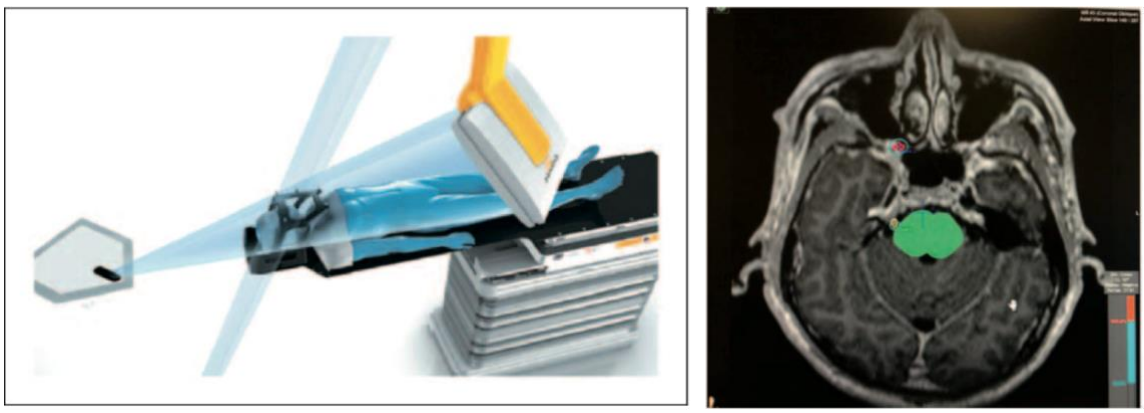
Three SUNCT patients were pain free after percutaneous balloon compression of the Gasserian ganglion with benefits ranging from 16 months to ten years of follow-up (Morales-Asín , et al., 2000; Hannerz , et al., 2002; Baabor , et al., 2010). Interestingly the SUNCT case with the longer lasting response to this procedure was a woman who presented to the authors' office with a six-week history of primary SUNCT (Baabor , et al., 2010). The patient was admitted into hospital and trials of NSAIDs, indomethacin 50 mg three times daily, carbamazepine up to 800 mg daily, corticosteroids, 100% oxygen via ventimask, opioids, and subcutaneous sumatriptan did not produce any benefits. The patient subsequently responded to percutaneous balloon compression of the Gasserian ganglion and was pain-free at 10 years follow-up.

However, lamotrigine, topiramate and gabapentin, which had been reported to be efficacious treatments in SUNCT, had not been tried in this case. Moreover, it can be difficult to establish whether the patient improved because of the procedure or because of spontaneous remission of an episodic form of SUNCT.

Gamma knife

Two SUNCT patients underwent gamma knife radiosurgery targeting the trigeminal nerve. The first experienced near complete pain relief for about two months, then the pain gradually recurred and he suffered from anesthesia dolorosa; the second reported no improvement (Black , et al., 2002). Two SUNCT patients underwent gamma knife targeting both the trigeminal nerve and the sphenopalatine ganglion. The first had complete pain resolution at 39 months follow-up, without medication (Effendi , et al., 2011); the second experienced only rare provoked attacks at four months' follow-up (Mathew , et al., 2012). A more recent case of refractory SUNCT treated with stereotactic radiosurgery using a non-invasive frameless technique, targeting both the trigeminal nerve and the sphenopalatine ganglion was described (Figure 3). At 16 months' follow-up, the patient was pain free with minimal side effects (Tan , et al., 2013), suggesting a better outcome of this procedure when both the trigeminal and parasympathetic pathways are targeted.

Figure 3. Non-invasive stereotactic radiosurgery targeting both trigeminal nerve and the sphenopalatine ganglion

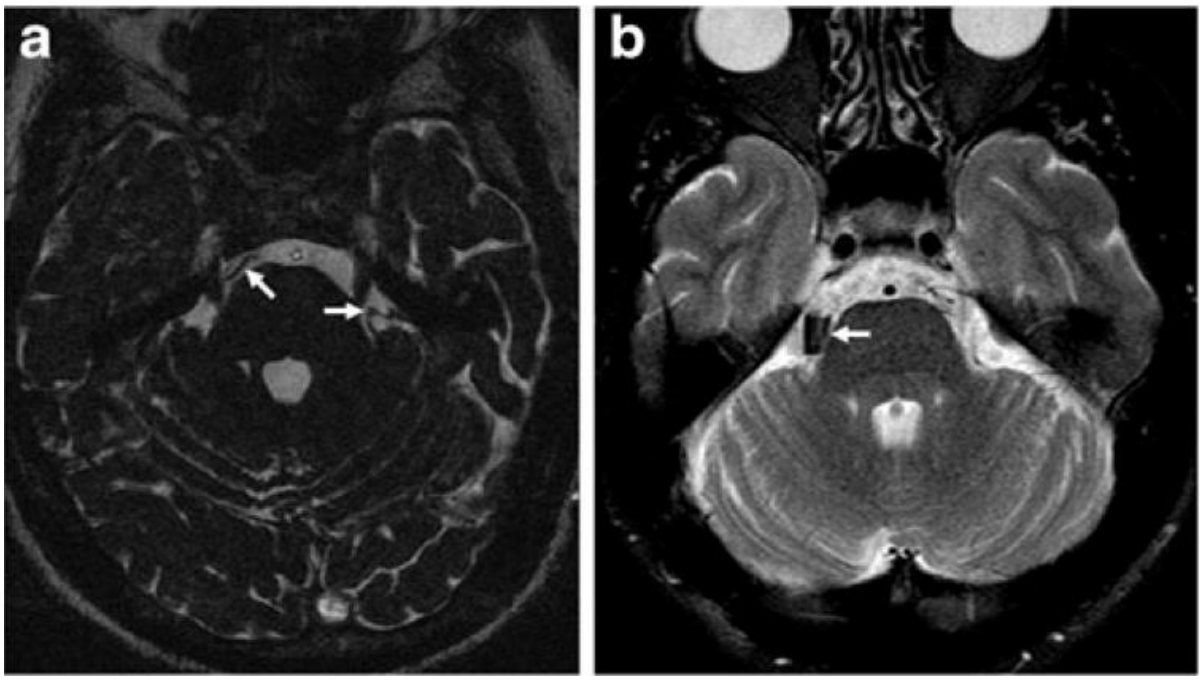


Left image: Novalis frameless radiosurgery system. *Right image*: image of the treatment plan showing the contoured trigeminal nerve (orange) and sphenopalatine ganglion (red) and placement of the isocenter and the 50% isodose line. Brainstem is contoured green (Figure reproduced from (Tan , et al., 2013).

Microvascular decompression of the trigeminal nerve

Trigeminal microvascular decompression is considered the surgical treatment of choice for refractory TN with evidence of trigeminal neurovascular conflict (Barker , et al., 1996). In view of the clinical overlap between TN, SUNCT and SUNA, Williams and Broadley systematically looked for trigeminal neurovascular conflict with dedicated trigeminal MRI scans and found a high proportion of ipsilateral vascular loops in contact with the trigeminal nerve in SUNCT and SUNA (88%, n=15/17). Ninety percent of the aberrant vessels were pressing on the symptomatic trigeminal nerve, compared to only 7% abutting on the asymptomatic nerve (Williams , et al., 2008). This supported the notion of microvascular decompression (MVD) being a potential treatment for these conditions. To date, ten case reports and a case series of nine SUNCT and SUNA patients, who underwent MVD of the trigeminal nerve, have been reported (Gardella , et al., 2001; Black , et al., 2002; Lagares , et al., 2005; Sprenger , et al., 2005; Guerreiro , et al., 2009; Irimia , et al., 2010; Williams , et al., 2010). Only in 12 cases the pattern of attacks was reported; 10 of 12 patients had a chronic form. Patients were considered resistant to multiple therapies, since they had failed different medical and surgical therapies (range: 3-16 therapies). After a median follow-up of 14 months (range: 0.5-32 months), 12 of 19 (63%) of cases were pain free, whereas in the remaining patients, the procedure had little or no effect. Two patients suffered from persistent complications, such as ataxia and hearing loss, whereas in five cases transient complications were noted (Figure 4). Although series with longer follow-ups would be ideal to assess the long-term efficacy of MVD for chronic medically intractable SUNCT/SUNA, at present this approach may be considered a valuable option in refractory patients with ipsilateral trigeminal nerve compression due to a vascular loop, though possible benefit should be weighed against operation-related risks of permanent neurological deficits.

Figure 4. Microvascular decompression of the trigeminal nerve in SUNCT



Axial MRI of the brainstem at the level of the trigeminal nerves. (a) CISS image showing bilateral aberrant arterial loops (arrows) preoperatively and (b) T2 image showing placement of a silicone sleeve around the right trigeminal nerve (arrow). (Figure reproduced from (Williams , et al., 2010)

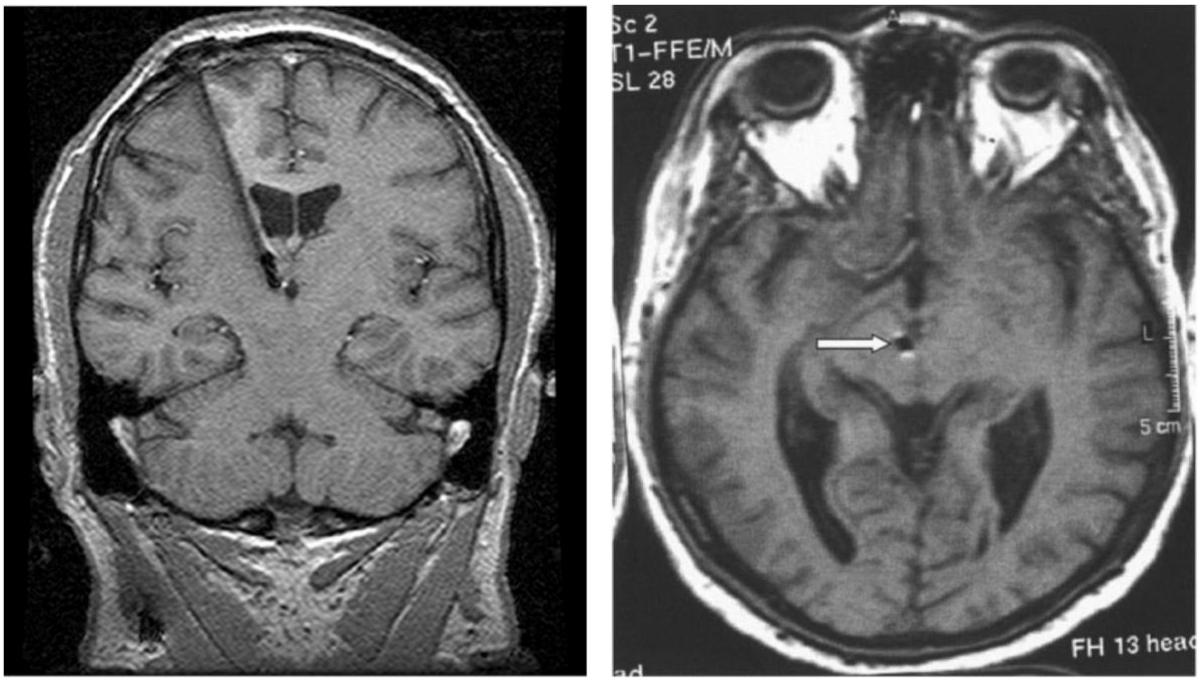
Central neurostimulation

Deep brain stimulation of the ventral tegmental area

In view of the functional imaging evidence of activation of the posterior hypothalamus region being linked to attacks of SUNCT (May , et al., 1999) and the broad experience in the use of posterior hypothalamic region DBS in patients with medically intractable CCH, three patients with intractable SUNCT have been treated with DBS of the posterior hypothalamus, which is now established to be the VTA. The outcome of the three patients was promising, with a significant and sustained decrease in attack frequency respectively at 18 months, 12 months and 15-month follow-up (Leone , et al., 2005; Lyons , et al., 2009; Bartsch , et al., 2011) (Figure 5). A recent case series of 11 SUNCT and SUNA patients treated with VTA DBS suggested the possible long-term efficacy of this approach in this condition. At the final follow-up, 82% of patients (9/11) reported at least 50% reduction in the frequency of the attacks. Improvements were also recorded in other outcomes such as quality of life, headache-related disability and affect measures. One patient required system removal and another IPG repositioning. These

data may suggest that VTA DBS has a role in the management of SUNCT and SUNA refractory to other therapies (Miller , et al., 2016).

Figure 5. Deep brain stimulation in SUNCT



Coronal (left) and axial (right) T-1 weighted MR images demonstrating the DBS lead in the posterior medial hypothalamus (Figure reproduced from Leone et al., 2005).

1.2.4.9. Pathophysiology of TACs

Pathophysiological hypotheses for TACs

Any pathophysiological construct for TACs must account for the three major clinical features characteristic of the various conditions that comprise this group: trigeminal distribution pain; ipsilateral autonomic features; and, the distinct circadian and circannual periodicity, especially in CH.

The pain-producing innervation of the cranium projects through branches of the trigeminal and upper cervical nerves to the trigeminocervical complex that is a functional brainstem unit within the trigeminal nucleus caudalis, from where the nociceptive pathways project to higher centers. This implies an integral role for the ipsilateral trigeminal nociceptive pathways in TACs. The ipsilateral autonomic features suggest transient cranial parasympathetic activation

(lacrimation, rhinorrhoea, nasal congestion and eyelid oedema) and sympathetic paralysis (ptosis and miosis). Animal experiments have demonstrated that stimulation of trigeminal system can lead to parasympathetic outflow via functional connectivity between the trigeminal nucleus caudalis and the superior salivatory nucleus (Goadsby , et al., 1988) that is the trigemino-autonomic reflex (Goadsby, et al., 1997). This reflex is activated as a physiologic response to cranial nociceptive input. Indeed, some degree of cranial autonomic symptomatology occurs with most primary headaches and facial pains and it is not specific for TACs only.

The cranial autonomic symptoms may be prominent in the TACs due to central disinhibition of the trigeminal-autonomic reflex. Anatomical studies in animals have identified connections between the trigeminal nucleus caudalis and the posterior hypothalamus, defined as trigemino-hypothalamic tract. This tract forms the afferent pathway to transmission of sensory information from the trigemino-cervical complex to the posterior hypothalamus (Malick , et al., 1988). In TACs, the prominent cranial autonomic symptoms might be due to a disinhibition of the trigemino-autonomic reflex by central functionally deranged structures. Supporting evidence has emerged from functional imaging studies (Goadsby, et al., 1997). Positron emission tomography studies in CH (May, et al., 1998), PH (Matharu , et al., 2006) and HC (Matharu , et al., 2004) and functional MRI studies in SUNCT demonstrated abnormal functional activation of the posterior hypothalamic region during spontaneous or triggered attacks of TACs (May , et al., 1999; Cohen, 2007). Importantly, the involvement of posterior hypothalamic structures may account for the rhythmicity or periodicity that is such a hallmark of CH. Hypothalamic activation is not seen in experimental trigeminal distribution head pain (May , et al., 1998). There is robust evidence for a role of the hypothalamus in mediating anti-nociceptive (Millan , et al., 1893; Dafny , et al., 1996) and autonomic responses (Lumb , et al., 1993). In fact, there is direct evidence from animal experimental studies for hypothalamic activation when intracranial pain structures are activated (Benjamin , et al., 2004). Moreover, the hypothalamic peptides Orexin A and B can elicit pro-nociceptive and anti-nociceptive effects in the trigeminal system (Bartsch , et al., 2004). These data have led to the suggestion that the TACs are probably due to an abnormality in the hypothalamus with subsequent trigeminovascular and cranial autonomic over-activation. An important consideration is that the different studies outlined above are unable to resolve the paramount question of whether the detected hypothalamic alterations are pathognomonic for TAC or whether they merely represent an epiphenomenon of different pain conditions in general. It has recently been argued

that hypothalamic derangements may not be specific to TACs (Holle , et al., 2011). Hypothalamic activation and structural alterations are not exclusively observed in TACs but can also be found in other primary headache disorders, including migraine (Denuelle , et al., 2007) and hypnic headache (Holle , et al., 2011). Interestingly, hypothalamic changes can even be observed in totally different pain conditions, such as angina pectoris, irritable bowel syndrome or even conditions that do not involve pain at all. Moreover, neuroendocrine changes can be detected not only in CH, but also in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome and migraine. Although the hypothalamus seems to play a key role in the pathophysiology of TACs, it is possible that it acts as a facilitator of trigeminal nociceptive signalling, rather than being the "TACs generator" (Leone , et al., 2009).

Pathophysiological hypotheses for SUNCT and SUNA

The anatomical and functional structures involved in producing pain in the trigemino-cervical distribution associated with ipsilateral cranial autonomic features are similar to those implicated in the other TACs, namely the trigemino-cervical complex and the trigemino-autonomic reflex.

In view of the prominent lacrimation and conjunctival injection during the painful attacks, studies on intraocular functions have been conducted. Intraocular pressure was found to be consistently elevated during attacks on the side of the pain as opposed to the asymptomatic side as well as pain free state. Similarly increased corneal temperature was detected during attacks (Sjaastad , et al., 1992). During the SUNCT ictal phase elevated blood pressure and bradycardia was noted in a few patients (Kruszewski , et al., 1991) along with normal ventilation and oxygen saturation levels (Kruszewski , et al., 1992). Some of these findings may possibly reflect vasodilation related to the parasympathetic outflow, rather than being considered causative factors in SUNCT pathogenesis.

Additionally, change in intracranial blood flow velocities were also tested in SUNCT by transcranial Doppler sonography. Middle cerebral artery (MCA) blood flow velocity was reduced during some attacks on the symptomatic side and to a lesser degree on the asymptomatic side. The reduced blood velocities normalized during the pain free state, suggesting a marked short-lived MCA vasodilation (Shen , et al., 1994). This initial evidence was not corroborated by a technetium-99m hexamethylpropylene amine oxime single-photon emission computed tomography (^{99m}Tc-HMPAO SPECT) study in two SUNCT patients during

four spontaneous attacks that showed normal tracer uptake and symmetrical perfusion (Poughias , et al., 1995).

Besides the two major features of TACs, namely the trigeminal distribution pain and ipsilateral autonomic features, pathophysiological constructs for SUNCT and possibly SUNA phenotypes should also account for the neuralgiform character of the pain, the triggerability of the pain via trigeminal stimulation ipsilaterally to the symptomatic side of the face and the lack of a refractory period after a triggered attack. Various hypotheses regarding the pathophysiology of SUNCT have been proposed. These hypotheses have attributed the primary pathology to an orbital venous vasculitis, a hypothalamic dysfunction and neurochemical derangements of the pituitary-hypothalamic axis. Recently it has been proposed that a neurovascular compression of the trigeminal sensory root at the root entry zone could also have a role in the pathophysiology of this condition.

Hypothalamic dysfunction

Similarly to the other TACs, during SUNCT attacks, a significant activation in the region of the ipsilateral inferior posterior hypothalamic grey was demonstrated in the first functional MRI study (May , et al., 1999). Subsequently Cohen extended the functional MRI scanning to nine patients with idiopathic SUNCT, two with idiopathic SUNA and one with SUNCT secondary to a brainstem abnormality during triggered and spontaneous attacks. In patients with primary SUNCT there was positive activation in the region of the posterior hypothalamus, which was bilateral in five patients and contralateral to the side of the attack in two patients. There was negative activation ipsilateral to the side of the pain in two patients. The patient with symptomatic SUNCT showed no hypothalamic activation. In the SUNA patients there was negative activation bilaterally (Cohen, 2007) (Figure 6). Sprenger and collaborators performed an fMRI study in a patient with right-sided SUNCT attacks triggered by cutaneous touch. They reported bilateral hypothalamic activation during the pain attacks. The authors noted ipsilateral brainstem activation in the region of the pontomedullary junction, which probably reflects spinal trigeminal nucleus activation (Sprenger , et al., 2005).

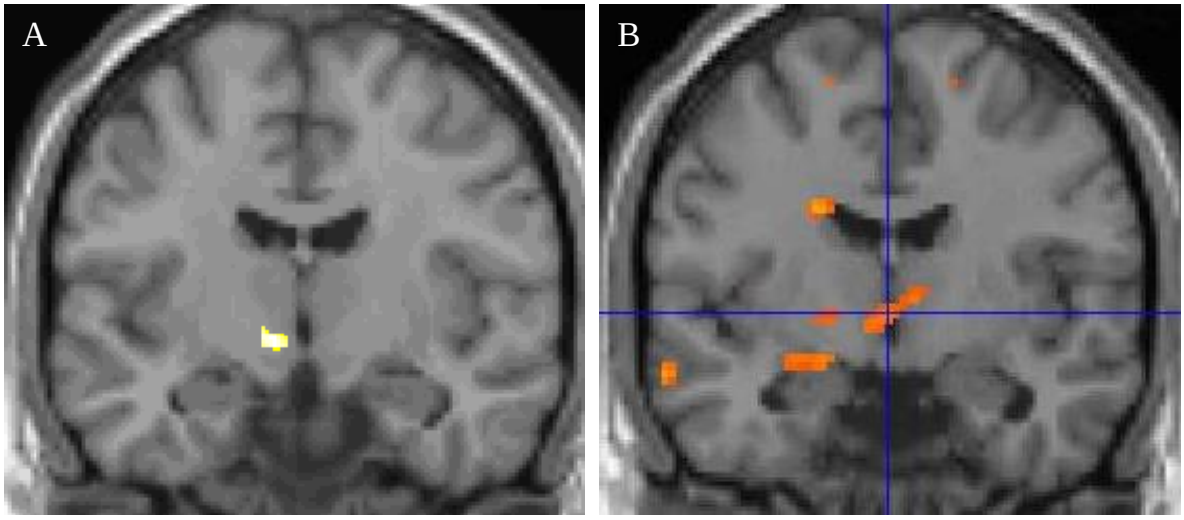
The functional neuroimaging evidence along with the initial promising experience of DBS targeting the posterior hypothalamus in three patients with SUNCT, support the paramount role of the hypothalamus in the pathophysiology of SUNCT. Similarly to the other TACs, it has

been postulated that a deranged hypothalamus could modulate the trigeminal-autonomic reflex activation threshold (Goadsby, et al., 1997), possibly via direct hypothalamic-trigeminal pathways (Malick , et al., 1988).

Trigeminal sensory root abnormality

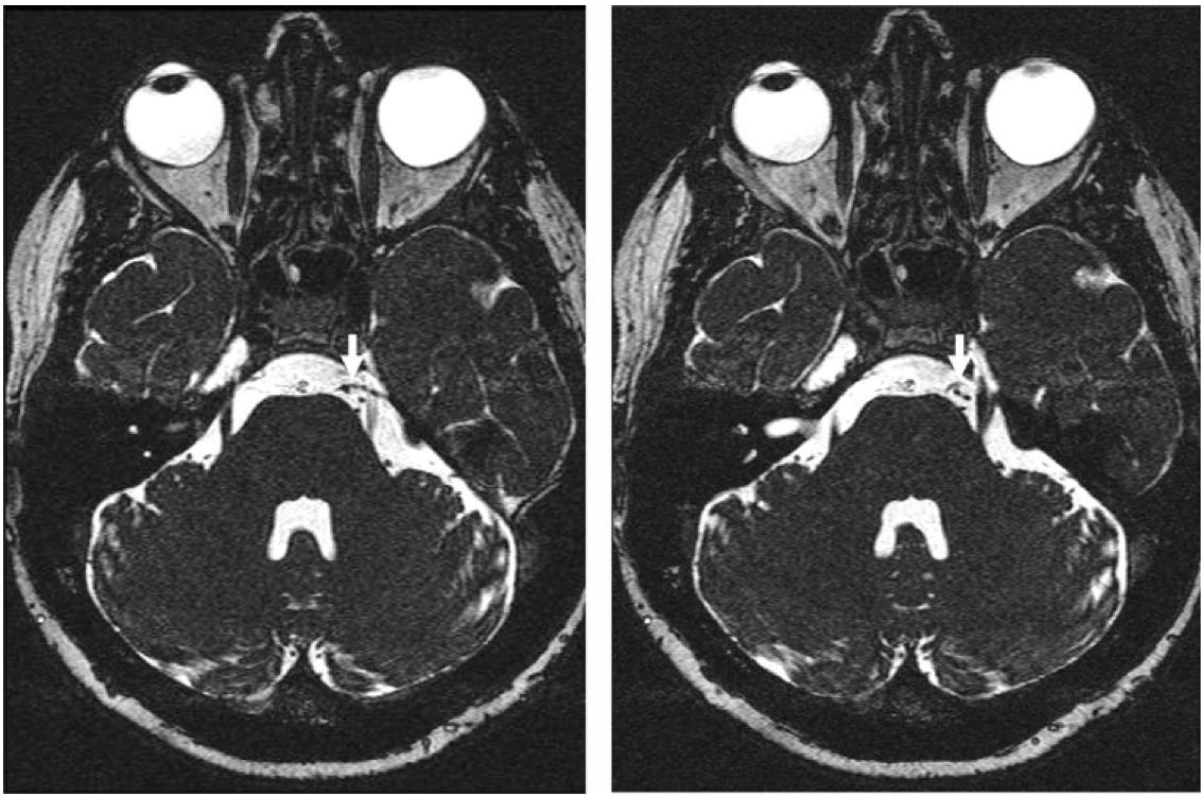
SUNCT shares clinical elements with CH, namely pain in the trigeminal distribution mainly in the ophthalmic trigeminal branch territory and prominent cranial autonomic features. However, many clinical features of SUNCT, namely duration, frequency, and character of the pain, along with presence of cutaneous triggers overlap with TN. Moreover, both SUNCT/SUNA and TN share similar responses to pharmacological treatments that modulate sodium channels such as carbamazepine, oxcarbazepine and lamotrigine. These similarities, along with the high proportion of patients showing trigeminal neurovascular conflict ipsilaterally to the side of the pain (Figure 7), as well as the encouraging results of MVD of the trigeminal nerve in some patients with SUNCT syndrome, support the notion that more peripheral mechanisms, may be involved in the complex pathophysiological mechanisms of this disorder (Sebastian , et al., 2013) (Figure 8). This would imply that SUNCT and SUNA may also share pathogenic mechanisms with TN, namely a demyelination of the trigeminal sensory root due to vascular compression. This abnormality would be responsible for the short-lived painful paroxysms and it would also be responsible for the ephaptic cross talk between fibres that drive sensation and nociceptive fibres, explaining the triggerability of the attacks in some SUNCT and SUNA patients. A complex interaction between more peripheral and central mechanisms may underpin the pathophysiology of SUNCT and SUNA. Further data are needed to confirm this hypothesis.

Figure 6. Functional magnetic resonance imaging studies showing hypothalamic activation in SUNCT



Reproduced from (A) (May , et al., 1999) and (B) (Cohen, 2007).
SUNCT, Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing

Figure 7. Neurovascular conflict with the trigeminal nerve in SUNCT syndrome



High resolution T2 constructive interference in the steady-state images: a neurovascular conflict of the posterior inferior cerebellar artery with the trigeminal sensory root ipsilaterally to the side of the pain is shown (Figure reproduced from Williams et al, 2010).

Figure 8. Schematic representation principal pathways and nuclei involved in the model of pain and autonomic features possibly involved in SUNCT syndrome

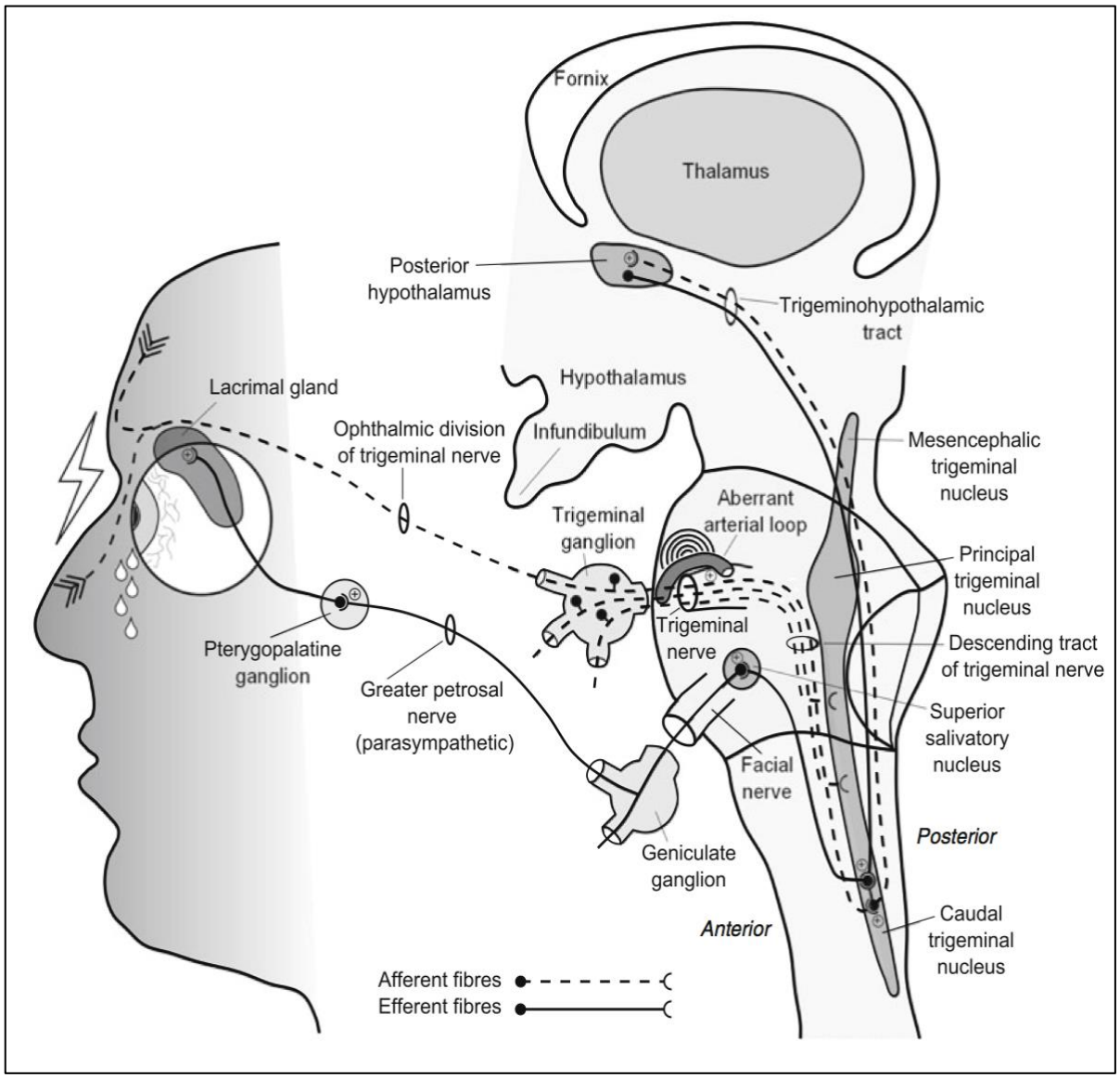


Figure reproduced from (Sebastian , et al., 2013)

Central neuroendocrine hypothesis

Headache is a common and disabling aspect of pituitary disease, especially of small, non-invasive functional tumours, particularly prolactinomas (Abe , et al., 1998). Trigeminal autonomic cephalalgias-like phenotype has been described in patients with headache related to pituitary tumours. Several cases of secondary SUNCT syndrome associated with pituitary

tumors namely micro- or macro- adenomas have been described (Massiou , et al., 2002; Matharu , et al., 2003; Levy , et al., 2003; Larner , 2006; Zidverc-Trajkovic , et al., 2009; Rozen , 2006; Rocha Filho , et al., 2006; Leroux , et al., 2006; Adamo , et al., 2008). In a large study, where patients with pituitary tumours and troublesome headaches were phenotyped, SUNCT, CH and HC represented 5%, 4% and 1% of the study group (Levy, et al., 2005). The pituitary tumors most commonly associated with SUNCT seem to be prolactinomas and growth hormone secreting tumors. However, in the largest SUNCT series published so far only 8% of patients were found to have pituitary tumors on MRI. However, the authors did not specify whether they requested specific pituitary fossa' sequences or whether they relied on routine MRI scanning (Cohen , et al., 2006). In one case series from Australia, where 17 SUNCT and seven SUNA patients were studied with MRI scans with specific trigeminal sequences, no pituitary lesions were detected (Williams , et al., 2008). However, a subsequent case series of six patients (five SUNCT and 1 SUNA patients) showed that all five patients with SUNCT syndrome were found to have pituitary adenomas, and the tumors were always ipsilateral to headache. The SUNA patients did not display any pituitary abnormality on MRI scans. Pituitary surgery was performed in an attempt to relieve headache in all SUNCT cases but one. Three patients improved dramatically after adenoma removal (Chitsantikul , et al., 2013). The authors suggested that one of the possible reasons for a low prevalence of pituitary tumors in previous series might have been the lack of detailed views of the pituitary fossa on MRIs. Three of their five patients had initial MRI scans reported as normal and the pituitary tumor was only discovered on pituitary MRI scanning.

The pathophysiology of headache related to pituitary tumors is complex and not completely understood. A prospective study in 63 patients with headache and pituitary tumors found no positive correlation of headache with pituitary tumor volume nor with cavernous sinus invasion, demonstrating that dural stretch and local cavernous sinus invasion are probably not the primary mechanisms behind pituitary tumor–associated headache in most patients (Levy , et al., 2004). It has been postulated that the mechanisms underlying headache associated with pituitary tumors involve derangements in hormonal function and hypothalamic neurotransmitters. This hypothesis highlights the importance of the dopamine-prolactin axis in the pathophysiology of SUNCT (Levy, et al., 2005). Dopamine agonists including bromocriptine, lisuride, quinagolide and cabergoline have been reported to induce SUNCT attacks in patients with pituitary prolactinoma (Massiou , et al., 2002). It is possible that perturbations in the dopamine-prolactin axis may be important in SUNCT and SUNA

syndromes. It is conceivable that specific neuroendocrine pathways involving the hypothalamic dopaminergic neurons may be capable of activating SUNCT pathophysiology at least in a subgroup of patients (Levy, et al., 2005).

1.3. Trigeminal Neuralgia

1.3.1. Introduction and background

Trigeminal neuralgia (TN) is a disorder characterized by recurrent unilateral brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve and triggered by innocuous stimuli. It may develop without apparent cause or be a result of another diagnosed disorder. TN is currently grouped together along with the painful trigeminal neuropathies, glossopharyngeal neuralgia, nervus intermedius neuralgia, occipital neuralgia and other forms of central facial pain within the "Painful cranial neuropathies and other facial pains" (Headache Classification Subcommittee of The International Headache, 2013).

1.3.2. Epidemiology

TN seems more common in women than in men (F:M ratio=3:2) (Katusic , et al., 1990; Maarbjerg , et al., 2014). However, in a large prospective series of 229 TN patients there was an even gender distribution (Rasmussen , 1990). The mean age of onset is after the fourth decade, with a peak onset in fifth to seventh decades. Katusic and collaborators found that the median age of onset in their patients was 67 years, with a range of 24 to 93 years (Katusic , et al., 1990). In a large prospective series of TN, the average age of onset of TN was 48 years (Rasmussen , 1990). A UK survey showed a peak incidence of TN between 45-59 years (Hall , et al., 2006). The annual incidence of TN is 4-5 per 100000 (Katusic , et al., 1990). However, recent surveys from UK and the Netherlands showed much higher incidences of 26.8 and 28.9 per 100000, respectively (Hall , et al., 2006; Dieleman , et al., 2008). Approximately 2% of the patients with multiple sclerosis (MS) complain about symptoms identical to those of TN (De Simone , et al., 2005).

1.3.3. Classification

The diagnostic criteria of TN and its sub-forms have evolved over time, reflecting progress in the understanding of the condition. Before the diagnostic criteria of TN were formally introduced in the ICHD classification in 1998, some of the authors based the diagnosis on the Rushton and Olafson's diagnostic criteria, which includes the presence of: brief paroxysms of severe pain confined to one or more divisions of the trigeminal nerve, unpredictable remissions and exacerbations of pain, lack of objective evidence of motor or sensory deficit of the involved nerve, and occurrence of trigger zones (Rushton , et al., 1965). In the ICHD-I (Headache Classification Committee of The International Headache Society, 1988), TN was classified in idiopathic and symptomatic forms. Symptomatic TN was further subdivided on the basis of the location of the abnormality causing the pain at the level of the nerve, the ganglion or the central nervous system (CNS). In the ICHD-II version (Headache Classification Subcommittee of The International Headache Society., 2004), TN was sub-classified as "Classical TN", where pathologies of the brain apart from vascular compression of the trigeminal nerve were thought to be responsible for the condition and "Symptomatic TN", where a demonstrable causative structural lesion was detected with appropriate investigations. In the recent beta version of the ICHD-III (Headache Classification Subcommittee of The International Headache, 2013), classical TN has been further subdivided in two forms: classical TN purely paroxysmal and classical TN with concomitant persistent facial pain, which refers to what was previously labeled as atypical TN or type 2 TN. This form is characterized by prolonged background pain in the affected area between paroxysms. The term symptomatic TN has been replaced by the term Painful trigeminal neuropathy. Table 12 outlines the current proposed diagnostic criteria for TN, according to ICHD-IIIβ.

Table 12. International Headache Society diagnostic criteria for Classical trigeminal neuralgia

A. At least three attacks of unilateral facial pain fulfilling criteria B and C:
B. Occurring in one or more divisions of the trigeminal nerve, with no radiation beyond the trigeminal distribution
C. Pain has at least three of the following four characteristics:
1. Recurring in paroxysmal attacks lasting from a fraction of a second to 2 minutes
2. Severe intensity
3. Electric shock-like, shooting, stabbing or sharp in quality
4. Precipitated by innocuous stimuli to the affected side of the face
D. No clinically evident neurological deficit
E. Not better accounted for by another ICHD-3 diagnosis

Adapted from The International Headache Society Classification Committee of (2013)

1.3.4. Clinical features

Although the phenotype of TN has been described for many centuries, the vast majority of the studies is retrospective in nature and based on postal questionnaires (PEET , et al., 1952; Katusic , et al., 1990; Loh , et al., 1998; Jainkittivong , et al., 2012). Additionally, some of the largest clinical series of TN were published pre-ICHD-I. Since the inclusion of the TN criteria in the IHS classification, some retrospective studies and one large prospective study have been published. The following summary of TN phenotype comprises a mixture of findings either pre- or post-ICHD.

Laterality and site of pain

In the large Peer and Schneider series, the right side was involved more frequently than the left by a ratio of 8:5 (PEET , et al., 1952). In Rasmussen's series, there was considerable preponderance of right-sided facial pain (64%) compared to patients with left-sided facial pain (34%). Four out of 229 patients reported bilateral pain (1.7%). Conversely, Katusic and

collaborators found no significant difference in the laterality of the pain; in their series, the right side was affected in 43, while the left side was affected in 30 patients (p=0.13). Bilateral involvement was noted in one patient, and in another patient the side involved was not stated. A recent Danish study conducted in a series of 158 TN patients, found that the pain was reported more often on the right side (56%) than on the left side of the face (41%). Five out of 158 patients reported bilateral pain (3%) (Maarbjerg , et al., 2014).

In Peet and Schneider's series of 689 TN patients, the maxillary division (V2) of the trigeminal nerve was involved alone in 16.5% of patients, the mandibular division (V3) alone in 15.8% and the ophthalmic division (V1) alone in 3.4%. The most frequently reported sites of pain were the maxillary and mandibular combined (37.3%). The ophthalmic and maxillary combined was reported in 13.9%; all three divisions combined in 12.7% and the ophthalmic and mandibular combined in 0.1% (Peet and Schneider, 1952). Similar findings were described in Katusic and collaborators' cohort, where the most frequently affected divisions of the trigeminal nerve were the maxillary (35% of patients) and mandibular (29%) alone, with 19% having both divisions affected. The least affected were the ophthalmic alone (4% of patients) and 1% of the patients had all three divisions affected together (Katusic , et al., 1990). In Rasmussen's series, the second and third trigeminal divisions combined were the most frequently reported pain territories (24%), followed by the mandibular division alone (22%). Only 5% of patients reported pain in the first trigeminal division (Rasmussen , 1991). In a more recent Danish study, 33% of the patients reported the pain in V2 and V3 together, 19% in V3 alone, 17% in V2 alone, 10% in V1-V2, 13% in V1-V2-V3 and 4% in V1 territory alone, supporting the predominant involvement of the maxillary and mandibular territories in the majority of TN patients (Maarbjerg , et al., 2014).

Character of the pain, frequency and duration of attacks

In Rasmussen's series, the character of the pain was described as shooting-cutting in 95% of patients, boring in 1%, dull in 1.7%, burning in 1.7%, pricking in 1.3% and throbbing in 0.4% (Rasmussen , 1990a). In a retrospective study of 188 TN patients, most patients described their attack as sharp pain (77.6%). Other pain descriptors included electric shock-like (19.1%), stabbing (9.6%), numbness (6.9%), throbbing (6.4%) and burning (4.2%). Also, no differences in the description of pain were reported between men and women (Jainkittivong , et al., 2012).

The frequency of occurrence and durations of attacks in TN is highly variable. In view of the

triggerability of the attacks, in most cases the daily frequency of attacks depends upon the number of activities that sufferers perform. The pain attacks in TN normally last seconds in the vast majority of patients (99.6%) and minutes in the remaining (Rasmussen , 1990). In Maarbjerg and collaborators 70% of patients suffered from series of paroxysms, which in most cases (89%) lasted less than 1 hour. A high percentage of patients (40%) suffered from more than 10 pain paroxysms per day (Maarbjerg , et al., 2014). Katusic and collaborators reported that the median number of pain episodes in their series of 75 TN patients was three, with a range of 1 to 11 attacks/day. The median length of episode was 49 days and the mean was 116 days, ranging from 1 to 1462 days (Katusic , et al., 1990). In Maarbjerg and collaborators' series, most patients experienced periods of remission (63%), but there was a great variety in the frequency of remission periods. Regarding the length of a remission period, 58 (37%) experienced months of remissions, and 100 (63%) experienced years of remissions (Maarbjerg , et al., 2014).

Intensity of the pain

TN pain intensity is known to be excruciating. However, moderate attacks have been reported. In a recent series of TN patients, 58% of the patients only reported that the intensity of their paroxysmal stabbing pain was on average 10/10 though the range was large (range VRS 2-10) (Maarbjerg , et al., 2014). This might be due to the fact that most patients with TN are medicated as soon as the diagnosis is established.

Trigger zone

One of the hallmark clinical features of TN is the triggerability of the attacks by innocuous stimulation of the face and intraoral mucosa ipsilaterally to the side of the pain. Light tactile stimulation seems to be the most effective stimulation to evoke pain in TN. Conversely, painful and thermal stimulation seem ineffective to elicit pain in TN (Kugelberg, et al., 1959).

In one of the first series of TN, Peet and Schneider found that only 31.6% of their TN patients reported one or more trigger zones. The commonest sites were: the upper lip 52%, ala nasae 42%, angle of the mouth 30%, nasolabial fold 22%, lower lip 2l%, malar eminence 18%, lower jaw 14%. Only 2.4% of all the patients had a trigger zone limited to the ophthalmic division (PEET , et al., 1952). However, the authors did not mention the proportion of patients who

could triggers attacks by cutaneous stimulation, or the types of triggers reported by their patients. Similarly, Kugelberg and Lindblom studied the site of the trigger zone in 30 TN patients. The trigger zone was most common in the nasolabial fold, on the upper lip, the lateral part of the lower lip, and the alveolar gingiva. Some patients had two trigger zones and some reported that their trigger zone had shifted from one point to another during the course of the disease. One patient stated that she had a trigger zone outside the trigeminal area, located in the ipsilateral axilla. In most patients, the trigger zone was small in diameter, whereas in some patients it was reported as diffuse (Kugelberg, et al., 1959).

Subsequently in another series, 96% of patients reported provoked TN attacks and only 4% reported only spontaneous attacks. The most frequently reported trigger factor was chewing and talking (76% of patients). The vast majority of patients, whom reported chewing as a trigger, experienced pain at the start of the mastication process (95%), whereas only in 5% the pain started late in the chewing process. Sixty-five percent of patients reported touching as a precipitating factor (65%). Of these, 50% (n=144 patients) identified a trigger zone. The trigger zones were localized at the nasal wing (37%), upper lip (25%), lower lip (20%), cavity of the mouth (17%), diffusely over an area of skin (16%), eyebrow (10%), corner of the mouth (6%). Other precipitating factors included cold (48%), movement of the head (2%), psychological factors (2%), heat (1%), abdominal contractions (1%) and pressure by denture (0.4%) (Rasmussen , 1991a). In a recent retrospective study, 183 out of 188 patients (97.3%) stated that their pain was initiated by physical stimuli in the facial area; the majority reacted to more than one type of stimulus (Jainkittivong , et al., 2012). The most common trigger was chewing (61.2%); other stimuli included speaking (47.3%), face washing (42.6%), face touching (39.9%), tooth brushing (30.3%), wind blowing (28.2%), mouth opening (21.8%), swallowing (8.5%) and hair combing (0.5%). The high proportion of patients with triggered attacks was also confirmed in a subsequent prospective study. Out of a total of 158 TN patients, 91% had trigger factors and 68% had also spontaneous attacks. The most frequent trigger factors were: chewing (73%), touch (69%), brushing teeth (66%), eating (59%), talking (58%), and cold wind (50%). A few patients reported some unusual trigger factors such as loud noises, emotional stress, physical strenuous exercise, and movement of the ipsilateral upper limb. In general, the area from which the pain could be triggered corresponded to the area of pain (79%). It was not clear in this study though what was the proportion of patients with both triggered and spontaneous attacks and the proportion of patients with triggered only and spontaneous only attacks (Maarbjerg , et al., 2014).

Refractory period

In the vast majority of TN patients, a triggered painful attack is normally followed by a period of seconds or minutes during which further attacks cannot be provoked. This phenomenon is called refractory period (Kugelberg, et al., 1959). The presence of a refractory period between triggers attacks in TN has been considered as a possibly clinically relevant difference compared to SUNCT (Headache Classification Subcommittee of The International Headache, 2013). However, it is not clear whether every patient with TN displays this clinical phenomenon or whether there is a minority of patients with TN that can trigger one attack after the other without any refractory periods in between.

Associated symptoms

The frequency of occurrence of cranial autonomic symptomatology in TN was poorly investigated in the old case series described in the literature. Rasmussen described 98 patients out of the 229 (43%) in whom the pain was accompanied by facial autonomic symptoms. Lacrimation ipsilaterally to the side of the pain was the most commonly described sign (31%), followed by rhinorrhea (9%), increased salivation (7%), facial swelling and flushing (5%). There was a slightly increased frequency of lacrimation in the groups where the pain was centred over the V1 and V2 trigeminal divisions; rhinorrhea, swelling and flushing were predominantly linked with pain in V2; salivation was linked with pain in V3. In 32% of cases lacrimation occurred together with one or more of the other autonomic symptoms, rhinorrhea occurred in 90%, salivation in 47%, and swelling and flushing in 62% (Rasmussen , 1991a). The fact that SUNCT syndrome was firstly being described around the time of publication of this study may explain why the authors may not have been aware of the possibility that patient with a TN phenotype with cranial autonomic symptoms may in fact have SUNCT or SUNA syndromes.

A Danish study published after the introduction of the latest revised version of the ICHD found that 31% (n=48/158) of their TN patients had experienced ipsilateral autonomic symptoms during attacks (Headache Classification Subcommittee of The International Headache, 2013). Conjunctival injection and/or tearing were the most frequent symptoms (22%). In 8/48 patients (16.7%%), the autonomic symptoms were pronounced in every attack. Out of these eight patients, one was diagnosed with both TN and SUNA, and one with both TN and SUNCT. One

patient was diagnosed with CH and TN. One patient did not fulfill the diagnostic criteria for any of the TACs. For the remaining four patients, it was not possible to conclude whether SUNCT/SUNA should be added to the diagnosis of TN. Similar to Rasmussen's series, patients with pain in V1 were more likely to report any cranial autonomic features (49%) (Maarbjerg , et al., 2014).

Other Authors have described cranial autonomic symptoms in association with V1 TN. Sjaastad and collaborators reported the occurrence of mild lacrimation in eight (42%), conjunctival injection in three (16%), and rhinorrhoea in two patients (11%) out of a series of 19 V1 TN patients. The combination of lacrimation, conjunctival injection and rhinorrhoea was reported in two patients (11%) (Sjaastad , et al., 1997). More recently a retrospective survey of 92 TN patients showed the presence of at least one autonomic symptom in 67% of the patients (Simms , et al., 2011).

Differential diagnosis

The differential diagnosis of TN encompasses a broad group of conditions characterised by unilateral short-lasting neuralgiform headache and facial pain attacks. The group includes dental pathologies, disorders of the jaw and the sinuses, salivary gland disorders, other forms of neuropathic pain involving the trigeminal territories, the TACs and persistent idiopathic facial pain. Table 13 summarises the conditions that should be considered in the differential diagnosis of TN (Obermann , et al., 2011; Zakrzewska , 2013). In many cases a definite diagnosis of TN requires a multidisciplinary input from many professionals including dentists, ear, nose and throat (ENT) specialists and neurologists.

Table 13. The differential diagnosis of trigeminal neuralgia

Dental causes	Dental caries Pulpitis Dental sensitivity Periodontal disorders Pericoronitis Cracked tooth Alveolar osteitis
Sinus causes	Maxillary sinusitis
Salivary gland causes	Salivary stone
Temporomandibular joint causes	Temporomandibular disorders
Neuropathic pain	Post-herpetic neuralgia Post-traumatic trigeminal neuropathy Painful trigeminal neuropathies Atypical odontalgia Burning mouth syndrome Glossopharyngeal neuralgia Nervus intermedius neuralgia
Trigeminal autonomic cephalalgias	SUNCT and SUNA syndromes Paroxysmal hemicrania Cluster headache Hemicrania continua
Other	Persistent idiopathic facial pain

SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

1.3.5. Medical management

There are numerous medical treatment options for TN. However, only few treatments are supported by robust evidence. Setting up clinical trials for TN can be challenging for various reasons including the rarity of the condition, which can prevent recruitment of sufficient numbers of patients, and the severity and disability of the pain which poses ethical issues related to the duration of the placebo phase. Furthermore, in view of the episodic pattern of occurrence of TN attacks, it can be difficult to establish whether an improvement of the condition is to be attributed to the treatment itself as opposed to a spontaneous improvement of the condition. These caveats are evident in the placebo-controlled crossover trials and comparative trials published, which are outlined in Tables 14.

Carbamazepine

Carbamazepine (CBZ) is the first-line treatment option for TN (dose: 200-1200 mg/day). The efficacy of carbamazepine is supported by four randomised double blind controlled trials (Class I or III) that included a total of 147 patients (Campbell, et al., 1966; Killian , et al., 1968; Nicol , 1969; Rockliff , et al., 1966). These studies demonstrated a very high rate of responders to the treatment amongst patients versus placebo. The main treatment outcomes assessed in these trials included: reduction in pain severity, pain paroxysms and the disappearance of triggers. The number needed to treat to obtain a significant improvement was 1.7-1.8. However, these trials, conducted several years ago, display some methodological limitations including the small sample in two of them, variable treatment outcomes and lack of extensive follow-ups.

Limitation in the use of carbamazepine includes the relatively low tolerability profile. The numbers-needed-to-harm (NNH) showed in these trials was of 3.4 for minor and of 24 for severe adverse events. In the largest randomised placebo-controlled trial, 50% of patients on carbamazepine experienced at least one side effect compared to 24% of the placebo group. However, only one patient on carbamazepine dropped out because of adverse events, namely a cutaneous rash (Campbell, et al., 1966). Another potential limitation in the use of carbamazepine is the known metabolic interaction with other medications, which can be problematic in elderly TN patients with other comorbidities (Cruccu , et al., 2008).

Oxcarbazepine

Oxcarbazepine (OXC) can also be used as initial treatment for TN. Its preference over CBZ is

mainly related to its accepted greater tolerability and decreased potential for drug interactions. Three double-blind randomised controlled trials including a total of 130 patients compared oxcarbazepine (OXC) 600–1800 mg/day to CBZ in TN patients (Beydoun, 2000). The reduction in number of attacks and global pain assessments were similar for both CBZ and OXC (88% of patients achieving a reduction of pain by >50%). However, no studies comparing OXC against placebo have been hitherto conducted (Cruccu , et al., 2008).

Baclofen

Baclofen was studied in a single-crossover double blind study. Ten patients were enrolled. The trial involved taking baclofen 10 mg three times a day with 10 mg increment every other day or placebo for a week. At the end of this phase, patients were given the other tablet for one more week. Seven out of ten patients obtained a significant reduction in painful paroxysms with baclofen, whereas none of patients on placebo reported any benefit. One patient dropped out because of side effects related to baclofen (Class II) (Fromm , et al., 1984).

Lamotrigine

Lamotrigine was tested in a double-blind placebo-controlled crossover trial in 14 patients with TN. Patients continued to take a steady dose of carbamazepine or phenytoin throughout the trial over a 31-day period. Patients were randomised (stratified by centre) to receive either LTG (LTG/PBO group) or placebo (PBO) (PBO/LTG group) for 14 days in the first arm of the study (days 1–14). Following a 3-day washout period on placebo (days 15–17), patients crossed over to receive the alternative medication (days 18–31). The maintenance dose of lamotrigine was 400 mg. Eleven of the 13 patients included in the analysis showed better efficacy on lamotrigine compared with placebo. This trial provided Class II evidence of efficacy of lamotrigine in TN (Zakrzewska , et al., 1997). More recently the effect of lamotrigine in TN was evaluated in a small crossover trial in 21 TN patients. Lamotrigine was compared to carbamazepine. Patients on carbamazepine at the time of enrolment were asked to discontinue the medication and after a three-day washout period to start titrating lamotrigine. Subjects on no medication were asked to start carbamazepine and then swap to lamotrigine. Each phase lasted 40 days. Twenty-one TN patients were included. The final titration dose for lamotrigine was 400 mg/day and for carbamazepine was 1,200 mg/day. Efficacy of the medications was assessed using a visual analogue scale (VAS) and verbal rating scale (VRS). Carbamazepine was effective in 90.5%

(19/21) of the patients as opposed to 62% (13/21) who benefitted from lamotrigine. The majority of lamotrigine responders (77%) obtained complete pain relief, as opposed to only 21% of the carbamazepine responders (Shaikh , et al., 2011).

The proportion of patients experiencing side effects on either drug was similar. Fourteen patients (67%) out of a total of 21 patients during therapy with the lamotrigine displayed side effects attributable to lamotrigine, whereas 12 out of 21 (57%) of the patients on carbamazepine displayed side effects attributable to carbamazepine. Five patients on lamotrigine developed a skin rash and two patients on carbamazepine developed a Steven-Johnson syndrome. However, in terms of the abnormal hematological, renal and hepatic values, 14% of patients on lamotrigine compared to 48% of patients on carbamazepine displayed deranged levels in one or more of these profiles.

Pregabalin

The effect of pregabalin in TN was studied in a prospective open-label single centre study conducted in a tertiary referral headache centre. Fifty-three patients were investigated. Of these, 47 (89%) had idiopathic TN and six (11%) had secondary TN. Thirty-nine patients had classical TN without concomitant chronic facial pain, whereas 14 patients had classical TN with concomitant chronic facial pain. The dose of pregabalin was titrated from 75 to 600 mg daily with a maximum dose increase of 75 mg/week for the first 2 weeks and 150 mg/week afterwards. Additional preventive medications such as carbamazepine or lamotrigine were permitted after eight weeks and considered in patients without complete pain relief while on 600 mg/day of pregabalin. Patients were followed-up after four weeks, eight weeks, after six months and after one year. Changes in TN symptoms were monitored with the aid of a pain diary. The primary outcome of the study was number of patients free of pain or with pain reduction > 50% and attack frequency reduction > 50% after eight weeks. The secondary outcome parameter was sustained pain relief after one year. After eight weeks of treatments, 74% of patients responded to treatment on a mean dose of 269.8 mg/day (range 150-600 mg/day). Of these, 25% experienced complete pain-free relief and 49% reported at least 50% pain reduction. The majority, 11 of the 13 patients experiencing complete pain relief at eight weeks of treatment, stayed pain free after one year. Fourteen patients (26%) did not respond to treatment. Patients without concomitant facial pain showed a much better response rate (32 of 39; 82%) compared with patients with concomitant chronic facial pain (seven of 14; 50%)

within the first eight weeks of treatment. Even when additional medication was started, the responder rate of those with concomitant facial pain showed a significantly lower response rate at one year compared to those without concomitant facial pain. Twenty-two patients (42%) reported side effects during treatment. This study showed encouraging long-term efficacy and tolerability of pregabalin in the management of TN (Obermann , et al., 2008).

Pregabalin was tested in a prospective multicentre observational study conducted in primary care in 65 patients with TN who did not respond to analgesic, antidepressant and other anticonvulsants. Pregabalin was used in monotherapy in 36 patients and as an add-on to paracetamol, opioids or non-steroidal anti-inflammatories (NSAIDs) in 29 patients for three months. The mean pregabalin dose was higher in the add-on group (234±107 mg/day) compared to the monotherapy group (196±105 mg/day). Pregabalin reduced the baseline pain intensity by 55%, with a response rate (pain relief ≥50%) of 59% of patients, 64% in the monotherapy group and 54% in the add-on group. Furthermore, within the 90-day treatment period, patients experience on average 35 pain-free days, 39 in the monotherapy group and 29 in the add-on group, suggesting that pregabalin alone could be an effective treatment for TN (Pérez , et al., 2009). However, the design of the study, in particular patients' selection has been criticized, suggesting that the effectiveness of pregabalin in TN should be studied in better designed trials (Cruccu , et al., 2013).

Pregabalin effect in TN was also compared to lamotrigine in a randomised open label crossover trial. Twenty-two patients with TN were enrolled and randomly allocated into two groups, one where patients were given lamotrigine and the other where they were given pregabalin. Both groups were kept on a steady dose of carbamazepine. Each group was crossed over to the other drug, after a two-week wash out period. The duration of the trial was a total of six weeks. The study showed that pregabalin was equally effective compare to lamotrigine and that both treatments were statistically superior to carbamazepine alone (Rustagi , et al., 2014).

Topiramate

The role of topiramate in the management of TN was evaluated in a randomised placebo-controlled crossover trial. However, the authors managed to enroll only three patients that completed the study. Patients entered a one-week baseline period, followed by two 12-week drug treatment periods separated and concluded by two-week washout periods. The treatments were given randomly, following this regimen: topiramate staring at 25 mg daily and titrated to

a maximum daily dosage of 800 mg or placebo. The primary outcome was change in pain intensity. Patient who responded to topiramate in the main study were offered the opportunity to enter a confirmatory comparison, which consisted of three 8-week segments. Within each segment, the patient took randomly four consecutive weeks of topiramate and four weeks of placebo under double-blind conditions. During the placebo-controlled phase, the pain intensity decreased by 31%, 42%, and 64% in the three patients, which was statistically superior to placebo. However, during the subsequent crossover confirmatory phases no pain reduction was noticed in the three patients taking topiramate, suggesting that methodologically more robust trials should be conducted to assess the efficacy of topiramate in TN (Gilron , et al., 2001). Further small trials have been studied topiramate in TN, though they were all published in the Chinese language.

Sumatriptan

Sumatriptan subcutaneous injections 3 mg has been tested against placebo in a crossover trial (Kanai , et al., 2006). Fifteen minutes after the injection of sumatriptan but not placebo, the baseline VAS decreased from 8.3 to 2.4 cm. Twenty out of 24 patients enrolled in the trial, benefited from sumatriptan (83.3%).

Botulinum toxin type A

Open label studies have suggested that Botulinum toxin type A (Botox®) may be effective in the management of TN. (Borodic , et al., 2002; Piovesan , et al., 2005; Türk , et al., 2005). Recent randomised double-blind placebo-controlled trials provided class I evidence of efficacy of Botulinum toxin type A (BoNT/A).

Wu et al studied 40 patients with classical TN according to the ICHD-2 criteria who failed to respond to conventional treatment (mean Visual Analog Scale or VAS score ≥ 4, mean attack frequency ≥ 4 per day). All the patients' medication was maintained during the study period. Patients were followed up for 12 weeks post-treatment. A period of 12 weeks was chosen as this is the typical duration of the motor effects of BoNT/A. Intradermal and/or subcutaneous injections of 75 U of BoNT/A (5 U/0.1 mL) or saline were applied at 15 points (0.1 mL per point). The primary endpoints were change in painful attack frequency and pain severity. Patients with ≥ 50% reduction in mean pain score at week 12 were defined as responders. The

primary end points were met and the responder rate in the BoNT/A group was superior (68%) to the one of the placebo group (15%). Shehata et al studied 20 subjects with classical TN in a randomised, single-blinded, placebo-controlled trial. The active treatment arm consisted of 10 patients who received 0.1 mL of BoNT/A (5 U/0.1 mL) applied subcutaneously per point (total dose ranged from 40 to 60 U) using a "follow the pain" method. After 12 weeks significant reductions in VAS scores (a decrease of 6.5 compared with 0.3 for saline) and the frequency of paroxysms were observed (Wu , et al., 2012).

Zúñiga et al studied the efficacy of BoNT/A in 36 patients suffering from classical TN in a randomised placebo-controlled trial. The BoNT/A group consisted of 20 subjects who received 50 U of the toxin subcutaneously in various sites 1 cm apart and 16 patients received placebo. Three months after the injection, significant differences were observed in the average VAS score for subjects treated with BTX and those treated with placebo (VAS 4.75 vs 6.94, respectively; t test, P = 0.01) (Zúñiga , et al., 2008).

Finally, Zhang et al conducted a randomised, double-blind, placebo-controlled trial testing the effects of different dosages of BoNT/A in 84 patients with classical TN who had failed to respond to established TN treatment. Patients were randomized to receive saline, 25 U/mL or 75 U/mL of BoNT/A intradermally and/or submucosally (total doses were divided by 20 and applied at 20 points). The VAS scores of both BoNT/A groups were lower than in the placebo group from the first to the eighth week ($p < 0.017$), and there was no difference between the 25 U and 75 U groups. Also, the number of responders (individuals with a reduction in mean pain score from baseline to endpoint > 50%) was higher for the active treatment groups ($p < 0.017$) and there was no difference between the groups that received different doses of BoNT/A (Zhang, et al., 2014). Overall these studies point towards a clear efficacy of BoNT/A in TN. Side effects included transient facial weakness and transient facial oedema.

Other medications

Pimozide has been reported to be more effective than CBZ (Lechin , et al., 1989) (Class II) while tocainide was reported to be as effective as CBZ (Lindström , et al., 1987) (Class III). Tizanidine, in a small group of patients (most having already undergone trigeminal surgery or taking concurrent medications), was more beneficial than placebo but its effect wore off within

1–3 months (Class III) (Fromm , et al., 1993). Small open label studies (Class IV) have suggested some therapeutic benefit from other antiepileptic drugs (clonazepam, gabapentin, valproate); however, these medications are generally added on other main treatments, such as CBZ or OXC, rather than used in monotherapy (Cruccu , et al., 2008).

Table 14. Summary of medical treatments trials versus placebo or versus carbamazepine in trigeminal neuralgia

	Evidence	**Dose range (mg/day)**	**Responder rate on active drug**	**Drop-out rate**
Carbamazepine	Class I	800-1200	88%	4/147 patients
Oxcarbazepine	Class II	600-1800	88%	0/48 patients
Lamotrigine	Class II	200-400	62-84.6%	0/14 patients
Baclofen	Class II	30-60	70%	1/10 patients
Pimozide	Class II	4-12	100%	0/48 patients
Tizanidine	Class III	12	80%	3/10 patients

1.3.6. Surgical treatments

Invasive surgical treatments are generally reserved for patients with debilitating pain refractory to a sufficient trial of established medications, namely CBZ and OXC. TN is usually associated with compression of the ipsilateral trigeminal nerve at the root entry zone by an aberrant vessel, ipsilaterally to the side of the pain. The proportion of TN patients with neurovascular conflict with the trigeminal nerve varies from 52% to 88% of patients (Majoie , et al., 1997; Benes , et al., 2005; Anderson , et al., 2006; Maarbjerg , et al., 2015). Barker and Jannetta described the long-term outcome of MVD in 1185 TN patients. In their cohort, the trigeminal root was compressed by the superior cerebellar artery in 75% of patients and by the anterior inferior cerebellar artery in 10% of patients. A vein contributed to the compression in 68% of patients and was the only compressing vessel in 12%. The vast majority of patients had only one

operation, though 11% of the cohort had a second operation after recurrence of TN. Immediate postoperative relief from TN was achieved in 82% of patients, partial in 16% and no relief in 2%. One year after the operation, 75% of patients were still pain free and 9% were experiencing a partial relief. With the inclusion of the final outcome of surgery for patients who had either one or two operations, ten years after operation, 70% were pain free and 4% had partial relief. The latter group did not require long-term treatments. The annual risk of recurrence (i.e., of transition from the group with excellent outcome to either the good-outcome or the poor-outcome group) was less than 2% five years after the operation and less than 1% after ten years. Operative complications included death in two patients, stroke in one patient, cerebral/cerebellar hematoma in four patients, facial paresis in 12 patients (permanent in two, transient in ten patients), hydrocephalus in two patients, ipsilateral hearing loss in 16 patients (mild in one patient, severe in 15 patients), severe facial numbness in 22 patients, cerebrospinal fluid leak in 20 patients, bacterial meningitis in five patients and chemical meningitis in 225 patients. Predictors of long-term response to MVD were: immediate postoperative relief, male sex, absence of venous compression of the trigeminal-root entry zone and duration of preoperative symptoms of less than eight years. The study demonstrated that MVD is an effective and relatively safe surgical treatment option for patients with TN refractory to medical management (Barker , et al., 1996).

A review of a large group of patients with typical (n=2003) and atypical TN (n=672) treated by MVD showed that the rate of complete postoperative pain relief was 84.1% and the rate of effective surgical pain control was 98.2% for classical TN patients, but for atypical TN patients (now labeled as classical TN with concomitant persistent facial pain), the rate of complete pain relief and effective pain control was 46.9% and 86.6%, respectively for 5 years or more follow-up (Tyler-Kabara , et al., 2002). In a subsequent study comparing the outcome of MVD in 45 typical TN versus 17 atypical TN, complete pain relief in the typical TN group was reported by 93.3% (42/45 patients) at a follow-up of 13 months or more after MVD. In the atypical TN group, complete pain relief was achieved by 23.5% only (4/17 patients) at about 13 months after MVD (Li , et al., 2005). Overall these findings support the notion that MVD is more effective in patients with classical TN purely paroxysmal, as opposed to those with classical TN with persistent concomitant facial pain, highlighting the importance of properly phenotyping patients with neuralgiform facial pain.

Surgical options for patients in whom MVD is contraindicated or not feasible because of the

absence of vascular loop, include: radiofrequency thermocoagulation, glycerol injection, or balloon compression. Efficacy of these procedures varies from 91% to 99% initially, with long-term recurrence rates of 10% to 25% (Peters , et al., 2002). For many patients, pain tends to recur within two to three years. Facial numbness frequently occurs as the result of these procedures and is of greatest concern for first division lesions because corneal anesthesia can lead to keratitis and loss of vision. Rates of anesthesia dolorosa range from 1% to 10% (Lopez, et al., 2004).

Gamma knife radiosurgery has attracted increasing interest because of its minimal invasiveness. A highly focused beam of 40 to 90 Gy of radiation is delivered stereotactically to a 4-mm target area encompassing the retrogasserian cisternal portion of the trigeminal nerve. Recent studies report initial pain relief in 81% to 92% and durable pain relief in 54% to 61% of patients (Kano , et al., 2010; Kondziolka , et al., 2010). The safety and efficacy of Gamma knife therapy was very recently reported for 497 patients with medically refractory classical TN who were never previously treated by Gamma knife. Of these, 456 patients (91.75%) were initially pain free after a median time of 10 days (range 1-180 days). Their probabilities of remaining pain free without medication at 3, 5, 7, and 10 years were 71.8%, 64.9%, 59.7%, and 45.3%, respectively. One hundred fifty-seven patients (34.4%) who were initially pain free experienced at least one recurrence, with a median delay of onset of 24 months (range 0.6-150.1 months). Severe facial hypoesthesia was reported in only three patients (0.6%) (Régis , et al., 2016). There is also Class IV evidence that in patients with medically refractory TN, early stereotactic radiosurgery as the initial procedure provides faster, better, and longer pain relief (Mousavi , et al., 2015).

1.3.7. Natural History

TN appears to be a lifelong disorder once it starts. The disorder usually involves bouts of daily attacks lasting weeks or months alternating with remission periods, which may last months to years. However, the natural progression of the disease may involve an increase in frequency of attacks and a shortening of remission periods. It has been proposed that patients with classical TN who are not treated properly may develop a constant inter-paroxysmal background pain overtime (Burchiel , et al., 2000). This group of patients is currently labeled as suffering with “Classical TN with concomitant persistent facial pain”, according to the recent revision of the IHS classification (Headache Classification Subcommittee of The International Headache,

2013). Studies on the medical and surgical management of this group of patients have shown a poorer response to sodium channel blockers, such as CBZ and OXC and to MVD, compared to patients with classical TN, purely paroxysmal. However, Obermann and collaborators recently challenged the theory on the natural history of TN. The authors demonstrated no difference in duration of disease between those who had classic TN and those with TN and constant background pain. The study also suggested that the pathophysiological substrate of classical TN with concomitant persistent facial pain may include a combination of trigeminal sensory root demyelination along with central sensitization possibly involving supraspinal pathways (Obermann , et al., 2007). This study supports the hypothesis that classical TN with concomitant persistent facial pain may in fact be a variant of TN rather than a result of TN disease duration.

1.3.8. Pathophysiology

The pathophysiology of TN is still a matter of debate. The current theory suggests that TN is caused by a proximal compression of the trigeminal sensory root near the brainstem (root entry zone) by a blood vessel (artery or vein). This mechanical compression may start a process of demyelination and remyelination (Rappaport , et al., 1997; Peker , et al., 2006), probably mediated by microvascular ischemic damages (Marinković , et al., 2007). These changes lower the excitability threshold of affected fibers and promote inappropriate ephaptic propagation towards adjacent fibers (Burchiel , 1980). Thus, tactile signals coming from the fast myelinated (A-β) fibers can directly activate the slow nociceptive (A-δ) fibers, resulting in the high-frequency paroxysms characteristic of TN. After a few seconds, these repetitive discharges spontaneously run out and are followed by a brief period of inactivity that is called “refractory period”, where triggering actions are not able to provoke pain.

While Jannetta and colleagues described 88% of their investigated patients having a nerve vessel conflict, 6% had MS and 6% showed a cerebellopontine angle tumor (Jannetta , 1967), more recent investigations demonstrated that not all patients who were considered to have TN had a nerve vessel conflict and that at least 25% of individuals without any clinical signs of TN had a nerve artery contact on MRI (Adamczyk , et al., 2007). A different study where MRI scans were performed for reasons different than facial pain, demonstrated that out of 220 investigated trigeminal nerves 110 (49%; 51 women and 57 men) showed some degree of compression (Kakizawa , et al., 2008). The immediate and sustained pain relief following MVD

surgery in the vast majority of patients indicates the key relevance of the trigeminal neurovascular compression mechanism. However, it is hard to explain why some patients experience recurrence of pain some years after the operation, why some patients do not respond to MVD in the first place and what is the underlying pain mechanism in those patients in whom no neurovascular conflict is demonstrated on detailed neuroimaging (Gronseth , et al., 2008). It was suggested that hyperexcitability of the compressed nerve may represent a risk factor for the development of TN, but on its own is not the only cause of the disease (Hamlyn , et al., 1992).

The remarkable clinical effect of sodium channels blockers in TN has suggested that an abnormal expression of voltage-gated sodium channels could constitute an important pathophysiologic correlate and that TN might be a sodium channelopathy. Nav1.7, Nav1.3 and Nav1.8 were found to be abnormally expressed in TN and possibly responsible for rapid activation and inactivation, as well as maintenance of the action potential (Siqueira , et al., 2009). Overtime, possible involvement of central mechanisms along with more peripheral mechanisms have been postulated to explain the hyperexcitability in the trigeminal system in TN. Sensitization of second-order wide dynamic range (WDR) neurons in lamina V of the dorsal horns and the trigeminal nerve nuclei due to hypersensitivity of tactile A-β fibers have been discussed as an additional pathophysiological mechanism. Since these WDR neurons receive convergent information from tactile (A-β) and nociceptive (A-δ and C) fibers, their sensitization could promote the perception of pain in response to cutaneous stimulation. Central facilitation was recently demonstrated in TN patients with additional constant dull background pain besides their typical TN attacks using pain-related evoked potentials and nociceptive blink reflex (Obermann , et al., 2007). This provides evidence for the involvement of supraspinal structures in TN.

Functional MRI studies in TN have demonstrated activation of areas of the pain neuromatrix and in particular activation of the spinal trigeminal nucleus, brainstem, thalamus, primary and secondary somatosensory cortices, anterior cingulate cortex (ACC) following painful stimulation of cutaneous triggered zones (Borsook , et al., 2007). The spinal trigeminal nucleus, brainstem and the ACC were not activated by non-painful stimulation (Moisset , et al., 2011). However, the role of activation of supraspinal structures in TN nociceptive processing needs to be further elucidated.

1.4. SUNCT, SUNA and trigeminal neuralgia: different disorders or variants of the same disorder?

SUNCT and SUNA are placed within the trigeminal autonomic cephalalgias (TACs) grouping, because of the combination of unilateral headache attacks in the trigeminal territory associated with cranial autonomic symptoms and the activation of the posterior hypothalamus during attacks demonstrated in functional neuroimaging studies. However, besides the occurrence of ipsilateral autonomic symptoms during attacks, there are few other similarities between SUNCT/SUNA and the other TAC syndromes. Conversely, the demographic characteristics, clinical features, neuroimaging findings and therapeutic treatments of SUNCT and SUNA overlap with trigeminal neuralgia, challenging the traditional view that they are separate disorders.

1.4.1. SUNCT, SUNA and Trigeminal neuralgia: classification criteria

Since their first appearance in the ICHD-2, the SUNCT diagnostic criteria showed several shortcomings, mainly linked to the criterion of the obligatory occurrence of lacrimation and conjunctival injection with the pain (Headache Classification Subcommittee of The International Headache Society., 2004). This criterion does not reflect the clinical presentation of SUNCT, in which a broader array of cranial autonomic symptoms occurs (Pareja , et al., 1997). Moreover, if the threshold of two cranial autonomic symptoms should be maintained, it is arguable that the association of any two amongst the array of cranial autonomic symptoms should have been suggested, rather than only conjunctival injection and lacrimation. Strikingly, compared to the other TACs' diagnostic criteria, the SUNCT criteria were the only ones in which the association of two rather than one cranial autonomic symptoms were obligatory for the diagnosis. Indeed, the criteria for cluster headache state that if the phenotype fulfills the other diagnostic criteria without any cranial autonomic features then a sense of restlessness is sufficient to make the diagnosis.

For the aforementioned reasons, the IHS Classification Committee considered that SUNCT syndrome may be a subset of a broader condition, SUNA. In SUNA, there may be cranial autonomic symptoms other than conjunctival injection and lacrimation, or just one of these symptoms may occur (Headache Classification Subcommittee of The International Headache

Society., 2004). However, reducing the threshold of cranial autonomic symptoms down to one led to the additional criterion of the absence of a refractory period in order to reinforce the difference between SUNA and V1 trigeminal neuralgia, in which attacks are often followed by a refractory period. Despite the broader SUNA criteria, only a few cases have been reported in the literature since 2004, hence the full phenotype still needs to be defined.

Since the publication of the ICHD-2 criteria, further studies have shed light on the clinical aspects of SUNCT and SUNA (Cohen , et al., 2006). In light of this, the IHS Classification Committee proposed a new set of diagnostic criteria for SUNCT and SUNA in the ICHD-3 beta version (Headache Classification Subcommittee of The International Headache, 2013). The new set of diagnostic criteria seems to have reinforced the diagnostic overlap between SUNCT/SUNA and the other TACs, by changing the frequency description of attacks to at least one daily, along with increasing the duration of the SUNCT/SUNA attacks up to 10 min. Conversely, despite evidence showing that 74% of SUNCT patients could trigger attacks by cutaneous stimulation, no such criterion was included (Cohen , et al., 2006). Moreover, the threshold of two cranial autonomic symptoms for the SUNCT criteria still remained unchanged. Disregarding the clinical overlap between SUNCT/SUNA and TN may continue to create confusion in clinical practice, preventing the publication of meaningful data that could shed light upon the neurobiology of these disorders.

1.4.2. SUNCT, SUNA and trigeminal neuralgia: the clinical phenotype

The difficulty of keeping SUNCT, SUNA and trigeminal neuralgia separate lies in their remarkable clinical overlap that includes neuralgiform character of the pain, very short duration, high daily frequency of attacks, and presence of attacks triggered by cutaneous stimulation. Moreover, in light of the recent description of the SUNA syndrome (Cohen , et al., 2006), the known clinical differences between SUNCT and trigeminal neuralgia such as the maximal intensity of the pain in the ophthalmic division of the trigeminal nerve, the association of pronounced cranial autonomic features with the pain, the absence of a refractory period following attacks provoked from trigger areas and the absence of a constant background pain between the paroxysmal attacks seem to suggest a continuum of symptoms rather than neurobiological differences between SUNCT, SUNA and TN (Table 15).

In the largest SUNCT and SUNA series published, 67% of SUNCT patients complained of

pain in V1 (ophthalmic nerve territory) and 33% complained of pain in V2 (maxillary nerve territory). In contrast, a higher proportion of SUNA patients reported the maximal intensity of the pain in V2 and V3 (mandibular nerve territory) (56% and 33%, respectively), suggesting a continuum with trigeminal neuralgia, in which the vast majority of patients report attacks in V2, V3 or both (Katusic , et al., 1990). Furthermore, it is possible that the high proportion of SUNCT patients with mainly V1 pain is a result of the mandatory association of the pain with conjunctival injection and tearing, decided by the IHS Classification Committee. Indeed, emerging evidence in SUNCT, SUNA and trigeminal neuralgia has suggested that the cranial autonomic symptoms tend to follow the site of the pain, with ocular symptoms occurring predominantly with pain in V1 and nasal symptoms with pain in V2 and V3 (Cohen , et al., 2006; Simms , et al., 2011). It is possible that if the SUNCT criteria allowed a more flexible combination of ocular and nasal cranial autonomic symptoms, more cases of SUNCT/SUNA with pain in V2 – V3 would be reported. Similarly, a reason why few patients with SUNCT/SUNA and pain in V2 – V3 have been reported might be because patients are often misdiagnosed with trigeminal neuralgia and therefore are not asked by physicians about the presence of associated symptoms. To support this hypothesis, a recent retrospective study in 92 TN patients who underwent MVD showed at least one cranial autonomic symptom in 67% of them regardless of the pain site (Simms , et al., 2011).

SUNCT is thought to be associated with numerous pronounced cranial autonomic symptoms unlike TN. However, when the threshold is reduced from at least two symptoms to one symptom (SUNA criteria), the clinical overlap with TN becomes more pronounced. TN with cranial autonomic symptoms has been reported in various clinical series. Sjaastad and colleagues reported the presence of lacrimation in eight of 19 (42%) patients with V1 trigeminal neuralgia; conjunctival injection and rhinorrhoea were also present in some patients (Sjaastad , et al., 1997). Subsequently, Pareja and collaborators recorded 26 attacks from two patients with V1 trigeminal neuralgia, 81% of which were accompanied by mild lacrimation. Strikingly, there was a relationship between attack duration and intensity of lacrimation, with slightly longer attacks (12 – 22 s) being accompanied by moderate lacrimation (Pareja , et al., 2002). The authors stated that the mild – moderate degree of cranial autonomic symptoms in TN was a clear-cut difference compared to the pronounced autonomic activation reported in SUNCT. However, there are no studies that have assessed the degree of autonomic activation in SUNCT. As shown for TN, given the wide range of duration of SUNCT/SUNA attacks, it may be possible that the degree of intensity and number of cranial autonomic symptoms varies

according to the duration of each attack. Short-lasting attacks may not be associated with pronounced cranial autonomic symptoms, as opposed to longer-lasting attacks. Although clinically meaningful, the different degrees of cranial autonomic activation in SUNCT, SUNA and TN, perhaps related to the different duration of attacks, may reflect a different degree of involvement of similar pathophysiological mechanisms rather than a distinctive neurobiological difference.

Another difference between SUNCT/SUNA and TN is in the presence of constant pain ipsilaterally to the side of the paroxysmal attacks. Approximately 50% of SUNCT and possibly SUNA patients report constant background headache (Cohen , et al., 2006). Conversely, in classical TN, by definition, patients must be pain free between attacks; otherwise a diagnosis of classical TN with concomitant persistent facial pain should be made. Compared to classical TN purely paroxysmal, the phenotype of TN with constant pain seems to be characterized by a higher occurrence of cranial autonomic symptoms (approximately 40% of patients); minor proportion of attacks triggered by cutaneous stimuli; and lower proportion of patients showing neurovascular compression on the trigeminal nerve and less impressive response to carbamazepine and MVD of the trigeminal nerve (Headache Classification Subcommittee of The International Headache, 2013). These clinical features seem remarkably similar to the clinical features of the subgroup of SUNCT/SUNA patients with constant pain. It is therefore possible that a significant proportion of patients with classical TN with concomitant persistent facial pain in fact suffer with SUNCT or SUNA with constant background pain. There has been a suggestion that the presence of migraine biology is accountable for the development of central sensitization and thus constant pain in SUNCT and SUNA (Cohen , et al., 2006). A similar mechanism could also account for TN with constant pain. Patients with TN and migraine biology would be more susceptible to central sensitization mechanisms that could influence the clinical presentation (background pain, cranial autonomic symptoms, and mainly spontaneous attacks) and perhaps the therapeutic outcome (less compelling response to carbamazepine and MVD), thus explaining the difference between classical TN and TN with constant pain.

Table 15. Clinical characteristics of SUNCT, SUNA and trigeminal neuralgia

	SUNCT	SUNA	Trigeminal Neuralgia
Gender ratio (M:F)	2:1; 1:1	0.5:1	1:2
Mean age of onset (years)	48	44-47	52
Site of pain	V1: 67% V2: 33% V3: 0%	V1: 56% V2: 56% V3: 33%	V1: 10% V2: 35% V3: 30%
Severity of pain	Severe to very severe	Severe to very severe	Very severe
Duration (seconds)	1-600	1-600	<1-120
Frequency/day	1-600	1-600	Triggerable
Autonomic features	Yes (numerous)	Yes (less numerous)	None (sparse)
Cutaneous/intraoral triggers	74%	NK	100%
Refractory period	Absent	Absent	Present
Background pain	47%	NK	Absent

SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; V1: Ophthalmic nerve territory; V2: Maxillary nerve territory; V3: Mandibular nerve territory; NK: not known due to insufficient data in literature.

1.4.3. The aetiology of SUNCT, SUNA and trigeminal neuralgia

The majority of SUNCT cases are idiopathic, but a significant minority of them seems to be secondary to intracranial abnormalities. Similar to secondary cases of other TACs (Cittadini, et al., 2009) and secondary TN (Love , et al., 2001; Leone , et al., 2004; Gazioğlu , et al., 2000), cases of SUNCT have been attributed to posterior fossa abnormalities and pituitary adenomas (Cohen , et al., 2006; Chitsantikul , et al., 2013). In addition, growing evidence supports the frequent occurrence of vascular compression of the trigeminal nerve close to the root entry zone ipsilaterally to the side of the pain. In a series of 24 SUNCT/SUNA cases, 17 patients were studied with dedicated MRI imaging of the trigeminal nerves. Neurovascular compression was detected in 15 of 17 patients (88%). In 90% of cases, a vascular loop was impinging on

the symptomatic trigeminal nerve, compared to only 7% in which the vascular loop was pressing on the asymptomatic nerve, suggesting that this finding was more than a mere chance association (Williams , et al., 2008). Should these data be confirmed in a larger sample of patients, it would support an aetiological overlap between SUNCT, SUNA and TN; indeed, TN seems to be associated with neurovascular compression of the trigeminal sensory root in the vast majority of patients.

1.4.4. The treatment of SUNCT, SUNA and trigeminal neuralgia

The treatment for SUNCT/SUNA and TN is divided into medical and surgical therapies. SUNCT, SUNA and TN respond to similar medications. Lamotrigine is considered the oral drug of choice for the preventive treatment of SUNCT and SUNA, despite the fact that this assumption is based on small open-label studies. Lidocaine is possibly even more effective, but its use is limited by the administration route and the side-effects profile (Lambru , et al., 2013). Evidence of efficacy has also been reported for topiramate and gabapentin (Cohen, 2007). The therapeutic response to carbamazepine has been reported in 33 SUNCT cases. Eleven patients (33%) reported a favourable response, the majority of which had only partial benefit (Matharu et al., 2003). However, the data on this treatment might have been biased by the selection of only those SUNCT and SUNA patients who were misdiagnosed with TN and failed the treatment with carbamazepine. Emerging evidence has shown a possible favourable effect in monotherapy or polytherapy of oxcarbazepine, which shares similar mechanisms of action with carbamazepine but seems to have a better tolerability profile (Dora , 2006; Marziniak , et al., 2009). Oxcarbazepine and carbamazepine are the drugs of choice for the prophylaxis of TN (Cruccu , et al., 2008). Moreover, evidence from a randomized placebo-controlled crossover trial also supports the efficacy of lamotrigine as an add-on therapy for the prevention of trigeminal neuralgia (Zakrzewska , et al., 1997). Interestingly, the study group consisted of patients who failed to respond to carbamazepine or phenytoin, strengthening the importance of lamotrigine in the prophylaxis of trigeminal neuralgia.

Despite the lack of homogeneous selection criteria for patients suitable for surgery, several ablative procedures on the trigeminal nerve known to be effective in TN have been attempted in SUNCT and SUNA, with mixed results (Lambru , et al., 2013). Remarkably, in view of the initial observations of the presence of neurovascular conflict with the trigeminal nerve in

SUNCT and SUNA syndromes, cases of patients treated with MVD of the trigeminal nerve have emerged. To date, 12/19 (63%) SUNCT and SUNA patients treated with MVD obtained a complete control of the headache at a mean follow- up of 14 months (range: 0.5 – 32 months) (Sebastian , et al., 2013). Larger series with longer follow-ups are required to confirm this promising result. Altogether, these findings suggest an overlap of medical and surgical treatments between SUNCT, SUNA and TN, supporting the hypothesis that these disorders may share underlying pathophysiological mechanisms.

1.4.5. The pathophysiology of SUNCT, SUNA and trigeminal neuralgia

Any pathophysiological construct on SUNCT and SUNA should account for their major clinical characteristics. It has been proposed that some of the clinical features of SUNCT/SUNA, namely the occurrence of pronounced cranial autonomic symptoms with the pain, imply a central disinhibition of the trigemino-autonomic reflex, similar to the other TACs (Goadsby, et al., 1997; Leone , et al., 2009). The cerebral structure implicated in the disinhibition mechanism is thought to be the posterior hypothalamus, known to have a modulatory role in the nociceptive and autonomic pathways, specifically the trigeminovascular nociceptive pathways (Bartsch , et al., 2004). Functional neuroimaging studies have showed activation of the posterior hypothalamus during SUNCT/SUNA attacks, supporting its paramount role in these disorders (May , et al., 1999; Cohen, 2007). However, this pathophysiological model can hardly explain the other key clinical features of SUNCT/SUNA, including the neuralgiform type of pain, the very short duration and high frequency of the attacks, the triggerability of the attacks, and the absence of a refractory period, which are unique characteristics for these disorders amongst the TACs and constitute the core of the clinical overlap with TN.

The pathophysiological model that accounts for the TN features revolves around a complex interaction of peripheral and central mechanisms. The ignition hypothesis highlights the role of focal demyelination of the trigeminal sensory root because of vascular compression near the root entry zone in generating spontaneous ectopic impulses responsible for the short-lasting spontaneous attacks (Devor , et al., 2002). Additionally, in the demyelination area ephaptic cross talking activities between fibers mediating light touching (A-b) and nociceptive fibers (A-d) may account for the attacks triggered by innocuous stimulation. Central mechanisms account for the occurrence of TN in patients with no structural damage on the trigeminal nerve,

besides explaining the mechanism of the refractory period following triggered attacks. The occurrence and the length of a refractory period are functions of the duration and intensity of the preceding attack, thus very short-lasting attacks seem not to be followed by a refractory period. This mechanism seems to be regulated by the trigeminal nucleus caudalis, highlighting the importance of central structures in TN (Kugelberg, et al., 1959).

The presence of a neurovascular conflict with the trigeminal nerve in a significant majority of patients may support similar peripheral mechanisms also in SUNCT/SUNA. A central disinhibition of the trigeminal nucleus caudalis may explain the lack of refractory periods in SUNCT/SUNA compared to TN.

Ultimately, SUNCT, SUNA and TN may be attributable to a unifying pathophysiological model characterized by different degrees of interaction between peripheral and central mechanisms, namely focal demyelination of the trigeminal sensory root and posterior hypothalamic dysfunction. Central mechanisms may be more pronounced in patients with at least two cranial autonomic symptoms and less pronounced in patients with one or no autonomic symptoms.

1.5. Conclusion

SUNCT and SUNA syndromes are considered TACs due to the occurrence of pain in the trigeminal territory associated with cranial autonomic symptoms. Functional neuroimaging studies demonstrated posterior hypothalamic activation during SUNCT attacks, supporting a shared pathophysiological model for the TACs. However, SUNCT and SUNA display a remarkable demographic and clinical overlap with TN. Growing evidence also supports aetiological similarities with TN because of the significant proportions of patients with SUNCT and SUNA showing a neurovascular conflict with the trigeminal nerve. Preliminary data demonstrate the efficacy of MVD of the trigeminal nerve in SUNCT and SUNA, suggesting the possible role of damage of the sensory root in the pathophysiology of these disorders. This underlying common mechanism could account for the striking clinical similarities between these conditions, supporting the hypothesis that SUNCT, SUNA and TN represent variants of the same disorder. This disorder would be characterized by unilateral short-lasting neuralgiform headache attacks with different degree of cranial autonomic activation, reflecting the different degree of involvement of central (posterior hypothalamic dysfunction) and

peripheral (trigeminal sensory root damage) mechanisms. This unifying hypothesis carries important nosological implications on whether this new clinical entity should belong to the TACs or the cranial neuralgias group.

1.6. Aims of the Thesis

The aim of the thesis is to detail the phenotype of SUNA syndrome and to compare it to that of SUNCT. The outcome of such a study may shed light on whether these two conditions need to be kept separate or whether they could be unified in the future revision of the IHS classification. This thesis also aims to study the proportion and the characteristics of neurovascular compression with the trigeminal nerve in SUNCT and SUNA syndromes, with the goal to examine the initial findings on this subject. Given the limited armamentarium of treatments for such disabling conditions, this thesis will study the efficacy of numerous medical treatments in a large series of SUNCT and SUNA patients, aiming to expand the medical treatment options for this disabling condition. Additionally, this study will aim to test two surgical procedures that have reported to be effective in the other TACs, namely occipital nerve stimulation and in TN, namely MVD, in a group of medically refractory SUNCT and SUNA patients. Finally, a comparison of demographic and clinical features between large series of SUNCT, SUNA and TN will be carried out aiming to shed light on whether SUNCT, SUNA and TN represent different clinical entities or variants of the same disorder.

Chapter 2. A Prospective Clinical and Radiological Study of Short-lasting Unilateral Neuralgiform Headache Attacks With Conjunctival

Injection And Tearing (SUNCT) Or Cranial Autonomic Symptoms (SUNA)

2.1. Abstract

Whereas the SUNCT clinical phenotype is well defined, that of SUNA is much less so. Despite the similar phenotypes, comparison between SUNCT and SUNA has hitherto not been possible due to the dearth of studies validating the phenotype of SUNA and therefore these two syndromes have been kept separate in the International Classification of Headache Disorders. To validate the clinical phenotype of SUNA and assess similarities and differences with the one of SUNCT, 133 patients with SUNA and SUNCT (SUNA=63 and SUNCT=70) underwent administration of a face to face semi-structured questionnaire capturing demographic and clinical characteristics. Both unadjusted and adjusted logistic regression analyses were used to identify predictors of patients suffering SUNA rather than SUNCT.

Of all the clinically relevant variables that characterise these disorders, a multivariate logistic regression analysis demonstrated a significant association between ipsilateral ptosis [OR: 3.37 (95% CI: 1.50, 7.66), p<0.0001] and rhinorrhoea [OR: 2.42 (95% CI: 1.09, 5.41), p=0.034] with SUNCT as opposed to SUNA. A significantly higher proportion of SUNCT patients (n=56, 80.0%) also reported marked lacrimation compared to SUNA patients (n=20, 46.5%) (P<0.001).

Since no major clinical differences between SUNCT and SUNA were found, bar the fact that SUNCT is characterised by more prominent cranial autonomic features, which is likely to merely reflect the current operational criteria that artificially separate these conditions, it was proposed that the two disorders be placed together in the single diagnostic category, SUNA, which encompasses cases of SUNCT. New diagnostic criteria for this unified syndrome were proposed. These criteria, applied to our cohort, correctly diagnosed all the patients, but two.

2.2. Introduction

Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) is a rare primary headache disorder first described in 1978 (Sjaastad, et al., 1978) and further characterised over subsequent years (Sjaastad , et al., 1989; Pareja , et al., 1997). The first diagnostic criteria for SUNCT, based on expert opinion, were proposed in 1997 (Goadsby, et al., 1997). In view of the clinical combination of unilateral pain in the trigeminal territory and ipsilateral cranial autonomic symptoms, the authors suggested placing SUNCT alongside cluster headache (CH) and paroxysmal hemicrania (PH) within the trigeminal autonomic cephalalgias (TACs). SUNCT was subsequently included in "Group 3" of the second edition of the International Classification of Headache Disorders (ICHD-2), while criteria for SUNA were outlined in the appendix section (Headache Classification Subcommittee of The International Headache Society., 2004). In the recently published revised version of the classification, SUNCT and SUNA have been encompassed within the group of the "Short-lasting unilateral neuralgiform headache attacks" and criteria for the episodic and chronic forms have been proposed (Headache Classification Subcommittee of The International Headache, 2013). Both the syndromes are currently defined by moderate or severe unilateral head pain in orbital, supraorbital, temporal and/or other trigeminal distribution, lasting for 1–600 seconds and occurring as single stabs, series of stabs or in a saw-tooth pattern. In SUNCT the pain must be accompanied by both ipsilateral conjunctival injection and lacrimation, whereas in SUNA only one or neither of conjunctival injection and lacrimation (tearing) should be present though the pain has to be accompanied by at least one cranial autonomic feature. Attacks have a frequency of at least one a day for more than half of the time when the disorder is active.

SUNCT and SUNA are believed to be rare with an estimated prevalence of 6.6 per 100,000 and an annual incidence of 1.2 per 100,000 (Williams , et al., 2008). To date, two reviews (Pareja , et al., 1997; Matharu , et al., 2003) and two prospective clinical series of SUNCT patients have defined the clinical phenotype of the syndrome (Cohen , et al., 2006; Williams , et al., 2008). In contrast, only a few patients with SUNA have been described in the literature thus far (Cohen , et al., 2006; Williams , et al., 2008; Lambru , et al., 2012; Chitsantikul , et al., 2013) and therefore the full clinical spectrum of the syndrome still needs to be defined. This has meant that valid comparisons of SUNCT and SUNA have been lacking and further

advances on the issue of whether they are separate syndromes or a unified entity have hitherto not been possible.

Moreover, similar to trigeminal neuralgia (TN), a significant proportion of SUNCT patients have been reported to display neurovascular conflict with the trigeminal nerve ipsilaterally to the side of the pain in a small study (Williams , et al., 2008). Some of those patients also benefited from treatment with microvascular decompression of the trigeminal nerve, suggesting a pathophysiological overlap between SUNCT, SUNA and TN (Williams , et al., 2010; Lambru , et al., 2014).

The aim of this chapter was to describe the clinical and demographic characteristics of a large clinic-based cohort of SUNA and SUNCT patients, and to compare and contrast these characteristics.

2.3. Methods

The study group was derived from 147 patients, of whom 66 had SUNA and 81 had SUNCT. However, 14 patients were excluded because they could not be followed-up for the following reasons: 11 were discharged from our clinic and three deceased for reasons not linked to the headache condition. The final study group consisted of 133 patients. The diagnosis of SUNCT or SUNA had initially been made according to the ICHD-3β criteria by two consultant neurologists and headache experts (M.M. and P.S.) at The National Hospital for Neurology and Neurosurgery from 2007 to 2012. Once the diagnosis was established, participants were invited to take part in the study and consent was taken. Participants were then administered a comprehensive standardized semi-structured questionnaire (see Appendix) in an outpatient clinical setting. The interview was conducted face to face by a single researcher (GL) and lasted between 60-90 minutes. If any diagnostic concerns were raised, patients were re-phenotyped at three to six-month intervals and appropriate investigations undertaken. These included trials of oral or intramuscular indometacin to rule out indometacin-responsive headaches (Headache Classification Subcommittee of The International Headache, 2013) and trials of sumatriptan 6 mg subcutaneous injections and high-dose and flow-rate oxygen to evaluate for the possibility of a diagnosis of cluster headache (Cohen, 2007). If any of the questions were not able to be answered by the participants, then that participant would be re-assessed normally between three

to six months. Data were collated in an electronic password protected spreadsheet and the participants files were updated if new or different clinical information became available.

Patients were asked to keep a headache diary for at least two weeks between appointments to obtain objective and reliable information about the duration and frequency of the headache attacks. Baseline headache characteristics were captured when participants were not on preventive treatments or while they were taking preventive medication, which were not effective. In addition, where possible, relatives (in particular partners) were questioned regarding the presence or absence of autonomic symptoms and other clinical features during acute attacks.

The study was approved by Northwick Park Hospital Research Ethics Committee, London, UK (REC no:11/LO/1709)

2.3.1. Statistical analysis

Baseline characteristics were compared between the cohorts of SUNA and SUNCT using Chi-squared tests or Fisher's exact tests for categorical variables and Student's t-tests or Mann Whitney U-tests depending on the distribution of the continuous variables. Both unadjusted and adjusted logistic regression analyses were used to identify predictors of patients suffering SUNA rather than SUNCT. Adjustments were made for characteristics that have previously been associated with either condition (i.e. site, quality of the pain, duration, frequency of the attacks and cranial autonomic symptoms). Statistical analyses were performed using STATA (Stata Corp. 2001. Stata Statistical Software: Version 12.1, College Station, Texas, USA). All reported p-values were two-sided and a significance level less than 5% was considered significant.

2.4. Results

2.4.1. Age, gender and duration of symptoms

The demographic characteristics of our cohorts of SUNA and SUNCT patients are shown in Table 16. Female were more represented than men in our cohort of patients. This gender preponderance was significantly more pronounced in SUNA compared to SUNCT patients

(p=0.042). It took a median of four years (IQR: 2-7.75 years) for the patients to obtain the correct diagnosis.

Table 16. Demographic characteristics of SUNA and SUNCT patients

		SUNA n (%)	**SUNCT n (%)**	**TOTAL n (%)**
Gender	Male	18 (28.6%)	32 (45.7%)	49 (36.8%)
	Female	45 (71.4%)	38 (54.3%)	84 (63.2%)
Mean (95% CI) age of onset (years)		45.03 (±14.1)	42.16 (±15.4)	43.52 (±14.8)
Age range of onset		16-72 years	13-76 years	13-76 years
Median duration of symptoms (range)		5 (1-31) years	8 (1-45) years	6 (1-45) years
Median time to make the correct diagnosis (range)		3 (0-30) years	3 (0-45) years	3 (0-45) years

CI: confidence interval; SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing;

2.4.2. Diagnoses made on previous clinical assessments

The majority of patients had previously been given a diagnosis of TN (Table 17). Of the 133 patients, 110 (82.7%) did not report any other comorbid headache disorder. Of the remaining 23 patients, nine had a diagnosis of chronic CH, three of HC, two of episodic CH, two of primary stabbing headache, two of new daily persistent headache, one patient of TN, one patient of trigeminal painful neuropathy, one patient of primary headache associated with sexual activity, one of tension-type headache and one of headache attributed to spontaneous intracranial hypotension.

Table 17. Diagnoses made prior to definitive diagnosis of SUNCT or SUNA

	SUNA n (%)	**SUNCT n (%)**	**TOTAL n (%)**
Trigeminal neuralgia	34 (54.0%)	34 (48.6%)	68 (51.1%)
Migraine	10 (15.9%)	17 (24.3%)	27 (20.3%)
Cluster headache	8 (12.7%)	16 (22.9%)	24 (18.1%)
Paroxysmal hemicrania	3 (4.8%)	0 (0.0%)	3 (2.3%)
Hemicrania continua	1 (1.6%)	0 (0.0%)	1 (0.8%)
Dental pathologies	6 (9.5%)	7 (10.0%)	13 (9.8%)
TAC not otherwise specified	0 (0.0%)	3 (4.3%)	3 (2.3%)
Stress/psychiatric conditions	0 (0.0%)	3 (4.3%)	3 (2.3%)
Horton arteritis	1 (1.6%)	1 (1.4%)	2 (1.5%)
Occipital neuralgia	0 (0.0%)	3 (4.3%)	3 (2.3%)
No diagnosis made	13 (20.6%)	9 (12.9%)	22 (16.5%)

Some patients were offered multiple diagnoses prior to the definitive diagnosis. SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; TAC: trigeminal autonomic cephalalgia

2.4.3. Precipitating events

Seventeen SUNA (25.8%) and 20 SUNCT (28.5%) patients reported possible precipitating events prior to the onset of symptoms. The remaining patients were not aware of any events that may have had a causative role in the exacerbation of their condition. A list of precipitating events is given in Table 18.

Table 18. Precipitating events

		SUNA n (%)	**SUNCT n (%)**	**TOTAL n (%)**	**Latency between event and onset of headache**
Period of extreme stress		2 (3.2%)	3 (4.3%)	5 (3.8%)	-2 SUNCT: 1 month -1 SUNCT: 3 weeks -2 SUNA: 1 month
Head injury		2 (3.2%)	3 (4.3%)	5 (3.8%)	-1 SUNCT: 3 weeks -1 SUNCT: 1 week -1 SUNCT: 24 hours -1 SUNA: 2 months -1 SUNA: 1 week
Infection	Flu symptoms	2 (3.2%)	0 (0.0%)	2 (1.5%)	-2 SUNA: 1 week
	Pneumonia	1 (1.6%)	0 (0.0%)	1 (0.8%)	-1 SUNA: 3 weeks
	Herpes simplex	0 (0.0%)	1 (1.4%)	1 (0.8%)	-1 SUNCT: 1 week
	Herpes Zoster	1 (1.6%)	1 (1.4%)	2 (1.5%)	-1 SUNCT: 2 months -1 SUNA: 1 month
	Bacterial tonsillitis	1 (1.6%)	0 (0.0%)	1 (0.8%)	-1 SUNA: 1 month
Surgical operation	Dental	1 (1.6%)	2 (2.9%)	3 (2.3%)	-1 SUNCT: 2 months -1 SUNCT: 1 week -1 SUNA: 1 week
	Eye	1 (1.6%)	0 (0.0%)	1 (0.8%)	-1 SUNA: 3 weeks
	Nasal	0 (0.0%)	1 (1.4%)	1 (0.8%)	-1 SUNCT: 1 month
Ischemic stroke		0 (0.0%)	2 (2.9%)	2 (1.5%)	-1 SUNCT: 1 week -1 SUNCT: 1 week
Therapeutic procedures	GON blockade	1 (1.6%)	0 (0.0%)	1 (0.8%)	-1 SUNA: 1 week
	IV DHE	0 (0.0%)	1 (1.4%)	1 (0.8%)	-1 SUNCT: 1 week
Chemotherapy		1 (1.6%)	0 (0.0%)	1 (0.8%)	-1 SUNA: 3 weeks
Pregnancy		1 (1.6%)	0 (0.0%)	1 (0.8%)	-1 SUNA: 1 week after childbirth

GON: greater occipital nerve; IV DHE intravenous dihydroergotamine; SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

2.4.4. Laterality of attacks

Thirty-one SUNA (49.2%) and 32 SUNCT patients (45.7%) had exclusively right-sided attacks; 24 SUNA (38.1%) and 27 SUNCT patients (38.6%) had exclusively left-sided attacks (p=0.820). Seven SUNA (11.1%) and 11 SUNCT patients (15.7%) had side alternating unilateral attacks; in eight patients, they were predominantly right-sided (SUNA, n=2; SUNCT, n=6), in nine patients they were predominantly left-sided (SUNA, n=4; SUNCT, n=5) and in one SUNA patient the attacks occurred equally on either side. One patient with side-alternating SUNA attacks also described bilateral attacks.

2.4.5. Site of attacks

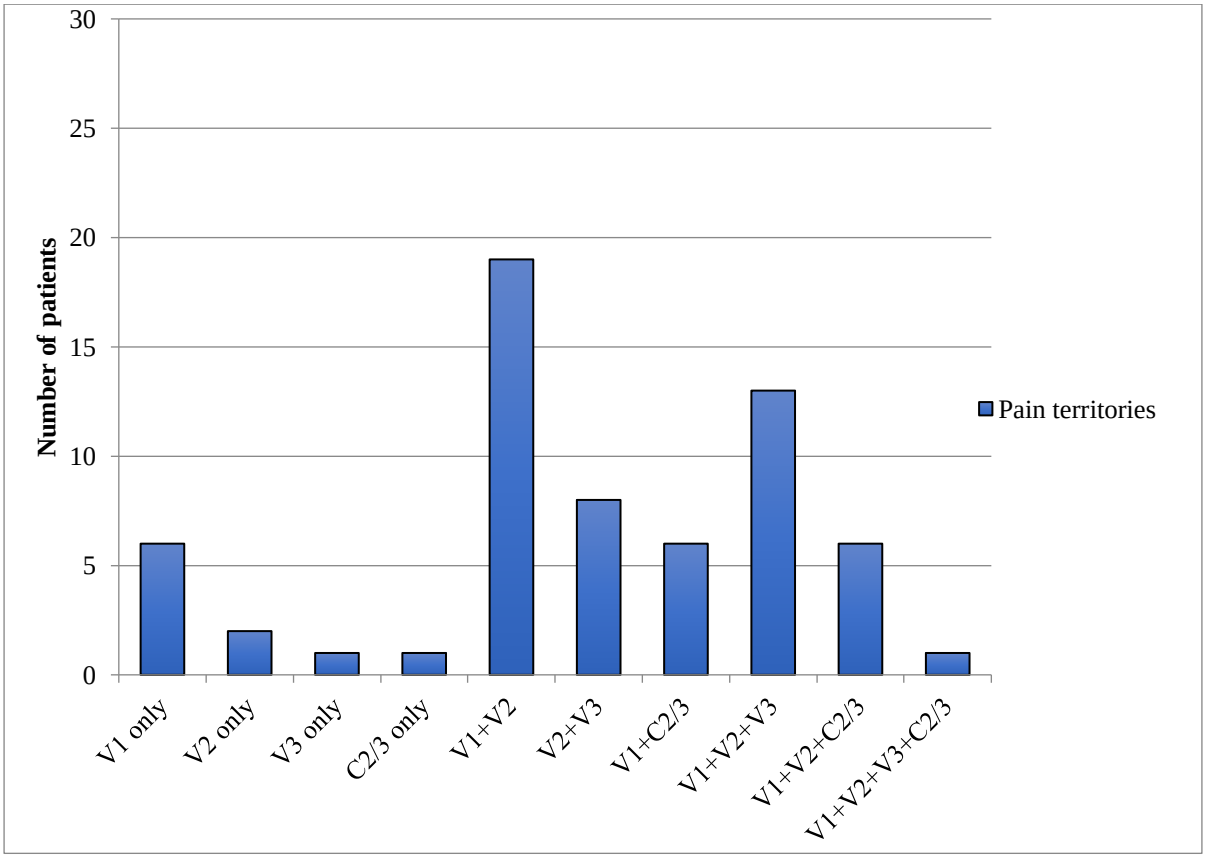
Fifty-one SUNA (81.0%) and 63 SUNCT (90.0%) patients had attacks in the distribution of the first branch of the trigeminal nerve (V_1) (p=0.136). In 40 SUNA patients (63.5%), V_1 constituted one of starting sites of the painful attacks whereas in 11 patients (17.5%) the pain started in another site and radiated to the V_1 territory. In 54 SUNCT patients (77.1%), V_1 constituted one of starting sites of the painful attacks whereas in nine patients (12.9%) the pain started in another site and radiated to V_1.

Forty-nine SUNA (77.8%) and 51 SUNCT (72.9%) patients experienced attacks in the distribution of the second branch of the trigeminal nerve, including the temple (V_2) (p=0.511). In 47 SUNA patients (74.6%), V_2 was one of the starting sites of the attacks whereas in two patients (3.2%), V_2 constituted a site where pain radiated. In 41 SUNCT patients (58.6%), V_2 was one of the starting sites of the attacks whereas in ten patients (14.3%), V_2 constituted a site where pain radiated.

Twenty-three SUNA (36.5%) and 20 SUNCT patients (28.6%) reported attacks in the distribution of the third branch of the trigeminal nerve (V_3) (p=0.005). In 18 SUNA patients (28.6%), V_3 was one of the principal locations of the pain whereas in five patients (7.9%), the pain started in another site and radiated to V_3. In 13 SUNCT patients (18.6%), V_3 constituted one the main pain sites whereas in seven patients (10%), V_3 was reported as a pain radiation site.

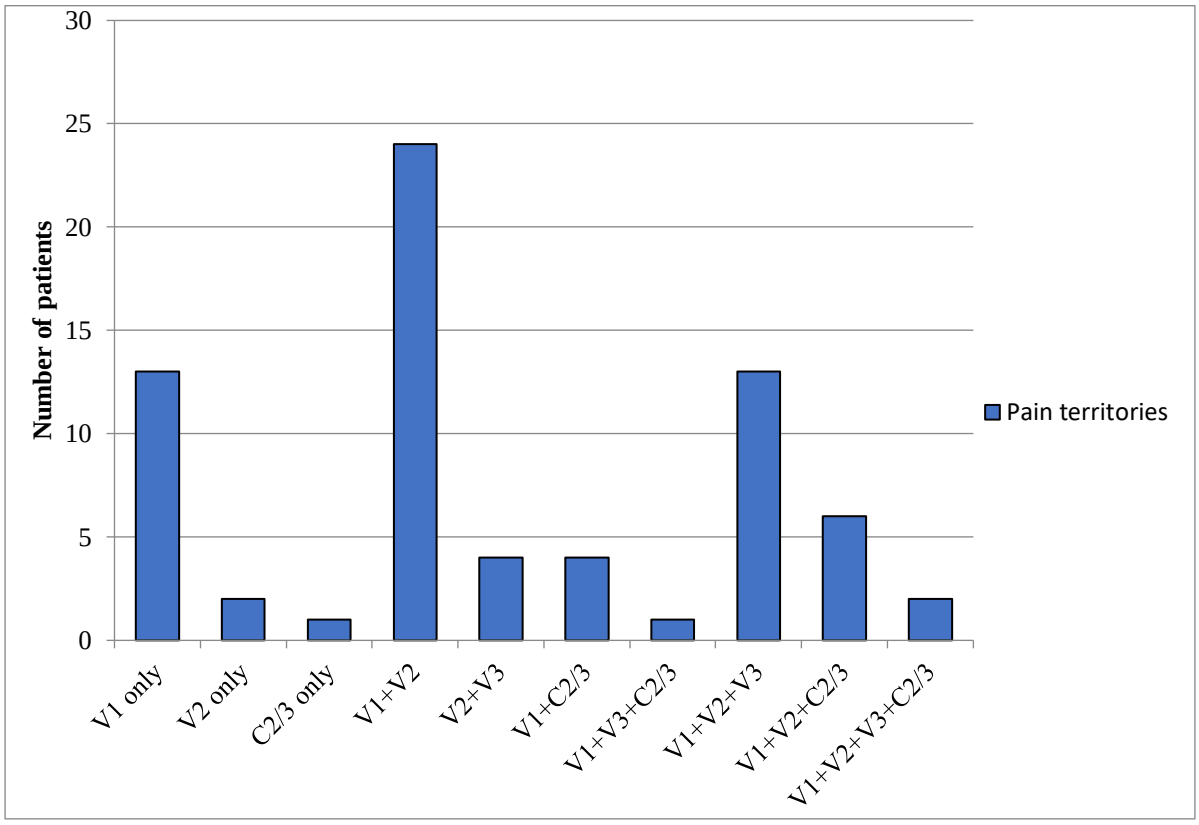
Extra-trigeminal territory pain (C_2-C_3) was reported in 14 SUNA (22.2%) and 14 SUNCT (20.0%) patients (p=0.753). In nine SUNA (14.3%) and 11 SUNCT patients (15.7%), C_2-C_3 was the only or the predominant pain site whereas in five SUNA (7.9%) and three SUNCT patients (4.3%), this territory was a pain radiation site. Figure 9 and 10 show the different pain distribution sites in SUNA and SUNCT patients, whereas a full list of attack sites is shown in Table 19.

Figure 9. Distribution of pain territories in SUNA patients



C2/3: second and third cervical roots territories; V1: ophthalmic trigeminal territory; V2: maxillary trigeminal territory; V3: mandibular trigeminal territory;

Figure 10. Distribution of pain territories in SUNCT patients



C2/3: second and third cervical roots territoriesV1: ophthalmic trigeminal territory; V2: maxillary trigeminal territory; V3: mandibular trigeminal territory;

Table 19. Site of the attacks

	SUNA n (%)	**SUNCT n (%)**	**P-value (<0.05)**
Peri-orbital	30 (47.6%)	47 (67.1%)	0.022
Retro-orbital	16 (25.4%)	29 (41.4%)	0.051
Forehead	23 (36.5%)	20 (28.6%)	0.328
Temporal	28 (44.4%)	31 (44.2%)	0.985
Parietal	13 (20.6%)	15 (21.4%)	0.910
Vertex	1 (1.6%)	4 (5.7%)	0.211
Occiput	14 (22.2%)	13 (18.6%)	0.601
Neck	0 (0.0%)	1 (1.4%)	-
Cheek	29 (46.0%)	30 (42.9%)	0.712
Side of nose	10 (15.9%)	7 (10.0%)	0.311
Ear	5 (7.9%)	6 (8.6%)	0.894
Retroauricular	1 (1.6%)	0 (0.0%)	-
Jaw	20 (31.8%)	13 (18.6%)	0.079
Upper teeth	5 (7.9%)	5 (7.1%)	0.862
Lower teeth	4 (6.4%)	3 (4.3%)	0.594
Upper lip	4 (6.4%)	5 (7.1%)	0.855
Lower lip	3 (4.8%)	3 (4.3%)	0.894
Chin	2 (3.2%)	1 (1.4%)	0.498

SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing;

2.4.6. Severity of the pain

The patients were asked to rate the average severity, along with the maximum and minimum severity of their attacks on a verbal rating scale (VRS) of 0 to 10, with 0 being no pain and 10 being very severe pain. The median severity of the pain was very severe in both groups with a VRS of 9 in SUNA (IQR: 8-10) and 10 in SUNCT (IQR: 8-10) (p=0.667). Only one SUNA (1.6%) and three SUNCT (4.3%) patients had an average severity of attacks of 6 on the VRS (moderate intensity).

2.4.7. Quality of pain

In our cohort, the most commonly described pain qualities were stabbing, sharp, electric shock-like or shooting (Table 20). All patients had at least one of these four qualities of pain. A pulsating nature to the pain was reported in only nine SUNA (14.3%) and ten SUNCT (14.3%) (p=1.000) and never as an isolated feature.

Table 20. Quality of pain

	SUNA n (%)	**SUNCT n (%)**	**P-value (<0.05)**
Stabbing	52 (82.5%)	57 (81.4%)	0.867
Sharp	38 (60.3%)	42 (60.0%)	0.970
Electric shock	21 (33.3%)	25 (35.7%)	0.773
Shooting	17 (27.0%)	22 (31.4%)	0.574
Burning	11 (17.5%)	13 (18.6%)	0.867
Pulsating	9 (14.3%)	10 (14.3%)	1.000
Jabbing	5 (7.9%)	5 (7.1%)	0.862
Pressure	4 (6.3%)	4 (5.7%)	0.877
Tightening	4 (6.3%)	0 (0.0%)	-
Dull	2 (3.2%)	1 (1.4%)	0.498

SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

2.4.8. Duration and profile of attacks

The SUNA group had mean attack duration of 158.5 seconds [±200.5, 95%CI: 107.9; median: 60 seconds; Inter-quartile range (IQR): 30-195 seconds] and SUNCT patients mean attack duration of 162.4 seconds (±194.5, 95%CI: 116.0; median: 90 seconds; IQR: 20-240 seconds) with no significant difference found between them (p=0.454). In all patients, the usual duration of attacks ranged from 1-900 seconds, although, in 23 patients (17.3%) some attacks could also last longer, up to one hour (range: 1200-3600 seconds). The vast majority of patients (n=131, 98.5%) patients had a usual duration of attacks ranging from 1-600 seconds, in line with the ICHD-3β criteria.

All patients reported attacks resembling at least one of the following profiles: single stabs, repetitive stabs (group of stabs), serrated or saw-tooth patterns (in which the pain would not return to baseline between attacks) (Matharu *et al*, 2003) and plateau-like patterns (Pareja and Sjaastad, 1994). Ten patients (SUNA: n=5; SUNCT: n=5) described their attack profile as plateau-like plus a superimposed stabbing component. In two of them that was the predominant attack profile. A substantial proportion of both SUNA and SUNCT patients described their attacks using more than one attack profile (Table 21). The median duration of single stabs was shorter than the median duration of the other attack profiles (Table 22 and Figure 11).

Table 21. Presence of isolated and multiple attack profiles

	SUNA n (%)	**SUNCT n (%)**	**TOTAL n (%)**
Single profile			
Single stabs	4 (6.4%)	1 (1.4%)	5 (3.8%)
Repetitive stabs	7 (11.1%)	12 (17.1%)	19 (14.3%)
Serrated stabs	8 (12.7%)	9 (12.9%)	17 (12.8%)
Plateau-like	3 (4.8%)	4 (5.7%)	7 (5.3%)
Two profiles	25 (39.7%)	34 (48.6%)	59 (44.4%)
Three profiles	13 (20.6%)	9 (12.9%)	22 (16.5%)
All four profiles	0 (0.0%)	1 (1.4%)	1 (0.8%)
Missing data	1 (1.6%)	0 (0.0%)	1 (0.8%)

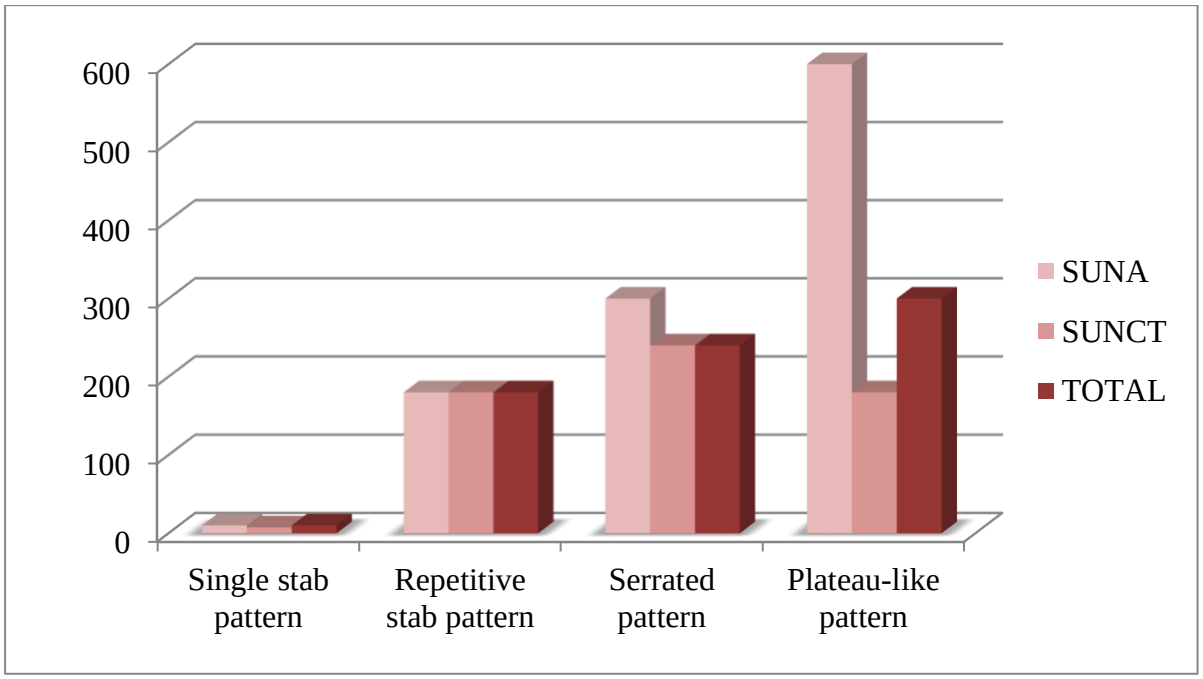
SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

Table 22. Frequency and duration of the different attack profiles in SUNA and SUNCT

	SUNA **n (%)** **Median duration (IQR)**	**SUNCT** **n (%)** **Median duration (IQR)**	**TOTAL** **n (%)** **Median duration (IQR)**
Single stabs	35 (55.6%) 10 sec (15-120 sec)	30 (42.9%) 7.5 sec (1-10 sec)	65 (48.9%) 10 sec (10-120 sec)
Repetitive stabs	33 (52.4%) 180 sec (60-450 sec)	45 (64.3%) 180 sec (40-270 sec)	78 (58.7%) 180 sec (60-300 sec)
Serrated stabs	31 (49.2%) 300 sec (60-345 sec)	33 (47.1%) 240 sec (40-240 sec)	64 (48.1%) 240 sec (60-240 sec)
Plateau-like	12 (19.1%) 600 sec (300-900 sec)	15 (21.4%) 180 sec (20-90 sec)	27 (20.3%) 300 sec (20-600 sec)
Missing data	1 (1.6%)	0 (0.0%)	1 (0.8%)

IQR: Inter-quartile range

Figure 11. Median attack profile duration in SUNA and SUNCT patients (in seconds)



SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing;

2.4.9. Frequency of attacks

In assessing the frequency of attacks, we considered single stabs, groups of stabs or serrated stabs as single episodes. The median attack frequency per day was 20 (IQR: 8-53 attacks/day; mean: 44.3, ±61.3) in the SUNA and 30 (IQR: 10-55 attacks/day; mean 48.7, ±52.3) in the SUNCT group (p=0.329). Seven SUNA (11.1%) and five SUNCT patients (7.1%) reported an average frequency of more than 100 attacks/day. All other SUNA and SUNCT patients (91.0%) had an average attack frequency ranging between 1 and 100 attacks/day.

2.4.10. Cranial autonomic symptoms

Eight SUNA patients (12.7%) reported conjunctival injection and 43 (68.3%) reported lacrimation during acute attacks. Besides the conjunctival injection and lacrimation, which exist as a significant clinical difference between SUNCT and SUNA by IHS diagnostic criteria definition, ptosis occurred more commonly in SUNCT patients (n=35, 50.0%) compared to SUNA patients (n=15, 23.8%) (p=0.001). Rhinorrhoea was also reported more in SUNCT (n=36, 51.4%) than SUNA (n=21, 33.3%) but the difference was not statistically significant (p=0.055). In SUNA, the cranial autonomic features were strictly unilateral ipsilateral to the pain in 53 patients (84.1%) and bilateral in 10 patients (15.9%). In SUNCT, the cranial autonomic symptoms were strictly unilateral ipsilateral to the pain in 57 patients (81.4%), bilateral in 12 patients (17.1%) and strictly unilateral contralateral to the pain in one patient (1.4%). It is noteworthy that facial sweating and flushing were the most frequently reported facial autonomic symptoms with bilateral appearance. Conversely, patients with bilateral facial symptoms seldom reported ocular and nasal symptoms. A detailed list of cranial autonomic symptoms is given in Table 23.

Table 23: Associated cranial autonomic symptoms

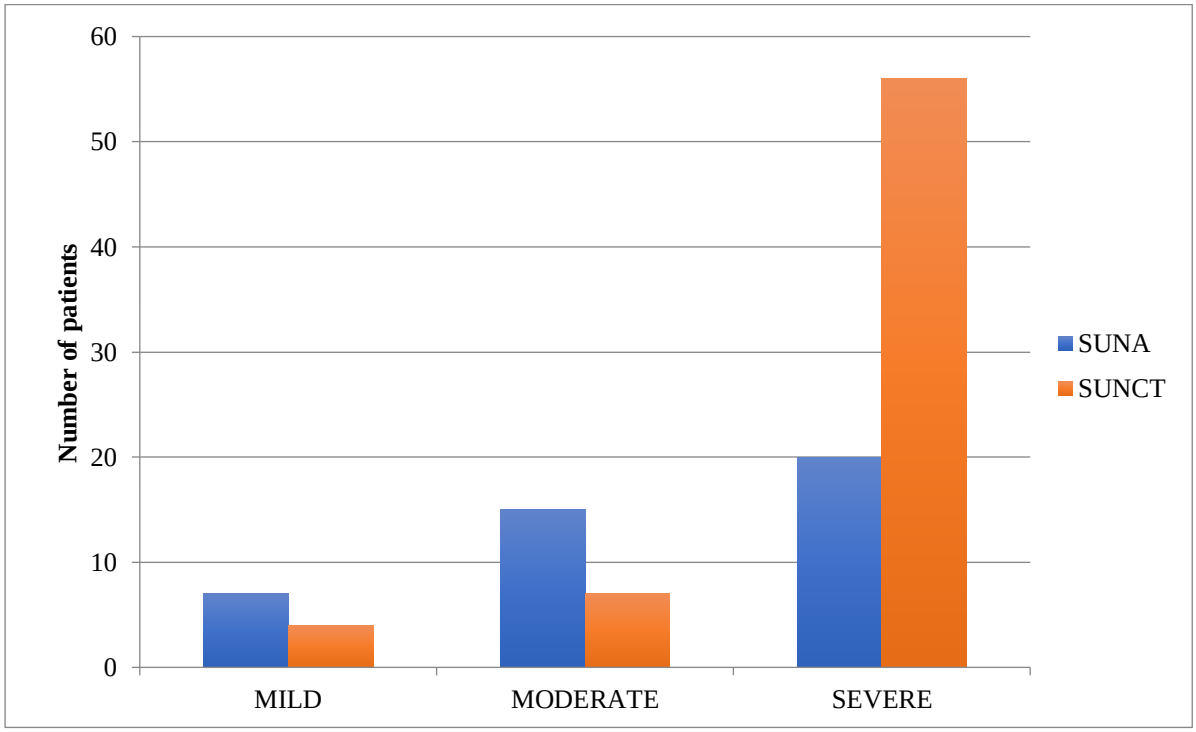
	SUNA n (%)	**SUNCT n (%)**	**P-value (<0.05)**
Conjunctival injection	8 (12.7%)	70 (100%)	-
Lacrimation	43 (68.3%)	70 (100%)	-
Ptosis	15 (23.8%)	35 (50.0%)	0.001
Eyelid oedema	8 (12.7%)	17 (24.3%)	0.087
Miosis	2 (3.2%)	6 (8.6%)	0.191
Rhinorrhoea	22 (33.3%)	36 (51.4%)	0.055
Nasal blockage	21 (33.3%)	28 (40.0%)	0.426
Facial sweating	20 (31.7%)	22 (31.4%)	0.968
Facial flushing	29 (46.0%)	29 (41.4%)	0.592
Facial swelling	6 (9.5%)	6 (8.6%)	0.848
Aural fullness	9 (14.3%)	15 (21.4%)	0.284

SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing;

The ICHD-II suggested that cranial autonomic features should be prominent features of an attack to allow SUNA to be differentiated from ophthalmic division TN (Headache Classification Subcommittee of The International Headache Society., 2004). However, the actual prominence of cranial autonomic symptoms has yet to be assessed properly in both SUNCT and SUNA. The scale previously used to assess lacrimation during first division TN was applied to our cohort to assess degree of lacrimation (Pareja , et al., 2002). The scale describes “mild lacrimation” as increased conjunctival brightness to increased conjunctival meniscus; “moderate lacrimation” as tears clearly seen but hardly overflowing the palpebral edge; “severe lacrimation” as tears running down the face. Amongst those with lacrimation

associated with the attacks, 20 SUNA patients (46.5%) reported a severe degree of lacrimation during the attacks compared to 56 SUNCT patients (80.0%). Twenty-two SUNA (51.2%) compared to only 11 SUNCT patients (15.7%) reported a mild or moderate degree of lacrimation (P<0.001). Data from one SUNA and three SUNCT patients is missing (Figure 12). The degree of conjunctival injection was not studied in view of the difficulty that patients have assessing its degree of severity.

Figure 12. Degree of lacrimation in SUNA and SUNCT patients



SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing;

2.4.11. Triggering of attacks

Thirty SUNA (47.6%) and 23 SUNCT patients (32.9%) had only spontaneous attacks, whereas two SUNA (3.2%) and three SUNCT patients (4.3%) had exclusively triggered attacks (p=0.082). Most of SUNA (n=31, 49.2%) and SUNCT (n=44, 62.9%) patients had both spontaneous and triggered attacks (p=0.112). Among patients with triggered attacks [SUNA n=33 (52.4%); SUNCT, n=47 (67.1%)], 29 with SUNA (88.0%) and 43 with SUNCT (91.5%) had attacks that could be provoked by various forms of cutaneous and/or intraoral stimulation.

Trigger areas were ipsilateral to the side of pain in all patients. Alcohol was not a trigger factor in our cohort. A list of trigger factors is outlined in Table 24.

Table 24: Trigger factors in SUNA and SUNCT patients with triggerable attacks

	SUNA n (%)	**SUNCT n (%)**	**P-value (<0.05)**
Chewing/eating*	21 (72.4%)	36 (87.8%)	0.207
Cold wind*	26 (90.0%)	35 (85.4%)	0.654
Light touch*	21 (72.4%)	31 (75.6%)	0.830
Brushing teeth*	21 (72.4%)	32 (78.0%)	0.678
Washing/Brushing hair*	19 (65.5%)	20 (48.8%)	0.185
Talking*	8 (27.6%)	21 (51.2%)	0.061
Washing face*	8 (27.6%)	19 (46.3%)	0.131
Blowing nose*	5 (17.2%)	8 (19.5%)	0.823
Shaving*	6 (20.7%)	3 (7.3%)	0.100
Swallowing*	4 (13.8%)	10 (24.4%)	0.288
Showering*	2 (6.9%)	3 (7.3%)	0.953
Valsalva Manoeuvres**	13 (39.4%)	14 (30.4%)	0.371
Neck movements**	4 (12.1%)	9 (19.6%)	0.401
Exercise**	3 (9.1%)	2 (4.4%)	0.379
Bright lights**	0 (0.0%)	4 (8.7%)	-
Loud noises**	3 (9.1%)	3 (6.5%)	0.650
Alcohol**	0 (0.0%)	0 (0.0%)	-
Strong smells**	0 (0.0%)	1 (1.4%)	-

*Frequencies and percentages for cutaneous/intraoral triggers refer to: SUNA = 29 patients and SUNCT = 41 patients (patients with headache attacks triggered only by cutaneous/intraoral stimulation).
** Frequencies and percentages for other triggers refer to SUNA = 33 patients and SUNCT = 46 patients (patients with headache attacks triggered by any triggers).
SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

2.4.12. Refractory period

Among patients with cutaneous triggers, 23 SUNA (79.3%) and 36 SUNCT (83.7%) patients could trigger an attack immediately after the cessation of the previous one thereby displaying no refractory period (p=0.633). Conversely, two SUNA (7.0%) and three SUNCT patients (7.0%) did experience a refractory period lasting approximately three and ten minutes in the two SUNA and two, three and five minutes in the three SUNCT patients. Four SUNA patients (13.7%) and three SUNCT (7.0%) were uncertain about the presence of a refractory period. We did not have the data on this issue for one SUNCT patient (2.3%).

2.4.13. Other associated symptoms

Behaviour during attacks. Forty-four SUNA (69.8%) and 49 SUNCT (70.0%) patients preferred to stay still during an attack (p=0.544). Patients with cutaneous triggers were far more likely to state a desire to stay still until the end of the attack, as they feared that any movement might worsen or trigger further attacks. On the other hand, 18 SUNA (28.6%) and 21 SUNCT patients (30.0%) felt restless and agitated during their headache. Data for one SUNA patient (1.6%) was incomplete.

Symptoms often associated with migraine. Twenty-one SUNA (33.3%) and 32 SUNCT (45.7%) patients reported at least one migrainous symptom during attacks (p=0.145). Nausea was present in ten SUNA (15.9%) and 11 SUNCT (15.7%) patients, whereas vomiting in just one SUNCT patient (1.4%) during some attacks. Unilateral photophobia ipsilateral to the side of the pain was reported by 12 SUNA (19.1%) and 19 SUNCT (27.1%) patients; one SUNA and two SUNCT patients complained of bilateral symptoms. Unilateral phonophobia was described by six SUNA (9.5%) and nine SUNCT (12.9%) patients; bilateral phonophobia was reported by one SUNA (1.6%) and one SUNCT patient (1.4%). One SUNA (1.6%) and five SUNCT (7.1%) patients reported osmophobia associated with at least some of their attacks while eight SUNA (12.7%) and 15 SUNCT (21.4%) patients reported motion sensitivity. Cutaneous allodynia during headache attacks was reported by nine SUNA (14.2%) and 10 SUNCT (14.3%) patients.

Aura. Aura symptoms have been reported in TACs (Matharu , et al., 2001; Bahra, et al., 2002; Peres , et al., 2002). In our cohort, two SUNA (3.0%) but no SUNCT patients experienced aura symptoms during some attacks. One patient experienced visual aura in the form of scintillating scotomata lasting ten minutes before subsiding. These symptoms occurred six to seven times

per annum. The second patient reported sensory symptoms in the form of paraesthesia involving the upper limb and half of the face contralateral to the side of the SUNA attack. These episodes lasted five to ten minutes, always at the onset of the pain and occurred with a frequency of three to four episodes per month. Neither of these two patients had a personal history of migraine but one did have a family history of migraine without aura.

Diurnal variation and predictability of attacks. Twenty-nine SUNA (46.0%) and 31 SUNCT patients (44.3%) experienced attacks exclusively during waking hours (p=0.839). Thirty-four SUNA (54.0%) and 38 SUNCT (54.3%) patients also experienced attacks during sleep. Among this group, no SUNA but three SUNCT patients had mainly nocturnal attacks and eight SUNA and two SUNCT patients experienced attacks equally during sleep and wakefulness. Data was not available on one SUNCT patient.

No SUNA (100%) and 63 SUNCT (90.0%) patients could not reliably predict the occurrence of their attacks. Five SUNCT patients (7.1%) experienced mostly random attacks along with some predictable attacks, which would occur at fixed times. In two SUNCT patients (2.9%) attacks were generally predictable: one patient stating that his attacks occurred consistently at 3am, 8am and 1pm every day and another patient at 1am and 10am.

2.4.14. Periodicity and chronicity of SUNCT and SUNA

According to the definition of episodic and chronic short-lasting unilateral neuralgiform headache attacks proposed in the ICHD-3β criteria (Headache Classification Subcommittee of The International Headache, 2013), 58 SUNA (92.1%) and 62 SUNCT patients (88.6%) in our cohort could be defined as chronic while five SUNA (7.9%) and eight SUNCT (11.4%) as episodic (p=0.498). The median number of bouts per year in the episodic SUNA group was four (range: 3-6 per year), each one lasting a median of two weeks (range: 1 week-1 month), with patients generally reporting that the remission periods were very variable (range: 7-11 months). The median number of bouts per annum in the episodic SUNCT group was 1.25 (range: 0.5-2 per year), lasting a median of three months each (range: 2 weeks to 10 months) and alternating with very variable remission periods (range: 3-14 months).

2.4.15. Interictal pain in SUNCT and SUNA

Twenty-seven SUNA (42.9%) and 37 SUNCT patients (52.9%) reported interictal background pain between exacerbations (p=0.249). Among these, 17 SUNA (63.0%) and 27 SUNCT (73.0%) patients stated that the onset of the interictal pain coincided with the original onset of the stabbing pain, whereas in the remaining patients the onset of the interictal pain occurred subsequently (p=0.393). Interictal pain occurred on the same side as the headache in 24 SUNA (88.9%) and 31 SUNCT patients (83.8%) while it was bilateral in three SUNA and six SUNCT patients (p=0.561). The location of the interictal pain corresponded to the site of the paroxysmal attacks in 17 SUNA (63%) and 18 SUNCT (48.7%) patients (p=0.255). The median severity of the interictal pain was mild for SUNA (VRS 3/10, range VRS: 2-7/10) and moderate for SUNCT (VRS 4/10, range VRS: 2-9/10) patients. Among SUNA with interictal pain, 22 patients (81.5%) had a constant background pain whereas in five patients (18.5%) the pain was perceived only immediately after a paroxysmal SUNA attack. Similarly, in SUNCT, the vast majority of patients (n=28, 75.7%) complained of a constant background pain with nine patients (24.3%) reporting interictal pain only following acute SUNCT attacks. The interictal pain following a SUNA or SUNCT attack could last from one minute up to six hours. Although in the vast majority of patients the interictal pain occurred on a daily basis, in the two patients with episodic SUNA and the three with episodic SUNCT who reported background pain, the pain occurred just during the bouts and disappeared during remission periods. Interictal pain was generally featureless.

It has been proposed that SUNCT and SUNA patients with a migraine biology (suggested by the presence of a personal and/or family history of migraine), especially those who overuse analgesics, may be at increased risk of developing interictal background pain (Cohen *et al.*, 2006). In our series, 40 SUNA (63.5%) and 32 SUNCT (45.7%) patients also suffered from migraine *(p=0.039).* Thirty-one SUNA (49.2%) and SUNCT (44.3%) patients had a first-degree family history of migraine (p=0.57). Forty-seven SUNA (74.6%) and 41 SUNCT patients (58.6%) had a personal and/or family history of migraine, though data were incomplete for six SUNA and three SUNCT patients. History of medication overuse headache, defined as the use of simple analgesics and non-steroidal anti-inflammatory (NSAID) medications on 15 or more days per month for at least three months or the use of triptans, ergots, opioids or combinations of them for at least ten days per month for at least three months (Headache Classification Subcommittee of The International Headache, 2013), was present in 19 SUNA

(30.2%) and 21 SUNCT (30.0%) patients (p=0.984). In our cohort of patients, 47 SUNA (74.6%) and 41 SUNCT (58.6%) patients had either personal or family history of migraine or both, suggesting a migraine biology (p=0.05). In order to assess the relationship between interictal pain and migrainous biology, we evaluated the proportion of patients with a migrainous biology who presented interictal background headache. Eighteen SUNA (38.3%) and 20 SUNCT patients (48.8%) with a migrainous biology developed interictal pain. Conversely, 29 SUNA (61.7%) and 21 SUNCT (51.2%) patients with a migraine biology did not (p=0.322). Data were incomplete for two SUNA and two SUNCT patients. Similarly, when considering the group with migraine biology and a previous history of analgesic overuse, seven out of 18 SUNA patients (38.9%) and nine out of 17 SUNCT (52.9%) had interictal pain (p=0.404).

2.4.16. Neurological examination findings and MRI findings

Eleven SUNA (17.5%) and 13 SUNCT patients (18.6%) had abnormal neurological examinations. A reduced sensation to pinprick in the distribution of the first (V1) and second (V2) branches of the trigeminal nerve was found in five SUNA and ten SUNCT patients. A single SUNA patient had hyperesthesia to pinprick in V2 and one SUNCT patient had a partial Horner's syndrome ipsilaterally to the side of the pain, which was extensively investigated, and no cause were found. Two SUNA patients with coexistent hemiplegic migraine had a mild persistent hemiparesis involving the upper and lower limbs ipsilaterally to the side of the pain. The remaining three patients had signs related to other pathologies including ischaemic stroke, Parkinson's disease and cervical myelopathy. All patients had neuroimaging scan of the brain. Apart from one SUNA patient who had a CT scan of the head rather than an MRI because of claustrophobia, the remaining patients had at least an MRI scan of the brain. Thirteen SUNA and seven SUNCT patients had the MRI scan in another hospital and another scan was not repeated at the time of the data analysis. The remaining MRI scans were performed with dedicated imaging of the pituitary fossa (SUNA=49; SUNCT=63). The outcome of the MRI scans is showed in Table 25.

Table 25. Magnetic resonance imaging results

	SUNA n (%)	**SUNCT n (%)**	**TOTAL n (%)**
MRI scan performed	62 (98.4%)	70 (100%)	132 (99.2%)
MRI scan with pituitary fossa sequences	49 (79.0%)	63 (90.0%)	112 (84.9%)
Pituitary abnormalities			
Microadenoma	2 (4.1%)	2 (3.2%)	4 (3.6%)
Macroadenoma	1 (2.0%)	0 (0.0%)	1 (0.9%)
Other abnormalities			
Non-specific white matter lesions	10 (16.1%)	13 (18.6%)	23 (17.4%)
Pineal cyst	0 (0.0%)	1 (1.4%)	1 (0.8%)
Mid-brain low grade astrocytoma	0 (0.0%)	1 (1.4%)	1 (0.8%)
Vascular loops pressing on facial and/or glossopharyngeal nerve	1 (1.6%)	1 (1.4%)	2 (1.5%)
Mature ischaemic strokes	1 (1.6%)	3 (4.3%)	4 (3.0%)
Cortical dysplasia	1 (1.6%)	0 (0.0%)	1 (0.8%)
Chronic sinus thrombosis	0 (0.0%)	1 (1.4%)	1 (0.8%)
Total abnormal intracranial appearances	16 (25.8%)	22 (31.4%)	38 (28.8%)

MRI: magnetic resonance imaging; SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

2.4.17. Clinical predictors for SUNA or SUNCT

Table 26 outlines the results of the unadjusted univariate logistic regression analysis for different demographic and clinical predictors for a diagnosis of SUNCT or SUNA. The clinical features were selected from the current diagnostic criteria for SUNCT and SUNA and from characteristics that were deemed clinically relevant according to our study. Female gender was significantly associated with SUNA [OR: 1.02 (95%CI: 1.02, 4.32), p=0.043]. The only clinical predictor for SUNCT rather than SUNA was the presence of ipsilateral ptosis during headache attacks [OR: 3.2 (95%CI: 1.51, 6.74), p=0.002]. A backward regression model was then applied

to the two cohorts and those variables that were thought to be clinically relevant were selected (Table 27). A multivariate logistic regression analysis on these variables, adjusted for age of onset of the headache and gender, confirmed the significant link between ptosis and SUNCT and also highlighted the association between ipsilateral rhinorrhoea and SUNCT [OR: 2.42 (95% CI: 1.09, 5.41), p=0.034]. The link between female gender and SUNA was not confirmed to be relevant.

Table 26. Unadjusted logistic regression analysis outlining demographic and clinical predictors for SUNCT compared to SUNA syndrome.

	SUNCT	**SUNA**	**p-value**
	Odds ratio (95% CI)	**Odds ratio (95% CI)**	
Gender; female versus male	0.46 (0.23, 0.98)	2.11 (1.02, 4.32)	*0.043*
Age of onset	0.98 (0.96, 1.01)	1.01 (0.99, 1.03)	0.263
Side of pain; Right Left Alternating/Bilateral	 Ref 1.09 (0.52, 2.3) 1.33 (0.47, 3.75)	 Ref 0.92 (0.44, 1.92) 0.75 (0.27, 2.11)	 0.820 0.588
Site of pain; V1 versus not V1 V2 versus not V2 V3 versus not V3 Extra-trigeminal versus not	 2.12 (0.78, 5.78) 0.77 (0.35, 1.70) 0.70 (0.34, 1.44) 0.88 (0.38, 2.01)	 0.47 (0.17, 1.29) 1.30 (0.59, 2.88) 1.44 (0.69, 2.98) 1.14 (0.50, 2.63)	 0.142 0.512 0.329 0.754
Quality of pain; Stabbing versus not Sharp versus not Electric versus not Shooting versus not Burning versus not Throbbing versus not	 0.93 (0.38, 2.25) 0.99 (0.49, 1.98) 1.11 (0.54, 2.27) 1.24 (0.59, 2.63) 1.08 (0.44, 2.61) 1.00 (0.38, 2.65)	 1.08 (0.44, 2.61) 1.01 (0.51, 2.03) 0.90 (0.44, 1.84) 0.81 (0.38, 1.71) 0.93 (0.38, 2.25) 1.00 (0.38, 2.65)	 0.868 0.970 0.773 0.574 0.868 1.000
Duration attacks; <1 min 1-2 min 2-3 min 3-4 min 4-5 min >5 min	 Ref 1.36 (0.49, 3.84) 1.17 (0.36, 3.83) 3.0 (0.30, 30.30) 0.75 (0.24, 2.4) 1.5 (0.48, 4.68)	 Ref 0.73 (0.26, 2.03) 0.85 (0.26, 2.81) 0.33 (0.03, 3.37) 1.33 (0.42, 4.25) 0.67 (0.21, 2.10)	 0.849
Attacks per day 1-10 attacks/day 12-25 attacks/day 30-60 attacks/day >60 attacks/day	 Ref 1.32 (0.51, 3.43) 2.59 (1.01, 6.62) 2.0 (0.76, 6.25)	 Ref 0.67 (0.29, 1.98) 0.39 (0.15, 0.98) 0.5 (0.19, 1.31)	 0.185
Cranial autonomic symptoms: Ptosis; yes versus not Eyelid oedema; yes versus not Blocked nose; yes versus not Rhinorrhoea; yes versus not Facial flushing; yes versus not Facial sweating; yes versus not Fullness of ear; yes versus not	 3.2 (1.51, 6.74) 2.2 (0.88, 5.53) 1.33 (0.66, 2.71) 1.97 (0.98, 3.97) 0.83 (0.43, 1.65) 0.99 (0.47, 2.05) 1.64 (0.66, 4.10)	 0.31 (0.15, 0.66) 0.45 (0.18, 1.14) 0.75 (0.37, 1.52) 0.51 (0.25, 1.02) 1.21 (0.61, 2.40) 1.01 (0.49, 2.11) 0.61 (0.25, 1.51)	 0.002 0.092 0.427 0.057 0.593 0.969 0.288
Behaviour; restless versus still	0.99 (0.47, 2.10)	1.01 (0.45, 2.12)	0.984

Type of attack; Spontaneous and triggered Spontaneous only Triggered only	 Ref 0.54 (0.27, 1.10) 1.06 (0.17, 6.70)	 Ref 1.85 (0.91, 3.77) 0.95 (0.15, 6.00)	 0.090 0.953
Headache pattern; Chronic Episodic	 Ref 1.50 (0.15, 4.84)	 0.67 (0.21, 2.16)	 0.500

CI: confidence interval; C2/3: second and third cervical roots territories; Ref: reference; **P*<0.05; SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; V1: ophthalmic trigeminal territory; V2: maxillary trigeminal territory; V3: mandibular trigeminal territory

Table 27. Multivariate logistic regression analysis adjusted for demographic and clinical variables considered potentially different between SUNCT and SUNA

	SUNCT	**SUNA**	**p-value**
	Odds ratio (95% CI)	**Odds ratio (95% CI)**	
Gender; female versus male	0.70 (0.32, 1.55)	1.43 (0.65, 3.20)	0.378
Cranial autonomic symptoms: Ptosis; yes versus not Rhinorrhoea; yes versus not	 3.37 (1.50, 7.66) 2.42 (1.09, 5.41)	 0.30 (0.13, 0.67) 0.41 (0.18, 0.92)	 *<0.0001* *0.034*
Type of attack; Spontaneous only	 0.50 (0.23, 1.08)	 2.02 (0.92, 4.40)	 0.078

Ref: reference; **p*<0.05; SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

2.5. Discussion

We report the first substantial case series of SUNA, characterising the demographic, clinical and radiological features of this rare syndrome. Hitherto, only a small series and a few case reports of SUNA have been reported and it has therefore not been possible to fully characterise this syndrome (Cohen , et al., 2006; Williams , et al., 2008; Lambru , et al., 2012; Chitsantikul , et al., 2013). Furthermore, we have conducted a comprehensive comparison between this case series of SUNA and the largest cohort of SUNCT described thus far. This study demonstrates

that there are no major clinical differences between SUNCT and SUNA, bar the fact that SUNCT is characterised by more prominent cranial autonomic features, which is likely to merely reflect differing degrees of autonomic symptomatology rather than any real biological diversity between the two conditions.

2.5.1. Demographic and clinical features of SUNA and SUNCT

2.5.1.1. Gender and Age

There is a female preponderance in our cohorts of SUNA and SUNCT, which is less pronounced in SUNCT, although this difference did not reach statistical significance. The female preponderance in SUNA confirms the preliminary findings reported in a small group of SUNA patients by Cohen et al (M:F=0.5:1) (Cohen , et al., 2006). However, the absence of a male preponderance in SUNCT challenges the traditional concept of SUNCT being considered a syndrome with a male preponderance (Pareja , et al., 1997; Cohen , et al., 2006). In this respect, it is interesting to observe that there has been a decrease in male:female ratio in cluster headache over time with the description of larger case series (Manzoni , 1998). The mean age of onset of SUNA and SUNCT is centred on the fifth decade. Overall, our demographic findings in SUNCT and SUNA suggest a demographic overlap with TN, with similar age of onset and a gender distribution (Katusic , et al., 1990).

2.5.1.2. Laterality of pain

Attacks of SUNA and SUNCT are typically strictly unilateral and side-locked with the exception of a small proportion of patients in whom attacks are strictly unilateral but side alternating. There is a preponderance for right sided attacks, which has also been reported in the other TACs and TN. One patient with SUNA has occasionally had bilateral attacks. The occurrence of bilateral attacks has been described in three cases of SUNCT (Zidverc-Trajkovic , et al., 2009; Bichuetti , et al., 2006; Kuhn , et al., 2005). In two cases, an underlying abnormality with a probable causal relationship was found, whereas in another case no brain abnormalities were identified, so the condition was considered idiopathic. Our case is the first idiopathic SUNA case with bilateral attacks and normal MRI study.

2.5.1.3. Site of pain

The majority of the patients with SUNA and SUNCT have pain centred on the ophthalmic and maxillary trigeminal territory though the pain also radiated to the mandibular trigeminal territory and extra-trigeminal (cervical) distribution in a significant minority of patients. Extra-trigeminal territory pain (C_2-C_3) was reported in 14 SUNA (22.2%) and 14 SUNCT (20.0%) patients (p=0.753). One SUNCT and one SUNA patient experienced the pain exclusively in the C2-C3 regions. Extra-trigeminal location of the painful headache episodes is not mentioned in the IHS criteria for any of the TACs and may lead to a different diagnosis, including occipital neuralgia. However, the SUNCT patient reported profuse ipsilateral lacrimation and conjunctival injection during the attacks, which makes the diagnosis of occipital neuralgia unlikely. The SUNA patient experienced retroauricular painful paroxysmal attacks associated with redness and sweating of the face, did not respond to GONB but responding transiently to IV lidocaine. Atypical location of the headache has been reported in other TACs. Boes and colleagues described two cases of paroxysmal hemicrania presenting as paroxysmal episodes of otalgia, suggesting that cervical painful input may activate the parasympathetic arm of the trigeminal-autonomic reflex, without provoking pain perception in the trigeminal territories (Boes , et al., 1998).

2.5.1.4. Severity and quality of pain

The pain of SUNA and SUNCT is usually very severe, thereby highlighting the devastating morbidity associated with these syndromes. The most commonly described pain qualities in both SUNA and SUNCT were stabbing, sharp, electric-shock like and shooting, reflecting the neuralgiform character of these syndromes. Though ICHD-II criteria required pulsating pain, this pain quality was relatively rare in our cohort. In line with our observations, the ICHD-IIIβ criteria removed the pulsating quality of the pain in SUNCT and SUNA.

2.5.1.5. Duration, frequency and temporal profile of attacks

In our cohorts of SUNCT and SUNA, all patients had an attack duration ranging from 1-900 seconds while 98.5% had an attack duration ranging between 1-600 seconds. ICHD-II specified attack duration of 5-240 seconds for SUNCT and 2-600 seconds for SUNA, while ICHD-IIIβ requires attack duration of 1-600 seconds for both SUNA and SUNCT. It seems reasonable to

retain the attack duration criteria of 1-600 seconds in future classification criteria to avoid inclusion of longer lasting TACs. We found that attacks may take on different profiles including single stabs, repetitive stabs, serrated stabs and plateau-like attacks in both SUNA and SUNCT.

In our cohorts, there was a wide variation in the attack frequency in both SUNA and SUNCT, ranging between few attacks per week and several hundred daily. ICHD-2 required an attack frequency of 3-200 daily for SUNCT and $\geq$1 daily for more than half of the time for SUNA. ICHD-3β specifies an attack frequency of at least one daily for more than half of the time when the disorder is active. Given the wide variation in attack frequency in these syndromes, the criterion specifying attack frequency is unhelpful and relatively meaningless. Removing this criterion will help simplify the diagnostic classification.

2.5.1.6. Cranial autonomic symptoms

Our study showed that patients reporting both conjunctival injection and lacrimation (SUNCT) are more likely to display a broader and more prominent array of autonomic features during an attack, as opposed to those experiencing either one of these features alone or none (SUNA). In addition, our data are in keeping with the suggestion that a stronger degree of activation of the facial parasympathetic pathway is more often associated with the occurrence of ocular sympathetic deficit (Drummond , 1988), explaining the more frequent occurrence of ptosis in SUNCT compared to SUNA. In view of the absence of any other significant differences in demographic, clinical and radiological characteristics, these differences are likely to reflect differing degrees of autonomic symptomatology rather than any real biological diversity between the two conditions. The degree of cranial autonomic symptomatology displayed by these two entities likely lies on a spectrum, with more prominent symptoms in SUNCT and less prominent symptoms in SUNA.

2.5.1.7. Triggers and Refractory Period

One of the most important clinical differences between SUNCT and SUNA versus the other TACs is the presence of attacks triggered by cutaneous/intraoral stimulation in the former. In our cohorts, the majority of patients with SUNA and SUNCT had triggered attacks. The most

prominent triggers were cutaneous and intraoral stimulation ipsilateral to the pain. These triggers are similar to the ones historically associated with TN painful exacerbations. Unlike TN, there was a general lack of refractory period between attacks in the vast majority of SUNA and SUNCT. This could serve as a good clinical feature to distinguish TN from SUNA and SUNCT. However, establishing the presence of a refractory period can be challenging in a clinical setting and despite several attempts to retrieve this clinical information accurately some patients may not be able to be certain about the presence of a refractory period. Furthermore, five patients in our cohort did experience a refractory period lasting a few minutes after triggered attacks, similarly to other three cases previously described in the literature (Paliwal , et al., 2012). These cases suggest that the presence of a refractory period by itself is not sufficient to discriminate between TN and SUNCT. Pathophysiological mechanisms responsible for the presence or absence of refractory periods may be shared between these two conditions and at times overlap.

2.5.1.8. Behaviour

Agitation and restlessness during attacks are clinical hallmarks of CH and to a lesser degree of PH (Bahra, et al., 2002; Cittadini , et al., 2008). A recent prospective study reported restlessness during attacks in 62% of SUNCT and 56% of SUNA patients (Cohen , et al., 2006). Our data suggests that the vast majority of SUNA and SUNCT patients preferred to stay still during attacks, which they mainly attributed to triggerability of the attacks by movement.

2.5.1.9. Interictal pain

Interictal background pain is traditionally thought not to be associated with SUNCT. However, Matharu and collaborators highlighted the presence of continuous and intermittent discomfort in a few SUNCT cases while in a recent series of SUNCT and SUNA patients, interictal pain was found in 47% and 22% respectively (Matharu , et al., 2003; Cohen , et al., 2006). We have described the interictal background pain reported by a significant proportion of SUNA and SUNCT patients. Similar to TN with concomitant pain (Obermann , et al., 2007), in SUNCT and SUNA the development of a persistent background pain seems not to be related to the duration of the disorder, since most patients reported simultaneous onset of stabbing and interictal pains. The chronic *ab initio* pattern along with the high load of attacks displayed by most SUNCT and SUNA patients might account for the development of a background pain at

early stages. Moreover, given the high prevalence of migraine in our SUNCT and SUNA group, it could be postulated that the susceptibility to a central nervous system disorder such as migraine, facilitates the occurrence of central sensitization and in turn the simultaneous occurrence of both the paroxysmal and the constant background pains in SUNCT and SUNA.

2.5.2. New proposed diagnostic criteria

On the basis of the direct comparison of the clinical phenotype of SUNA and SUNCT, we propose that the distinction between these two syndromes be abandoned and that they be placed under a single diagnostic category named SUNA. This nomenclature would allow the wide array of autonomic features that can accompany the headaches to be considered. ICHD-3β encompasses SUNCT and SUNA under the category of "short-lasting unilateral neuralgiform headache attacks" but this term would be a misnomer as it potentially also describes TN and does not highlight the autonomic features which are central for the diagnosis of SUNCT and SUNA.

Of the 70 SUNCT patients, only three (4.3%) satisfied the ICHD-2 diagnostic criteria. The main reasons for failing to fulfil these criteria can be found in the limited array for cranial autonomic symptomatology allowed; the location of the pain, which is confined to V_1 and the temple; and, the frequency and duration of the attacks, which can be longer than stated in the criterion B. According to our data, the ICDH-3β diagnostic criteria for SUNCT have improved upon the previous version, particularly by extending the site of the pain to the three trigeminal divisions, increasing the array of cranial autonomic features and the range of attack duration. These changes have been reflected in the higher number of SUNCT patients who fulfilled the ICDH-3 β diagnostic criteria (N=35; 50%). However, the updated criteria do not account for pain in non-trigeminal locations and for the plateau-like profiles, which were reported by a few patients in our cohort (Figure 13).

Of the 63 SUNA patients, 15 (23.8%) satisfied the ICHD-2. The higher proportion of patients fulfilling these diagnostic criteria reflects the broader array of cranial autonomic symptoms and the longer duration of attacks allowed for SUNA. The ICHD-3β diagnostic criteria for SUNA were met by 35 patients (55.6%), which is a similar proportion to the one found in SUNCT patients (Figure 14).

The diagnostic yield of the criteria can be refined further. ICHD-3β specifies that patients should have attacks occurring as single stabs, series of stabs or in a saw-tooth pattern. However, some patients have a plateau-type pain profile without having any of the profiles mentioned in the criteria. We propose that instead of a criterion based on pain temporal profile, a criterion on the quality of pain (stabbing, sharp, electric-shock like, shooting) is more meaningful and better captures the neuralgiform character of the pain. ICHD-3β specifies an attack frequency of at least one daily for more than half of the time when the disorder is active. Given the wide variation in attack frequency in these syndromes, the criterion specifying attack frequency is unhelpful. Removing this criterion will help simplify the diagnostic classification. Furthermore, triggering by innocuous stimuli to the affected side of the face with the lack of refractory period is a key feature of these syndromes and merits inclusion in the diagnostic criteria. On the basis of these considerations, we propose a set of new diagnostic criteria for this single unified entity, SUNA (Table 28). These criteria, applied to our cohort, correctly diagnosed all the patients, but two, who reported an average attacks duration of 900 seconds.

This study has some limitations. The duration and frequency of occurrence of the headache attacks were subjectively estimated by the patients and only seldom objectively measured. However, in view of the variable duration of the attacks and often the multiple number of daily attacks, it is difficult to ask patients to produce headache-specific diaries and headache diaries used for other conditions (migraine and CH) may not be entirely appropriate to SUNCT and SUNA.

2.6. Conclusion

The demographic and clinical characteristics of SUNA have been detailed and refined. The clinical phenotype of SUNA did not differ significantly from SUNCT, apart from a different degree of activation of the parasympathetic system and dysfunction of the ocular sympathetic system, possibly due to the different number of autonomic features set up for SUNCT and SUNA in their diagnostic criteria. Based on our data, SUNCT and SUNA could be considered as a single clinical entity under the name SUNA, a term that highlights the occurrence of a broad array of cranial autonomic features besides conjunctival injection and lacrimation. The diagnostic criteria of this unified entity, SUNA, have been proposed.

Moreover, the demographic, clinical and pathophysiological overlap between SUNCT, SUNA and TN supported by our data, may challenge the traditional view that consider them separate disorders. SUNCT, SUNA and TN may constitute a continuum of the same disorder. This unifying hypothesis carries important nosological implications on whether SUNCT and SUNA should belong to the TACs or the cranial neuralgias group.

Figure 13. Comparison of ICHD-2 and ICHD-3β diagnostic criteria in our cohort of SUNCT patients

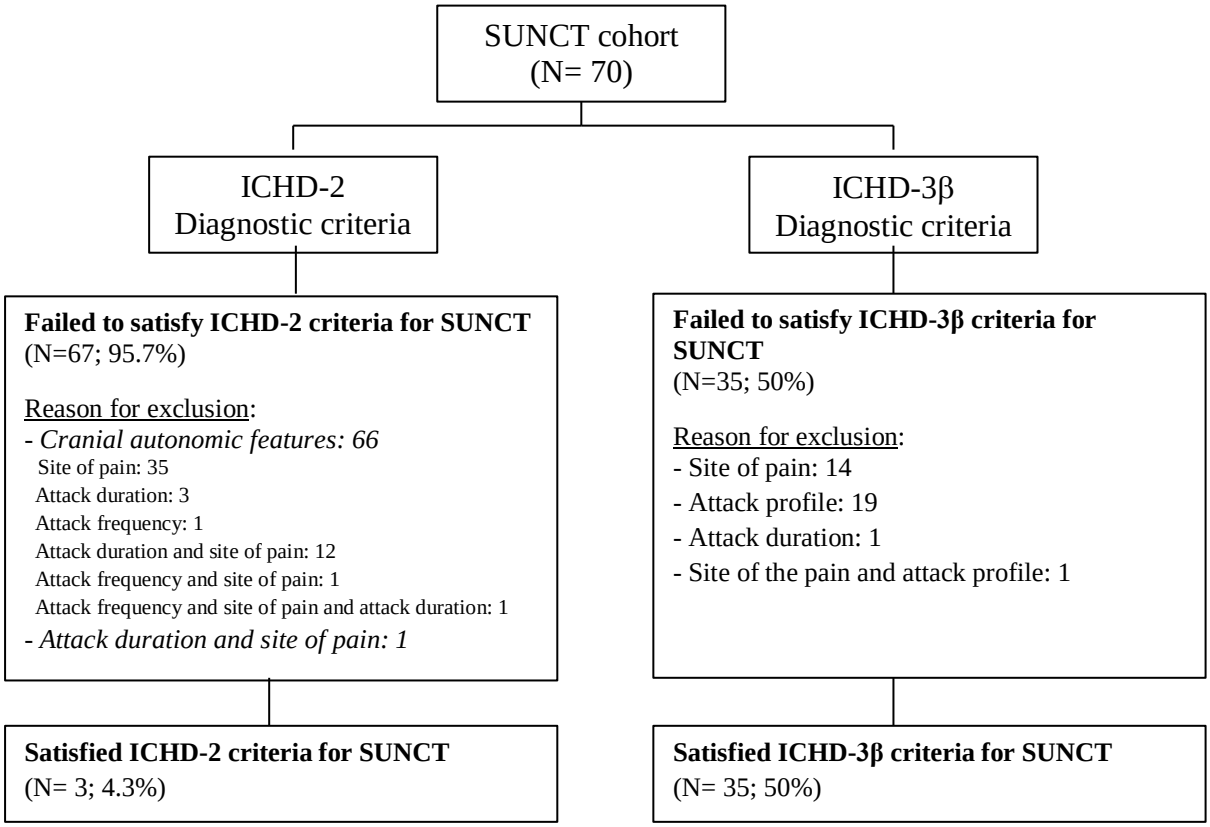
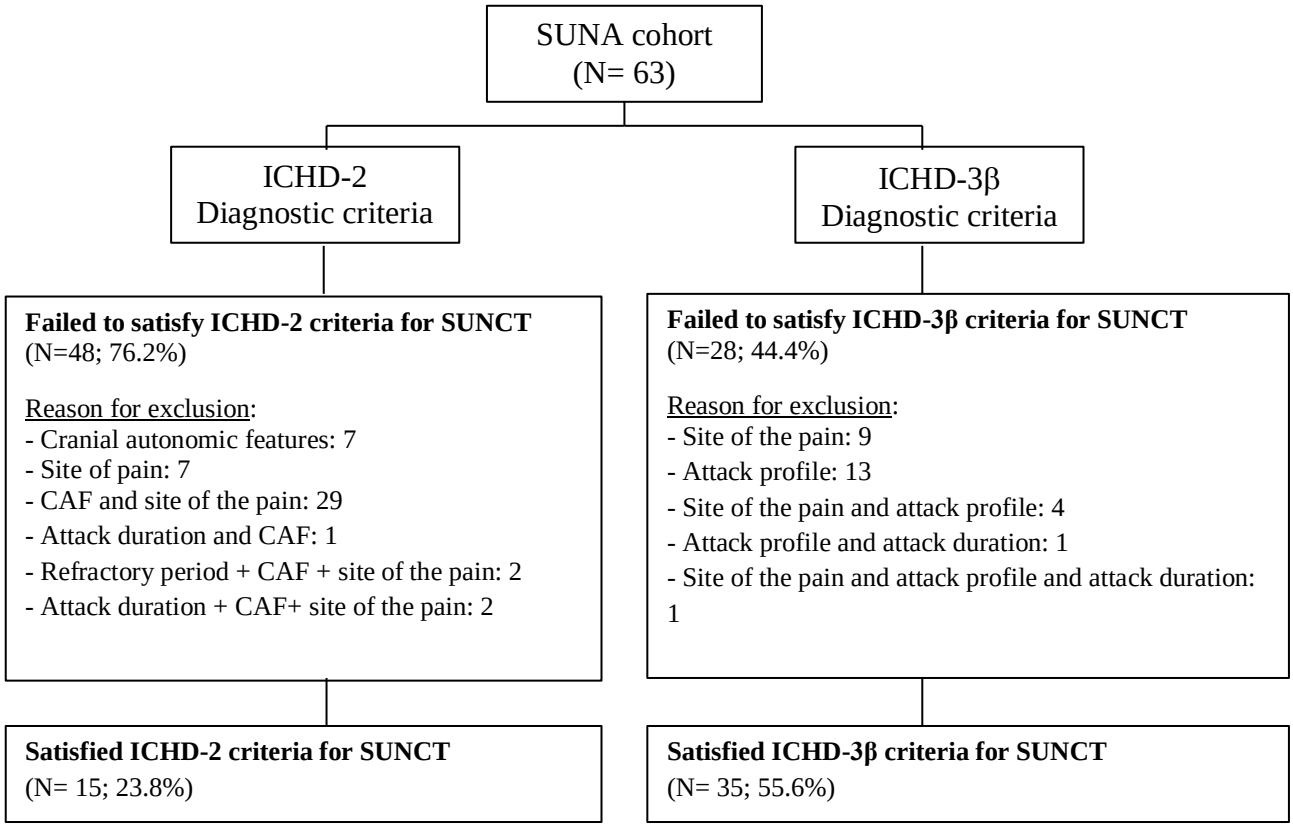


Figure 14. Comparison of ICHD-2 and ICHD-3 diagnostic criteria in our cohort of SUNA patients



ICHD, International classification for headache disorders; SUNA, Short-lasting unilateral headache attacks with autonomic symptoms

Table 28. Proposed criteria for unified diagnosis of SUNA

A. At least 20 attacks of unilateral head pain fulfilling criteria B–E
B. Occurring in the first division of the trigeminal nerve, with possible radiation to the second and third divisions of the trigeminal nerve and with possible radiation beyond the trigeminal distribution
C. Pain has at least three of the following five characteristics: 1. Attacks lasting 1-600 seconds 2. Moderate or severe intensity 3. Stabbing, sharp, electric shock-like or shooting in quality 4. Precipitated by innocuous stimuli to the affected side of the face 5. No refractory period follows attacks triggered by innocuous stimuli to the affected side of the face or head
D. At least one of the following cranial autonomic symptoms or signs, ipsilateral to the pain: 1. Conjunctival injection and/or lacrimation 2. Nasal congestion and/or rhinorrhoea 3. Miosis and/or ptosis 4. Eyelid oedema 5. Forehead and facial sweating 6. Forehead and facial flushing 7. Sensation of fullness in the ear
E. Not better accounted for by another ICHD-3 diagnosis

SUNA, Short-lasting neuralgiform headache attacks with autonomic symptoms; ICHD-3, International classification of headache disorders

Chapter 3. Trigeminal Neurovascular Contact in SUNCT and SUNA: A Prospective Structural Magnetic Resonance Study

3.1. Abstract

Emerging data points towards a possible pathophysiological and therapeutic relevance of trigeminal NVC in SUNCT and perhaps in SUNA, similarly to TN. The aim of this study was to assess the prevalence and significance of trigeminal NVC in a large cohort of SUNCT and SUNA. MRI examinations were performed to consecutive SUNCT and SUNA patients. The standard imaging protocol included high spatial and nerve-cistern contrast resolution imaging acquisitions of the cisternal segments of the trigeminal nerves and vessels. MRI studies were evaluated blindly and graded according to the presence, location and degree of neurovascular contact. The degree of contact was graded as: simple contact, distortion or atrophy. Severe neurovascular contact was defined as contact with distortion and/or atrophy.

Seventy-nine patients (53.7%) (45 SUNCT; 34 SUNA) were included. A total of 82 symptomatic trigeminal nerves (47 in the SUNCT group and 35 in the SUNA group) and a total of 76 asymptomatic trigeminal nerves (43 in the SUNCT group and 33 in the SUNA group) were analysed. In the SUNCT and SUNA cohorts, the prevalence of neurovascular contact on the symptomatic trigeminal nerves was higher (57.3%; n=47/82) than the prevalence of neurovascular contact on the asymptomatic trigeminal nerves (25%; n=19/76) ($P \leq 0.001$). Severe neurovascular contacts were considerably more prevalent on the symptomatic side (47.6%; n=39/82), compared to the asymptomatic side (11.8%, n=9/76) ($P \leq 0.001$). In SUNCT, severe neurovascular contacts were considerably more prevalent on the symptomatic compared to the asymptomatic nerves [53.2% versus 14.0%, OR: 4.16 (95%CI: 2.55, 20.02) $P \leq 0.001$]. In SUNA, severe neurovascular contacts were considerably more prevalent on the symptomatic compared to the asymptomatic nerves [42.9% versus 12.1%, OR: 3.75 (95%CI: 2.78, 34.96), P=0.005]. There was no statistically significant difference in the proportion of neurovascular contacts on the symptomatic nerves between SUNCT

[29/47 (61.7%)] and SUNA [20/35 (57.1%)] (P=0.67). Similarly, there was no statistically significant difference in the proportion of severe neurovascular conflict between SUNCT and SUNA [25/47 (53.2%) versus 15/35 (42.9%)] (P=0.35)]. The analysis of radiological predictors associated with the symptomatic side, indicated that the presence of a vascular contact and its location at the root entry zone were strong predictors for the nerve to be symptomatic rather than asymptomatic. These findings support the aetiological importance of trigeminal neurovascular contact in SUNCT and SUNA, further expanding their overlap with TN. The therapeutic relevance of this novel findings will be discussed in Chapter 5.

3.2. Introduction

SUNCT and SUNA are encompassed within the TACs' group in view of the presence of overlapping clinical characteristics, namely unilateral pain in the ophthalmic trigeminal distribution and the prominent cranial autonomic symptomatology. Furthermore, functional neuroimaging findings during SUNCT attacks suggest a pivotal role of the posterior hypothalamus in SUNCT and possibly SUNA, similarly to the other TACs (Cohen, 2007). However, the significance of ictal hypothalamic activation is currently unknown. The broad demographic and clinical overlap as well as the similar response to medical management between SUNCT, SUNA and TN, has led to growing interest in exploring the presence of shared pathophysiological mechanisms as the basis of these similarities. The effect of vascular loops in contact with the trigeminal nerve ipsilaterally to the side of the pain is thought to constitute one of the pivotal pain mechanisms in TN. This finding is seen in about 47–90 % of TN cases and the vascular compression often occurs at the region of the root entry zone (REZ) (Love , et al., 2001). The pathophysiological importance of the trigeminal neurovascular conflict (NVC) is corroborated by the long-term efficacy of trigeminal microvascular decompression procedure, which is the gold standard surgical approach in TN (Barker , et al., 1996).

A meta-analysis of MRI studies showed that NVC on the symptomatic side is strongly linked with TN (88.7%) compared to the control nerves (35.8%) (OR = 16.6; 95% CI = 11.8–23.3; P < .0001). Similarly, NVC at the root entry zone (REZ) (REZ was defined as the proximal 6-mm segment of the nerve adjacent to the pontine belly) on symptomatic nerves were predictive for TN compared to those on asymptomatic nerves (OR = 14.7; 95% CI = 8.3–25.8; P < .0001). Conversely there was no significant difference between non-REZ NVC on symptomatic and asymptomatic nerves (OR = 0.8; 95% CI = 0.4–1.7) (P = .58) (Antonini , et al., 2014). A recent study conducted in 135 TN patients aimed to assess the degree of contact, localization (REZ or distal) and type of blood vessel (artery or vein) using a 3 Tesla (T) MRI scanning protocol. The authors found that 70% of patients had bilateral neurovascular contact. However neurovascular contact on the symptomatic (89%) was more prevalent compared to the asymptomatic side (78%) (P = 0.014). 'Severe neurovascular contact' was defined as a neurovascular contact with displacement or atrophy of the nerve. Severe neurovascular

contacts were considerably more prevalent on the symptomatic compared to the asymptomatic side (53% versus 13%) ($p<0.001$). Prevalence of neurovascular contact in the REZ was similar on the symptomatic and asymptomatic side (81% versus 70%, $P = 0.1$), but neurovascular contact involving an artery was more prevalent on the symptomatic side (74% versus 56%, $P = 0.001$). The authors concluded that the presence itself of any type of trigeminal NVC was not specific for classical TN as they were highly prevalent on both the symptomatic and the asymptomatic side. However, in view of the strong association between a severe NVC and the symptomatic side, a severe neurovascular contact could be considered a major aetiological factor in TN, unlike a non-severe NVC on the symptomatic (Maarbjerg , et al., 2015). These findings suggest that although trigeminal NVC is of great importance in the pathophysiology of TN, other unknown mechanisms may play a role.

Emerging data points towards a possible pathophysiological and therapeutic relevance of trigeminal NVC also in SUNCT and perhaps in SUNA. Several case reports of trigeminal NVC on the symptomatic side in subjects with SUNCT have been described (Table 29). Amongst the more recent case series of SUNCT and SUNA patients, only in one study, dedicated views of the trigeminal nerves were obtained (Williams , et al., 2008). In this case series where dedicated fine cut constructive interference steady state (CISS) images of the trigeminal nerves were obtained, 15/17 (88%) patients with SUNCT showed an arterial loop. Blinded analysis of the symptomatic versus asymptomatic side indicated that 90% of these vessels were contacting the symptomatic trigeminal nerve, while only 7% were contacting the asymptomatic nerve (Williams and Broadley, 2008). Other series have found a much lower incidence of aberrant vessels (2–8%), but in one of these series, dedicated views of the trigeminal nerve were not obtained (Matharu, MS; personal communication) and the other was a literature review of cases in whom for the vast majority such images were similarly not obtained (Cohen , et al., 2006; Matharu , et al., 2003) (Table 30).

In view of these results coming from case reports and small case series, we assess in this chapter the prevalence and the significance of trigeminal NVC in a large cohort of SUNCT and SUNA.

Table 29. Neurovascular conflict in SUNCT and SUNA patients: case reports

	Age of onset/Sex	**Diagnosis**	**Pain laterality**	**NVC**
Ertsey et al. 2000	- 68/M	- SUNCT	- R	- SCA
(Gardella , et al., 2001)	- 43/F	- SUNCT	- R	- SCA
(Köseoglu , et al., 2005)	- 48/M	- SUNCT	- L	- AICA
(Lagares , et al., 2005)	- 54/F	- SUNCT	- L	- SCA
(Sprenger , et al., 2005)	- 47/M	- SUNCT	- R	- SCA
(Zidverc-Trajkovic , et al., 2005)	- 68/M	- SUNCT	- L	- VA
(Jacob , et al., 2008)	- 29/M	- SUNA	- R	- VL
(Guerreiro , et al., 2009)	- 57/M	- SUNCT	- L	- SCA
(Irimia , et al., 2010)	- 54/M	- SUNCT	- L	- SCA
(Maggioni , et al., 2010)	- 40/F	- SUNCT	- R	- Artery
(Bartsch , et al., 2011)	- 67/M	- SUNCT	- R	- SCA
(Chaila , et al., 2011)	- 45/M	- SUNCT	- L	- SCA
(Paliwal , et al., 2012)	- 60/M - 55/M - 64/M	- SUNCT - SUNCT - SUNCT	- R - R - R	- VL - SCA - SCA
(Rinaldi , et al., 2013)	- 60/F	- SUNA	- R	- SCA
(Lambru , et al., 2015)	- 43/M - 33/F	- SUNA - SUNCT	- R - R	- SCA - Arterial

SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing;; SUNA: short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms; M: male; NVC: neurovascular conflict; F: female; L: left; R: right; AICA: anterior inferior cerebellar artery; SCA: superior cerebellar artery; VA: vertebral artery; VL: vascular loop

Table 30. Neurovascular conflict in SUNCT and SUNA patients: case series

	Age of onset/Sex	**Diagnosis**	**Pain laterality**	**NVC**
(Cohen , et al., 2006) (Total=52)	- N/A - N/A - N/A	- SUNCT - SUNCT - SUNCT	- Unilateral - Unilateral - Bilateral	- VL - Bilateral VL - VL
(Williams , et al., 2008) (Total= 17)	- 43/F - 53/M - 46/F - 47/F - 17/F - 46/F - 19/F - 58/M - 19/M - 55/M - 65/F - 58/M - 32/F - 54/M - 54/M	- SUNCT - SUNCT - SUNCT - SUNCT - SUNCT - SUNA - SUNCT - SUNA - SUNCT - SUNA - SUNCT - SUNA - SUNCT - SUNA - SUNCT	- Bilateral - L - R - R/L - Bilateral - L - L - R - L - R - R - L - R - L - L	- Bilateral SCA - AICA + V - SCA - Bilateral A - Bilateral A - AICA + V - A - SCA + V - SCA - SCA - SCA - A - Bilateral A - SCA - A
(Cação , et al., 2016) (Total=15)	- 50/F - 48/M - 32/M - 57/F	- SUNCT - SUNCT - SUNCT - SUNCT	- L - R - R - L	- NVC - NVC - NVC - NVC

A: artery; AICA: anterior inferior cerebellar artery; F: female; M: male; NVC: neurovascular conflict; L: left; R: right; SCA: superior cerebellar artery; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; SUNA: short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms; V: vein; VL: vascular loop

3.3. Methods

The study group consisted of 147 patients with SUNCT and SUNA according to the ICHD-3**β** diagnostic criteria. As part of their assessment, consecutive Magnetic Resonance Imaging (MRI) examinations were performed. These images were retrospectively reviewed by a consultant neuroradiologist blinded to the diagnosis and lateralisation of symptoms. Exclusion criteria were patients with MRI brain without high-resolution cisternal imaging, patients with abnormal MRI scans and patients who

could not have an MRI brain because of implanted devices (i.e. ONS).

MRI examinations were performed on a 1.5-Tesla GE Signa Excite (GE Medical Systems, Milwaukee), 1.5-Tesla Siemens Avanto (Siemens, Erlangen) or 3.0-Tesla Siemens Trio (Siemens, Erlangen) MRI scanner. The standard imaging protocol included high spatial and nerve-cistern contrast resolution imaging acquisitions of the cisternal segments of the trigeminal nerves and vessels, with 3D Fast Imaging Employing Steady-State Acquisition (FIESTA; TE: 1.5ms, TR: 4.9ms, NEX: 4), 3D Constructive Interference in Steady State (CISS; TE: 5.3ms, TR: 10.6ms, Excitations: 1), or 3D Sampling Perfection with Application optimized Contrasts using different flip angle Evolution (SPACE; TE: 132ms, TR: 1000ms, Excitations: 2). The slice thickness of all examinations ranged from 0.5 mm to 1 mm. High resolution axial and coronal T2-weighted sequences through the trigeminal nerves were also obtained with acquisitions a slice thickness of 2 mm, in order to assess intrinsic signal hyperintensity. When present, Time-Of-Flight Magnetic Resonance Angiography (TOF MRA) was used to confirm the location of the cerebellar arteries and veins in close proximity to the cisternal segments of the trigeminal nerves on the high-resolution images; high signal within vessels on this sequence were considered arteries and the contrary, veins.

All MRI studies were reviewed and analysed on Coronis high-resolution 3-megapixel monitors (Barco Inc, California) on IMPAX 6 Picture Archiving and Communication System (AGFA Healthcare NV, Belgium) by the same experienced neuroradiologist (I.D.) who was blinded to the diagnosis and the laterality of the headache. Vascular contact with the cisternal segments of the trigeminal nerves was assessed on both sides on multiplanar reformats of the source high-resolution data. Neurovascular contact was defined on the analysis of imaging by no perceptible CSF signal intervening the silhouette of the vascular structure (arterial or venous) and the cisternal segment of the trigeminal nerve. Contact with the root entry zone (REZ) was the proximal 4 mm of the cisternal segment of the trigeminal nerve as it emerged from the pons (De Ridder , et al., 2002).

In addition to the presence or absence of contact and involvement of the REZ, we also assessed for the degree of neurovascular contact and type of vessel involved. The degree of contact was graded as: simple contact, distortion or atrophy. Distortion was defined as indentation or displacement of the trigeminal nerve at the site of the

neurovascular contact. Atrophy was defined as reduced volume of the trigeminal nerve at the site of the neurovascular contact. Severe neurovascular contact was defined as contact with distortion and/or atrophy. MRI studies without high-resolution cisternal imaging or which were incomplete or of poor diagnostic quality were excluded.

The study was approved by Northwick Park Hospital Research Ethics Committee, London, UK (REC no:11/LO/1709)

3.3.1. Statistical analysis

Unadjusted and adjusted multilevel logistic regression models, to account for diagnoses, were used to investigate whether presence of vascular contact, degree of contact, site of contact within the trigeminal sensory root and type of vessel involved, were associated with the symptomatic as opposed to asymptomatic trigeminal nerves in SUNA and SUNCT. We used the binomial approximation to the normal distribution to compare the proportions between symptomatic and asymptomatic nerves.

Statistical analyses were performed using ST A T A (Stata Corp. 2001. Stata Statistical Software: Version 12.1, College Station, Texas, USA). All reported *P*-values were two-sided and a significance level less than 5% was considered significant.

3.4. Results

Seventy-nine patients (53.7%) had high-resolution cisternal imaging MRI scans according to our protocol (45 SUNCT; 34 SUNA). Of the remaining 68 patients, 38 patients did not have high-resolution cisternal imaging MRI scans due to incorrect MRI protocol, 26 had not had trigeminal nerve imaging at our centre and either declined further imaging or were not able to have an MRI scan as they had an occipital nerve stimulator in situ, three were excluded as they had abnormal MRI scans (mid-brain low grade astrocytoma, posterior fossa ischaemic strokes) one declined an MRI scan due to claustrophobia.

Of the 79 adequately imaged SUNCT and SUNA patients, 45 had right-sided attacks (26 SUNCT; 19 SUNA), 31 had left-sided attacks (17 SUNCT; 14 SUNA) and three

had unilateral side-alternating attacks (2 SUNCT; 1 SUNA). A total of 82 symptomatic trigeminal nerves, 47 in the SUNCT group and 35 in the SUNA group and a total of 76 asymptomatic trigeminal nerves, 43 in the SUNCT group and 33 in the SUNA group, were analysed.

3.4.1. Neurovascular conflict in the SUNCT and SUNA cohorts

In the SUNCT and SUNA cohorts, the prevalence of neurovascular contact on the symptomatic trigeminal nerves was higher (57.3%; n=47/82), than the prevalence of neurovascular contact on the asymptomatic trigeminal nerves (25%; n=19/76) (P≤0.001). Severe neurovascular contacts were considerably more prevalent on the symptomatic side (47.6%; n=39/82), compared to the asymptomatic side (11.8%, n=9/76) (P≤0.001). The prevalence of neurovascular contact within the REZ on the symptomatic trigeminal nerves was higher (83.0%; n=39/47) compared to the asymptomatic trigeminal nerves (68.4%; n=13/19), but the difference was not statistically significant (P=0.19). The vessels involved in neurovascular contact on the symptomatic nerves in SUNCT and SUNA were predominantly arteries (76.6%; n=36/47) rather than veins (23.4%; n=11/47) (P≤0.001). Similarly, the vessels involved in neurovascular contact on the asymptomatic trigeminal nerves in the SUNCT/SUNA cohort were predominantly arteries (63.2%; n=12/19).

3.4.2. Neurovascular conflict in the SUNCT cohort

The presence of trigeminal neurovascular conflict and its characteristics on the symptomatic and asymptomatic nerves is outlined in Table 31. There was a significantly higher prevalence of neurovascular contact on the symptomatic compared to the asymptomatic trigeminal nerves [61.7% versus 23.3%, OR: 5.31, (95%CI: 2.51,18.55), *P*≤0.001]. Severe neurovascular contacts were considerably more prevalent on the symptomatic compared to the asymptomatic nerves [53.2% versus 14.0%, OR: 4.16 (95%CI: 2.55, 20.02) P≤0.001]. Neurovascular contact at the REZ was more prevalent on the symptomatic compared to the asymptomatic nerves in SUNCT. Although arterial contacts were more prevalent than vein contacts, there was no statistically significant difference between symptomatic and asymptomatic nerves.

Similarly, there was no significant difference in the location of the contacts between symptomatic and asymptomatic nerves.

Table 31. Summary characteristics of trigeminal neurovascular contacts by symptomatic and asymptomatic nerves in SUNCT

	Symptomatic trigeminal nerves (n=47)	**Asymptomatic trigeminal nerves (n=43)**	**OR* (95% CI)**	**P-value**
Vascular loop				
Yes	29/47 (61.7%)	10/43 (23.3%)	5.31 (2.51,18.55)	≤0.001
No	18/47 (38.3%)	33/43 (76.7%)	Ref.	
Site of Contact:				
REZ	24/27 (88.9%)	7/10 (70.0%)	6.50 (0.33,13.42)	0.002
Peripheral[a]	3/27 (11.1%)	3/10 (30.0%)	Ref.	
Degree of NVC:				
Severe[b]	25/47 (53.2%)	6/43 (14.0%)	4.16 (2.55,20.02)	≤0.001
Simple	4/47 (8.5%)	4/43 (9.3%)	Ref	
No contact	18/47 (38.3%)	33/43 (76.7%)		
Type of vessel:				
Artery	20/29 (69.0%)	8/10 (80.0%)	0.90 (0.07, 3.65)	0.857
Vein	8/29 (27.6%)	2/10 (20.0%)	Ref.	
Missing data	1/29 (3.4%)	-	-	-

*OR comparing the odds of each category on having a symptomatic nerve vs. asymptomatic.
NCV: neurovascular conflict; Ref: reference; REZ: root entry zone;
[a] Defined as >4mm from the site of entry of the trigeminal nerve into the pons
[b] Defined as indentation and/or distortion and/or atrophy

3.4.3. Neurovascular conflict in the SUNA cohort

The presence of a trigeminal neurovascular conflict and its characteristics on the symptomatic and asymptomatic nerves is outlined in Table 32. There was a significantly higher prevalence of neurovascular contact on the symptomatic compared to the asymptomatic trigeminal nerves [57.1% versus 27.3%, OR: 3.55 (95%CI: 1.82,16.47), *P*<0.015]. Severe neurovascular contacts were considerably more prevalent on the symptomatic compared to the asymptomatic nerves [42.9% versus 12.1%, OR: 3.75 (95%CI: 2.78, 34.96), P=0.005]. Similarly to SUNCT, the arterial contacts were more prevalent than venous contacts; there was no statistically significant difference between symptomatic and asymptomatic nerves. Similarly, there was no

significant difference in the location of the contacts between symptomatic and asymptomatic nerves.

Table 32. Summary characteristics of trigeminal neurovascular contacts by symptomatic and asymptomatic nerves in SUNA

	Symptomatic trigeminal nerves (n=35)	**Asymptomatic trigeminal nerves (n=33)**	**OR* (95% CI)**	**P-value**
Vascular loop				
Yes	20/35 (57.1%)	9/33 (27.3%)	3.55 (1.82,16.47)	0.015
No	15/35 (42.9%)	24/33 (72.7%)	Ref.	
Site of Contact				
REZ	15/20 (75.0%)	7/9 (77.8%)	1.28 (0.44,18.56)	0.71
Peripheral[a]	5/20 (25.0%)	2/9 (22.2%)	Ref.	
Degree of NVC				
Severe[b]	15/35 (42.9%)	4/33 (12.1%)	3.75 (2.78,34.96)	0.005
Simple	5/35 (14.3%)	5/33 (15.2%)	2.42 (0.68,8.68)	0.174
No contact	15/35 (42.9%)	24/33 (72.7%)	Ref.	
Type of vessel				
Artery	14/20 (70.0%)	4/9 (44.4%)	1.30 (0.19-0.81)	0.110
Vein	6/20 (30.0%)	5/9 (55.5%)		

*OR comparing the odds of each category on having a symptomatic nerve vs. asymptomatic.
NCV: neurovascular conflict; Ref: reference; REZ: root entry zone;
[a] Defined as >4mm from the site of entry of the trigeminal nerve into the pons
[b] Defined as indentation and/or distortion and/or atrophy

3.4.4. Neurovascular conflict: comparison between SUNCT and SUNA cohorts

There was no statistically significant difference in the proportion of neurovascular contacts on the symptomatic nerves between SUNCT [29/47 (61.7%)] and SUNA [20/35 (57.1%)] (P=0.67). Similarly, there was no statistically significant difference in the proportion of severe neurovascular conflict between SUNCT and SUNA [25/47 (53.2%) versus 15/35 (42.9%)] (P=0.35)]. The comparison of the other variables showed no significant difference between the two cohorts of patients.

3.4.5. Analysis of predictors for symptomatic nerves unadjusted and adjusted for diagnosis

Table 33 outlines the results of the analysis of radiological predictors associated to the symptomatic side, unadjusted and adjusted for the diagnosis of SUNCT and SUNA. The estimates of odds ratio indicate that the presence of a vascular contact is a strong predictor for the nerve to be symptomatic rather than asymptomatic. Similarly, the estimates of odds ratio indicate that the presence of a severe contact at the REZ is strongly associated with the nerve being symptomatic rather than asymptomatic.

Table 33. Analysis of radiological predictors for symptomatic compared to asymptomatic nerves

	Unadjusted OR (95%CI)	**Adjusted for diagnosis OR (95%CI)**
Vascular loop		
Yes	4.45 (2.25-8.8) p<0.001	4.45 (2.25-8.8) p<0.001
No	Ref	
Site of Contact		
REZ	3.87 (1.5-9.98) p=0.005	3.81 (1.47-9.98) p=0.006
Peripheral[a]	Ref	
Degree of NVC		
Severe[b]	4.0 (1.27-12.66) p=0.019	4.0 (1.23-12.82) p=0.021
Simple	Ref	
Type of vessel		
Artery	1.27 (0.49-3.23) p=0.629	1.27 (0.50-3.26) p=0.616
Vein	Ref	

NCV: neurovascular conflict; Ref: reference; REZ: root entry zone;
[a] Defined as >4mm from the site of entry of the trigeminal nerve into the pons
[b] Defined as indentation and/or distortion and/or atrophy

3.5. Discussion

This is the first prospective, consecutive blinded MRI study, conducted in a large cohort of patients, demonstrating that trigeminal neurovascular contact ipsilaterally to the side of the pain is a common neuroanatomical variant in SUNCT and SUNA. The presence

of any type of neurovascular contact was significantly more prevalent on the symptomatic side compared to the asymptomatic, suggesting that this anatomical finding may be contributory to these conditions. There was no significant difference in the prevalence of neurovascular contacts between SUNCT and SUNA, enforcing the likelihood that the two conditions belong to the same clinical entity. In the vast majority of cases, the neurovascular contact was severe and much more prevalent on the symptomatic side than on the asymptomatic side. The site of the neurovascular contact was predominantly the REZ and was generally caused by an artery in both SUNCT and SUNA. We also demonstrated that a severe trigeminal neurovascular contact at the REZ is highly associated with the pain side in SUNCT and SUNA. These findings have implications in clinical practice, highlighting the importance of MRI scans with dedicated trigeminal views to shed light on the aetiology of these disorders and potentially for management reasons.

The rate of NVC was lower than that coming from a series of 24 SUNCT and SUNA cases, where 17 patients were studied with dedicated MRI imaging of the trigeminal nerves. Neurovascular compression was detected in 15 of 17 patients (88%). In 90% of cases, a vascular loop was impinging on the symptomatic trigeminal nerve, compared to only 7% in which the vascular loop was pressing on the asymptomatic nerve (Williams , et al., 2008). The higher prevalence of neurovascular contact in their series could be explained by the small size of the sample. Moreover, the authors did not detail the scanning protocol and did include in the definition of vascular loop also cases where a contact was only observed. It is therefore possible that they overestimated the prevalence of vascular loops.

The association between a severe neurovascular contact and the symptomatic side raises the possibility that a severe neurovascular contact is an aetiological factor in SUNCT and SUNA, similarly to TN. Maarbjerg and colleagues have recently studied neurovascular contact in classical TN and reported that there was a high prevalence of severe neurovascular contact on the symptomatic (53%) compared to the asymptomatic side (13%). It is remarkable that their finding in TN is similar to that of our cohorts of SUNA and SUNCT. These findings in SUNA, SUNCT and TN have implications for the aetiology of these disorders, suggesting an overlap in the underlying

pathophysiological basis of these disorders (Sesso, 2001; Lambru , et al., 2014). However, in both our and Maarbjerg et al studies, only about half of the patients displayed a severe neurovascular contact on the symptomatic side and since several studies in TN patients have shown a high prevalence of neurovascular contacts in non-TN individuals (Peker , et al., 2006), it could be argued that this neuroanatomical finding may not be the only etiologically relevant factor for these disorders. Our data suggest that severe neurovascular contacts at the REZ may play an important aetiological role in SUNCT and SUNA, similarly to what has been demonstrated in TN (Maarbjerg , et al., 2015). Other factors may also play a role in the pathophysiology of SUNCT and SUNA. Lambru and colleagues described a co-occurrence between SUNCT/SUNA and hemiplegic migraine (HM) in ten subjects. This association raises the possibility of a common denominator implicated in the pathogenesis of both conditions, with ion channel dysfunction being an attractive hypothesis. It is noteworthy that the most effective treatments of SUNCT/SUNA (lamotrigine and oxcarbazepine) modulate sodium channel function among others, and that sodium channel dysfunction is capable (at least in Familial HM series) of generating hemiplegic aura (Lambru , et al., 2012). It is possible that ion channels dysfunction may increase susceptibility to the SUNCT/SUNA phenotype and the presence of a neurovascular contact in a subgroup of patients may increase vulnerability of the trigeminal nerve to trigger factors, allowing precipitation and perpetuation of the condition overtime.

Further evidence that severe neurovascular contact plays a pivotal role in SUNCT and SUNA should come from long-term headache freedom after trigeminal microvascular decompression (MVD). Initial encouraging evidence from single case reports and a small case series suggest that trigeminal MVD in patient with a severe neurovascular conflict on the symptomatic nerve could be beneficial in SUNCT and SUNA (Sebastian , et al., 2013), though larger studies with longer follow-ups will be required to confirm the efficacy of this surgical procedure in these conditions.

3.6. Summary

This Chapter describes the largest MRI study with dedicated trigeminal sequences in SUNCT and SUNA. It demonstrates the important role of neurovascular contact

ipsilaterally to the side of the pain, without significant differences between SUNCT and SUNA. It supports the possibility that this neuroanatomical finding plays an important role in the pathophysiology of SUNCT and SUNA. Along with the clinical similarities between SUNCT and SUNA demonstrated in chapter 2, these findings further enforce the concept that SUNCT and SUNA should no longer be considered separate entities. Furthermore, the radiological overlap with TN along with the initial encouraging results of MVD of the trigeminal nerve in some patients with SUNCT syndrome support the notion that more peripheral mechanisms, may be involved in the complex pathophysiological mechanisms of SUNCT and SUNA (Sebastian , et al., 2013). This would imply that a subgroup of SUNCT and SUNA may also share pathogenic mechanisms with TN, namely demyelination of the trigeminal sensory root due to vascular compression. This abnormality would be responsible for the short-lived painful paroxysms and it would also be responsible for the ephaptic cross talk between fibres that drive sensation and nociceptive fibres, explaining the triggerability of the attacks in some SUNCT and SUNA patients. A complex interaction between more peripheral and central mechanisms may underpin the pathophysiology of SUNCT and SUNA. Further data are needed to confirm this hypothesis.

Chapter 4. The medical treatment of SUNCT and SUNA syndromes: a prospective exploratory study

4.1. Abstract

The management of SUNCT and SUNA is considered challenging due to paucity of data and lack of knowledge of its biological mechanisms. To assess the efficacy of medical treatments in these conditions, the response to treatments was evaluated in a prospective exploratory study. A semi-structured questionnaire was administered face to face to 161 consecutive SUNCT and SUNA patients. Treatment outcome was classified as: ineffective (no improvement), mild (<50% improvement), good (≥50% improvement) and excellent improvement (pain-free or almost pain-free). Responders were defined as those patients who obtained a good or excellent improvement from a given treatment.

Lamotrigine was found to be the most effective treatment (responders: SUNCT= 53.5%, SUNA= 57.9%) followed by oxcarbazepine (responders: SUNCT= 44.8%, SUNA= 47.0%) in both groups of patients; duloxetine and topiramate were more effective in SUNCT rather than SUNA (duloxetine responders: SUNCT= 45.0%, SUNA: 11.8%; p= 0.027; topiramate responders: SUNCT= 33.3%, SUNA= 10.7%; p= 0.028). Amongst transitional treatments intravenous lidocaine given at a dose ranging from 1.3 to 3.3 mg/kg/h for 7–10 days, with an infusion speed that varies from from 60 to 240 mg/h, led to a significant, albeit short-lasting, headache improvement in 83.3% SUNCT (n=25) and in 76.5% SUNA (n=13) patients (p=0.73). A greater occipital nerve block (GONB) injecting a mixture of steroid and local anaesthetic was tried in 77 patients. A 50% or more headache improvement was obtained by 27.3% (n=21) in our cohorts of patients, without any significant difference between SUNCT (24.4%; n=11) and SUNA (37.0%; n=10) patients (p=0.42). In those who benefited from the procedure, the improvement lasted for a median of 21 days (IQR: 53 days; range: 1 to 150 days). We found intravenous dihidroergotamine able to worsen or even to precipitate a de novo SUNCT/SUNA when administered for a different primary headache disorder. In conclusion, SUNCT and SUNA seem to respond to sodium channel blockers, similarly to TN. These findings delineate a treatment algorithm of SUNCT and SUNA and further expand the overlap between SUNCT, SUNA and TN.

4.2. Introduction

The management of SUNCT and SUNA syndromes has historically been considered challenging. The rarity of SUNCT has meant that the majority of published treatment studies have been conducted in single cases or small case series. As far as SUNA is concerned, only the therapeutic outcome of a small series of patients has hitherto been reported (Cohen, 2007). It is therefore still unclear whether medications effective in SUNCT are also effective in SUNA.

To date there are no randomised placebo-controlled double-blind trials conducted in the pharmacological management of SUNCT and SUNA. Difficulties in setting up such trials may include slow and incomplete participants' enrolment due to the rarity of the conditions, leading to underpowered studies. Moreover, conducting placebo-controlled trials in such excruciating conditions poses ethical issues related to the use of a placebo compound and the duration of the placebo phase. Since preventive treatments normally used in headache management require relatively slow titration and high daily dosages, a short controlled phase may not allow proper drug titration, hence masking the full potential of a treatement.

Given the clinical overlap between the other TACs and TN, a plethora of medical and injectable treatments deemed to be effective have been tried in SUNCT and much less frequently in SUNA, with inconsistent results (Pareja , et al., 2013).

In this chapter we conducted a prospective exploratory study of preventive medical treatments tested in a large cohort of SUNCT and SUNA patients, with the aims of:

1) Describing the outcome of oral long-term and short-term preventive treatments, previously reported to be effective in SUNCT, in a large series of SUNCT and SUNA patients.

2) Describing the response to preventive treatments in a large series of SUNA and comparing it to the one of SUNCT patients.

3) Reporting the outcome of therapies for which there is no evidence of efficacy in SUNCT and SUNA.

4.3. Methods

4.3.1. Study design and study population

This study was a prospective single centre open-label observational study aiming to assess the effectiveness and tolerability of preventive treatments in SUNCT and SUNA patients. Consecutive patients with a diagnosis of SUNCT and SUNA, according to the ICHD-2 and ICDH3β diagnostic criteria, who attended our headache and facial pain outpatient clinics between 2010 and 2013, were included in the study. Details on medical treatments were collected directly from patients in outpatient or inpatient settings using a semi-structured standardised questionnaire (see Appendix) and, when necessary, from the clinical notes or telephone follow-ups. Data were subsequently entered onto a clinical electronic database SPSS version 21 (IBM® SPSS® Statistics). Data including demographics, headache clinical characteristics, type of medication, dose, side effects, length of the trial, and reasons for discontinuation (when appropriate) were captured. Patients were usually followed-up at three or six-monthly intervals with telephone follow-up in the interim, if needed. This allowed us to assess the outcome of a certain treatment and monitor its effect overtime.

4.3.2. Data collection and treatments outcome

Patients' estimate of benefit was used to evaluate the outcome of medication trials in view of the absence of standardised diaries designed to capture the multiple (sometimes hundreds) short-lasting daily SUNCT and SUNA attacks.
Patients' baseline daily attacks frequency, severity and duration were recorded in the research questionnaire and compared to the same clinical parameters after each treatment trials, looking for any changes.

Headache improvement was defined as reduction in daily attacks frequency and/or intensity and/or duration. Treatment improvement was classified as: mild (<50% improvement), good (≥50% improvement) and excellent (pain-free or almost pain-free). Responders were defined as those patients who obtained a good or excellent improvement from a given treatment.

To assess differences in treatment responses between SUNCT and SUNA, we compared responders to treatments between the two groups of patients.

Most treatments were tried in monotherapy, though sometimes combination of two or more treatments was required when the first medication was only partially beneficial. All treatments outcomes were assessed prospectively, with the exception of carbamazepine and gabapentin, which had in some occasions been tried by other clinicians by the time the patients were referred to our service. However, we only included outcomes on these two medications if the information provided was detailed and accurate as well as being confirmed by the patients.

The study was approved by Northwick Park Hospital Research Ethics Committee, London, UK (REC no:11/LO/1709)

4.3.3. Statistical analysis

All data were analysed using Statistical Package for the Social Sciences, SPSS version 21 (IBM® SPSS® Statistics). Chi square test and Fisher's exact test were used for categorical variables. Paired sample T-test was used for non-categorical variables. All reported p-values are two-sided and a significance level less than 5% was considered significant.

4.4. Results

The demographic and clinical characteristics of the cohort of SUNCT and SUNA patients are summarised in Table 34. There was a preponderance of female patients, particularly in SUNA. The vast majority of patients displayed a chronic pattern with daily or daily severe headache attacks occurring on a median frequency of 22 attacks/day, each lasting a median of 60 seconds.

Table 34. Demographic and clinical features of the SUNCT and SUNA cohorts

		SUNCT (N=85)	SUNA (N=76)	TOTAL (N=161)
Gender	**Male**	40 (47.1%)	23 (30.3%)	63 (39.1%)
	Female	45 (52.9%)	53 (69.7%)	98 (60.9%)
Median age of onset in years		41 (range: 13-76)	45 (range: 16-72)	42 (range: 13-76)
Median headache duration in years		8 (range: 1-45)	6 (range: 1-32)	6 (range: 1-45)
Headache course	**Episodic**	10 (11.8%)	7 (9.2%)	17 (10.6%)
	Chronic	75 (88.2%)	69 (90.8%)	144 (89.4%)
Laterality	**Right**	41 (48.2%)	39 (51.3%)	80 (49.7%)
	Left	31 (36.5%)	28 (36.8%)	59 (36.6%)
	Side-variable	13 (15.3%)	8 (10.5%)	21 (13.0%)
	Bilateral	0 (0%)	1 (1.3%)	1 (0.6%)
Median attack frequency daily		30 (range: 0.1-250)	20 (range: 2-250)	22 (range: 0.1-250)
Median attack severity (VRS)		10 (range: 6-10)	9 (range: 4-10)	9 (range: 4-10)
Median attack duration (Seconds)		120 (range: 5-1200)	60 (range: 1-900)	60 (range: 1-1200)
Missing data		-	1 (1.3%)	1 (0.6%)
Attack triggerability	**T + S**	53 (62.4%)	40 (52.6%)	93 (57.8%)
	S only	27 (31.8%)	31 (40.8%)	58 (36.0%)
	T only	5 (5.9%)	4 (5.3%)	9 (5.6%)
Missing data		-	1 (1.3%)	1 (0.6%)

S:spontaneous attacks; S only: spontaneous attacks only; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; T: triggered attacks; T only: triggered attacks only; VRS: verbal rating scale (0= no pain, 10= worst pain)

4.4.1. Therapeutic outcomes: oral preventive treatments

Several treatments were tried in our cohorts. Some of them, including lamotrigine, topiramate, carbamazepine, oxcarbazepine and gabapentin, were tried because of initial evidence of efficacy reported mainly in SUNCT (Cohen, 2007). Other medications such as pregabalin, duloxetine, lacosamide and mexiletine, which are not supported by any published evidence, were tried on the basis of their mechanisms of action and/or their favourable tolerability profile. Table 35 outlines the number of patients who tried each medication, the median doses, therapeutic outcomes for each medication tried, as well as the proportion of patients who discontinued the medications because of unacceptable side effects. Figure 13 outlines the comparison between responders to oral medications in the SUNA and SUNCT cohorts.

Lamotrigine

Lamotrigine was tried by the majority of our SUNCT and SUNA patients (n=134/161, 84.5%) at a median dose of 250 mg/day (IQR: 250 mg; range: 25-700mg) for a median of eight months at the time of the assessment (range: 15 days to 7 years; data on duration for which drug was taken were incomplete for 16 patients). Lamotrigine led to a headache improvement in 97 of 128 patients in our cohorts [75.8%, missing data (md): 6 patients]: 54 SUNCT (73.0%) and 43 SUNA patients (71.7%) (p=0.749). A 50% or more benefit was observed in 53.5% of SUNCT (n= 38) and 57.9% of SUNA patients (n=33) (p=0.621). One patient experienced a worsening of SUNCT while on lamotrigine and therefore she discontinued it. Data on efficacy were incomplete for three SUNCT and three SUNA patients. The medication was tolerated by 83.3% of SUNCT patients (n=55), though it was discontinued because of side effects in 14.9% (n=11) of SUNCT patients. Similarly, lamotrigine was tolerated by 81.4% of SUNA patients, though it had to be discontinued because of side effects in 18.3% (n=11) patients. Data on drug tolerability were incomplete for 11 patients.

Carbamazepine

Carbamazepine was tried by 87 patients at the median dose of 600 mg/day (IQR: 500 mg; range: 100-2000 mg) for a median of 7.5 months at the time of the assessment (range: 1 month to 25 years). Carbamazepine led to a headache improvement in 42 out of 84 patients in our cohorts (50.0%, md: 3 patients): 16 SUNCT (37.2%) and 26 SUNA (63.4%) patients (*p=0.016*). A 50% or more headache improvement was observed in

36.6% of SUNA (n=15) compared to 16.3% of SUNCT patients (n=7) (*P=0.034*). Amongst all patients who trialled carbamazepine, in both SUNCT and SUNA, approximately 20% of patients had to discontinue the trial because of unbearable side effects.

Gabapentin

Gabapentin was tried in 80 SUNCT and SUNA patients at a median dose of 1800 mg/day (IQR: 1800 mg; range: 200-4800 mg) for a median trial duration of six months at the time of the assessment (range: 1 month to 11 years). Gabapentin led to a headache improvement in 26 of 80 patients in our cohorts (32.5%): 32% of SUNCT (n=16) and 33.3% of SUNA patients (n=10) (p=0.76). The majority of SUNCT and SUNA patients either reported a mild improvement or no improvement at all on gabapentin. A 50% or more headache improvement was observed in 10% of SUNCT (n=5) and SUNA (n=3) patients (p=1.0). Side effects led to treatment discontinuation in a greater proportion of SUNA (19.4%, n=6) compared to SUNCT patients (8.7%, n=4).

Topiramate

Topiramate was tried in 79 patients at a median dose of 200 mg/day (IQR: 300 mg; range: 25-800 mg) for a median duration of four months at the time of the assessment (range: 1 month to 5 years). Topiramate led to a headache improvement in 36 of 76 patients in our cohorts (47.4%; md: 3 patients): 26 SUNCT (54.2%) and 10 SUNA (35.7%) patients (*p=0.12*). A greater proportion of SUNCT (33.3%, n=16) compared to SUNA patients (10.7%, n=3) obtained at least 50% or more headache improvement (*p=0.028*). The majority of SUNCT and SUNA patients though reported a mild improvement or no improvement at all on topiramate. One SUNCT and one SUNA patients reported a worsening of the attacks while on topiramate. Side effects led to discontinuation of the medications in 35.4% of SUNCT (n=17) and 22.6% of SUNA patients (n=7).

Pregabalin

Pregabalin was tried in 66 patients. However, data were not satisfactory for most outcomes in one patient, hence 65 patients were considered for the analysis. Pregabalin was tried in our cohort at a median daily dose of 500 mg/day (IQR: 375 mg; range: 25-600 mg). The median duration of the trial at the time of the assessment was four months

(range: 1 month to 5 years). Similar to gabapentin, pregabalin led to headache improvement in a small proportion of patients: 19 of 64 in our cohorts (29.7%, md=2 patients), 11 SUNCT (30.6%) and eight SUNA (28.6%) patients (p=0.863). A 50% or more headache improvement was observed in 11.1% of SUNCT (n=4) and 10.7% of SUNA patients (n=3) (p=0.959). No patients exposed to pregabalin reported an excellent headache benefit. Moreover, the proportion of patients who discontinued pregabalin because of tolerability issues, was slightly higher than the proportion of patients who discontinued gabapentin (SUNCT: 16.2% vs 8.2%; SUNA: 20.7% vs 19.4%).

Oxcarbazepine

Oxcarbazepine was tried by 63 SUNCT and SUNA patients at a median daily dose of 1200 mg (IQR: 600 mg; range: 300-3600 mg) for a median duration of four months (range: 1 week to 5 years) at the time of the assessment. Oxcarbazepine led to a headache improvement in 45 of 63 patients in our cohorts (71.4%): 69% of SUNCT (n=20) and 73.5% of SUNA (n=25) patients (p=0.689). A 50% or more headache improvement was observed in 44.8% of SUNCT (n=13) and 47.0% of SUNA patients (n=16) (p=0.859). The proportion of patients who had to discontinue oxcarbazepine due to side effects was 17.2% (n=5) of SUNCT and 29.4% (n=10) of SUNA patients.

Of the 63 patients who tried oxcarbazepine, 47 (72.3%) patients (SUNCT=21; SUNA=26) previously used carbamazepine. Of these, 11 patients did not tolerate carbamazepine (17.5%). Only one patient who did not tolerate carbamazepine had responded to it but was swapped to oxcarbazepine because of tolerability issues. Of the remaining 33 patients who tolerated carbamazepine, 12 were responders and 19 were non-responders. It is likely that responders experienced side effects, which were not severe enough to discontinue the medication, but enough to warrant a replacement with another medication, in this case with oxcarbazepine. Of the 12 responders to carbamazepine, eight (66.7%) also responded to oxcarbazepine, whereas four reported a marginal or no response at all to the latter medication.

Duloxetine

Duloxetine was tried in a more challenging-to-treat subgroup of patients who had failed to respond or tolerate medications such as lamotrigine, topiramate, carbamazepine, and gabapentin. Duloxetine was tried in 37 patients at a median dose of 90 mg/day (IQR: 30 mg; range: 30-120 mg/day), for a median follow-up of four months (range: 3 weeks to 1 year) at the time of the assessment. Duloxetine led to a headache improvement in 18 of 37 patients in our cohorts (48.6%), 60.0% of SUNCT (n=12) and in 35.3% of SUNA patients (n=6) (p=0.134). A 50% or more headache improvement was observed in 45.0% of SUNCT (n=9) and 11.8% of SUNA (n=2) patients (*P=0.027*). One SUNCT patient reported a worsening of the headache while of duloxetine. Unacceptable side effects led to drug discontinuation in 25.0% of SUNCT (n=5) and 17.6% of SUNA (n=3) patients.

Mexiletine

Mexiletine was tried in 15 patients at a median daily dose of 850 mg/day (IQR: 600 mg; range: 400-1220 mg). At a median follow-up of four months (range 1month-4 years) nine patients in our cohorts (60%), 75% of SUNCT (n=6) and 42.9% of SUNA (n=3) patients (p=020) reported a headache improvement. A 50% or more headache improvement was obtained by 37.5% (n=3) of SUNCT and 28.6% of SUNA (n=2) patients (p=0.71). Side effects led to drug discontinuation in 25% (n=2) of SUNCT and 57.1% (n=4) of SUNA patients.

Lacosamide

Lacosamide was tried in nine patients, refractory to most of the other medications reported in this study at a median dose of 250 mg/day (IQR: 175 mg; range: 100-400 mg). At a median follow-up of three and a half months (range: 1 month to 14 months) one SUNCT and one SUNA obtained a 50% or more headache improvement. Two SUNCT patients could not tolerate the medication and had to discontinue it.

Table 35. Doses, duration of trials, therapeutic outcome and discontinuation of oral preventive treatments in SUNCT and SUNA

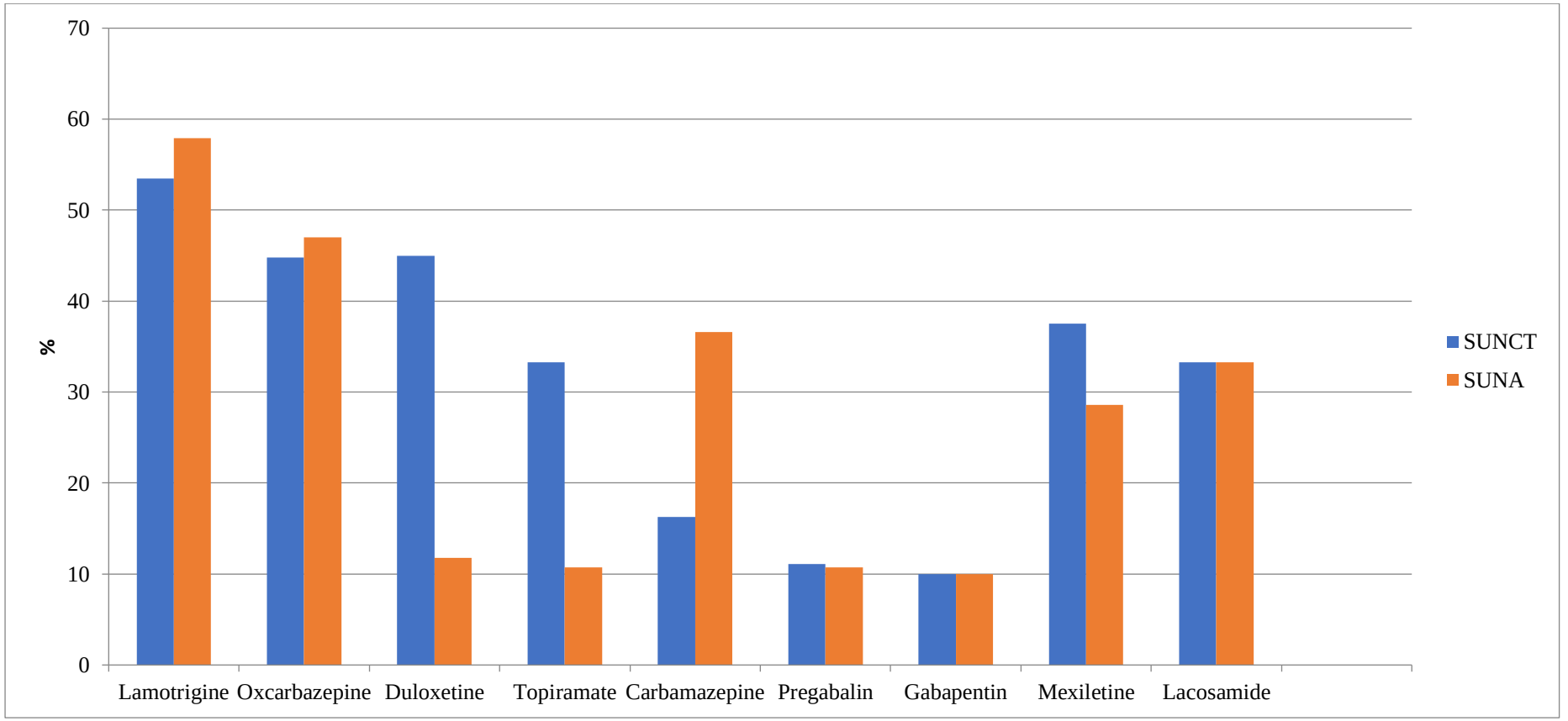
		Median dose mg (range)	**Mild Improvement N (%)**	**Good Improvement N (%)**	**Excellent improvement N (%)**	**Non-responders N (%)**	**Treatment discontinuation N (%)**
Lamotrigine (Total: 134)	SUNCT (n=74)	200 (25-700)	16 (21.6%)	30 (40.5%)	8 (10.8%)	17 (23.0%)	11 (14.9%)
	m.d.	12 (16.2%)	3 (4.1%)				6 (8.3%)
	SUNA (n=60)	300 (25-600)	10 (16.7%)	22 (36.7%)	11 (18.3%)	14 (23.3%)	11 (18.3%)
	m.d.	4 (6.7%)	3 (5.0%)				5 (7.8%)
Carbamazepine (Total: 87)	SUNCT (n=44)	600 (100-1600)	9 (20.5%)	6 (13.6%)	1 (2.3%)	27 (61.4%)	9 (20.5%)
	m.d.	10 (22.7%)	1 (2.3%)				1 (2.2%)
	SUNA (n=43)	700 (200-2000)	11 (26.8%)	12 (29.3%)	3 (7.3%)	15 (36.6%)	8 (20.0%)
	m.d.	5 (11.6%)	2 (4.7%)				3 (7.0%)
Gabapentin (Total: 80)	SUNCT (n=50)	1800 (300-4500)	11 (22.0%)	4 (8.0%)	1 (2.0%)	34 (68.0%)	4 (8.2%)
	m.d.	9 (18.0%)	0 (0%)				4 (8.0%)
	SUNA (n=30)	1800 (200-4800)	7 (23.3%)	3 (10.0%)	0 (0%)	20 (66.7%)	6 (19.4%)
	m.d.	5 (16.7%)	0 (0.0%)				2 (6.7%)

		Median dose mg (range)	Mild Improvement N (%)	Good Improvement N (%)	Excellent improvement N (%)	Non-responders N (%)	Treatment discontinuation N (%)
Topiramate (total: 79)	SUNCT (n=48)	200 (50-800)	10 (20.8%)	15 (31.3%)	1 (2.1%)	22 (45.8%)	17 (35.4%)
	m.d.	1 (2.1%)	0 (0%)				0 (0%)
	SUNA (n=31)	200 (25-700)	7 (22.6%)	3 (9.7%)	0 (0%)	20 (64.5%)	7 (22.6%)
	m.d.	3 (9.7%)	3 (9.7%)				2 (6.5%)
Pregabalin (Total: 66**)**	SUNCT (n=37)	500 (25-600)	7 (18.9%)	4 (10.8%)	0 (0%)	25 (67.6%)	6 (16.2%)
	m.d.	4 (10.8%)	1 (2.7%)				4 (10.8%)
	SUNA (n=29)	300 (75-600)	5 (17.2%)	3 (10.3%)	0 (0%)	20 (69.0%)	6 (20.7%)
	m.d.	5 (17.2%)	1 (3.6%)				4 (13.8%)
Oxcarbazepine (Total: 63)	SUNCT (n=29)	1200 (300-2400)	7 (24.1%)	12 (41.4%)	1 (3.4%)	9 (31.0%)	5 (17.2%)
	m.d.	1 (3.4%)	0 (0.0%)				0 (0.0%)
	SUNA (n=34)	1200 (600-3600)	9 (26.5%)	13 (38.2%)	3 (8.8%)	9 (26.5%)	10 (29.4%)
	m.d.	3 (8.8%)	0 (0.0%)				2 (5.9%)

		Median dose mg (range)	Mild Improvement N (%)	Good Improvement N (%)	Excellent improvement N (%)	Non-responders N (%)	Treatment discontinuation N (%)
Duloxetine (total: 37)	SUNCT (n=20)	90 (30-120)	3 (15.0%)	7 (35.0%)	2 (10.0%)	8 (40.0%)	5 (25.0%)
	m.d.	0 (0%)	0 (0.0%)				4 (20.0%)
	SUNA (n=17)	90 (30-120)	4 (23.5%)	1 (5.9%)	1 (5.9%)	11 (64.7%)	3 (17.6%)
	m.d.	1 (5.9%)	0 (0.0%)				5 (29.4%)
Mexiletine (total: 15)	SUNCT (n=8)	600 (400-1200)	3 (37.5%)	3 (37.5%)	0 (0%)	2 (25%)	2 (25%)
	m.d.	1 (12.5%)	0 (0%)				0 (0%)
	SUNA (n=7)	950 (400-1200)	1 (14.3%)	2 (28.6%)	0 (0%)	4 (57.1%)	4 (57.1%)
	m.d.	0 (0%)	0 (0%)				0 (0%)
Lacosamide (total: 9)	SUNCT (n=4)	200 (100-400)	0 (0%)	1 (33.3%)	0 (0%)	2 (66.7%)	2 (50.0%)
	m.d.	0 (0%)	1 (25.0%)				0 (0%)
	SUNA (n=5)	300 (200-400)	0 (0%)	0 (0%)	1 (33.3%)	2 (66.7%)	0 (0%)
	m.d.	1 (20.0%)	2 (40.0%)				2 (40.0%)

m.d.= missing data; N= number; SUNA= short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; SUNCT= short-lasting neuralgiform headache attacks with conjunctival injection and tearing;

Figure 15. Comparison between SUNCT and SUNA responders to oral medical treatments



SUNCT: Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injections and Tearing; SUNA: Short-lasting Unilateral Neuralgiform headache attacks with autonomic symptoms

4.4.2. Therapeutic outcome: injectable preventive treatments

These treatments aim to produce a rapid suppression of headache attacks for a limited period of time while waiting for the beneficial effect of a preventive treatment to become evident. Additionally, they can be used to give some relief to patients who present with breakthrough headache attacks. Table 36 summarises the outcome and duration of improvement of intravenous (IV) lidocaine and greater occipital nerve blockade (GONB) tested in our study cohorts. Tables 37-39 summarise our experience with IV dihydroergotamine (DHE) in SUNCT and SUNA.

4.4.2.1. Intravenous lidocaine

Our protocol consists of using IV lidocaine ranging from 1.3 to 3.3 mg/kg/h for 7–10 days, with an infusion speed that varies from from 60 to 240 mg/h according to the outcome and side effects. Twenty-four hours ECG monitoring is mandatory during the infusion in view of the potential risk of cardiac arrythmia (Lambru , et al., 2013).
A 50% or more headache improvement during IV lidocaine infusion was obtained by 83.3% SUNCT (n=25) and in 76.5% SUNA (n=13) patients (p=0.73). Data was incomplete for one SUNCT patient. The majority of responders with SUNCT (n=19/25) and SUNA (10/13), experienced the maximum benefit with an average infusion speed of 120 mg/h. In 58.6% of patients with SUNCT (n=17/29) and 41.2% of SUNA (n=7/17) who benefited from IV lidocaine, the attacks recurred immediately after the end of the infusion period, whereas in the remaining responders the median duration of the improvement was 10 days (range: 3-90 days; SUNCT= median 11 days; IQR: 16 days; range 3-90 days; SUNA=median 10 days; IQR: 25 days; range 4-30 days). Data was incomplete for two SUNCT patients. One SUNCT and two SUNA patients had to discontinue the lidocaine infusion because of unacceptable side effects, such as cognitive slowing and paranoid thoughts.

4.4.2.2. Greater occipital nerve blockade

A greater occipital nerve blockade (GONB) was performed using a mixture of methylprednisolone 80 mg and 2 ml of lidocaine 2% delivered around the GON territory ipsilaterally to the side of the pain. Two patients received bilateral injections

in view of their headache laterality. The infiltration technique used to perform a GONB consists of a mixture of methylprednisolone 80 mg and 2 ml of 2% lidocaine, injected in the suboccipital area at a point lying on the medial third of a line drawn between the inion and mastoid process ipsilateral to the pain. The needle is inserted until it starts to touch bone. One-third of the solution is then injected in that area, one-third is injected slightly medially and one-third slightly laterally (Lambru, et al., 2014).

A GONB was tried in 77 patients. A 50% or more headache improvement was obtained by 27.3% (n=21) in our cohorts of patients, without any significant difference between SUNCT (24.4%; n=11) and SUNA (37.0%; n=10) patients (p=0.42). Data were incomplete for one SUNCT and four SUNA. In those who reported some improvement after the procedure, the improvement lasted for a median of 21 days (IQR: 53 days; range: 1 to 150 days). SUNA reported longer median duration of benefit compared to SUNCT (30 days vs 21 days; $p<0.05$) patients. Four SUNCT (8.9%) and five SUNA (18.5%) patients reported worsening of headache after the procedure. The headache worsened for a median of eight days in SUNCT (IQR: 11 days; range: 7-21 days) and for a median of nine days in SUNA patients (IQR: 29 days; range: 9-60 days).

Table 36. Outcome and duration of response to intravenous lidocaine and greater occipital nerve blockade

		Mild benefit N (%)	**Good Benefit N (%)**	**Excellent benefit N (%)**	**Responders N (%)**	**Median duration of benefit in days (range)**	**Non-responders N (%)**
IV Lidocaine (Total: 58)	SUNCT (n=31)	4 (13.3%)	11 (36.7%)	14 (46.7%)	25 (83.3%)	11 (3-90)	0 (0%)
	SUNA (n=17)	1 (5.9%)	6 (35.3%)	7 (41.2%)	13 (76.5%)	10 (4-30)	3 (%)
GONB (Total: 77)	SUNCT (n=46)	4 (8.9%)	7 (15.6%)	4 (8.9%)	11 (24.4%)	21 (1-90)	26 (57.8%)
	SUNA (n=31)	4 (14.8%)	6 (22.2%)	4 (14.8%)	10 (37.0%)	30 (7-150)	9 (56.3%)

GONB: greater occipital nerve blockade; IV: intravenous; SD: standard deviation; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms

4.4.2.3. Intravenous dihydroergotamine

Following an initial observation that patients with coexistent chronic migraine (CM) or CH and SUNCT/SUNA receiving IV DHE for the former had complained of dramatic worsening of the latter, we reviewed the case notes of patients assessed between 2008 and 2013 with CM or CH co-existent with SUNCT/SUNA, who underwent at least a trial of IV DHE. Diagnoses were assigned according to the ICHD-II (Headache Classification Subcommittee of The International Headache Society., 2004). Data on the outcomes were gathered from our detailed clinical notes that included copies of the headache diaries that patients admitted for IV DHE are asked to fill prior to, during and after admission. Patients who required repeated courses of IV DHE and reported exacerbations of SUNCT/SUNA whilst on treatment were also prospectively assessed by the same researcher (G.L.) on the ward. The DHE protocol we use is outlined in Table 37.

Table 37: Intravenous Dihydroergotamine regimen for chronic migraine and cluster headache

DAY 1	First dose: 0.5 mg in 100 mL of normal saline over 1 hour
DAY 2–5	Second dose, 8 hours later: 0.75 mg in 250 mL of normal saline over 1 hour. Third and subsequent doses: 1 mg in 250 mL of normal saline over 1 hour every 8 hours for 10 doses with the goal of a cumulative total dosage of 11.25 mg (±1 mg)
Nausea management	Ondansetron: 4 mg IV every 8 hours, 30 minutes before each DHE infusion. Domperidone 10–20 mg orally or by suppository Metoclopramide, if necessary.

IV: intravenously; mL: millilitre; DHE: Dihydroergotamine

The study group consisted of 24 patients with a diagnosis of chronic SUNCT (n= 8) or SUNA (n= 16) coexistent with CM (n= 19) or CCH (n= 5), who had been treated with IV DHE. All the patients were offered the treatment with the aim of improving their

refractory CM or CCH. In 16 out of 24 patients (Table 38), IV DHE had no effect (66.7%); in one patient with CM and SUNCT, IV DHE was significantly effective for the former, but only marginally beneficial for the latter. IV DHE led to a dramatic worsening of the SUNCT/ SUNA in five patients, and it triggered a de novo onset SUNA in two patients (n=7, 29.2%). The main clinical features of the different headaches, investigations, treatments and outcome of IV DHE are summarised in Tables 39 and in Figure 16.

Table 38. Principal diagnosis, headache comorbidities and treatment' outcome in those whose SUNCT/SUNA did not worsen with intravenous dihydroergotamine

	Diagnosis 1	Diagnosis 2	Number of IV DHE treatments	Outcome of IV DHE on CM/CCH	Outcome of IV DHE on SUNCT/SUNA
1	SUNA	CM	Every 4 monthly since 2008	Pain free for 3 months	Ineffective
2	SUNA	CM	1 (2009)	Ineffective	Ineffective
3	SUNA	CM	1 (2008)	Ineffective	Ineffective
4	SUNA	CM	2 (2009)	Ineffective	Ineffective
5	SUNA	CM	1 (2009)	Pain free for 3 weeks	Ineffective
6	SUNA	CM	1 (2008)	30% reduction in headache severity for 2 weeks	Ineffective
7	SUNA	CM	1 (2008)	Ineffective	Ineffective
8	SUNA	CCH	1 (2009)	50% reduction in headache frequency for 1 month	Ineffective
9	SUNCT	CM	Every 4 monthly (2008)	75% improvement for 3-5 months	20% improvement for 1 month
10	SUNCT	CCH	1 (2008)	Ineffective	Ineffective
11	SUNCT	CM	2 (2009)	Pain free for 2 weeks	Ineffective
12	SUNCT	CM	2 (2009-2010)	Pain free for 1 month	Ineffective
13	SUNCT	CM	1 (2009)	80% reduction in headache severity	Ineffective
14	SUNCT	CM SHM	1 (2009)	Ineffective	Ineffective
15	SUNA	CM	2 (2008, 2009)	Ineffective	Ineffective
16	SUNA	CM	2 (2010, 2011)	Pain free for 1 week	Ineffective
17	SUNA	CM	1 (2010)	Ineffective	Ineffective

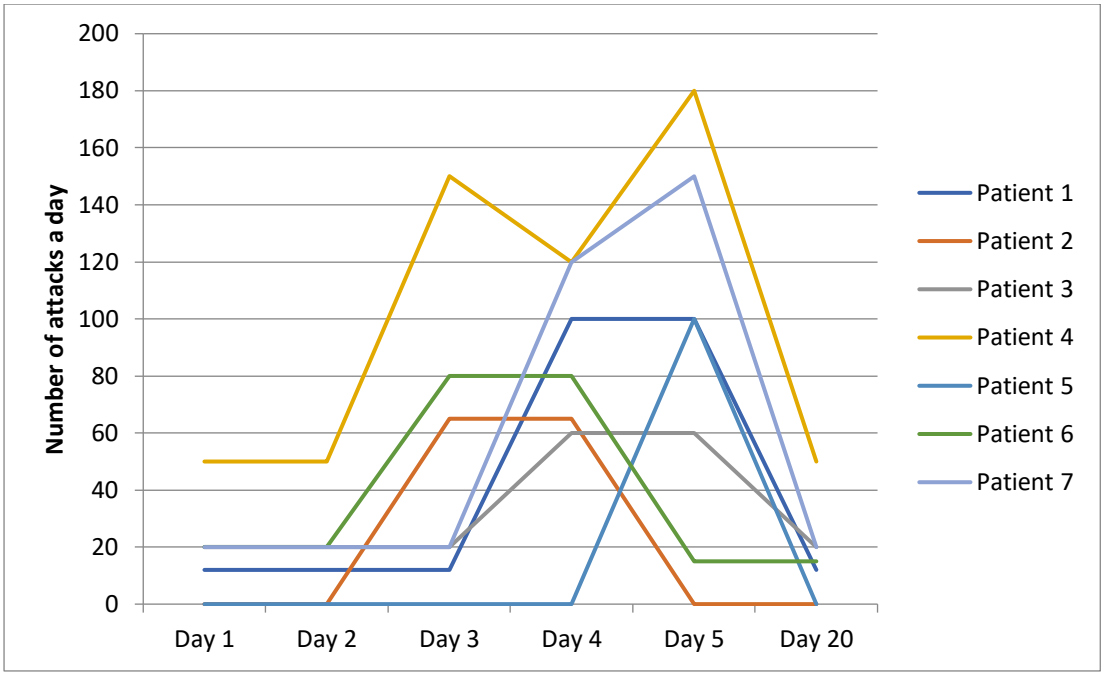
SUNCT: Short lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing; SUNA: Short lasting Unilateral Neuralgiform headache attacks with cranial Autonomic symptoms; CM: chronic migraine; CCH: chronic cluster headache; SHM: sporadic hemiplegic migraine

Table 39: Clinical characteristics of SUNCT/SUNA whose headache worsened during intravenous dihydroergotamine

	Diagnosis	**Sex**	**Age of onset**	**Site of pain**	***Duration**	****Frequency**	**CAS**	**Triggers**
1	Chronic SUNA	F	37	V1	120-180	10-15	L, BN, AF	S + T
2	Chronic SUNCT	F	55	V1	20-300	60-70	L, CI	S
3	Chronic SUNA	F	55	V1, V2	30-120	12-30	L, EO, FR	S + T
4	Chronic SUNCT	F	51	V1, C2-3	180-600	15-80	L, P, BN	S
5	Chronic SUNA	M	44	V1	30-45	20-30	L, BN	S
6	Chronic SUNA	F	40	V1-2, C2	30-300	20-50	L, P	S
7	Chronic SUNCT	F	34	V1, V2, V3	30-120	40-50	L, CI, P	S + T

AF: aural fullness; BN: blocked nose; C: cervical; CI: conjunctival injection; EO: eyelid oedema; F: female; FR: facial redness; L: lacrimation; M: male; P: ptosis; RN: runny nose; S: spontaneous; T: triggered by cutaneous stimulation; V1: ophthalmic division of the trigeminal nerve; V2: maxillary branch of the trigeminal nerve; V3: mandibular branch of the trigeminal nerve.
*Duration: duration of attacks in seconds
**Frequency: frequency of attacks/day

Figure 16. Timing of exacerbation of SUNCT/SUNA during intravenous dihydroergotamine infusion in patients who reported a worsening/new onset of the condition.



Patient 1: A 41-year-old woman was referred to our headache service in 2008 for a headache disorder that fulfils the criteria for CM. Unfortunately, she failed trials of propranolol, amitriptyline, dosulepin, topiramate, sodium valproate, gabapentin, pregabalin, flunarizine and methysergide. Bilateral greater occipital nerve blocks were moderately effective for three to four weeks. She was offered the first IV DHE treatment in 2009. This led to a complete suppression of the migraine for six weeks. Given the limited management options, the treatment had been repeated every three to four months since. In 2010, with no precipitant triggers, a new headache began. The headache phenotype fulfilled the ICHD-II criteria for chronic SUNA (Headache Classification Subcommittee of The International Headache, 2013). An MRI scan of the head with pituitary and trigeminal views was normal. In December 2010 she had a further course of IV DHE for her CM. While the CM improved similarly to the previous times, she experienced a dramatic worsening of the SUNA attacks from day 4 (cumulative DHE dose: 9.25 mg), with three to four attacks/hour lasting two to three minutes each, both spontaneous and triggered by cutaneous stimulation, which disrupted her regular eating and intake of fluids. This exacerbation of SUNCT lasted

for two weeks, before the headache gradually subsided. Subsequently, she had three more courses of IV DHE, as it was the only effective treatment for the migraine, followed by seven days of IV lidocaine (1.5–3.5 mg/kg/h) due to the consistent worsening of the SUNA. An occipital nerve stimulator (ONS) was implanted in 2012 with dramatic improvement of the SUNA and 50% reduction in migraine days.

Patient 2: A 58-year-old woman presented to our headache service in 2010 with a nine-year history of a chronic daily headache fulfilling the ICHD-II criteria for CM (Headache Classification Subcommittee of The International Headache, 2013). She had trials of propranolol, atenolol, amitriptyline, gabapentin, pregabalin, topiramate, methysergide and Onabotulinum toxin type A, with no appreciable improvement. She was therefore admitted for a course of IV DHE in May 2011. She derived a 50% reduction in migraine days from the infusion for a period of six weeks. The treatment was repeated four months later with expected initial improvement in the migraine. However, a new headache started from day three (cumulative DHE dose: 6.25 mg). The new headache phenotype fulfilled the IHS criteria for SUNCT. The DHE infusion was discontinued and the patient was started on IV lidocaine for seven days, with suppression of the attacks during the infusion and for the following two weeks. Subsequently the headache relapsed, leaving the patient with daily SUNCT attacks since then. A 50% reduction in attack frequency was achieved on lamotrigine 500 mg/day. Since DHE was the only treatment providing transient but significant improvement of her CM, she had four further IV DHE treatments four months apart, which consistently led to a dramatic worsening of the SUNCT attacks from days 3–4 of the infusion that were treated with a seven-day course of IV lidocaine.

Patient 3: A 60-year-old woman was referred to our headache service for the management of a headache disorder, which started at the age of 33 with the features of chronic cluster headache (CCH). The CH was managed with a combination of verapamil, topiramate and three monthly greater occipital nerve blocks. However, in 2009, with no precipitating triggers, a new headache began. A diagnosis of chronic SUNA was made after paroxysmal hemicrania was ruled out with an indometacin test. Lamotrigine at high dose as well as carbamazepine and oxcarbazepine did not produce any meaningful benefit. Duloxetine 120 mg/day led to a 50% reduction in the SUNA attack frequency. An MRI scan of the head with pituitary and trigeminal sequences was

normal. In July 2010 she was admitted for an IV DHE treatment for her CCH. Although the CH attacks subsided for eight weeks after discharge, the SUNA attacks worsened dramatically from day 4 of infusion. The attack frequency increased to 60/day on day 4 and for the following two weeks, before they settled. Three months later she had the second IV DHE treatment, which similarly to the first, led to a worsening of the SUNA attacks from day 4. The patient was commenced on IV lidocaine for seven days with complete suppression of the SUNA attacks. Since then, she had further five IV DHE treatments, three months apart, followed by IV lidocaine for seven days, as soon as the SUNA worsened. Since 2012, her SUNA and CCH have been successfully managed with an ONS.

Patient 4: A 55-year-old woman was referred to our headache service for the management of a headache disorder that started at the age of 40 and became progressively more frequent, until it was occurring on a daily basis. At that time, she used to take codeine and paracetamol on a daily basis. The headache had the features of CM and medication-overuse headache (MOH). The CM was managed with a combination of sodium valproate (2 gr daily) and pregabalin (600 mg daily) with partial benefit. In 2010 a new headache disorder, fulfilling the IHS diagnostic criteria for SUNCT, began. The headaches were strictly unilateral on the left side, centred over the retro-orbital region and radiating to the occiput. The SUNCT attacks have been occurring on nearly daily basis with no significant remissions since the onset, suggesting a chronic form. An MRI scan of the head with pituitary and trigeminal sequences was unremarkable. In 2011 she had her first IV DHE treatment for CM management. The headache improved during the infusion and she obtained a 70% reduction in headache days, according to her headache chart, for further six weeks after discharge. The SUNCT attacks remained unchanged. In 2012 she repeated the DHE infusion treatment. From day 3 (DHE cumulative dose: 6.25 mg) she went into a 'SUNCT status', with multiple attacks per hour occurring relentlessly throughout the day for 10 days, before they subsided. She had IV DHE treatments two more times since, followed by IV lidocaine for seven days to control the SUNCT worsening.

Patient 5: A 46-year-old man was assessed in our headache clinic for the management of CCH, which began at the age of 43 with no precipitants. His CH management included high-dose and flow oxygen for the acute attacks (he could not tolerate

sumatriptan 6 mg injections) and verapamil 960 mg, which was moderately effective for CH prevention. The negative indometacin trial ruled out indomethacin-responsive headaches. An MRI scan of the head showed an arterial (superior cerebellar artery) loop pressing on the trigeminal nerve ipsilaterally to the side of the pain. In view of the disappointing response to lithium, topiramate, methysergide, sodium valproate, melatonin, baclofen, greater occipital nerve blocks, which were beneficial for a week only, he was offered an admission for IV DHE. During the infusion period he did not experience any CH attacks, but remarkably, at day 5, after the last DHE dose (cumulative dose: 10.25 mg), he started complaining of a new-onset headache with the features of SUNA. A few hours later the patient was commenced on IV lidocaine, with complete resolution of the SUNA attacks by day seven and no further attacks for the following ten days. Subsequently the SUNA attacks relapsed and have been occurring regularly since. The patient is currently managing the SUNA and the CH attacks with oral preventive treatments and ONS.

Patient 6: A 44-year-old woman has been under our care for two types of chronic daily headaches possibly secondary to a craniopharyngioma operated at the age of 7. The first headache condition has the features of CM complicated by medication overuse. The second headache type fulfilled the ICHD-II criteria for chronic SUNA. Over time she had a few MRI scans which showed stable post-operative changes. Her pituitary function tests showed slightly reduced thyroid-stimulating hormone (TSH) levels. In 2010 she underwent her first IV DHE treatment, which was highly beneficial for the CM, with 60% reduction in headache days for three weeks. However, from day 3 of DHE infusion, her SUNA attacks worsened dramatically, from a baseline of 20/day (last two weeks prior to IV DHE), to approximately 80–100 on day 3. For this reason, she was started on IV lidocaine for eight days, which led to an 80% reduction in the SUNA attacks frequency. She had further five IV DHE treatments every four months, followed by seven days of IV lidocaine to suppress the consistent worsening of the SUNA attacks.

Patient 7: A 39-year-old woman was referred to our service for the management of a chronic headache disorder, which fulfilled the ICHD-II criteria for CM. In 2009, with no precipitants, a new headache developed. A diagnosis of chronic SUNCT was made. An MRI scan of the head with pituitary and trigeminal sequences showed an arterial

loop distorting the trigeminal nerve ipsilaterally to the side of the pain. The combination of lamotrigine and topiramate led to a significant improvement for the SUNCT, though it only marginally helped the CM. However, other preventive treatments including amitriptyline, gabapentin, pregabalin, sodium valproate and greater occipital nerve blocks proved to be ineffective or not tolerated. For this reason, a trial with IV DHE was offered. During the infusion period and for the subsequent eight weeks after discharge, the migraine improved significantly. From day 4 (cumulative DHE dose: 9.25 mg), the SUNCT attacks frequency worsened dramatically to approximately 120 attacks on day 4 and ranging between 100 and 150 during the subsequent two weeks, before they subsided. The patient had five further IV DHE treatments, three months apart, with similar outcome and therefore the DHE treatment was always followed by seven days of IV lidocaine, which promptly suppressed the SUNCT exacerbation.

4.5. Discussion

The aims of this open-label prospective study were to assess the effectiveness and tolerability of medical treatments in SUNCT and SUNA as well as to establish whether SUNCT and SUNA patients respond differently to medical treatments. Our findings suggest that lamotrigine and IV lidocaine are the medications of choice for both SUNCT and SUNA patients and that sodium channel blockers may be the most promising class of drugs in the prevention of headache in these conditions. Response to treatments did not differ between SUNCT and SUNA patients except for topiramate and duloxetine, which were effective in a greater proportion of SUNCT compared to SUNA, and carbamazepine, which was effective in a greater proportion of SUNA compared to SUNCT.

The strengths on this study include the large number of patients included and the prospective nature of the study. These elements have allowed us to study the effect of medications in the largest cohorts of SUNCT and SUNA patients ever described and to compare the response to medical treatments between SUNCT and SUNA cohorts.

The study also has numerous limitations. The main limitation is the lack of a placebo arm. It is possible that the outcome of certain drugs has been exaggerated, partially reflecting a placebo effect. To try and minimise this, we used 50% cut off improvement

that we considered as a clinically relevant outcome measure, to define responders. This, along with the duration of improvements in patients with a protracted preceding chronic phase, may have reduced the likelihood that responders benefited significantly from a medication only by chance. Furthermore, open-label trials have the important role of providing evidence in rare disorders, where conducting randomised-controlled trials can be difficult for reasons related to recruiting participants and ethical issues due to administration of placebo. Another limitation includes the lack of objective tools to collect evidence of headache improvement. In the vast majority of patients, the outcomes of treatment trials were obtained were patients' subjective opinion. However, this caveat reflects the lack of a disease specific and patient-friendly headache charts for SUNCT and SUNA as well as for other short-lasting neuralgiform disorders, namely TN. It is imperative that future research should focus on validating headache diaries specific for short-lasting headache and facial pain conditions like SUNCT, SUNA and TN. Finally, our study group included predominantly patients with the chronic subtypes of SUNCT and SUNA, hence our findings may not be relevant in patients with the episodic form of these conditions. However, the vast majority of SUNCT and SUNA patients display a chronic pattern making our results meaningful for the majority of them.

One of the caveats of the IV DHE study includes its retrospective design. However, patients who required courses of IV DHE and reported exacerbations of SUNCT/SUNA whilst on treatment were assessed with daily clinical observations during admissions. Additionally, their headaches pattern was monitored with prospectively filled headache diaries.

4.5.1. Oral treatments

Our findings confirmed the initial observation that lamotrigine may be the most effective drug for SUNCT, suggesting that it should be considered the first line treatment for this condition. The proportion of responders in our study was slightly less prominent compared to another prospective open-label study conducted in 25 patients, where lamotrigine was found to be effective in 68% of them. However, the definition of efficacy was not detailed in that study, making it difficult to directly compare with our study. Unlike the outcome reported in four SUNA patients from a previous study

(Cohen, 2007), our data confirmed that lamotrigine is the most effective drug in SUNA patients as well, with a similar proportion of responder to SUNCT.

Interestingly, oxcarbazepine was the second most effective medication in SUNCT and SUNA patients. Oxcarbazepine has been reported to be effective in two case reports only thus far. Our findings support the view that oxcarbazepine should be considered as a second option in patients not responding or not tolerating lamotrigine, or as an add-on treatment to lamotrigine, when lamotrigine alone is not sufficient to control the headache. Interestingly carbamazepine was effective in a smaller proportion of patients compared to oxcarbazepine and SUNA patients showed a significantly better response to carbamazepine compared to SUNCT. The difference in outcome between carbamazepine and oxcarbazepine might partly reflect their different tolerability profiles. Furthermore, the different response rate of SUNCT and SUNA to carbamazepine may constitute a selection bias. Indeed, since a significant proportion of SUNA patients was previously diagnoses with TN, it is possible that those who did not report a significant response to carbamazepine were then referred to our clinic where the diagnosis was changed to SUNA. Conversely carbamazepine may not have been considered early in the management of SUNCT patients, given that the majority of them were referred from other neurologists who have traditionally been informed that carbamazepine is ineffective in SUNCT, hence it is possible that carbamazepine was tried in a subgroup of SUNCT patients more refractory to treatment; this may account for the less remarkable outcome.

Unlike the outcome of a previous study where topiramate was effective in 11/21 (52%) SUNCT patients, only a third of SUNCT patients responded to topiramate and a significantly lower proportion of SUNA patients reported meaningful benefit in our study (Cohen, 2007). Similar to the figures of patients on carbamazepine, a significant proportion of SUNCT and SUNA patients had to discontinue topiramate due to side effects. The poor tolerability profile of this drug might have therefore contributed to the disappointing outcome in this study.

A case series where 22 SUNCT and 5 SUNA patients were treated with gabapentin, reported that SUNA may respond better (60 %) than SUNCT (45 %) to this medication (Cohen, 2007). In another series of eight SUNCT patients treated with gabapentin in

monotherapy, five patients became headache free after one month of treatment and three obtained a significant reduction of the headache load (Etemadifar , et al., 2008). These encouraging results were not confirmed in our study, where only approximately 10% of patients benefited significantly from this drug. Very similar outcomes were reported by patients treated with pregabalin, suggesting that perhaps both drugs might be helpful mainly in combination with another drug, rather than in monotherapy (Marziniak , et al., 2009).

In view of positive data in the management of neuropathic pain, duloxetine was tested in 43 SUNCT and SUNA patients (Wernicke , et al., 2006). Surprisingly the proportion of responders to duloxetine was higher than the proportion of responders to topiramate and carbamazepine, suggesting a possible role of duloxetine in management of SUNCT. Moreover, a significantly greater proportion of SUNCT responded to duloxetine compared to SUNA. This difference may be due to the small patient size treated. In view of the better tolerability profile of duloxetine compared to topiramate, our data suggest that duloxetine may be a preferable option to topiramate in patients who fail lamotrigine or oxcarbazepine.

In view of the striking effect of sodium channel blockers, such as lidocaine and lamotrigine in SUNCT and SUNA management, we tested the efficacy of lacosamide and mexiletine. Lacosamide is a novel anti-epileptic drug, which has been shown to be possibly effective in the treatment of painful diabetic neuropathy (Wymer , et al., 2009). Mexiletine is a lidocaine derivative that belongs to the class of 1B antiarrhythmic drugs (Marmura , 2010). Their main mechanism of action in pain disorders involves blocking of voltage-gated sodium channels, although lacosamide enhances the slow-inactivating state of voltage-gated sodium channels, sparing the fast inactivating ones (Niespodziany , et al., 2013). Both the drugs were effective in a significant proportion of SUNCT but also SUNA patients. However, they displayed a poor tolerability profile, with a high discontinuation rates amongst patients. Nonetheless, given that the group of patients that tried both these medications was refractory to all the above-mentioned treatments, these drugs might be considered in refractory cases, where otherwise more invasive approaches would be considered.

The different medical treatments tested in our SUNCT and SUNA patients were stratified in a three-tier algorithm taking into account both the efficacy and side effect profile of these treatments (Table 40).

Table 40. Proposed Algorithm for medical management of SUNCT and SUNA

	Medications (maximum dose)
1st line treatment	Lamotrigine (up to 700 mg/day)
2nd line treatments	Oxcarbazepine (up to 2400 mg/day) Duloxetine (up to 120 mg/day) Carbamazepine (up to 1600 mg/day) Topiramate (up to 800 mg/day)
3rd line treatments	Gabapentin (up to 4800 mg/day) Pregabalin (up to 600 mg/day) Lacosamide (up to 400 mg/day) Mexiletine (up to 1200 mg/day)

GONB: greater occipital nerve blockade; IV: intravenous; SD: standard deviation; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms

4.5.2. Injectable treatments

Our data on IV lidocaine are in line with the results of previous series, showing excellent response in the vast majority of SUNCT and SUNA patients (Cohen, 2007; Matharu , et al., 2003). Other authors administered lidocaine either as an IV infusion, or as a subcutaneous injection for a mean infusion time of six to eight days. Thirteen of their 14 patients had excellent results, with most patients becoming headache-free, suggesting that either route of infusion could be successfully employed (Williams , et

al., 2008). In terms of duration of improvement, in approximately 40% of our patients the benefit lasted for the duration of the infusion only, though in the remaining responders a median length of response of 10 days was shown.

Preliminary data on the outcome of blockade of the greater occipital nerve has been reported as temporary or partially effective procedure in nine SUNCT and SUNA patients (Cohen, 2007). Our findings were less impressive than that reported by Cohen and collaborators. It is possible that this difference is due to the different patients group size. However, when effective, the benefit can last a median of 21 days in SUNCT and 30 days in SUNA patients.

IV DHE has a long history of efficacy in CM, including the medically intractable forms as showed in several open-label and retrospective trials (Raskin , 1986; Silberstein , et al., 1992). IV DHE has also been reported to be effective in CH. Open-label studies in episodic and chronic CH suggested a rapid and sustainable efficacy in the vast majority of patients (Mather, et al., 1991; Magnoux, et al., 2004). However, little is known about the efficacy of DHE in the other TACs (Miller , et al., 2014). To the best of our knowledge, only one case of a SUNCT patient who failed to respond to IV DHE (3 mg) has been reported (Goadsby, et al., 1997). In view of the lack of any published data supporting the efficacy of DHE in SUNCT and SUNA, it is not routine practice to treat these patients with IV DHE. We therefore studied a group of patients who tried IV DHE for the management of their refractory CM or CCH who also suffered with SUNCT or SUNA. While IV DHE led to a remarkable improvement of the baseline primary headache (CM or CCH) in a significant proportion of our refractory patients, it was essentially ineffective in SUNCT and SUNA. Furthermore, in almost a third of our patients IV DHE improved the baseline headache disorder but led to consistent exacerbations of the SUNCT/SUNA condition. These findings suggest that DHE may not represent an effective treatment option for SUNCT and SUNA syndromes; therefore, it should not be considered amongst the armamentarium of transitional treatments for these conditions. Physicians should be careful about administering IV DHE in patients with SUNCT and SUNA as it can worsen these syndromes; additionally, all patients receiving this treatment should be cautioned that IV DHE can lead to de novo onset of SUNCT/SUNA. Interestingly, none of the patients who did not benefit from DHE reported a worsening of the SUNCT/ SUNA. This may be purely

coincidental. It would be rather unlikely that the improvement of the baseline CM or CCH has simply unmasked the coexistent SUNCT/SUNA syndromes, leading to a consequent amplification of the latter. The concomitant coexistence of more than one primary headache disorder in the same individual is usually characterised by a specific response to diagnosis-specific treatments, allowing clear differentiation between headache disorders (Totzeck , et al., 2014). Conversely, it may be possible that certain DHE neurochemical effects are responsible for the exacerbations of SUNCT and SUNA during infusion. DHE has a complex pharmacology. It interacts with multiple receptors, including serotonin, dopamine and a-adrenoceptors, with different degrees of affinity (Silberstein , et al., 2003). Preclinical studies have demonstrated the ability of DHE to prevent the development of neurogenic inflammation in the dura by blocking the peripheral C or A delta fibres (Markowitz , et al., 1988). This effect, similar to the mode of action of triptans, is thought to be facilitated by the high affinity of DHE for 5-HT_{1B} and 5-HT_{1D} receptors located on the dural sensory fibres (Buzzi , et al., 1991). DHE has been shown to be able to bind to central nervous system structures, including the brainstem, dorsal horn of the cervical spinal cord and the cerebral cortex (Goadsby , et al., 1991), as well as possibly acting within the trigeminal nucleus caudalis to inhibit trigeminal neuron activity (Hoskin , et al., 1996). The inhibition of peripheral and possibly central sensitisation via modulation of serotoninergic circuits may explain DHE efficacy in migraine and partly also in CH. SUNCT and perhaps SUNA pathophysiology is thought to be similar to CH and the other TACs, involving a derangement in the hypothalamic-trigeminal circuits, perhaps leading to an abnormally activated trigemino-autonomic reflex (Goadsby, et al., 1997). Nonetheless, neither IV DHE, nor subcutaneous sumatriptan 6 mg, which are highly effective in CH seem to display any effect in SUNCT/SUNA syndromes (Magnoux, et al., 2004; The Sumatriptan Cluster headache Study Group, 1991; Lambru , et al., 2013). It could be argued that the enhanced neuronal serotoninergic tone produced by DHE might be of only marginal importance in SUNCT/SUNA pathophysiology, thus explaining why DHE is ineffective. However, other mechanisms might help explain the opposite therapeutic response of DHE in CH compared to SUNCT/ SUNA. Ergot alkaloids are potent dopamine receptors agonists, with full intrinsic activity at D2 and D3 receptors whereas they are fairly weak antagonists or partial agonists at D1 receptors (Silberstein , et al., 2003). Dopaminergic pathways are thought to play an important role in the pathophysiology of primary headaches including CH, where a downregulation of

hypothalamic dopaminergic neurons has been demonstrated in endrocrinological studies (Lepper , et al., 2013). Hence one possible hypothesis is that dopamine agonists, such as DHE, might help restore the decreased sensitivity of dopaminergic neurons in the hypothalamus in CH patients. The role of the central dopaminergic system in SUNCT and SUNA is unknown. Dopamine agonists including bromocriptine, lisuride, quinagolide and cabergoline have been reported to induce SUNCT attacks in patients with pituitary prolactinoma (Ferrari , et al., 1988; Massiou , et al., 2002; Levy , et al., 2003; Levy, et al., 2005; Larner , 2006). The worsening effect of DHE in some of our patients could support the importance of neuroendocrine mechanisms involving the dopamine prolactin axis in modulating SUNCT and SUNA. However, none of our patients had neuroradiological or laboratory evidence of prolactinoma or hyperprolactinemia. Nonetheless our findings raise the possibility that perturbations in the dopamine-prolactin axis may be important even in primary SUNCT/SUNA syndrome. It is conceivable that specific neuroendocrine pathways involving the hypothalamic dopaminergic neurons may be capable of activating SUNCT pathophysiology at least in a subgroup of patients. According to this hypothesis, antidopaminergic drugs may then be useful in at least a sub-group of SUNCT and SUNA patients, by restoring the balance in the dopamine neurons. However, there are no data in the literature on this subject. In this study, domperidone was used in variable daily doses for the management of nausea, not only by all the patients who worsened with IV DHE, but also by the remaining patients included in this study. Moreover, domperidone only minimally penetrates the blood-brain barrier, so it would be difficult to postulate any involvement of this drug in the worsening of the SUNCT/ SUNA attacks in our patients. Metoclopramide was rarely needed by most of our patients.

In summary, the scarcity of reports on potentially effective medications, has prevented the delineation of effective management options for SUNCT and SUNA. Open-label observational studies are important for generating hypotheses on medications that could be studied in future better-designed clinical trials. Our study supported, in a large cohort, the efficacy of medications that were reported to be beneficial in previous studies, such as lamotrigine and shed light on the possible role of other drugs with very little or no evidence of efficacy in the literature, such as oxcarbazepine and duloxetine. The ultimate confirmation of the utility of these drugs in the management of SUNCT and SUNA syndromes should come from randomized double-blind, placebo-controlled

clinical trials. However, generating meaningful data from placebo-controlled trials in rare painful disorders is often challenging, for methodological reasons related to low numbers of patients to recruit and for ethical reasons, such as exposing patients with a severe pain disorder to placebo for extended periods.

4.5.3. Mechanisms of action of drugs effective in SUNCT and SUNA and pathophysiological implications

The clinical similarities between SUNCT, SUNA and TN, have led to testing neuromodulators with a known effect in neuropathic pain as prophylactic therapies. Whereas drugs like topiramate, gabapentin and pregabalin have yielded rather disappointing effects in SUNCT/SUNA and TN, drugs such as, lamotrigine, oxcarbazepine, IV lidocaine and carbamazepine, have been reported to be effective in all these disorders. Moreover, duloxetine, lacosamide and mexiletine seem to be new promising therapeutic tools in SUNCT and SUNA treatment, though they have not been reported in TN yet. Amongst their multiple mechanisms of action, all these drugs have in common the inhibition of voltage-gated sodium channels that in turn inhibiting the release of glutamate from glutamatergic neurons (Bhattacharya , et al., 2009). In addition, lidocaine, lamotrigine, carbamazepine and oxcarbazepine have been shown to be able to inhibit nicotinic acetylcholine (Ach) -evoked current in neurons, suggesting their contribution in inhibition of parasympathetic ganglionic transmission (Cuevas , et al., 1994; Zheng , et al., 2010; Di Resta , et al., 2010).

A novel pathophysiological model that accounts for the clinical similarities between SUNCT, SUNA and TN, has been recently proposed (Lambru , et al., 2014). According to this model, SUNCT, SUNA and TN pathophysiology may be characterized by different degrees of interaction between peripheral and central mechanisms, namely focal demyelination of the trigeminal sensory root, due to vascular compression, disinhibition of the trigemino-autonomic reflex and posterior hypothalamic region dysfunction. Differences in the clinical phenotype between SUNCT, SUNA and TN in terms of presence and degree of cranial autonomic symptomatology, site and duration of the attacks and their triggerability may reflect different degree of involvement of similar central and peripheral pathways. In this context, the efficacy of sodium channels

blockers in SUNCT and SUNA and TN suggest a common denominator in the pathogenesis of these conditions, with sodium channels dysfunction being an attractive candidate. In TN, a downregulation of Nav1.7 and upregulation of Nav1.3 has already been reported (Siqueira , et al., 2009). In addition, the relatively high efficacy of lamotrigine in SUNCT/SUNA and carbamazepine in TN may be attributed to further mechanisms, perhaps their different effect on cholinergic parasympathetic pathways at central (hypothalamic) and peripheral (sphenopalatine ganglion) levels of the two drugs.

4.6. Conclusion

SUNCT and SUNA seem to have similar responses to pharmacological treatments. The higher proportion of SUNCT responders with topiramate and duloxetine along with the higher response of SUNA with carbamazepine may be due to patient selection bias. It also possible that since the SUNA patients experienced less cranial autonomic symptoms and often described pain in V2-V3, they responded better to carbamazepine because they may share biological mechanisms with TN. Lamotrigine should be considered the drug of choice for the management of SUNCT and SUNA. Oxcarbazepine, duloxetine and topiramate can be useful options for patients who fail to respond to lamotrigine or as add-on options. IV lidocaine is an extremely effective treatment for patients with frequent, severe attacks, but it may not be available in every hospital. Conversely, GONB is a more minimally invasive procedure but only effective in 1/3 of patients. When effective though, it may produce significant headache relief for a clinically relevant duration of time. IV DHE seems to be ineffective and in some cases, may exacerbate the SUNCT/SUNA headache phenotype, hence should be not offered in SUNCT and SUNA. Ultimately more definitive answers on the management of SUNCT and SUNA should come from controlled studies. SUNCT and SUNA response to drugs is similar to TN and differs from the other TACs. The efficacy of sodium channels blockers in the former conditions raises the possibility that one of the biological hallmarks in SUNCT, SUNA and TN may be a dysfunction in certain sodium channels. Thus, sequencing of sodium channel genes in SUNCT/SUNA patients may provide additional insight into this complex disorder and eventually lead to the development of more specific drugs, which can convincingly relieve the symptoms of these highly disabling conditions.

Chapter 5. The Surgical Management of SUNCT and SUNA: Prospective Single Centre Open-label Studies

5.1. Abstract

A small undetermined proportion of chronic SUNCT and SUNA patients can be intractable to medical therapies. The surgical management of SUNCT/SUNA is controvartial and little is known on the role of surgical treatments deemed effective in other TACs and in TN. We present outcomes of two uncontrolled open-label prospective studies respectively in a group of medically-intractable SUNCT and SUNA with occipital nerve stimulation (ONS) and in another group of medically-intractable SUNCT and SUNA with trigeminal microvascular decompression (MVD). ONS at a median follow-up of 38 months (range 24-55 months) led to a marked headache improvement in eight of the nine patients implanted (89%). Four of nine patients became and remained completely pain-free for the whole duration of the follow-up except when the stimulator was switched off or malfunctioned. Four patients reported a marked improvement in their condition but were not rendered pain-free. Two of these four patients estimated that their headaches had improved by 95%, while the headache score, derived from the prospective headache diaries, showed an improvement of 97% and 98% in these patients. The other two patients estimated that their headaches had improved by 50-60%, though the headache scores revealed an improvement of 81% and 96%. One patient did not report any benefit from the stimulator at 24 months' follow-up and opted to have the ONS explanted. Trigeminal MVD was tried in ten SUNCT and SUNA patients with MRI evidence of ipsilateral trigeminal neurovascular conflict. At a mean follow-up fo 19.6 months (range: 12-36 months), seven patients (70%) became headache free after the operation. Five of the seven patients (71.4%) remained headache-free at the last follow-up. The remaining two patients were headache-free respectively for 9 and 12 months before the headache relapsed. There were no major surgical and post-surgical complications. These studies support that ONS and trigeminal MVD may be safe and effective therapies for refractory SUNCT and SUNA patients who failed conventional treatments.

5.2. Introduction

The vast majority of patients with SUNCT and SUNA syndromes display a chronic headache pattern, with attacks occurring daily or nearly daily, thereby having a significant impact on the quality of life of the majority of these patients. In addition, the limited arsenal of effective medical treatments means that a significant minority of sufferers prove to be refractory to medical management. The extent of this problem is not as clearly defined as in other commoner primary headache disorders such as migraine and CH and no consensus on the definition of "refractory" SUNCT and SUNA exists, it is nonetheless commonly observed in clinical practice that a significant proportion of SUNCT and SUNA patients are refractory to medical management. For these patients, surgical approaches need to be considered. Evidence on surgical options available in SUNCT and SUNA are limited and quality of the studies rather poor (Lambru , et al., 2013).

Several destructive or invasive approaches targeting the trigeminal nerve have been tried in these patients. The effectiveness of these procedures is uncertain as the reported results are often conflicting and the follow-up period is generally very limited. These procedures are also known to be associated with various complications including corneal anesthesia, anesthesia dolorosa, jaw deviation, diplopia, and vestibular disturbance (Harries , et al., 2011).

Neurostimulation therapies that entail stimulation of peripheral or central nervous system targets have emerged as promising approaches for the management of medically intractable headache disorders. Based upon the finding of posterior hypothalamic region activation in SUNCT (May , et al., 1999), three medically intractable SUNCT patients treated with ventral tegmental (VTA) area deep brain stimulation (DBS) have been reported in the literature. The therapy led to a significant improvement of the headache load at follow-ups ranging between 12 to 18 months, with only minor adverse events, suggesting that DBS of the VTA (previously considered to be the posterior hypothalamic region), could be a therapeutic option for medically refractory SUNCT and SUNA patients (Leone , et al., 2005; Lyons , et al., 2009; Bartsch , et al., 2011). Recently the first case series of 11 SUNCT and SUNA patients treated with VTA DBS with a long follow-up was published. The vast majority of patients (82%) benefited

significantly from the surgery with only one patient requiring removal of the system due to wound infection (Miller , et al., 2016). However, given the potentially fatal complications of DBS, peripheral neurostimulation targets have been more recently tested in TACs. Open label case series using ONS has shown promising evidence of safety and efficacy in the management of refractory CH and HC (Magis, et al., 2012). In view of the clinical and pathophysiological similarities between the TACs and SUNCT/SUNA, it is reasonable to postulate that ONS may also be beneficial for medically refractory SUNCT and SUNA syndromes.

Another surgical approach that finds its rationale in the clinical similarities between SUNCT, SUNA and TN, is microvascular decompression (MVD) of the trigeminal nerve. To date, there are ten case reports and one case series of nine patients with SUNCT/SUNA who have had trigeminal MVD. Twelve out of nineteen (63%) SUNCT and SUNA patients treated with trigeminal MVD reported complete relief of headaches at a mean follow-up of 14 months (range: 0.5 – 32 months). Transient complications were reported in five cases (wound infection, chest infection, vertigo, jaw pain and dural sinus bleed). More persistent symptoms of hearing loss and ataxia were seen in 2/19 (11 %) of cases (Sebastian , et al., 2013).

In this chapter we sought to determine the following:

1. Long-term safety and efficacy of ONS for the management of medically refractory SUNCT and SUNA syndromes.

2. Safety and efficacy of MVD of the trigeminal nerve in SUNCT/SUNA.

We hypothesised that both the procedures may have an important role in the surgical management of these conditions.

5.3. Occipital nerve stimulation in SUNCT and SUNA

5.3.1. Methods

5.3.1.1. Case material

Patients with medically intractable, chronic SUNCT and SUNA under our care were offered an occipital nerve stimulator. The diagnosis of SUNCT was established according to International Classification of Headache Disorders (ICHD-2) criteria, while the proposed appendix criteria were used for the diagnosis of SUNA (Headache Classification Subcommittee of The International Headache Society., 2004). All patients fulfilled the standard diagnostic criteria, except for one SUNA patient who had facial redness and sweating but none of the cranial autonomic features delineated in the standard criteria. While all patients fulfilled the standard diagnostic criteria for duration of attacks, some patients also had longer lasting attacks, which have been described in the largest clinical series of SUNCT and SUNA patients (Cohen , et al., 2006). All patients had a trial of oral indometacin or a modified indo-test (100 or 200 mg of intramuscular indomethacin versus saline placebo) (Matharu , et al., 2004) to rule out indomethacin-responsive headaches. Patients with attacks lasting longer than four minutes also had trials of high flow oxygen and subcutaneous sumatriptan, which can be beneficial in cluster headache but are ineffective in SUNCT and SUNA.

Patients were considered suitable for ONS if they had highly disabling, medically intractable, chronic SUNCT or SUNA for at least two years. Unlike in cluster headache, the concept of medically refractory SUNCT/SUNA is not clearly defined in the literature (Mitsikostas, et al., 2014). In this study patients were considered medically refractory if they failed to respond to adequate trials, at appropriate doses for an appropriate length of time, of lamotrigine, topiramate, gabapentin, pregabalin, and one of either carbamazepine or oxcarbazepine. These agents were selected on the basis of the available evidence of the efficacy of these agents (Cohen, 2007; Williams , et al., 2008) and our experience. A failed trial was defined as an unsatisfactory response,

development of intolerable side effects, or contraindication to the use of the agent.

A temporary stimulation trial is performed for several days before the permanent implantation in some centers, with a view to improving the selection of candidates for permanent stimulation. This practice is not used at our unit and therefore it was not a selection criterion. Similarly, most patients had a greater occipital nerve blockade (GONB), with a mixture of 2 mL of 2% lidocaine and methylprednisolone 80 mg, but the response to the GONB was not a selection criterion. The patients were given implants on compassionate grounds. The study was an audit of outcomes, and as such, it did not require ethics board approval under UK guidelines. All patients gave written informed consent.

5.3.1.2. Surgical procedure

The anatomy of the nerves of the occipital region has been well described (Natsis , et al., 2006). There are three nerves that innervate the occipital region, namely the greater, lesser and least occipital nerves. The greater occipital nerve is a branch of the C2 spinal root. It proceeds between the inferior oblique and the semispinalis capitis muscle in a superomedial fashion. The nerve then crosses above the rectus capitis posterior major muscle and arises medial to the semispinalis capitis muscle, which it occasionally pierces. It then penetrates through the trapezius muscle to join the occipital artery. It provides innervations to an occipito-parietal area 6–8cm wide and ascending paramedially from the subocciput to the vertex (Poletti , 1991). The lesser occipital nerve is composed of branches of the C2 and C3 spinal roots. It runs lateral to the greater occipital nerve, crossing over the sternocleidomastoid muscle, and courses superolaterally towards the region behind and above the ear. The medial branch of the posterior division of the C3 root gives off a branch called the least occipital nerve, which pierces the trapezius and ends in the skin of the lower part of the back of the head. It lies medial to the greater occipital nerve and communicates with it. There is an anatomical and functional overlap of trigeminal and cervical afferents throughout the trigeminocervical complex from the level of the caudal trigeminal nucleus to at least the C2 segment (KERR , et al., 1961). This convergence explains how nociceptive

activation at either end of this structure can result in both trigeminal and cervical distribution pain.

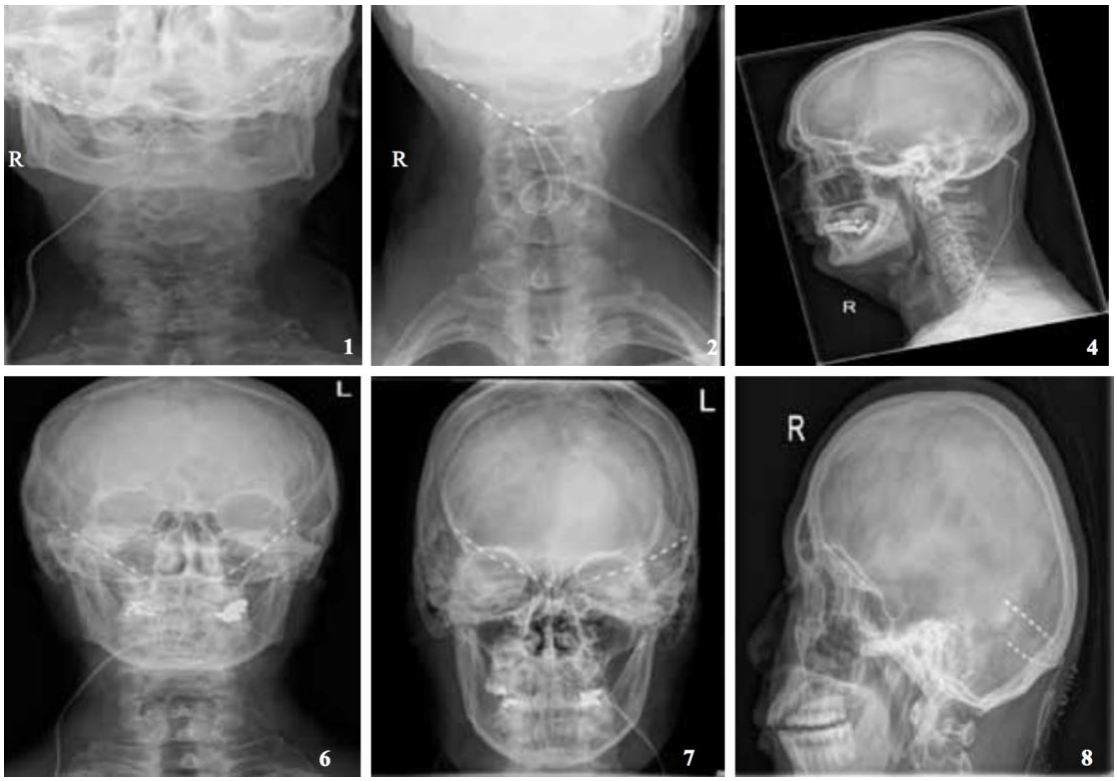
Bilateral ONS electrodes, leads, and battery were implanted after informed consent was obtained. The implant technique has evolved overtime in our center. In earlier SUNCT and SUNA cases, the insertion point was at the spinous process of C1, passing laterally and superiorly, using a Tuohy needle curved to follow the cervical fascia. However, in order to reduce possible complications such as unwanted stimulation of the neck muscles, which can limit the amplitude of stimulation that can be applied and erosion of the electrode tip through the skin, the implantation level in more recent cases has been aimed at stimulating the greater occipital nerve, as it emerges superior to the nuchal line. This means that the electrode is superior to the cervical muscles, thus reducing the chance of unwanted muscle stimulation. Since the electrode can be passed in the loose subgaleal plane at this level, we did not use a sharp insertion technique (Tuohy needle) but instead passed the electrodes using a blunt plastic tube, thus reducing the chance that the tip would be tunnelled closer to the skin than intended, at the extreme lateral tip of the electrode. Figure 15 illustrates patients operated with the earlier technique, where electrodes originated from the level of the spinous process of C1 (Cases 1, 2, 4, 6) and those implanted using the later technique, with electrodes placed superior to the nuchal line (Cases 7 and 8). It is unlikely that this difference in the implant technique could account for a difference in therapeutic outcome since the target is still stimulation of the greater occipital nerve. The difference was only aimed to reduce ONS-related adverse events.

A single-stage procedure in 2 parts was used to allow an intraoperative stimulation trial. The first part was performed under local anesthetic and gentle sedation, with care taken to avoid anesthetizing the occipital nerves. The patient was placed in a lateral position and a sterile field was established. A midline posterior cervical incision was made and bilateral cylindrical-style, octad electrodes (Medtronic, Minneapolis, MN) were introduced using the two different techniques described above. A dual program pulse generator (Medtronic Prime Advanced® Medtronic) was then used to test stimulation and confirm that paresthesias were felt bilaterally. The second part of the insertion was done under a general anesthetic. The electrodes were looped and anchored to the cervical fascia, then tunneled to a lateral cervical or subclavicular skin crease

intermediate incision. A left subclavicular or abdominal incision was made (according to the patient's preference) to form a pocket to implant the pulse generator. Electrodes were tunneled to the intermediate incision and a pair of extension leads (Medtronic) was attached. Silicone sheaths were used to protect the lead connections. A topical antibiotic cover with gentamicin was introduced around the pocket and the incisions were closed.

Patients were provided remote controls and instructed how to use them to communicate with the implanted pulse generators. They could adjust their stimulator settings with the remote control, although the pulse generators were programmed to provide continuous stimulation. Patients could turn the stimulator on or off, and vary the pulse width, frequency, or amplitude, although most of them tended only to vary the amplitude. The polarity of the electrodes was adjusted during follow-up visits to achieve comfortable bilateral paresthesias in the occipital region. Patients remained in the hospital for several days after implantation before being discharged.

Figure 17. Electrodes placement in SUNCT and SUNA patients treated with occipital nerve stimulation



X-rays for patients 3, 5 and 9 are not available. However similar electrode positioning have been used.

5.3.1.3. Follow-up and Data Collection

Data were collected prospectively from patients' records, outpatient visits, inpatient admissions, mail, and telephone and included demographics, diagnosis, previous and current treatments, ONS settings, pre- and post-implantation headache characteristics, patients' estimates of change in headaches, and complications. Patients were asked to fill in a headache diary in order to record the frequency, severity on a verbal rating scale (VRS; 0 = no pain to 10 = very severe pain) and duration of attacks for four weeks before implantation and two weeks prior to each postoperative outpatient follow- up visit. These sessions were scheduled every three months for the first year and every six months thereafter. Extra visits or phone consultations were scheduled as required. These prospectively collected data were used at each follow-up to calculate a "headache score," which has been validated elsewhere (Levy , et al., 2004), using the following formula: Σ (duration X severity) of each attack for a 2-week period. This score takes into account not only changes in the frequency of attacks, but also any variation in severity and duration of attacks, giving a comprehensive measure of the response to the treatment. Since specific tools for measuring the disability of TACs have not been alidated yet, disability was assessed and monitored using the Migraine Disability Assessment Scale (MIDAS) (Stewart , et al., 1999) and the Headache Impact Test-6 (HIT-6) (Kosinski , et al., 2003). MIDAS and HIT-6 have been used extensively to assess primary headache disorders and have already been used to assess the disability of patients with CH and hemicrania continua (HC) treated with ONS (Schwedt , et al., 2007; Burns , et al., 2008). As per the recommendations by Leone and collaborators (Leone , et al., 2007), quality of life and mental state were assessed pre- and post-surgery. The Short Form 36 (SF- 36) was used to assess health-related quality of life at baseline and after stable improvements in those who responded, or after a year of continuous stimulation in those who did not respond (Mueller , et al., 2011). The Hospital Anxiety (HAD-A) and Depression (HAD-D) scales were used to evaluate the presence and degree of anxiety and depression before and after surgery (Mykletun , et al., 2001). All data were collated at baseline and after every postoperative follow-up in an electronic database (Microsoft Excel® spreadsheet, Microsoft Corporation, Redmond, WA).

5.3.2. Results

Five women and four men with a median age at the operation of 52 years (range: 33–74 years) received stimulator implants (Table 41). Six patients had SUNCT and 3 had SUNA. The median duration of the disorder was 7 years. Three SUNCT and one SUNA patient presented with the episodic form, which subsequently evolved into the chronic form. The remaining patients were chronic from the onset. The median duration of the chronic phase was 4 years. Table 42 shows the headache frequency, severity, and duration characteristics as reported by the patients prior to ONS. All patients had a brain magnetic resonance imaging scan, which revealed evidence of ipsilateral neurovascular conflict in 2 patients (Cases 1 and 6).

Table 41. Patient demographics

	Age at time of implant	Sex	Subtype of diagnosis	Duration from onset to time of implant (years)	Duration of chronic phase at time of implant (years)
1	74	M	Secondary chronic SUNCT	7	4
2	61	F	Primary chronic SUNA	4	4
3	44	M	Primary chronic SUNCT	7	7
4	52	M	Secondary chronic SUNCT	17	9
5	53	F	Secondary chronic SUNCT	7	4
6	56	M	Primary chronic SUNCT	8	8
7	34	F	Primary chronic SUNA	2	2
8	33	F	Secondary chronic SUNA	6	3
9	49	F	Primary chronic SUNCT	22	22
Median (range)	52 (33-74)	M=4 F=5	SUNCT=6 SUNA=3	7 (2-22)	4 (2-22)

F: female; M: male; Primary chronic: chronic form of disorder from onset; Secondary chronic: episodic form of disorder that subsequently evolved into chronic form; SUNA: short-lasting unilateral neuralgiform headache attacks with cranial autonomic features; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

Table 42. Clinical features

	Diagnosis	Side/Site of the attacks	Quality of pain	Duration of attacks seconds (range)	Frequency of attacks/day (range)	Triggered spontaneous or both, attacks
1	SUNCT	R/V1	Stabbing, burning, sharp	660 (120-900)	46 (0-97)**	B
2	SUNA	L/V1	Stabbing, sharp, pulsating	240 (120-600)	33 (8-52)	B
3	SUNCT	R/V1	Stabbing	32 (20-1920)	30 (16-40)	B
4	SUNCT	L(R)/V1 + occipital	Stabbing, jabbing, sharp	120 (60-360)	12 (3-20)	S
5	SUNCT	L/V1-V2	Stabbing	25 (5-75)	90 (48-150)	T
6	SUNCT	R(L)/V1	Stabbing, sharp	120 (60-600)	30 (6-103)	S
7	SUNA	R/V1-V2	Shooting, sharp	5 (1-1800)	20.5 (16-42)	B
8	SUNA	L(R)/V1 + occipital	Stabbing, sharp	120 (5-600)	79 (5-154)	S
9	SUNCT	R/V1+ retro auricular	Stabbing, shooting, burning	10 (5-1800)	72 (18-96)	S

B: both Triggered and spontaneous attacks; F: female; L: left side; (L): Attacks can present occasionally on the left side; M: male; R: right side; (R): Attacks can present occasionally on the right side; REZ: root entry zone; S: Spontaneous attacks only; SCA: superior cerebellar artery; T: Attacks triggered from triggers zones; V1: Cutaneous territory innervated by the first division of the trigeminal nerve; V2: Cutaneous territory innervated by the second division of the trigeminal nerve; **Patient 1 had a maximum of 3-5 pain free days /month

All patients failed to obtain sustained or substantial benefit from preventive medications administered as single or combination therapy, as well as from drugs such as pregabalin, mexiletine, and melatonin, which although lacking published evidence of efficacy, can occasionally be effective in these disorders (Table 43). All patients

showed a very good, albeit short-lived, response to intravenous lidocaine, while only three patients obtained transient benefit from GONB. Five patients had a single-blinded placebo-controlled indomethacin test and four had a course of oral indomethacin at doses of 150 to 225 mg daily, showing no effect on their SUNCT/SUNA attacks (Table 44). Three out of seven patients who had a GONBs, experience some headache improvement. However, when the procedure was repeated it did not lead to any appreciable improvement (Table 45). Seven patients tried subcutaneous sumatriptan 6 mg or high-flow oxygen inhalation or both to abort their SUNCT/SUNA attacks without any appreciable benefit.

Table 43. Preventive treatments tried in SUNCT and SUNA patients without significant improvement and respective doses (total mg per day)

	LMG	**TPM**	**GBP**	**PGB**	**CBZ**	**OXC**	**MXT**	**MLT**	**Other drugs (mg/day)**
1	350	175	4500	500	NK	NT	NT	12	Amitriptyline (NK) Lithium (NK)
2	300	700	2400	350	1600	NT	1200	9	Amitriptyline 25 Tizanidine (NK)
3	400	200	3600	600	NK	NK	NT	NT	Amitriptyline 20 Sertraline 100
4	300	75	900	300	NT	1200	NT	12	VPA 600 Propranolol (NK)
5	400	150	3000	600	NK	1500	600	9	Phenytoin (NK) Propranolol 120
6	50	125	3000	300	300	NT	NT	12	VPA 600 Pizotifen 1.5 Propranolol 160
7	250	150	3600	600	NT	1500	NT	15	Amitriptyline 50 VPA 1000
8	200	200	3600	400	NT	1200	NT	12	Amitriptyline 50 Pizotifen 3
9	500	400	3600	600	NK	2400	1200	NT	Amitriptyline 150 VPA 800

For this group, side effects were the usual reason for not attaining maximum doses. NK: dose not known; NT: not tried. CBZ: carbamazepine; GBP: gabapentin; LMG: lamotrigine; MLT: melatonin; MXT: Mexiletine; PGB: pregabalin; TPM: topiramate

Table 44. Acute and transitional treatments tried for SUNCT and SUNA, and therapeutic responses: indometacin and lidocaine infusion

	Indometacin (duration of trial)	**Lidocaine infusion (given over 7-10 days)**		
		SUNCT/SUNA improvement	**Number given**	**Duration of response**
1	225 mg (2 weeks)	Pain free	2	During infusion only
2	225 mg (3 weeks)	Pain free	1	During infusion only
3	150 mg (2 weeks)	Moderate improvement	1	During infusion only
4	225 mg (4 weeks)	Pain free	1	During infusion only
5	100 mg (indo-test)	Pain free	1	During infusion only
6	100 mg (indo-test)	Moderate improvement	1	During infusion and 2 weeks afterwards
7	100 mg (indo-test)	Moderate improvement	1	During infusion only
8	100 mg (indo-test)	Moderate improvement	1	During infusion only
9	200 mg (indo-test)	Pain free/Moderate improvement	4	During infusion only

Indo-test: double blinded intramuscular indometacin vs normal saline [22] ; SUNA: short-lasting unilateral neuralgiform headache attacks with cranial autonomic features; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

Table 45. Transitional treatments tried for SUNCT and SUNA, and therapeutic responses: greater occipital nerve blockades

	GON injection (lidocaine and steroids)		
	SUNCT/SUNA improvement	**Side of injection**	**Duration of response**
1	Yes	R×2	3 days/no response
2	Yes	L×2	5 days/no response
3	No	R	-
4	No	L	-
5	NT	-	-
6	Yes	R×2	3 days/no response
7	NT	-	-
8	No	L	-
9	No	R	-

GON: greater occipital nerve blockade; L: left side; NT: not tried; R: right side; SUNA: short-lasting unilateral neuralgiform headache attacks with cranial autonomic features; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing;

The characteristics of SUNCT and SUNA attacks pre- and post-ONS, derived from prospective diaries, are listed in Table 46. At a median follow-up of 38 months (range 24-55 months) after the stimulator implantation, eight of the nine patients (89%) reported a marked improvement of their condition. Four of nine patients became and remained completely pain-free for the whole duration of the follow-up except when the stimulator was switched off or malfunctioned. Four patients reported a marked improvement in their condition but were not rendered pain-free. Two of these four patients estimated that their headaches had improved by 95%, while the headache score, derived from the prospective headache diaries, showed an improvement of 97% and 98% in these patients. The other two patients estimated that their headaches had improved by 50-60%, though the headache scores revealed an improvement of 81% and 96%. One patient did not report any benefit from the stimulator at 24 months'

follow-up and opted to have the ONS explanted. All patients, except the one who failed to respond, would recommend the use of ONS to another patient in a similar situation.

Table 46. Effect of occipital nerve stimulation on SUNCT/SUNA attack frequency, severity and duration

	Follow-up after ONS (months)	Median frequency/day (range)		Median severity on Verbal Rating Scale (range)		Median duration in seconds (range)		Daily headache score		Percentage of improvement of the headache score	Patients estimation of benefit
		Before	After	Before	After	Before	After	Before	After		
1	43	46 (0-97)	Pain free	7 (3-10)	Pain free	660 (120-900)	Pain free	50135	0	100%	100%
2	55	33 (8-52)	Pain free	10 (7-10)	Pain free	240 (120-600)	Pain free	15904	0	100%	100%
3	24	30 (16-40)	Pain free	9 (7-10)	Pain free	32 (20-1920)	Pain free	13741	0	100%	100%
4	52	12 (3-20)	1 (0-2)	7 (5-10)	5 (4-8)	120 (60-360)	120 (53-360)	2444	97	96%	60%
5	55	90 (48-150)	41 (26-50)	10 (8-10)	5 (4-10)	25 (5-75)	23 (3-68)	5592	1075	81%	50%
6	38	30 (6-103)	Pain free	8 (5-10)	Pain free	120 (60-600)	Pain free	12235	0	100%	100%
7	28	21 (16-42)	7 (0-12)	7 (5-8)	5 (3-8)	5 (1-1800)	5 (1-20)	1920	64	97%	95%
8	28	79 (5-154)	9/week (6-12/week)	10 (7-10)	8 (6-10)	120 (5-600)	120 (5-240)	15049	287	98%	95%
9	24	72 (18-96)	74 (15-91)	10 (6-10)	10 (6-10)	10 (5-1800)	10 (5-1500)	11038	11019	0%	0%
Median (range)	38 (24-55)	33 (0-154)	1 (0-97)	9 (3-10)	5 (3-10)	120 (5-1800)	5 (1-1500)	12235	64	98% (Mean 87%)	99% (Mean 78%)

There was a marked improvement in health-related quality of life, disability, and affective scores following ONS. The median baseline scores in all SF-36 domains were low, particularly in role functioning-physical (RP), bodily pain (BP) and social functioning (SF). Following ONS, patients reported a remarkable improvement in all 8 domains, with mean scores similar to the British normative SF-36 mean scores for adults aged 55-64 years old (Table 47).

Table 47. Effect of occipital nerve stimulation on health-related quality of life

	SUNCT/SUNA patients		British normative data
	Pre-ONS Mean, ±SD, median (range)	Post-ONS Mean, ±SD, median (range)	Mean, ±SD
PF	52±22 60 (30-85)	79±26 85 (30-100)	80±22
RP	0±0 0 (0)	64±48 100 (0-100)	79±36
BP	4±5 0 (0-10)	60±37 50 (10-100)	79±24
GH	30±28 10 (10-80)	71±18 70 (40-100)	68±23
V	27±28 10 (0-60)	59±30 75 (0-80)	63±20
SF	14±20 0 (0-50)	75±37 100 (0-100)	87±23
RE	33±33 33 (0-100)	81±38 100 (0-100)	86±30
MH	35±22 44 (0-64)	77±34 88 (0-100)	78±17

PF, Physical Functioning; RP, Role Functioning-Physical; BP, Bodily Pain; GH, General Health; VT, Vitality; SF, Social Functioning; RE, Role Functioning-Emotional; MH, Mental Health.

The median baseline MIDAS and HIT-6 scores were 182 (range 150–270) and 74 (range 68–78), respectively; these scores are consistent with severe disability. When the response to ONS had reached a plateau, the median MIDAS and HIT-6 scores had reduced to 20 (range 0–180) and 52 (range 36–78), respectively, which are consistent with moderate disability. The anxiety (HAD-A) and depression (HAD-D) scores were within the severely impaired range for the majority of patients at baseline. Following ONS, the median HAD-A score reduced from 13 (range 8–16) to 6 (range 0–18) while the median HAD-D score reduced from 11 (range 8–16) to 5 (range 0–16).

Patients who responded to ONS were able to discontinue or reduce their preventive medications for SUNCT/SUNA. Six of the nine patients were able to discontinue all preventive treatments. One patient (Case 7) was able to maintain significant improvement of her SUNA with a slight reduction of the doses of lamotrigine from 250 mg (pre-ONS) to 100 mg (post-ONS) and oxcarbazepine from 1500 mg (pre-ONS) to 1200 mg (post-ONS), but further reduction led to recrudescence of attacks; he therefore opted to continue on the reduced doses of these agents. Case 5 reported a marked benefit with ONS but was unable to reduce the dose of mexiletine (600 mg) without a worsening of attacks.

Most patients obtained a clear benefit from the stimulator after a few days (median 11 days), though it took a few months to achieve maximum improvement (median 3.5 months). To ensure that the clinical improvement was related to ONS, the stimulator was switched off (with patient consent) in Patients 1, 3 and 5, which in all cases led to a worsening of the attacks within 48 hours. There was also worsening of the headaches in Patients 1, 2, 4, and 7 following battery failure; in most cases this was experienced within 1–5 days of failure though, interestingly, Case 2 remained pain-free for 3 months after the battery ran out, following 34 months of continuous stimulation. Case 9, who was unresponsive to ONS, did not report any change in her headache when the stimulator was switched off. The other two patients declined to switch the stimulator off.

The range of stimulation parameters and the patterns of use are reported in Table 7. The stimulator was switched on continuously in all patients. The patients experienced occipital paresthesia, which is known to be a requirement for clinical effect. Four patients reported adverse events from ONS (Table 48). Electrode migration was noted

in one patient (Case 4), which led to a marked worsening of the headache. Interestingly, a month after surgery, Case 1 developed a continuous background pain of moderate intensity at the same site as the SUNCT attacks, with superimposed exacerbations of up to an hour associated with ipsilateral conjunctival injection and lacrimation. A diagnosis of HC was confirmed by a double-blind indotest. The patient was started on oral indometacin and became completely pain-free, but the HC recurred every time reduction of the indomethacin dose was attempted. Case 9 had lead site pain and variable occipital paresthesia, which failed to improve despite trials of various stimulation parameters. She opted to have the ONS explanted after 24 months as she had not derived any benefit. In Patients 1, 2, 4, and 7 the battery discharged after 23, 34, 26, and 25 months, respectively. In these cases the battery was replaced with a rechargeable one (Restore Advanced®, Medtronic).

Table 48. Occipital nerve stimulation parameter settings and complications

	Amplitude (V)	Frequency (Hz)	Pulse width (µs)	Complications	Action taken
1	1.9-3.1	100	450	-New onset of HC -Infection over the ONS scar site -Battery discharged after 23 months	-Started Indometacin 150 mg/day -Resolved with oral antibiotics -Replaced with a rechargeable battery
2	0.8	60	450	-Battery discharged after 34 months	-Replaced with a rechargeable battery
3	1.0-1.8	70	450	None	None
4	1.5-2.5	70	450	-Electrode migration -Skin erosion and exposed electrode -Battery discharged after 26 months	-Surgical revision -Surgical revision -Replaced with a rechargeable battery
5	0.9-1.6	100	450	-None	
6	0.3	130	450	-None	
7	1.5-3.2	70	450	-Battery discharged after 25 months	-Replaced with a rechargeable battery
8	0.4-2.1	65	450	-Moderate neck stiffness. Severe pulling pain over the leads due to muscle recruitment	- Surgical revision
9	0.4-1.3	30-130	450	-Lead site pain and variable paraesthesia over the occiput	-No improvement after various trails of different stimulation parameters; ONS explanted after 24 months

Hz: Hertz; mg: milligrams; µs: milliseconds; ONS: occipital nerve stimulation; V: voltage

5.3.3. Discussion

This is the first case series that provides evidence for long-term effectiveness of occipital nerve stimulation in medically intractable SUNCT and SUNA. The remarkable improvement obtained by 8 out of 9 patients provides evidence, albeit on an open-label basis, that ONS may have a role in the management of chronic, medically refractory SUNCT and SUNA. This is borne out by the substantial reduction in disability and improvement of quality of life and affective scores seen in these responders. Additionally, most of the responders were able to stop or reduce preventive medications for SUNCT or SUNA.

A limitation of this observational study is the absence of a control group, raising the possibility that the effect of ONS in this patient group might be attributable to placebo or natural history. However, blinding with ONS is particularly challenging since it seems that occipital paresthesia is a requirement for clinical effect. Several observations in this report suggest more than natural history or a placebo effect, including: a protracted preceding chronic phase, lack of response to several other treatments, the relatively robust response rate, sustained long-term improvement, and the rapid deterioration and recovery after technical failures.

A particular strength of this study is the relatively long duration of follow-up. In most of the series published hitherto, patients were followed for a period ranging from 13.5 to 17.5 months (Burns , et al., 2007; Burns , et al., 2008; Palmisani , et al., 2013). The importance of long-term follow-up was highlighted by Fontaine and collaborators who, in a series of 13 chronic cluster headache patients treated with ONS, reported a patient who completely lost therapeutic benefit initially obtained with ONS at 16 months follow-up (Fontaine , et al., 2011). The results of our series indicate a robust and long-lasting improvement from continuous stimulation over a median follow-up period of 38 months. With the stimulator working properly, none of our patients reported a loss of the improvement achieved, suggesting that ONS has a long-lasting reliability and consistency in this patient group.

Other series of ONS for headache demonstrated that it is a relatively safe procedure with no reports of any serious adverse events. Common complications reported include electrode migration, lead site pain, myofascial incision site pain, neck stiffness, battery

site pain, and contact dermatitis. In this case series with a median follow-up of 38 months, there were a range of complications including electrode migration, skin erosion resulting in electrode exposure, infection, lead site pain, muscle recruitment, and neck stiffness. Four of the 9 patients needed a new battery during the follow-up period. Battery depletion is not strictly a complication but it does require a further operation. However, given the recent availability of rechargeable batteries, the need for repeat operations for new batteries in the future will be reduced.

There is sparse literature on the ability of a percutaneous trial to predict the long-term benefit of an ONS implant (Palmisani , et al., 2013). There are 3 multicenter randomized control trials of ONS in primary headaches, all of which have been conducted in chronic migraine (Lipton, et al., 2009; Saper , et al., 2011; Silberstein , et al., 2012). A subgroup analysis of data from the PRISM study reported that a favorable response to a percutaneous treatment trial was moderately predictive of a 12- week response (Lipton, et al., 2009). However, this study has only been reported in abstract form and just the short-term data are available, making it difficult to ascertain the actual importance of trial stimulation in predicting a response to ONS. Moreover, it is arguable that longer periods of stimulation in those who failed the trial might have resulted in a benefit in the longer term, given that ONS usually induces improvements over weeks or months (Fontaine , et al., 2011). A large randomized controlled trial of ONS in 177 patients with chronic migraine reported that 89% of them demonstrated a favorable response to a percutaneous trial; these patients then had a permanent device implanted, but only 17% responded favorably (defined as a > 50% reduction in mean visual analog score [VAS]) at 12 weeks (Silberstein , et al., 2012). It is interesting to compare this with the ONSTIM study of ONS in chronic migraine, in which all patients had permanent implants, without percutaneous trial stimulation. This study reported that 39% of them responded favorably (defined as a > 50% reduction in headache days or > 3-point reduction in VAS) at 12 weeks (Saper , et al., 2011).

The open-label series of ONS in headache disorders also report a relatively high response (> 80%) to trial stimulation, in keeping with response rates reported in randomized controlled trials (Schwedt , et al., 2007; Palmisani , et al., 2013; Brewer , et al., 2013; Mueller , et al., 2013). This reported benefit of a short percutaneous trial might represent a placebo effect in a cohort of patients who have high expectations

from surgery after failing most available treatments. However, the ability of a trial test to select long-term favorable responders appears poor in controlled studies, especially given that more than 80% of patients go onto full implantation anyway. In our study, the majority of patients obtained a significant response after a median of 3.5 months from the implant. By using a 1–2 weeks' trial, we would have excluded patients that would have benefited from ONS. Hence, a stimulation trial does not appear to be a reliable predictor of long-term success with ONS in headache disorders. Larger prospective ad hoc studies are needed to further clarify this issue.

Given the costs and level of invasiveness, identifying predictors for response to ONS has been a subject of interest. Initial evidence coming from a small study suggested that GONB was not a predictor of favorable response to ONS in patients with medically intractable, chronic primary headaches (Schwedt , et al., 2007a). In our study, GONBs were performed in 7 out of 9 patients (Table 4). Three (Patients 1, 2, 6) out of 7 patients responded to the first procedure, but did not derive any improvement from the second one. They all became pain-free with ONS. Among those who did not respond favorably to GONB (Patients 3, 4, 8, 9), 3 patients obtained a favorable response from ONS (respectively 100%, 96%, and 98% improvement of the headache score), whereas one patient did not respond favorably to ONS treatment. This data, although coming from a small series of patients, suggests that the response to GONB may not be considered a predictor of the therapeutic effect from ONS. However, these finding were not confirmed in a large open-label study conducted after our analysis, which looked at predictors of response in refractory chronic primary headaches including 20 patients with short-lasting neuralgiform headache attacks. Indeed, the study demonstrated that a previous positive response to GON block was associated with a positive response to ONS (Miller , et al., 2017).

The mechanisms by which peripheral neurostimulation mediates the antinociceptive effect are poorly understood. Several sites of action within the peripheral and central nervous system have been proposed, including the peripheral nerve, spinal segmental level and supraspinal levels. It is likely that peripheral neurostimulation exerts its effect by multiple mechanisms and that these mechanisms may differ in the various headache and pain syndromes. Direct effects of neurostimulation on peripheral nerve fibre

excitability have been described, including transient slowing of conduction velocity, increase in electrical threshold and decrease in response probability (Ignelzi , et al., 1979). However, ONS did not significantly modify pain thresholds in CCH, which argues against a diffuse analgesic effect (Magis, et al., 2007).

A widely accepted theory for the antinociceptive effect of neurostimulation is the gate-control theory of pain which proposes that the activation of large diameter afferent nerve fibres in the spinal dorsal horn inhibit onward transmission in small diameter primary afferent nociceptive fibres, thereby preventing the nociceptive signals from reaching the higher neural centres and being interpreted as pain (Melzack , et al., 1965). Indeed, a number of physiological studies have confirmed that afferent activity set up by peripheral neurostimulation blocks nociceptive transmission in the spinal cord (Garrison , et al., 1996; Chung , et al., 1985; Woolf , et al., 1982). The explanation for the antinociceptive effect of spinal cord stimulation (SCS) model, according to the gate-control theory is that nociceptive input from the periphery could be inhibited at the first dorsal horn relay by stimulation-induced antidromic activation of collaterals of large dorsal column fibres projecting onto the same spinal segment (Dubuisson , 1989; Foreman , et al., 1975). However, the gate theory does not adequately explain some of the animal and human experimental data and therefore several additional mechanisms of action for neurostimulation have been postulated. Some of the theories proposed include: activation of supraspinal mechanisms; alteration of putative neurotransmitter levels; and blockade of sympathetic mechanisms (Meyerson , et al., 2000; Krames , 1999).

The involvement of supraspinal sensory pathways is a requisite for the orthodromic transmission of the activation resulting from neurostimulation. The key issues are whether the ascending and descending pain pathways are involved in mediating an antinociceptive effect and, if so, then which supraspinal structures are involved. Antinociception in animal models produced by sensory afferent stimulation is reduced by spinal transaction, thus implicating the involvement of supraspinal mechanisms (Woolf , et al., 1980). Similarly, with SCS it has been argued that the inhibitory effects on nociceptive transmission in the spinal dorsal horn cannot be entirely attributed to antidromic activation of the dorsal columns because they persist after dorsal column transection caudal to the stimulating electrode (Saadé , et al., 1985). Furthermore, on

the basis of animal studies, various supraspinal structures have been proposed as candidates for mediating the antinociceptive effect including the periaqueductal grey (PAG) and thalamus (Stiller , et al., 1995; Nyquist , et al., 1973).

A positron emission tomography (PET) study investigated the effect of SCS in patients with refractory angina pectoris (Hautvast , et al., 1997). The study was performed when the patients were not in pain and therefore the regional cerebral blood flow changes reflect the effects of SCS solely. During stimulation, activation was noted in the PAG, dorsomedial and the pulvinar nuclei of the thalamus, prefrontal cortex, medial temporal gyrus, posterior caudate nuclei and posterior cingulate cortex, while a relative decrease in regional cerebral blood flow was observed in the insulae and anterior cingulate cortex. Furthermore, a functional magnetic resonance imaging study in three patients with chronic pain syndromes showed primary and secondary somatosensory cortex and anterior cingulate cortex activation with SCS (Kiriakopoulos , et al., 1997).

A PET study investigated the brain structures modulated by ONS in chronic migraine (Matharu , et al., 2004). Eight patients with a marked beneficial response to bilateral ONS were studied in three states: during stimulation when the patient was pain free; during pain with the ONS switched off; and during partial stimulation and varying levels of pain and paraesthesia. Stimulation suppressed the headache within 30 min and pain recurred within 20 min of switching off the device. Stimulation evoked local paraesthesia, the presence of which was a criterion of pain relief. There were significant changes in regional cerebral blood flow in the dorsal rostral pons, anterior cingulate cortex and cuneus correlated to pain scores, and in the anterior cingulate cortex and left pulvinar correlated to stimulation-induced paraesthesia scores. The activation pattern in the dorsal rostral pons in this study is highly suggestive of a role for this structure in the pathophysiology of chronic migraine. However, this brainstem region may also be a locus for neuromodulation by ONS. The PAG has long been proposed as a candidate for mediating the antinociceptive effects of neurostimulation. Stiller and collaborators performed microdialysis studies on transmitter release in the PAG of rats receiving SCS. They observed that SCS affected a decrease in gamma-aminobutyric acid (GABA) levels but not of serotonin or substance P. As GABA neurons in the PAG exert a tonic depressive effect on the activity in descending pain inhibitory pathways, the authors proposed that a decreased GABA level in this region following repeated SCS

might indicate increased pain inhibition (Stiller , et al., 1995).

Magis and colleagues studied 10 patients with medically intractable CCH treated with ONS and 39 drug-free healthy volunteers using 18- fluorodeoxyglucose (FDG) PET (Magis , et al., 2011). The 10 patients with CCH underwent an 18 FDG PET scan after ONS, at delays varying between 0 and 30 months. All were scanned with ongoing ONS and with the stimulator switched off. After 6–30 months of ONS, three patients were pain free and four had a reduction of attack frequency of at least 90% (patients who responded). In all patients compared with controls, several areas of the pain matrix showed hypermetabolism, including the ipsilateral hypothalamus, midbrain and ipsilateral lower pons. All normalized after ONS, except for the hypothalamus. Switching the stimulator on or off had little influence on brain glucose metabolism. The perigenual anterior cingulate cortex was hyperactive in patients who responded to ONS compared with those who did not respond. These results may support the hypothesis that ONS exerts its beneficial effects via slow neuromodulatory processes in the central pain matrix. The finding of a possible selective perigenual anterior cingulate cortex (PACC) in patients who responded raises the possibility that ONS activates descending pain control systems in a top-down manner and restores an equilibrium in antinociceptive opioidergic pathways. The study also reported persistent hypermetabolism of the ipsilateral posterior hypothalamus outside of an attack, which might be a hallmark of cluster headaches and also explains why attacks rapidly recur after interruption of ONS.

SUNCT/SUNA have clinical and pathophysiological features that overlap with CH and TN, suggesting an underlying complex pathophysiology characterized by an interaction between peripheral and central structures of the brain (Goadsby, et al., 1997; Lambru , et al., 2014). Patients with SUNCT and SUNA treated with ONS showed better outcomes, compared to the series of patients with CH already published, in terms of a higher proportion of those who responded favorably (n = 8/9 [89%] in our series versus n = 61/91 [67%] in CH series as well as rate and degree of improvement (Magis, et al., 2012). This effect might reflect differences in the biology of SUNCT/SUNA and CH, with the former possibly characterized by a prominent involvement of more peripheral areas of the nociceptive system. Furthermore, besides a slow neuromodulatory process of areas belonging to the pain matrix, which has been suggested to be the main

mechanism of action of ONS in primary headaches, a plastic modulation of structures, like the trigeminocervical complex, might explain the rapid and substantial improvement observed in the majority of patients with SUNCT and SUNA (Lambru , et al., 2014).

In conclusion, this study shows a beneficial response to ONS in patients with chronic, medically intractable SUNCT or SUNA, which then continued over a median follow-up of 38 months. There was a substantial reduction in headache-related disability and improvement of affective symptoms. The stimulator proved to be safe and generally well tolerated. Given the potential adverse events of other surgical procedures and their inconsistent results, ONS might be considered the surgical option of choice for medically intractable, chronic SUNCT and SUNA. The efficacy of ONS in SUNCT and SUNA further extends the potential therapeutic spectrum of action of this surgical procedure, strengthening its role in the management of chronic, medically refractory primary headache disorders.

5.4. Microvascular decompression of the trigeminal nerve in SUNCT and SUNA

5.4.1. Methods

5.4.1.1. Case material

Ten patients three females and seven males were included in the case series. Seven patients had an IHS diagnosis of chronic SUNCT and three of chronic SUNA. The mean duration of the condition at the time of the operation was 5.5 years (range: 5-13 years). In the absence of any published consensus, we used the definition of refractory or intractable SUNCT and SUNA that was previously employed in the ONS study (Lambru , et al., 2014). Patients were considered medically refractory SUNCT and SUNA when they failed to respond or tolerate adequate dosages of lamotrigine, topiramate, oxcarbazepine or carbamazepine, pregabalin or gabapentin, duloxetine and greater occipital nerve blockades. Intravenous lidocaine normally leads to a transitional headache improvement in SUNCT and SUNA patients and it improved the headache in all our patients, though the benefit lasted mainly for the duration of the infusion therapy. All candidates for trigeminal MVD had MRI scans with high-resolution sequences of the trigeminal nerves showed significant neurovascular compression ipsilaterally to the side of the pain (Table 49). We offered MVD rather than ONS when patients decided not to wait for funding for ONS or funding was declined.

5.4.1.2. Outcome measures

Pre-and post-operative data were prospectively collected from patient records and outpatient visits. Frequency, severity and duration of attacks at baseline were compared to headache characteristics at follow-ups post-MVD. Use of preventive medications and adverse events following the operation were also assessed. Finally, patients' opinion on the efficacy of the procedure was evaluated.

5.4.1.3. MRI protocol

The MRI protocol is detailed in Chapter 2. In summary, MRI examinations were performed on a 1.5-Tesla GE Signa Excite (GE Medical Systems, Milwaukee), 1.5-Tesla Siemens Avanto (Siemens, Erlangen) or 3.0-Tesla Siemens Trio (Siemens, Erlangen) MRI scanner. The standard imaging protocol included high spatial and nerve-cistern contrast resolution imaging acquisitions of the cisternal segments of the trigeminal nerves and vessels, with 3D Fast Imaging Employing Steady-State Acquisition (FIESTA; TE: 1.5ms, TR: 4.9ms, NEX: 4), 3D Constructive Interference in Steady State (CISS; TE: 5.3ms, TR: 10.6ms, Excitations: 1), or 3D Sampling Perfection with Application optimized Contrasts using different flip angle Evolution (SPACE; TE: 132ms, TR: 1000ms, Excitations: 2). Vascular contact with the cisternal segments of the trigeminal nerves was assessed on both sides on multiplanar reformats of the source high-resolution data. Neurovascular contact was defined by our neuroradiologist (I.N.) on the analysis of imaging by no perceptible CSF signal intervening the silhouette of the vascular structure (arterial or venous) and the cisternal segment of the trigeminal nerve. Contact with the root entry zone (REZ) was considered by our neuroradiologist the proximal 4 mm of the cisternal segment of the trigeminal nerve as it emerged from the pons (De Ridder , et al., 2002).

Table 49. MRI scan findings in SUNCT and SUNA patients undergoing microvascular decompression of the trigeminal nerve.

	Type of vessel	Degree of compression	Site of contact
1	SCA	Distortion	REZ
2	SCA	Contact	REZ
3	AICA	Contact	REZ
4	SCA	Distortion	REZ
5	SCA	Indentation	REZ
6	SCA + VEIN	Distortion	REZ
7	AICA	Contact	REZ
8	SCA	Distortion	REZ
9	SCA	Distortion	REZ
10	SCA	Contact	REZ and distally

AICA: anterior inferior cerebellar artery; REZ: root entry zone; SCA: superior cerebellar artery

5.4.2. Results

The baseline demographic and clinical characteristics of these patients is summarised in Table 50. All patients were considered medically refractory, since they failed to respond to adequate trials, at appropriate doses for an appropriate length of time, of lamotrigine, topiramate, gabapentin, pregabalin, at least one of either carbamazepine or oxcarbazepine and duloxetine (Table 51). GONBs and IV lidocaine only provided transient improvement of the condition. A failed trial was defined as an unsatisfactory response, development of intolerable side effects or contraindication to the use of the medication.

Table 50. Demographic and clinical characteristics of SUNCT and SUNA patients who underwent microvascular decompression of the trigeminal nerve

	Gender	Diagnosis	Headache duration	Laterality	Site	Triggers
1	F	SUNCT	6 years	Right	V2-V3	S
2	M	SUNCT	12 years	Right	V1-V2	T
3	F	SUNCT	7 years	Left	V1-V2-C2	S + T
4	M	SUNCT	6 years	Right	V1-V2	T
5	M	SUNCT	13 years	Right	V1-V2-C2	S + T
6	M	SUNCT	7 years	Left	V1-V2	S
7	F	SUNCT	8 years	Right	V1-V2	S
8	M	SUNA	7 years	Right	V1-V2-V3	T
9	M	SUNA	5 years	Left	V1-V2	S + T
10	M	SUNA	5 years	Right	V1	S + T

F: female; M: male; SUNA: short-lasting unilateral neuralgiform headache attacks with cranial autonomic features; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; S: spontaneous attacks; T: Attacks triggered from triggers zones; V1: Cutaneous territory innervated by the first division of the trigeminal nerve; V2: Cutaneous territory innervated by the second division of the trigeminal nerve; V3: Cutaneous territory innervated by the third division of the trigeminal nerve.

Table 51. Preventive treatments tried in SUNCT and SUNA patients without significant improvement and respective doses (total mg per day)

	LMG	TPM	GBP	PGB	CBZ	OXC	MXT	DUL	Other drugs (mg/day)
1	200	150	900	150	400	1200	600	100	Baclofen 45; Lacosamide 400; Tizanidine 24; IV lidocaine; GONB
2	200	100	NK	500	NK	600	1200	NT	Melatonin 9; prednisolone; GONB; verapamil
3	NK	300	2400	100	300	NT	NT	30	Lacosamide 100; GONB IV lidocaine; Melatonin 15 Indometacin 225
4	400	400	2700	225	600	1050	NT	12	Indometacin 200; Melatonin 5; GONB; IV lidocaine
5	200	250	NT	150	800	1200	NT	NT	GONB
6	350	25	300	600	NK	2400	NT	30	IV lidocaine; GONB
7	800	200	2700	50	NK	600	400	NT	IV lidocaine; GONB; Indometacin 225; Melatonin 15
8	800	400	1800	600	400	NT	NT	90	-
9	400	200	3600	600	NK	1200	NT	90	IV lidocaine; GONB; Indometacin
10	200	75	NT	NK	800	NT	NT	100	Amitriptyline 20; VPA 1600

CBZ: carbamazepine; DUL: duloxetine; GBP: gabapentin; GONB: greater occipital nerve blockade; IV: intravenous; LMG: lamotrigine; MXT: mexiletine; NK: not known; NT: not tried; OXC: oxcarbazepine; PGB: pregabalin; TPM: topiramate; VPA: sodium valproate

All patients underwent a MVD according to Jannetta's procedure (Figure 16). Intraoperatively, a vascular loop contacting the REZ of the trigeminal sensory root was found in all ten cases. Table 52 summarises the outcome from MVD surgery.

Figure 18. Intraoperative image of the pons showing a vascular loop contacting the trigeminal sensory root at the root entry. Intraoperative image after Teflon is positioned.

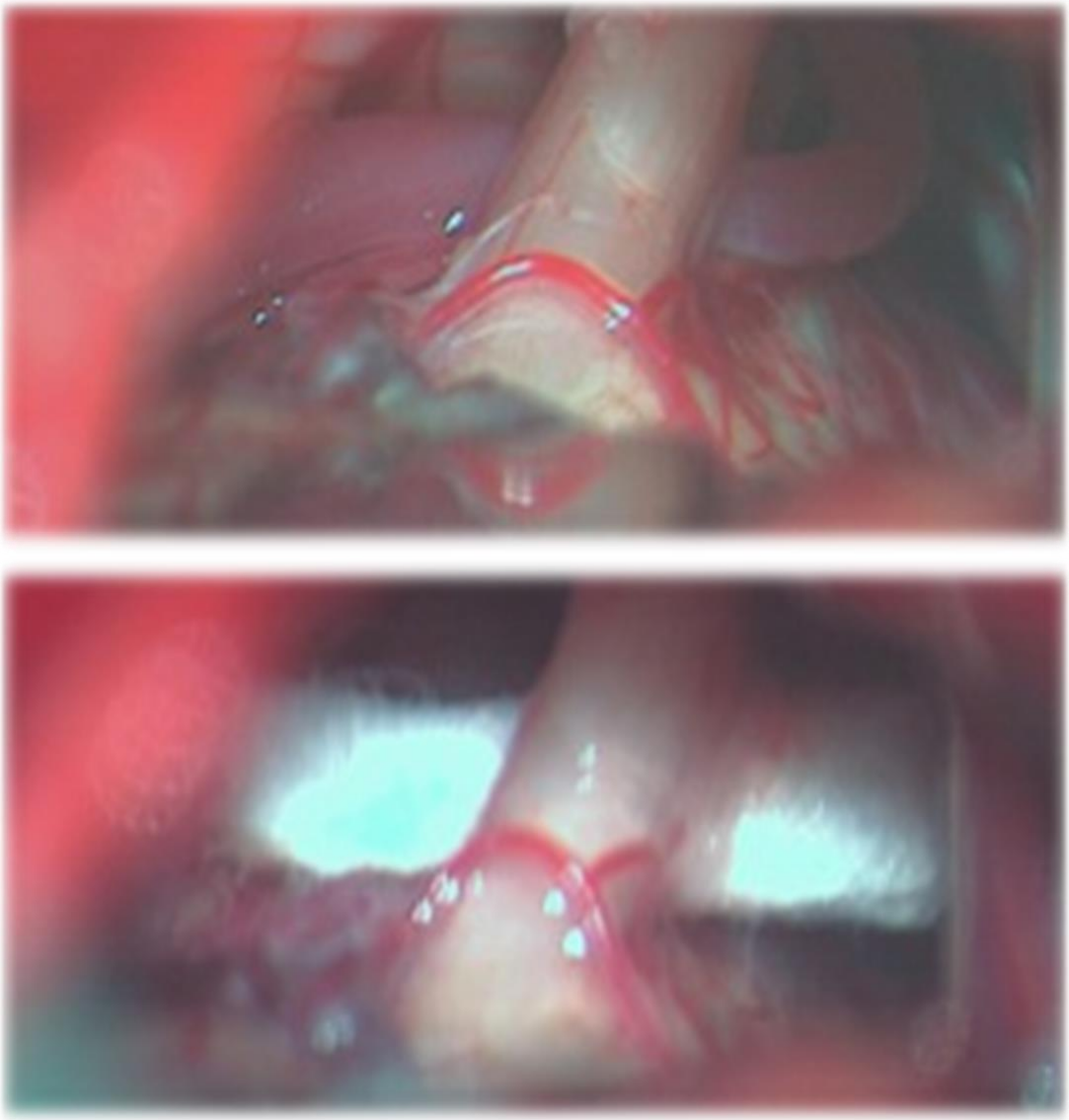


Table 52. Outcome from trigeminal microvascular decompression surgery in SUNCT and SUNA patients

	Attacks frequency (per day)		**Attacks severity (1-10/10)**		**Attacks duration (seconds)**		**Follow-up (months)**
	Pre-MVD	Post-MVD	Pre-MVD	Post-MVD	Pre-MVD	Post-MVD	
1	20-40	2/week	10/10	5-7/10	120-180	3-5	36
2	30-100	Pain-free	8-10/10	Pain-free	10-600	Pain-free	16
3	20-60	2-3	7/10	5/10	30-240	30-240	12
4	30-40	Pain-free	10/10	Pain-free	2-15	Pain-free	16
5	60-100	60-100	9-10/10	9-10/10	10-20	10-20	24
6	100-120	1/week	10/10	5-8/10	30-300	2-5	17
7	20-50	Pain-free	8/10	Pain-free	10-60	Pain-free	17
8	60-100	Pain-free	10/10	Pain-free	60	Pain-free	12
9	40-60	10-30	8-10/10	5-7/10	20-30	20-30	34
10	50-75	Pain-free	10/10	Pain-free	180-1200	Pain-free	12

*Patient 1 became pain free for 9 months before pain relapsed.

**Patient 5 became pain free for 12 months before pain relapsed.

MVD: microvascular decompression

Seven patients (70%) became headache free after the operation. Five of the seven patients (71.4%) remained headache-free at the last follow-up. The remaining two patients (patient 1 and 5) were headache-free respectively for 9 and 12 months before the headache relapsed. A post-operative MRI brain did not show any further vascular conflict. When returned, the headache attacks were less frequent, less severe and shorter-lasting in patient 1, whereas the headache load returned to the same level in patient 5. Low dose of carbamazepine (200 mg/day) enabled a sufficient control of SUNCT attacks in this case. Low dose of carbamazepine was not effective in keeping the pain under control prior to the operation in the same patient. The other three patients (patient 3, 7 and 9) reported a marked improvement post-operatively, with an improvement ranging between 50-90%. The patients who became and remained pain-free were able to discontinue their prophylactic medications. There were no major surgical and post-surgical complications. One patient experienced a transient CSF leak and one patient developed neuropathic pain around the scar area.

5.5. Discussion

MVD of the trigeminal nerve is an established relatively safe surgical technique for refractory TN according to the international guidelines (Cruccu , et al., 2008). Our series suggests that MVD of the trigeminal nerve may also be an effective surgical treatment for medically refractory SUNCT/SUNA syndrome, when there is an evidence of vascular contact of the trigeminal nerve at the REZ. At a median follow-up of 16.5 months, 80% of our patients experienced a meaningful improvement of their conditions, which is in keeping with the figures for MVD in TN patients at 1-year follow-up (Barker , et al., 1996). Two of our patients reported a relapse of their condition within a year from the operation. However, in both cases their headache condition remained significantly more manageable than baseline, with and without the aid of adjunctive pharmacological treatments. Overall the outcome of trigeminal MVD in our series is similar to the outcome of the only other series of SUNCT/SUNA patients operated with the same procedure (Williams , et al., 2010). The consistency of promising results in two series of patients coming from different centres suggest that this procedure may have an important role in the management of refractory forms of SUNCT/SUNA syndrome. However, in view of the short follow-up of our preliminary study, caution in interpretation of our data is required and our patients need to be followed up overtime

to establish the rate of relapse per annum. However trigeminal MVD may be considered a good surgical option for refractory SUNCT and SUNA with MRI evidence of a vascular loop, in view of the immediate pain relief in responders, no need of programming and the lack of hardware-related adverse events. Consersely, ONS may be a better option than MVD for older persons who could not tolerate a major invasive operation and for patients who suffer from alternating side headache attacks. While ONS can theoretically be used in every patient, only patients with a demonstrable trigeminovascular conflict ipsilateral to the pain would be suitable for MVD. On the other hand, the overall data on the 29 patients with SUNCT/SUNA treated with trigeminal MVD (19 published and 10 from this study) makes this procedure the most widely used in refractory cases, hence a reasonable option to consider in patients with neurovascular conflict, though more long-term efficacy data from larger series are required.

The immediate relief from pain achieved from MVD in our and other series, raises the question about the pathophysiological role of the sensory root entry zone compression in SUNCT and SUNA. In view of the clinical similarities with TN, it is possible that in SUNCT/SUNA the vascular compression near the REZ may generate spontaneous ectopic impulses responsible for the short-lasting spontaneous attacks. Furthermore, the cross-talk activities between fibers mediating light touching (A-β) and nociceptive fibers (A-δ) may account for the attacks triggered by innocuous stimulation. Unlike TN, in SUNCT/SUNA the pain is accompanied by cranial autonomic symptomatology, which implies hyperactivation of the trigemino-autonomic reflex. It is unknown whether this overactive trigemino-parasympathetic reflex is due to lack of central inhibition mediated by deranged posterior hypothalamic function, or whether it is due to irritation of the trigeminal arm of the trigemino-autonomic reflex by a vascular compression, or both. The general absence of reported episodes of cranial autonomic symptoms without pain, may indicate that the peripheral trigger plays an important role in maintaining the overactivity of the reflex at least in some patients.

This study suggests the efficacy of MVD in the management of medically refractory SUNCT/SUNA patients. The main limitation of this study includes the relatively short

follow-up. However, our preliminary findings, along with the other cases reported in the literature, may suggest that trigeminal MVD, along with ONS could be considered as the first-line surgical options for medically refractory cases. This study also draws attention on new potential neuronal targets involved in the pathophysiology of this disorder, supporting a pathophysiological overlap between SUNCT/SUNA and TN. These conditions may constitute a clinical continuum due to a complex interaction between central and more peripheral mechanisms perhaps responsible for the clinical and therapeutic similarities and differences between them.

5.6. Summary

This chapter describes the efficacy and safety of ONS in a series of nine medically refractory SUNCT/SUNA patients and the safety and efficacy of trigeminal MVD in another series of ten medically refractory chronic SUNCT/SUNA patients. Both the procedures showed a remarkable outcome in most patients at follow-ups of variable lengths. These findings support the possible effectiveness of two therapeutic options for the management of patients with SUNCT/SUNA refractory to medical management. In view of the outcome of both the procedures, it is reasonable to propose that ONS and trigeminal MVD should be the first line treatments for refractory forms of SUNCT/SUNA. Caveats of these treatments include the high costs for ONS and the limitation of MVD to those patients with MRI evidence of neurovascular conflict with the trigeminal nerve ipsilaterally to the side of the pain. The efficacy of non-destructive approaches, such as ONS and trigeminal MVD should discourage the use of ablative procedure of the trigeminal pathway to treat refractory cases.

Although the efficacy of ONS is seen in several primary and secondary headache disorders, thus implying non-specific pain relief mechanisms, the outcome of trigeminal MVD in SUNCT/SUNA may potentially shed light on novel mechanisms involved in the pathophysiology of this disorder that warrants further research.

Chapter 6. A prospective study comparing the clinical phenotype of SUNCT/SUNA and trigeminal neuralgia

6.1. Abstract

Several clinical aspects suggest a striking clinical overlap between SUNCT/SUNA and TN. However, no direct clinical comparisons of these disorders has hitherto been conducted. To evaluate similarities and differences between SUNA (according to the new criteria of Chapter 2) and TN the demographic and clinical phenotype of 133 SUNA patients was compared to the one of consecutive 79 TN patients. Patients underwent administration of a face to face semi-structured questionnaire capturing demographic and clinical characteristics. Both unadjusted and adjusted logistic regression analyses were used to identify predictors of patients suffering SUNA rather than TN.

The clinical comparison highlighted several similarities and some clinical predictors of SUNA rather than TN such as: pain location in V1(OR: 11.29 95%CI: 3.92, 35.50, p<0.001), spontaneous only attacks (OR: 44.40, 95%CI: 4.50, 437.83, p=0.001) and a chronic pattern (OR: 13.19, 95%CI: 4.04, 43.08, p<0.001). Equally we found some clinical predictors for TN rather than SUNA. They included: duration of the attacks <1 minute (OR: 7.95, 95%CI: 2.30, 27.57, p=0.001) and the presence of a refractory period in between triggered attacks (OR: 0.06; 95%CI: 0.02, 0.28, p-value <0.001). On the basis of this analysis we proposed new diagnostic criteria for trigeminal neuralgia. In conclusion, these findings suggest that SUNA and TN constitute different variant of a clinical continuum that could be named "Short-lasting trigeminal neuralgiform attacks". This clinical view will hopefully open novel research directions towards a better understanding of the complex biological mechanisms underlying these similar disorders.

6.2. Introduction

The ICHD 3β classifies short lasting neuralgiform headache attacks and TN in different diagnostic categories. Short lasting neuralgiform headache attacks are subclassified into SUNCT and SUNA, and are included among the TACs, whereas TN is classified under the painful cranial neuropathies and other facial pains (Headache Classification Subcommittee of The International Headache, 2013). The TN diagnostic criteria have been based upon relatively old, methodologically poor studies (PEET , et al., 1952; Rasmussen , 1990; Jainkittivong , et al., 2012). More recently the Danish headache group conducted a series of studies in TN, including a detailed prospective clinical analysis of 158 face to face interviewed TN patients (Maarbjerg , et al., 2014).

The proposed SUNCT and SUNA diagnostic criteria have been updated since 2004 on the basis of a prospective study conducted on a good-sized cohort of SUNCT but only a small number of SUNA patients (Cohen , et al., 2006). The comparison between the IHS diagnostic criteria for the Short-lasting unilateral neuralgiform headache attacks and classical TN highlights what are considered the distinguishing features between these disorders (Table 53). They include: the moderate or severe pain intensity in SUNCT/SUNA compared to the severe intensity of the TN episodes; the longer duration of SUNCT/SUNA attacks compared to the very short TN attacks; the presence of at least one cranial autonomic feature ipsilateral to the side of the pain during attacks in SUNCT/SUNA and the absence of any cranial autonomic features during TN attacks. Furthermore, attacks can be precipitated by innocuous stimulation of the affected side of the face in TN, whereas no triggers are mentioned for SUNCT/SUNA attacks. However, in the comments of the diagnostic criteria, the IHS Classification Committee states that SUNCT/SUNA attacks are usually triggerable. Moreover, the prospective series of patients published between the publication of the ICHD-2 and the ICDH-3β, suggested that extra-trigeminal pain location can occur in almost 30% of the SUNCT patients (the SUNA group was too small to comment on findings) (Cohen , et al., 2006). The current proposed diagnostic criteria for TN do not mention the association between pain and cranial autonomic features, which could lead to diagnostic confusion for those SUNCT/SUNA patients that could conceivably be classified as TN, if the TN criteria

are fulfilled despite association with cranial autonomic features. (Headache Classification Subcommittee of The International Headache, 2013).

A careful evaluation of the proposed ICHD-3β diagnostic criteria, reveals the difficulty in keeping SUNCT, SUNA and TN separate in view of their remarkable clinical overlap in most domains of their phenotypic presentation. Since the largest prospective clinical phenotype studies in TN took place before SUNCT and SUNA were recognized as independent clinical conditions, they did not evaluate in details clinical features that could distinguish TN from SUNCT/SUNA, hence preventing any indirect comparison between these conditions. Moreover, no SUNCT and SUNA series have been compared to TN series to formally establish the presence of any significant phenotypical difference between these disorders.

In this chapter we aim to compare the clinical characteristics of a large cohort of SUNCT/SUNA patients with the ones of a large cohort of TN patients to determine the presence of clinical significant differences between these disorders.

Table 53. Comparison of International Classification of Headache Disorders 3 beta diagnostic criteria for classical trigeminal neuralgia and short-lasting unilateral neuralgiform headache attacks

	SUNCT	**SUNA**	**Trigeminal neuralgia**
Number of attacks	At least 20	At least 20	At least 3
Intensity	Moderate or severe	Moderate or severe	Severe
Pain location	V1-V2-V3	V1-V2-V3	V1-V2-V3
Pain duration	1-600 seconds	1-600 seconds	Faction of a second to 120 seconds
Pain quality	Stabbing	Stabbing	Electric shock like, shooting, stabbing or sharp
Associated autonomic features	Conjunctival injection and lacrimation	≥1 cranial autonomic symptoms/signs	None
Triggers	-	-	Precipitated by innocuous stimuli to the affected side of the face
Attacks frequency	≥1 attack/day for more than half of the time when the disorder is active	≥1 attack/day for more than half of the time when the disorder is active	-

SUNA: Short-lasting neuralgiform headache attacks with autonomic symptoms; SUNCT: Short-lasting neuralgiform headache attacks with conjunctival injection and tearing; V1: ophthalmic trigeminal territory; V2: maxillary trigeminal territory; V3: mandibular trigeminal territory;

6.3. Methods

The SUNCT and SUNA study group includes the 133 patients phenotyped in Chapter 2 (for methodological details see Chapter 2). The study conducted in chapter 2 demonstrated the lack of significant clinical differences between SUNA and SUNCT, hence it was decided to amalgamate these two groups of patients for the purposes of this study. Furthermore, it was proposed that as SUNCT is likely to be a subset of SUNA, all these patients can be classified in the unified diagnosis of SUNA. In this

chapter, the previously diagnosed SUNCT or SUNA patients were unified under the term SUNA. As outlined in chapter 2, ICHD-3β encompasses SUNCT and SUNA under the category of "short-lasting unilateral neuralgiform headache attacks" but this term would be a misnomer as it potentially also describes TN and does not highlight the autonomic features which are central for the diagnosis of SUNCT and SUNA. Hence, we have opted to use the term "SUNA" to encompass this group rather than "short-lasting unilateral neuralgiform headache attacks"

The TN study group consisted of consecutive patients seen at the Facial Pain clinic within the National Hospital for Neurology and Neurosurgery from 2010 to 2012. Diagnosis was based on ICDH-2 criteria (Headache Classification Subcommittee of The International Headache Society., 2004). The Facial Pain clinic is a tertiary referral clinic in the UK and receives patients from all over the Country, referred by general practitioners, dentists, maxillo-facial surgeons as well as neurologists and neurosurgeons. All patients were interviewed face to face by a single researcher (GL) using a comprehensive standardized semi-structured questionnaire (Appendix) and data were collated onto an electronic database (SPSS). In view of the potential high attack load during an active pain period, headache/facial pain charts were not used in this study. If any patients could not accurately report any of the clinical features needed, or could not remember because they were out of a bout of TN attacks, they were re-phenotyped at three to six-month intervals during their clinical follow-ups to ensure collection of accurate information.

The study was approved by Northwick Park Hospital Research Ethics Committee, London, UK (REC no:11/LO/1709).

6.4. Statistical analysis

Baseline characteristics were compared between the cohorts of SUNA and TN using Chi-squared tests or Fisher's exact tests for categorical variables and Student's t-tests or Mann Whitney U-tests depending on the distribution of the continuous variables. Both unadjusted and adjusted logistic regression analyses were used to identify predictors of patients suffering SUNA rather than TN. Adjustments were made for characteristics that have previously been associated with either condition (i.e. site,

quality of the pain, duration, frequency of the attacks and cranial autonomic symptoms). Statistical analyses were performed using STATA (Stata Corp. 2001. Stata Statistical Software: Version 12.1, College Station, Texas, USA). All reported *P*-values are two-sided and a significance level less than 5% is considered significant.

6.5. Results

The clinical and demographic characteristics of a SUNA cohort (n=133) were compared to those of a TN cohort (n=80). However, one TN patient was excluded from the final analysis because of incomplete clinical information provided. Of the 79 TN patients included in the analysis, 70 patients had classical TN purely paroxysmal and nine patients had classical TN with concomitant persistent facial pain.

6.5.1. Age, gender and duration of symptoms

The demographic characteristics of our cohorts are shown in Table 54. Female were more represented than men in both the SUNA and TN cohort of patients. There was no statistically significant difference in the proportion of female in the two cohorts. The mean age of onset of TN was approximately a decade later than the SUNA onset ($p<0.0001$).

Table 54. Demographic characteristics of SUNA and SUNCT patients

		SUNA n (%)	**Trigeminal Neuralgia n (%)**	**p-value (<0.05)**
Gender	Male	50 (37.6%)	31 (39.2%)	0.811
	Female	83 (62.4%)	48 (60.8%)	
Mean (95% CI) age of onset (years)		43.52 (±14.8)	53.33 (±13.3)	<0.001
Age range of onset		13-76 years	19-83 years	-
Median duration of symptoms (range)		6 (1-45) years	8 (1-39) years	-

CI: confidence interval; SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing;

6.5.2. Diagnoses made on previous clinical assessments

The majority of patients with SUNA had previously been given a diagnosis of TN (n=68, 51.1%). A proportion of patients with TN were correctly diagnosed before coming to our clinic (n=18, 22.8%). However dental pathologies were incorrectly diagnosed in 19 patients (24.1%) and a non-specific diagnosis of facial pain was proposed in 34 patients (43.0%). Data on this subject was missing for 7 patients (8.9%).

6.5.3. Precipitating events

Unlike the SUNA cohort (n= 37, 27.8%), only nine of 79 TN patients reported precipitating events prior to the onset of symptoms (11.4%). These included facial trauma, flu-like symptoms and dental procedures performed before the facial pain started rather than once it had already occurred. The remaining 70 TN patients were not aware of any events that may have had a causative role in the exacerbation of their condition.

6.5.4. Laterality of attacks

Sixty-three SUNA patients (47.4%) and 49 TN patients (62%) had exclusively right-sided attacks (p=0.038); 51 SUNA (38.3%) and 28 TN (35.4%) patients had exclusively left-sided attacks (p=0.672). A significant higher proportion of SUNA (n=18, 13.5%) compared to TN patients (n=2, 2.5%) had side alternating unilateral attacks (one patient predominantly centred over the right hand side and one patient had side alternating unilateral attacks equally distributed between sides) (p=0.008). None of the TN patient had bilateral attacks. Table 55 outlines the comparison between SUNA and TN laterality of attacks.

Table 55. Laterality of attacks in SUNA and trigeminal neuralgia

	SUNA (numbers)	**Trigeminal Neuralgia (Numbers)**	**p-value (<0.05)**
Right-sided	63	49	0.038
Left-sided	51	28	0.672
Alternating (Unilateral)	18	2	0.008
Bilateral	1	0	-

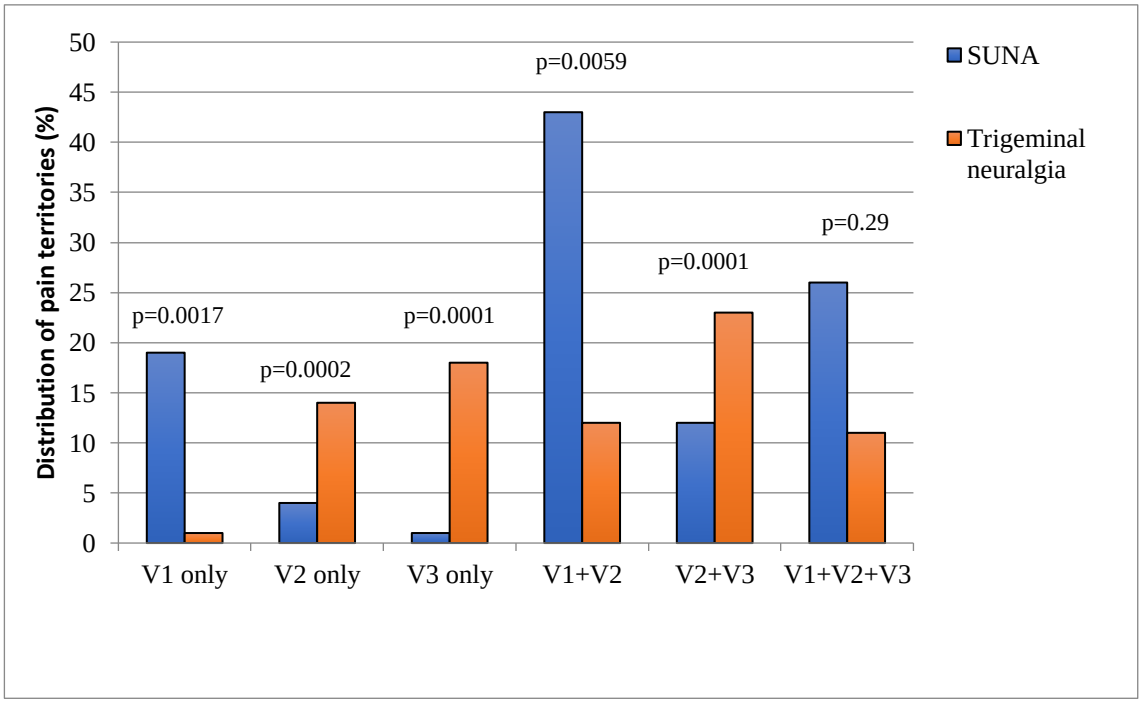
SUNA**:** short-lasting unilateral neuralgiform headache attacks with autonomic symptoms

6.5.5. Site of attacks

Figure 17 outlines the difference in pain distribution within the trigeminal territories between the SUNA and TN cohorts. Pain exclusively in the V1 territory was reported by a higher proportion of SUNA patients (n=19, 14.3%) compared to TN patients (n=1, 1.3%). Conversely, pain in V2 only and in V3 only was reported by a significantly higher number of TN patients (V2: n=14, 17.7%; V3: n=18, 22.8%) compared to SUNA patients (V2: n=4, 3.0%; V3: n=1, 0.8%). A significantly higher proportion of SUNA (n=43, 32.3%) compared to TN patients (n=12, 15.2%) reported pain in both V1 and V2 trigeminal territories, whereas a significantly higher proportion of TN patients (n=23, 29.1%) experienced pain in both V2 and V3 territories compared to SUNA

patients (n=12, 9.0%). A similar proportion of SUNA (n=26, 19.5%) and TN patients (n=11, 13.9%) reported pain in all trigeminal territories. Extra-trigeminal territory pain (C_2-C_3) was reported in 28 SUNA (21.1%) patients. None of the TN patients reported pain in extra-trigeminal territories. A full list of attack sites is shown in Table 56.

Figure 19. Distribution of pain territories in SUNA and TN cohorts



SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; a; TN: trigeminal neuralgi**V1**: ophthalmic trigeminal territory; **V2:** maxillary trigeminal territory; **V3**: mandibular trigeminal territory

Table 56. Site of the attacks in SUNA and trigeminal neuralgia cohorts

	SUNA N (%)	**Trigeminal neuralgia N (%)**	**p-value (<0.05)**
Peri-orbital	77 (57.9%)	15 (19%)	<0.001
Retro-orbital	45 (33.8%)	2 (2.5%)	<0.001
Forehead	43 (32.3%)	28 (35.4%)	0.642
Temporal	59 (44.4%)	19 (24.1%)	0.003
Parietal	28 (21.1%)	1 (1.3%)	<0.001
Vertex	5 (3.8%)	1 (1.3%)	0.289
Occiput	27 (20.3%)	0 (0%)	-
Neck	1 (0.8%)	0 (0%)	-
Cheek	59 (44.4%)	53 (67.1%)	0.001
Side of nose	17 (12.8%)	10 (12.7%)	0.979
Ear	11 (8.3%)	0 (0%)	-
Retroauricular	1 (0.8%)	0 (0%)	-
Jaw	33 (24.8%)	47 (59.5%)	<0.001
Upper teeth	10 (7.5%)	25 (31.6%)	<0.001
Lower teeth	7 (5.3%)	18 (22.8%)	<0.001
Upper lip	10 (12.7%)	9 (6.8%)	0.339
Lower lip	5 (6.3%)	6 (4.5%)	0.223
Chin	4 (5.1)	3 (2.3%)	0.755

SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms;

6.5.6. Severity of the pain

The patients were asked to recall the average severity, along with the maximum and minimum severity of their attacks when they were not on effective treatments. A verbal rating scale (VRS) of 0 to 10, with 0 being no pain and 10 being very severe pain was used. The median severity of the pain was very severe in both groups with a VRS of 10

in the SUNA (IQR: 8-10) and 8 in the TN group (IQR: 8-10) (*P*=0.04, Z-score: 2.0). A significantly higher proportion of TN (n=9, 11.4%) compared to SUNA patients (n=4, 3.0%) reported an average severity of attacks of 6 on the VRS (moderate intensity) (p=0.002).

6.5.7. Quality of pain

In our cohorts, the most commonly described pain qualities were stabbing and sharp. The pain descriptors "electric-shock like" and "shooting" were significantly more represented in the TN group than in the SUNA group (Table 57). All patients had at least one of the above four qualities of pain. A pulsating nature to the pain was reported in 19 SUNA (14.3%) and 14 TN patients (17.7%) and never as an isolated feature.

Table 57. Quality of pain

	SUNA n (%)	**Trigeminal neuralgia n (%)**	**p-value (<0.05)**
Stabbing	109 (82.0%)	63 (79.7%)	0.691
Sharp	80 (60.2%)	44 (55.7%)	0.524
Electric shock	46 (34.6%)	56 (70.9%)	0.001
Shooting	39 (29.3%)	36 (45.6%)	0.016
Burning	22 (16.5%)	7 (8.9%)	0.115
Pulsating	19 (14.3%)	14 (17.7%)	0.504
Jabbing	10 (7.5%)	0 (0%)	-
Pressure	8 (6.0%)	1 (1.3%)	0.097
Tightening	4 (3.0%)	0 (0%)	-
Dull	3 (2.3%)	0 (0%)	-
Ache	0 (0%)	2 (2.5%)	-

SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms;

6.5.8. Duration and profile of attacks

The SUNA group had a median duration of attacks of 60 seconds (mean duration: 160.5 seconds ±196.7, range: 1-900 seconds) whereas the TN group had a median duration of attacks of 15 seconds (mean duration: 47.7 seconds ±87.6, range: 1-600 seconds) (P=

<0.001, Z-score: 6.4). The vast majority of SUNA patients (n=131, 98.5%) had a usual duration of attacks ranging from 1-600 seconds, in line with the ICHD-3β criteria. However, 37 (27.8%) patients reported some longer lasting attacks ranging from 900 to 3600 seconds.

All but four TN patients (n=75, 94.9%) had a usual attack duration ranging from 1-120 seconds, in line with the ICHD-3β criteria. However, 25 TN patients (31.6%) reported some longer lasting attacks ranging from 180 to 900 seconds.

The comparison between different attack profiles in SUNA and TN patients is outlined in Table 58 and 59. A higher proportion of TN compared to SUNA reported a single stab profile (p<0.001). Conversely, a higher proportion of SUNA compared to TN reported attacks following the plateau-like profile (p=0.006). Of those who reported only one attack profile, a single stab profile was reported by a significantly higher proportion of TN patients compared to SUNA (p=0.001). A substantial proportion of both SUNA and TN patients described their attacks using more than one attack profile. The proportion of SUNA patients that reported three attack profiles was significantly higher than the one of the TN group (p=0.031).

Table 58. Frequency and duration of the different attack profiles in SUNA and TN

	SUNA **n (%)** **Median duration (IQR)**	**Trigeminal neuralgia** **n (%)** **Median duration (IQR)**	**p-value*** **(<0.05)**
Single stabs	65 (48.9%) 10 sec (10-120 sec)	62 (78.5%) 5 sec (1-120 sec)	<0.001
Repetitive stabs	78 (58.7%) 180 sec (60-300 sec)	42 (53.2%) 60 sec (3-7200 sec)	0.436
Serrated stabs	64 (48.1%) 240 sec (60-240 sec)	30 (38.0%) 105 sec (4-600 sec)	0.150
Plateau-like	27 (20.3%) 300 sec (20-600 sec)	5 (6.3%) 60 sec (60-600 sec)	0.006
Missing data	1 (0.8%)	1 (1.3%)	0.708

IQR: Inter-quartile range; SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; *P-value relates to the differences in number of events between SUNA and trigeminal neuralgia.

Table 59. Presence of isolated and multiple attack profiles

	SUNA n (%)	**Trigeminal neuralgia n (%)**	**p-value (<0.05)**
Single profile	48 (36.1%)	25 (31.6%)	0.510
Single stabs	5 (3.8%)	13 (16.5%)	0.001
Repetitive stabs	19 (14.3%)	4 (5.1%)	0.036
Serrated stabs	17 (12.8%)	5 (6.3%)	0.136
Plateau-like	7 (5.3%)	3 (3.8%)	0.626
Two profiles	59 (44.4%)	46 (58.2%)	0.054
Three profiles	22 (16.5%)	5 (6.3%)	0.031
All four profiles	1 (0.8%)	0 (0%)	-
Missing data	1 (0.8%)	0 (0%)	-

SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

6.5.9. Frequency of attacks

In assessing the frequency of attacks, we considered single stabs, groups of stabs or serrated stabs as single episodes. The median daily attack frequency was 25 in the SUNA group (mean: 46.6 attacks/day ±56.6; range: 1-250) and 15 in the TN group (mean: 23.1±23.9; range: 2-100). However, in the TN patients, the frequency of the attacks was countable by 57 out of 79 patients (72.2%); the remaining 22 patients stated that the attacks were so frequent that they could not count them. Conversely the number of the attacks was countable in every SUNA patients, although in patients with numerous attacks an estimate of the attacks per hour multiplied per number of hours of pain per day, was provided. For this reason, a statistical comparison of the attack frequency between the two groups was not performed. In fact, assuming that the 22 TN patients had >100 attacks/day, the proportion of patients with an average frequency of more than 100 attacks/day was higher in TN (27.8%) than in SUNA (n=12, 9.0%) ($p<0.001$).

6.5.10. Cranial autonomic symptoms

Although cases of TN with cranial autonomic features have been described prior to the publication of the latest version of the classification, the ICHD-3β does not include the cranial autonomic features domain in the TN diagnostic criteria (Rasmussen , 1990a; Sjaastad , et al., 1997; Simms , et al., 2011). In our cohort 10 TN patients reported lacrimation during some of the attacks (12.7%). Of these, the degree of lacrimation was mild in nine and moderate in one patient. One patient reported ipsilateral lacrimation, conjunctival injection and blocked nose with few of the attacks and another patient reported ipsilateral lacrimation and rhinorrhoea seldom associated with the pain. Of the 10 patients with TN and some degree of cranial autonomic activation, the pain also involved the V1 territory in six patients (60%). This percentage is remarkably higher compared to the involvement of the V1 territory in the remaining of the TN cohort (30.4%), suggesting a link between pain location and type of autonomic feature, which is this cohort was mainly lacrimation. Using the cut-off of 120 seconds for TN attack duration, our data showed that seven out of ten patients who reported some degree of autonomics had attacks lasting ≤120 seconds and only three patients experienced autonomic features during longer lasting attacks. In these patients the duration of the attacks was 180 seconds, 600 seconds and 180 seconds and followed a serrated pattern in one and a repetitive stabs pattern in two of them. This support initial evidence suggesting that the occurrence of cranial autonomic features was not associated with longer attacks duration (Haviv , et al., 2016). Table 60 summarises the main clinical features of the group of TN patients with cranial autonomic features.

Table 60. Clinical features of trigeminal neuralgia with cranial autonomic features

	Trigeminal neuralgia with cranial autonomic features
Gender	Female: male = 5:5
Age of onset	Median=53.5 years old (range: 30-70 years old)
Pattern	Chronic: episodic = 5:5
Pain side	Right: left = 8:2
Pain intensity	Severe: moderate = 9:1
Attacks duration	Median = 30 seconds (IQR: 56, range: 2-80 seconds)
Attack frequency:	Median = 9/day (IQR: 24/day, range: 5-70/day; attacks were not countable in 4 patients)
Behaviour during attacks	Still: restless = 10:0
Attacks triggered/spontaneous	Both triggered and spontaneous: triggered only = 9:1
Refractory period	Yes: no = 1:1 (7 patients were unsure; 1 md)
Interictal pain	Yes: no = 5:5
Response to CBZ	≥50% improvement = 5 patients ≤50% improvement = 1 patient md: 2 patients; not tried = 2 patients
MRI findings	Trigeminal conflict: YES:NO = 6:4 (in one case conflict is bilateral)

CBZ: carbamazepine; md: missing data: MRI: magnetic resonance image

6.5.11. Triggering of attacks

The comparison between the proportions of patients with spontaneous and/or triggered attacks in SUNA and TN patients is outlined in Table 61. A significantly higher proportion of SUNA compared to TN patients had spontaneous attacks only ($p<0.001$). Conversely a significantly higher proportion of TN compared to SUNA patients had triggered attacks only ($p<0.001$). Among SUNA patients with triggered attacks (n=80, 60.2%), 72 (90%) had attacks that could be provoked by various forms of cutaneous and/or intraoral stimulation. All TN patients with triggered attacks (n=74, 93.7%) had attacks that could be provoked by various forms of cutaneous and/or intraoral

stimulation. Trigger areas were ipsilateral to the side of pain in all patients. A list of trigger factors is outlined in Table 62.

Table 61. Proportion of patients with spontaneous, triggered or both

	SUNA	**Trigeminal neuralgia**	**p-value (p<0.05)**
Spontaneous and triggered	75 (56.4%)	55 (70.5%)	0.055
Spontaneous only	53 (39.8%)	4 (5.1%)	<0.001
Triggered only	5 (3.8%)	19 (24.4%)	<0.001
Missing data	0 (0%)	1 (1.3%)	-

SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms;

Table 62. Trigger factors in SUNA and TN patients with triggerable attacks

	SUNA n (%)	**Trigeminal neuralgia**	**p-value (p<0.05)**
Cold wind	61 (76.3%)	40 (54.1%)	<0.001
Chewing/eating	57 (71.3%)	67 (90.5%)	0.002
Brushing teeth	53 (66.3%)	65 (87.8%)	0.001
Light touch	52 (65.0%)	62 (83.8%)	0.007
Washing/Brushing hair	39 (48.8%)	8 (10.8%)	<0.001
Talking	29 (36.3%)	42 (56.8%)	0.010
Washing face	27 (33.8%)	33 (44.6%)	0.167
Swallowing	14 (17.5%)	3 (4.1%)	0.016
Blowing nose	13 (16.3%)	8 (10.8%)	0.325
Shaving	9 (11.3%)	16 (21.6%)	0.081
Showering	5 (6.3%)	1 (1.4%)	0.116
Valsalva Manoeuvres	27 (34.2%)	7 (9.5%)	<0.001
Neck movements	13 (16.5%)	8 (10.8%)	0.325
Exercise	5 (6.3%)	2 (2.7%)	0.291
Bright lights	4 (5.1%)	0 (0%)	-
Loud noises	6 (7.6%)	0 (0%)	-
Alcohol	0 (0.0%)	0 (0%)	-
Strong smells	1 (0.8%)	0 (0%)	-
Stress	3 (3.8%)	5 (6.8%)	0.400
Moving/vibrations	7 (8.8%)	7 (9.5%)	0.878
Cold/hot weather	3 (3.8%)	2 (2.7%)	0.714

*Frequencies and percentages for cutaneous/intraoral triggers refer to: SUNA = 70 patients and TN = 74 patients (patients with headache attacks triggered only by cutaneous/intraoral stimulation).

** Frequencies and percentages for other triggers refer to SUNA = 80 patients and TN 74 patients (patients with headache attacks triggered by any triggers).

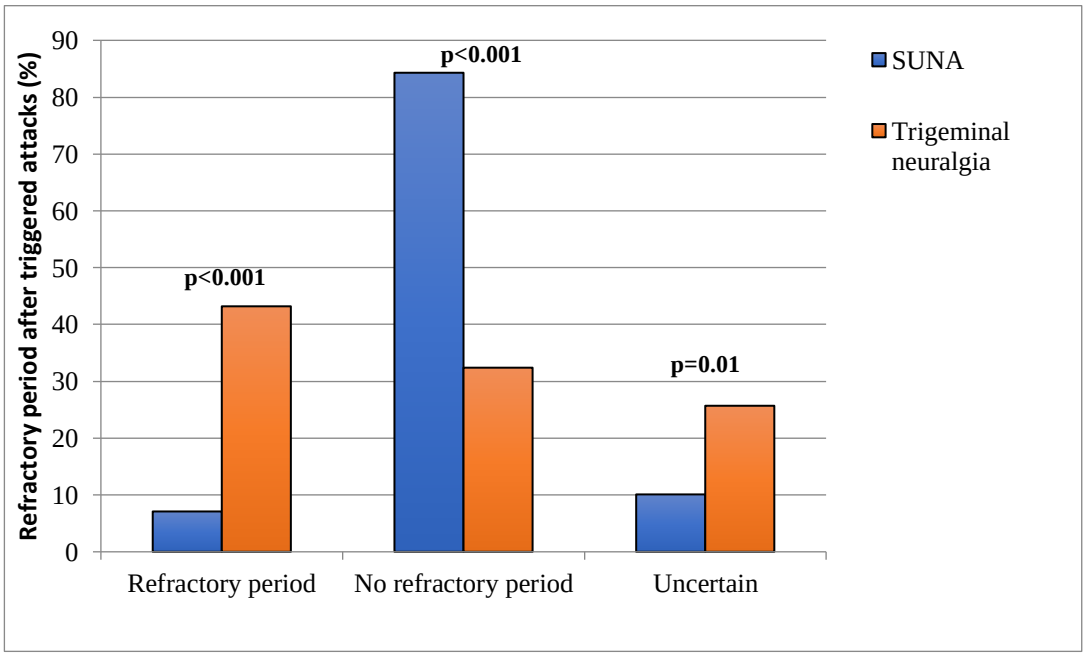
SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; SUNCT: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; TN: trigeminal neuralgia

6.5.12. Refractory period

Among patients with cutaneous triggers, 59 SUNA (81.9%) and 24 TN (32.4%) could trigger an attack immediately after the cessation of the previous one, thereby displaying no refractory period (p<0.001). Conversely, five SUNA (6.9%) and 32 TN patients (43.2%) did experience a refractory period (p<0.001). Seven SUNA (9.7%) and 19 TN patients (25.7%) were uncertain about the presence of a refractory period (p=0.011). We did not have the data on this subject for one SUNA patient (1.4%) (Figure 18).

The mean duration of the refractory period was 240 seconds in SUNA and 189.5 seconds (median 150 seconds, range: 10-900 seconds) in TN patients (p=0.23, Z-score: -1.1). However only 20 of the 32 TN patients who reported a refractory period could confidently remember the average duration of the refractory periods (62.5%).

Figure 20. Refractory period after triggered attacks in SUNA and TN



SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms;

6.5.13. Other associated symptoms

Behaviour during attacks. Ninety-three SUNA (70.5%) and 72 TN (91.1%) patients preferred to stay still during an attack. On the other hand, 39 SUNA (29.5%) and 7 TN patients (8.9%) felt restless and agitated during the pain episodes ($p<0.001$). Data for one SUNA patient (0.8%) was incomplete.

Symptoms often associated with migraine. Fifty-three SUNA (39.8%) patients reported at least one migrainous symptom during attacks. Two TN patients reported migrainous symptoms during some of the attacks. One patient reported nausea and one ipsilateral photophobia. Both patients had a personal and family history of migraine.

Aura. In our cohort, two SUNA (1.5%) and no TN patients experienced aura symptoms during some attacks.

Diurnal variation and predictability of attacks. Sixty SUNA (45.5%) and 49 TN patients (64.5%) experienced attacks exclusively during waking hours. Seventy-two SUNA (16.7%) and 27 TN (35.5%) patients also experienced attacks during sleep. Among this group, three SUNA and one TN patient had mainly nocturnal attacks. Data was not available for one SUNA and three TN patients.

One hundred and twenty-six SUNA (94.7%) and all TN patients (100%) could not reliably predict the occurrence of their attacks. Five SUNA (3.8%) experienced mostly random attacks along with some predictable attacks, which would occur at fixed times. In two SUNA patients (1.5%) attacks were generally predictable: one patient stating that his attacks occurred consistently at 3am, 8am and 1pm every day and another patient at 1am and 10am. Only one TN patient (1.3%) stated that her attacks were mostly random with one predictable attack, which would occur at 4 am.

6.5.14. Periodicity and chronicity of SUNA and trigeminal neuralgia

According to the definition of episodic and chronic short-lasting unilateral neuralgiform headache attacks proposed in the ICHD-3β criteria (Headache Classification Subcommittee of The International Headache, 2013), 120 SUNA (90.2%) in our cohort could be classified as chronic and 13 (9.8%) as episodic. Although the ICDH-3β criteria for TN do not subdivide the condition in chronic and episodic, TN is considered a recurrent episodic disorder. In our cohort, 43 patients displayed an episodic pattern

(54.4%) and 34 a chronic pattern (43.0%); of the latter group, 21 patients reported a chronic pattern from the onset of the condition and in 13, the condition started as episodic and became chronic over time. Two patients could not make any statement on their facial pain pattern, since they had always been on preventive medications.
The median number of bouts per year in episodic SUNA and "episodic" TN were two (SUNA range: 1 every two years to 12 per year) (TN range: 1-6 per year), each one lasting a median of 2.75 months in SUNA (range: 1 week to 16 months) and three months in TN (range: 15 days to 10 months).

6.5.15. Interictal pain in SUNA and trigeminal neuralgia

Sixty-four SUNA (48.1%) patients reported interictal background pain between exacerbations. In the TN cohort, 70 patients had classical TN purely paroxysmal and nine patients had classical TN with concomitant persistent facial pain. Twenty-three TN patients (29.1%) reported some degree of intermittent interictal background facial pain: these included all patients with TN with concomitant persistent facial pain and 14 of the 70 patients with classical TN purely paroxysmal (20.3%). Data were incomplete for one patient. In 14 of the 23 TN patients (60.9%) the interictal pain coincided with the original onset of the stabbing pain, similarly to the SUNA group (63.0%). In the remaining TN patients, two reported the onset of interictal background pain when the condition became chronic and two reported the onset of interictal pain 13 and 15 years after the onset of the paroxysmal pain.

In our TN cohort, 40 patients had a personal history of migraine (50.6%; 2 missing data) and 43 patients (56.6%; 3 missing data) had a migraine biology (suggested by the presence of a personal and/or family history of migraine). A migraine biology was significantly more represented in the SUNA (n=88 patients, 71%) rather than the TN cohort (p=0.037).

6.5.16. MRI findings in trigeminal neuralgia

Seventy-two TN patients had an MRI scan of the brain, though not all of them had the investigation within our National Health Service (NHS) Trust. This prevented us from systematically compare the MRI findings in the TN cohort with the ones of the SUNA

cohort. Twenty-one patients had no NVC conflict (29.2%), 33 had an ipsilateral NVC (45.8%), which was caused by an artery in 31 of 33 patients. Five patients had a contralateral loop (6.9%) and 13 patients a bilateral loop (18.1%). A total of 46 patients (63.9%) had either a unilateral loop ipsilateral to the pain side, or bilateral loops. With the available data we could not comment on the severity of the contact. Data on MRI scans was missing for 7 patients.

6.5.17. Clinical predictors for SUNA or trigeminal neuralgia

Table 63 outlines the results of the unadjusted univariate logistic regression analysis for different demographic and clinical predictors for a diagnosis of SUNA or TN. The clinical features were selected from the diagnostic criteria for SUNA and TN and from characteristics that were deemed clinically relevant based on this study's outcomes. Clinical predictors for SUNA rather than TN included age of onset, alternating side of the attacks, occurrence of pain in the ophthalmic trigeminal division, duration of attacks longer than 5 minutes, plateau-like profile of the attacks, the presence of spontaneous only attacks and the chronic pattern. Clinical predictors for TN included occurrence of pain in V3, electric shock-like and shooting quality of pain, duration of the painful attacks of <1-minute, single stabs profile of the attacks and the presence of triggered only attacks.

A backward regression model was then applied to the two cohorts and those variables that were predictive for SUNA or TN according to the unadjusted logistic regression analysis in Table 11, were selected The quality of pain variable was not included in the adjusted analysis. This is because the electric shock-like, shooting, stabbing and sharp are all together included under domain C of the IHS diagnostic criteria of TN, hence of limited predictive value. A multivariate logistic regression analysis on these variables, adjusted for age of onset of the headache and gender, confirmed that pain in V1 is a predictor for SUNA; that attacks duration <1 minute is a predictor for TN, but that different attacks profile are not linked with one of the other condition; spontaneous only attacks and triggered only attacks are predictors respectively for SUNA and TN and a chronic pattern of occurrence the disorder is a predictor for SUNA rather than TN (Table 64).

The variable “refractory period” was analysed separately from the rest of the clinical variables, since it was applicable only for those SUNA and TN patients who reported attacks triggered by cutaneous stimulation: n=146 patients, n=71 SUNA patients and n=75 TN patients. Data was missing for one SUNA patient. The univariate regression analysis for this subgroup of patients showed highly statistically significant association between TN and the presence of a refractory period [OR: 0.06; 95%CI: 0.02, 0.28, p-value <0.001]. Similarly, there was a highly statistically significant association between SUNA and the absence of a refractory period [OR: 16.7; 95%CI: 3.6, 50.0, p-value <0.001].

Table 63. Unadjusted logistic regression analysis outlining demographic and clinical predictors for SUNA compared to trigeminal neuralgia syndrome.

	SUNA	**Trigeminal neuralgia**	**p-value**
	Odds ratio (95% CI)	**Odds ratio (95% CI)**	
Gender; female versus male	0.93 (0.53, 1.67)	1.07 (0.60, 1.89)	0.811
Age of onset	1.05 (1.03, 1.07)	0.95 (0.93, 0.97)	<0.001
Side of pain; Right Left Alternating/Bilateral	 Ref 1.42 (0.78, 2.56) 7.3 (1.64, 33.25)	 Ref 0.70 (0.39, 1.28) 0.14 (0.03, 0.61)	 0.250 0.009
Site of pain; V1 versus not V1 V2 versus not V2 V3 versus not V3	 13.75 (6.95, 27.21) 0.96 (0.50, 1.84) 0.25 (0.14, 0.44)	 0.07 (0.036, 0.14) 1.04 (0.54, 2.00) 4.00 (2.27, 7.27)	 <0.001 0.901 <0.001
Quality of pain; Electrick shock versus not Shooting versus not Stabbing versus not Sharp versus not	 0.21 (0.12, 0.39) 0.49 (0.27, 0.88) 1.15 (0.57, 2.33) 1.20 (0.68, 2.11)	 4.60 (2.52, 8.41) 2.01 (1.13, 3.60) 0.87 (0.43, 1.75) 0.83 (0.47, 1.46)	 <0.001 0.018 0.691 0.525
Duration attacks; <1 min 1-2 min 2-3 min 3-4 min 4-5 min >5 min	 0.22 (0.11, 0.44) 0.87 (0.38, 1.98) Ref 2.43 (0.26, 2.22) 4.54 (1.01, 20) 10.0 (7.69, 1.28)	 4.44 (2.27, 8.67) 1.15 (2.27, 2.63) Ref 0.41 (0.45, 3.76) 0.22 (0.05, 0.99) 0.10 (0.13, 0.78)	 <0.001 0.739 Ref 0.433 0.500 0.028
Pain profiles; Single stabs versus not Repetitive stabs versus not Serrated pattern versus not Plateau-like versus not	 0.27 (0.14, 0.50) 1.34 (0.76, 2.35) 1.54 (0.87, 2.71) 3.81 (1.40, 10.34)	 3.76 (1.99, 7.10) 0.75 (0.43, 1.31) 0.65 (0.37, 1.15) 0.26 (0.10, 0.71)	 <0.001 0.308 0.138 0.009
Type of attack; Spontaneous and triggered Spontaneous only Triggered only	 Ref 9.70 (3.31, 28.44) 0.19 (0.67, 0.54)	 Ref 0.10 (0.03, 0.30) 5.26 (1.49, 1.85)	 <0.001 0.002
Headache pattern; Episodic Chronic	 Ref 11.67 (5.64, 24.17)	 0.09 (0.04, 0.18)	 <0.001

CI: confidence interval; Ref: reference; min: minute; SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; V1: ophthalmic trigeminal territory; V2: maxillary trigeminal territory; V3: mandibular trigeminal territory;

Table 64. Multivariate logistic regression analysis adjusted for demographic and clinical variables considered potentially different between SUNA and trigeminal neuralgia

	SUNA	**Trigeminal neuralgia**	**p-value**
	Odds ratio (95% CI)	**Odds ratio (95% CI)**	
Site of pain; V1 versus not V1 V3 versus not V3	 11.29 (3.92, 35.50) 0.81 (0.29, 2.29)	 0.088 (0.31, 0.26) 1.24 (0.44, 3.51)	 <0.001 0.689
Duration attacks; <1 min >5 min	 0.13 (0.36, 0.44) 2.39 (0.17, 33.32)	 7.95 (2.30, 27.57) 0.42 (0.30, 5.86)	 0.001 0.518
Pain profiles; Single stabs versus not Plateau-like versus not	 0.71 (0.25, 1.99) 3.36 (0.73, 15.60)	 1.42 (0.50, 3.98) 0.30 (0.06, 1.38)	 0.510 0.121
Type of attack; Spontaneous and triggered Spontaneous only Triggered only	 2.94 (0.65, 13.27) 44.40 (4.50, 437.83) Ref	 0.34 (0.08, 1.53) 0.02 (0.00, 0.22)	 0.161 0.001
Headache pattern; Episodic Chronic	 Ref 13.19 (4.04, 43.08)	 0.076 (0.02, 0.25)	 <0.001

CI: confidence interval; Ref: reference; min: minute; SUNA: short-lasting unilateral neuralgiform headache attacks with autonomic symptoms; V1: ophthalmic trigeminal territory; V2: maxillary trigeminal territory; V3: mandibular trigeminal territory;

6.6. Discussion

In this study we compared substantial cohorts of SUNA and TN patients. Clinical differences and similarities between these disorders have hitherto come only from indirect comparison between small series of SUNCT and SUNA patients and old trigeminal neuralgia studies. This study for the first time performed a direct comparison of the clinical features of both conditions. This comparison aimed to formalise differences and similarities that could help physicians in the diagnostic process of patients with short-lasting neuralgiform headache attacks and in turn improve their treatment.

6.6.1. Demographic and clinical features of SUNA and trigeminal neuralgia

6.6.1.1. Gender and age

This study did not support gender predilection as a useful distinguishing feature between SUNA and TN. Indeed, a female preponderance in both SUNA and TN cohorts was found. TN begins approximately a decade later than SUNA, supporting preliminary findings that reported the average age of onset of SUNCT and SUNA in the fifth decade (Cohen , et al., 2006). However a retrospective analysis of the age at symptoms onset in 219 classical TN patients, showed that individuals with TN and absence of trigeminal NVC have a earlier symptoms onset (mean of 42.6 years) compared to those with trigeminal NVC (mean 51.1 years). This difference was statistically significant (Ko, et al., 2015). These initial evidence suggest that NVC is neither sufficient nor necessary for the development of TN, similarly to the current understanding of SUNA pathophysiology.

6.6.1.2. Laterality of pain

Unlike in TN, side-alternating cases of SUNCT have been reported (Cohen , et al., 2006; D'Andrea , et al., 2001; Sabatowski , et al., 2001). In our cohorts the presence of unilateral but side alternating headache attacks, albeit rare, was linked with SUNA rather than TN. The possible pathophysiological mechanisms that may explain the the occurrence of unilateral side-alternating attacks in SUNA may reside in the different predilection of central as opposed to more peripheral mechanisms likely to be of importance in SUNA pathophysiology. An fMRI study has shown that hypothalamic activation during SUNCT/SUNA attacks is not always unilateral ipsilateral to the pain side, but it could be bilateral or contralateral (Cohen, 2007). Additionally, severe trigeminal neurovascular conflicts are associated with the symptomatic nerve in SUNA according to our findings. It is therefore conceivable that in some patients with alternating unilateral attacks with a one-sided vascular contact, the presence of bilateral

or contralateral hypothalamic activation may be responsible for attacks side shifting.

6.6.1.3. Site of pain

The current IHS diagnostic criteria for both SUNCT, SUNA and TN state that the pain location for these disorders can involve any branches of the trigeminal nerve. Studies in SUNCT and TN have consistently demonstrated a predilection for V1 in SUNCT/SUNA and for V2 and V3 in TN (Pareja , et al., 1997; Cohen , et al., 2006; Rasmussen , 1991). This was confirmed in our study, which showed that pain in V1 is a clinical predictor for SUNA rather than TN. Despite several studies demonstrating cases of isolated V1 TN, it is still unclear whether the phenotype of these conditions modifies overtime manifesting features more in keeping with TN, such as radiation of pain in V2-V3 trigeminal territories or in keeping with SUNA, such as combination of pain and cranial autonomic activation (Rasmussen , 1991; Maarbjerg , et al., 2014).

6.6.1.4. Severity of the pain

One of the ICHD-3β diagnostic criteria for TN state that the painful attacks have to be severe. This contrasts with the level of severity of the short-lasting neuralgiform headache attacks criteria, where the level of pain can be moderate as well as severe (Headache Classification Subcommittee of The International Headache, 2013). Our findings demonstrate that a moderate level of pain can be seen in TN patients as well as in SUNA patients. Our data therefore do not support the use of pain intensity to discriminate between SUNA and TN.

6.6.1.5. Duration of attacks

The attacks duration outlined by the ICHD-3β diagnostic criteria for the Short-lasting unilateral neuralgiform headache attacks and for TN ranges respectively between 1-600 seconds and between a fraction of a second to 120 seconds (Headache Classification Subcommittee of The International Headache, 2013). The importance of attack duration in TN has been studied in a cohort of 81 patients divided into a short-lasting attack group and long-lasting attack group, according to the duration of the attacks (short

group= duration of attacks less than 2 minutes; long group= duration of attacks more than 2 minutes). The clinical features of the two groups were compared. Individuals with long attack duration were more likely to report interictal background pain and attacks while asleep. However, there was no difference in the proportion of patients with associated autonomic symptoms reported in both groups as well as pain location and duration of the condition. The Authors speculated that TN with long attack duration may be part of the SUNCT/SUNA spectrum, since a significant proportion of these patients also reported interictal background pain and cranial autonomic features accompanying the pain (Haviv , et al., 2016). This may also explain why the group of patients with longer-lasting attacks responded less to established TN medications used in this trial including carbamazepine, baclofen and gabapentin. Interestingly, lamotrigine, the drug of choice in SUNA was rarely employed in this study (Benoliel et al, 2016).

In this context, our findings suggesting that attacks lasting <1 minute and >5 minutes were predictors for TN and SUNA, respectively, and thereby suggest the notion that patients with longer lasting attacks may belong to the SUNA clinical spectrum.

6.6.1.6. Cranial autonomic symptoms

Autonomic symptoms have been reported in several case series of TN, perhaps in a less intense and consistent fashion than in SUNA (Sjaastad , et al., 1997; Rasmussen , 1991a; Simms , et al., 2011). In line with previous studies, a small proportion of our TN patients reported some level of autonomic activation. In most cases this included one single autonomic feature, mild in intensity and sporadic occurrence. Interestingly even patients with V2-V3 pain location reported cranial facial autonomic features. This characteristic was also reported in a previous study, suggesting that not only in patients with V1 TN, a diagnosis of SUNA should be excluded, rather in every TN patient, even those with pain in V2-V3, the association with cranial autonomic features is possible (Simms , et al., 2011). This renders the differential diagnosis between TN and SUNA even more complex and their overlap more prominent.

It has been suggested that the presence of autonomic symptoms may not be a function of pain intensity nor related to attacks duration (Sjaastad , et al., 1997; Haviv , et al., 2016). Using the same cut-off for longer attacks of 120 seconds, our data were in

keeping with the latter finding, showing that the majority of TN patients that experienced some cranial autonomic symptoms had ≤120 seconds.

It remains unknown why TN can be accompanied by cranial autonomic activation. It has been postulated that since first division nociceptive input results in cranial parasympathetic activation and cranial autonomic features are present in migraine, the other TACs and experimental head pain, they could also be expected in V1 TN. In this context, it has been suggested that the difference between SUNCT and V1 TN would not be outlined by the presence of cranial autonomic symptoms but rather the degree of intensity and their consistency (Goadsby , et al., 2001). However, it could also be speculated that the short-lasting neuralgiform headache attacks group constitute a clinical spectrum of disorders, which encompasses core clinical features including the neuralgiform type of pain, the very short duration and high frequency of the attacks, the triggerability of the attacks, and the presence of a refractory period. This disorder manifests itself with different degrees of cranial autonomic signs that if pronounced, reflect the SUNA phenotype, whereas if sparse, the TN one (Lambru , et al., 2014).

6.6.1.7. Triggers and Refractory Period

The vast majority of patients in both cohorts reported spontaneous as well as triggered attacks, which were mainly innocuous cutaneous/intraoral stimulations. However, the presence of cutaneous triggered attacks only predicted a diagnosis of TN, whereas the presence of spontaneous attacks only predicted a diagnosis of SUNA. Furthermore, certain triggers such as cold air drafting on the symptomatic side of the face, hair brushing and swallowing were significantly more frequently reported by SUNA patients. Conversely, chewing, light touch, brushing teeth, talking were significantly more prevalent in the TN cohort. This is the first study suggesting that certain triggers may have a predilection for SUNA or TN. It is difficult to advance any pathophysiological explanation for this difference. It is noteworthy that triggers directed to upper part of face or head predominate in SUNA while those that were directed to the lower part of the face predominate in TN; this is probably reflective of the distribution of pain. Furthermore, neurophysiological studies using conventional trigeminal reflexes and trigeminal laser evoked potentials in TN associated with a

trigeminal neurovascular contact showed a profile in keeping with possible unilateral dysfunction of small nociceptive fibres, namely Aδ fibres, which improved after trigeminal microvascular decompression (Truini, et al., 2007; Obermann , et al., 2007). Preliminary neurophysiological studies in a small group of SUNCT revealed no nociceptive afferents abnormalities. However, the Authors did not specify if patients had attacks triggered by cutaneous stimulation or whether MRI scans revealed any trigeminal neurovascular conflict (Truini , et al., 2006). It is possible that in SUNA patients, alongside a dysfunction in Aδ fibers, there is an involvement of C-fibers responsible for cold/wind-triggered attacks as well as the interictal dull background headache, which occurs frequently in SUNA patients according to our findings.

The absence of a refractory period after attacks triggered by innocuous cutaneous stimulation in SUNCT and SUNA has been proposed as one of the key clinical difference from TN, where patients are known to be able to keep stimulating the trigger area without evoking any further pain (Kugelberg, et al., 1959). However, this historical notion was not supported by robust evidence. Our study demonstrates the clinical validity of the concept of a refractory period applied for SUNA as well as for TN and confirms preliminary findings from other studies (Cohen , et al., 2006; Rasmussen , 1991a). However, it demonstrates that about 1/3 of TN patients do not report a refractory period between triggered attacks. This is a novel finding, which contrasts with the traditional view expressed in the TN literature and enforces the overlap between SUNA and TN.

The refractory phase is thought to be caused by a neuronal hyperpolarization mechanism, which prevents cutaneous stimulation to cross-talk to nociceptive afferents for a variable amount of time (Devor , et al., 2002). This phenomenon possibly reflects healthy brainstem and diencephalic antinociceptive circuits. The absence of a refractory period in SUNA may be caused by a derangement of these antinociceptive structures like the hypothalamus, which are perhaps also impaired in those TN patients who do not report a refractory phase. Future studies will need to address this hypothesis.

6.6.1.8. Interictal pain

TN patients in whom the paroxysmal pain is associated with background pain have traditionally been labelled as "Atypical TN" and more recently as classical TN with concomitant persistent facial pain. The presence of a constant background pain seems to occur in patients who experience other "atypical" clinical features, namely longer attacks duration (Haviv , et al., 2016), less triggerability and poor medical and surgical treatment response (Headache Classification Subcommittee of The International Headache, 2013). Recent studies on consecutive TN patients showed that the occurrence of concomitant persistent facial pain is frequent, ranging between 29-49% of TN patients (Maarbjerg , et al., 2014; Haviv , et al., 2016). In SUNA, approximately half of patients report background interictal pain, according to our and others' SUNA series (Cohen , et al., 2006). However, SUNA with background pain is not considered an atypical subtype of SUNA with purely paroxysmal attacks, partly because of lack of comparative studies between SUNA with and without background pain and partly because the presence of background pain is an accepted clinical feature for the other TACs (Marmura , et al., 2012). Given the higher prevalence of migraine biology in SUNA compare to TN, it could be postulated that the susceptibility to a central nervous system disorder such as migraine, facilitates the occurrence of central sensitization and in turn the simultaneous occurrence of both the paroxysmal and the constant background pains more in SUNA rather than in TN patients.

6.6.1.9. Chronic and episodic subtypes

TN is considered a recurrent disorder with a relapsing remitting pattern of occurrence. However, a recent large prospective study showed that 37% of TN patients displayed a chronic pattern (Maarbjerg , et al., 2014). Similarly, in our cohort, 43% of patients had a chronic unremitting subtype. However, unlike SUNCT and SUNA, there is no mention of episodic or chronic subtypes for TN in the ICHD-3β (Headache Classification Subcommittee of The International Headache, 2013). We also demonstrated that the chronic pattern is predictive of SUNA rather than TN. Together these data suggest that the periodicity of occurrence of SUNA and TN is a meaningful clinical characteristic to help direct the diagnosis and stratify patients for treatments.

On this basis, it would be reasonable to subdivide TN into episodic and chronic similarly to the current SUNCT and SUNA criteria.

6.6.1.10. Trigeminal neuralgia diagnostic criteria analysis

Our clinical findings from the TN cohort were applied to the TN ICHD-3β diagnostic criteria. Of the 79 TN patients, 75 fulfilled the criteria, whereas four did not (5.1%). Three out of these four patients did not fulfilled the criteria because of attacks duration longer than 120 seconds and moderate attacks intensity. One patient because of moderate attacks intensity and lack of triggerable attacks. It is noteworthy that none of these four patients reported cranial autonomic features with the paroxysmal attacks, so a diagnosis of SUNA was ruled out; two patients reported pain in V1 trigeminal territory but not as the sole pain location; three patients did not report any interictal background pain and one reported some interictal pain; two patients had a family or personal history of migraine, hence displaying a migraine biology; finally three patients had a good or excellent response to carbamazepine, whereas for one patient data on the medications history was not available. Based on these clinical non-ICHD-3β features, we thought the diagnosis of TN was the most reasonable one. Furthermore ten TN patients reported mild lacrimation with some attacks. All the other clinical features were in keeping with the TN ICHD-3β diagnostic criteria, so it was decided to keep them within the TN group instead of considering them SUNA where cranial autonomic features normally occur with the majority of the attacks (Table 60).

According to our findings, the current TN diagnostic criteria could be refined to reflect more accurately the clinical differences with SUNA that emerged in this study. We propose a change in criterion A, since we think that three attacks may not be sufficient to support a robust diagnosis of TN in view of its complex phenotype and differential diagnosis. In view of the fact that the majority of patients with cranial autonomic signs or symptoms had pain in V1 associated with lacrimation, we propose criterion D, which does not allow a diagnosis of TN to be made in presence of associated cranial autonomic symptoms. Finally, since the presence of a refractory period is associated with TN according to our analysis, we propose, similarly to the framework of the proposed SUNA criteria (Chapter 2), to include the statement regarding the presence of refractory

periods following triggered attacks under Criterion C to reflect this clinical link. We acknowledge that some patients do not persevere with the cutaneous stimulation that triggered the initial attack, in view of its intensity, hence for some patients this criterion may not be relevant. However, when the clinical information on a refractory period is available, it may facilitate the differential diagnosis between TN and SUNA. The new proposed TN diagnostic criteria are outlined in Table 65 and reflect the complexity of this disorder, which emerged from our study.

To complete the TN clinical profile that arose from our analysis, we propose the inclusion of some clinically relevant features that may help distinguishing TN from SUNA further. Firstly, since pain in V1 is a predictor for SUNA rather than TN, we propose the inclusion of a statement suggesting that in TN the pain has a predilection for the second and/or third divisions of the trigeminal nerve, with possible radiation to the first trigeminal nerve division, We also proposed to include in the TN diagnostic criteria' notes that in TN there is a predilection for an episodic relapsing remitting pattern of occurrence rather than chronic. Furthermore, the TN diagnostic criteria' notes should highlight that patients with attacks exclusively triggered by innocuous cutaneous stimuli are more likely to have TN. Similarly, the SUNA diagnostic criteria' notes should mention the predilection for the pain to occur more frequently in the first division of the trigeminal nerve, with possible radiation to the second and third divisions; the predilection for a chronic pattern of occurrence, rather than episodic and the likelihood that patients with exclusively spontaneous attacks are more likely to have SUNA. Furthermore, since the presence of interictal pain has now been confirmed as an established clinical feature of SUNA, occurring in approximately half of patients, the possible presence of interictal pain should be reflected in the SUNA diagnostic criteria' notes. Future studies will need to establish whether the presence of interictal pain is associated with different clinical, radiological and therapeutic outcomes compared to SUNA patients with paroxysmal pain only.

Table 65. Proposed criteria for unified diagnosis of trigeminal neuralgia

A. At least *20 attacks* of unilateral facial pain fulfilling criteria B–E

B. Occurring in one or more divisions of the trigeminal nerve, with no radiation beyond the trigeminal distribution

C. Pain has at least three of the following *five* characteristics:

1. Attacks lasting a fraction of a second to 120 seconds
2. Severe intensity
3. Electric shock-like, shooting, stabbing or sharp in quality
4. Precipitated by innocuous stimuli to the affected side of the face
5. *A refractory period can follow attacks triggered by innocuous stimuli to the affected side of the face*

D. No cranial autonomic signs or symptoms accompany the paroxysmal attacks.

E. No clinically evident neurological deficit.

F. Not better accounted for by another ICHD-3 diagnosis

This study has some limitations. The duration and frequency of occurrence of the headache attacks were subjectively estimated by the patients and only seldom objectively measured. However, in view of the variable duration of the attacks and often the multiple number of daily attacks, it is difficult to ask patients to produce headache-specific diaries and headache diaries used for other conditions (migraine and CH) may not be entirely appropriate to TN.

6.7. Conclusion

A detailed comparison of demographic and clinical characteristics in SUNA and TN has been conducted. The need for such as study came from the notion that the two conditions share several clinical characteristics that are otherwise not commonly seen in the other TACs. The laterality, trigeminal distribution of pain and the associated cranial autonomic features are characteristics that SUNA shares with the other TACs as well as with TN. Conversely, the neuralgiform quality of pain, the very short duration of attacks, the triggerability by cutaneous stimulation and the concept of a refractory period are features shared solely between SUNA and TN. This striking similarity have instigated more interest in the TN phenotype, with recent studies revisiting what was

thought to be an established disorder. TN is more complex than previously thought to be the case. Recent studies have highlighted certain clinical features in TN patients, such as the presence of cranial autonomic signs, the frequent occurrence of interictal pain, and the variable duration of the paroxysms (Maarbjerg , et al., 2014; Haviv , et al., 2016), which become relevant in the context of the clinical overlap with SUNA and call into question whether TN and SUNA should be considered distinct entities or rather a continuum of the same disorder (Lambru , et al., 2014). One school of thoughts believes that SUNCT, SUNA and TN are distinct disorders, which overlap in view of the fact that the symptoms are driven by the trigeminal system, which is the final common pathway for these conditions (VanderPluym , et al., 2015). This hypothesis does not explain why SUNCT and SUNA share many more clinical features with TN as opposed to the other TACs, which also use the trigeminal system as final pathway. Another school of thoughts proposed a broader nosological concept where SUNCT, SUNA and TN constitute different aspect of the same entity (Lambru , et al., 2014). The cornerstone clinical domains of this continuum include: the unilateral occurrence of pain; the neuralgiform quality of the pain; the trigeminal distribution of pain; the short-lasting duration of painful paroxysms (1 seconds to 600 seconds); the association of pain and cranial autonomic features; the triggerability of paroxysms by cutaneous/intraoral innocuous stimulation; and, the refractory period. Additionally, the response to sodium channel blockers and the radiological association with trigeminal neurovascular conflict complete the clinical spectrum. Differences between the clinical entities that constitute this spectrum exist and reflect different expressions of the shared clinical domains. This study demonstrates that different sites of the pain, attacks duration, triggerability of attacks, presence of a refractory period and headache pattern are predictors for SUNA or TN. To this list we should add the presence of cranial autonomic features, which can occur in a proportion of TN patients as demonstrated in several studies (Rasmussen , 1991a; Sjaastad , et al., 1997; Simms , et al., 2011; Maarbjerg , et al., 2014; Haviv , et al., 2016). We proposed that patients with clinical features otherwise fulfilling the TN criteria but with pain associated with cranial autonomic signs and symptoms are now classified as SUNA. In the context of a clinical continuum, these differences may help stratifying patients for management purposes including medical and surgical approaches, rather than forcing them into different diagnostic categories largely dictated by the need to maintain some diagnostic barriers. This proposed concept may also stimulate further research onto the understanding of

hybrid forms of facial pain with some features of SUNA and TN, which currently have no place in the IHS classification, expanding the knowledge of these complex disorders.

Chapter 7. Discussion

This thesis investigated and compared the clinical aspects of SUNA, SUNCT and TN by prospectively phenotyping large cohorts of patients. This study tried to answer unresolved questions of pivotal importance from a clinical, therapeutic, pathophysiological and nosological perspectives.

7.1. Are SUNCT and SUNA different entities or variants of the same clinical entity?

Since the publication of the diagnostic criteria in the IHS classification in 2004, SUNCT was considered a subtype of a broader entity called SUNA, where the association with one cranial autonomic feature was sufficient to meet the diagnostic criteria (Headache Classification Subcommittee of The International Headache Society., 2004). However, up to now only case reports and small series of patients with SUNA had been described calling into question the existence of this condition (Sjaastad , 2008). The clinical characteristics of SUNA were described in this study and SUNA was validated as a clinical entity. A variety of reasons could account for its rare occurrence. The reduced cut-off number of cranial autonomic features to one, means that the diagnostic distinction from TN became less defined. It is therefore possible that a significant proportion of SUNA patients is misdiagnosed as TN, which is a condition diagnosed and managed by multiple specialists including dentists, neurosurgeons, maxillo-facial surgeons, ENT and pain specialists as well as neurologists; many of these specialities are unaware of SUNCT and SUNA as these are relatively recently described entities and the bulk of the literature is published in neurology journals. This may explain the small number of SUNA patients referred to a headache or neurology clinic.

Our findings suggest that the clinical phenotype of SUNA does not differ significantly from the one of SUNCT, apart from a different degree of activation of the parasympathetic system and dysfunction of the sympathetic system, largely reflecting the different number of autonomic features decided by the IHS Classification Committee for SUNCT and SUNA.

In view of the clinical similarities with TN, growing interest around the association between SUNCT/SUNA and MRI findings of ipsilateral trigeminal neurovascular conflict have been reported (Favoni , et al., 2013). However, the extent and the nature of this association have been unknown. Our study demonstrated that trigeminal neurovascular contact ipsilateral to the side of the pain is a common neuroanatomical variant in SUNCT and SUNA. Furthermore, we demonstrated that a severe neurovascular conflict at the REZ was significantly associated with the symptomatic trigeminal nerve without any significant difference between SUNCT and SUNA. Based on these findings, it could be postulated that severe neurovascular conflict plays an important aetiological role in these disorders, at least in patients who demonstrate evidence of neurovascular conflict, and that SUNCT and SUNA display a pathophysiological overlap.

The medical treatment of SUNCT and SUNA has been considered challenging in view of limited quality data. Chapter 4 provided the largest open-label prospective evidence on medical treatments' outcome in SUNCT and SUNA patients. Our results demonstrate the remarkable efficacy of sodium channel blockers, namely lamotrigine as an oral drug and lidocaine as intravenous formulation, which are the drugs of choice for SUNCT and SUNA. Oxcarbazepine and duloxetine were found to be effective as well as to a lesser extent carbamazepine, possibly due to patients' selection bias issues. Less impressive results were reported by the use of gabapentinoids and topiramate, which may be helpful as add on treatments to the first and second line treatments. Lacosamide and mexiletine were also found to be effective in a small number of patients, though a significant proportion of patients discontinued the treatments in view of tolerability issues. No significant differences between SUNCT and SUNA were observed in the outcomes of the most effective treatments, namely lamotrigine, oxcarbazepine and IV lidocaine. Furthermore, no significant differences were demonstrated in the outcomes of two series of patients with medically refractory SUNCT and SUNA patients who underwent trials of ONS and trigeminal MVD. These data suggest a therapeutic overlap between SUNCT and SUNA.

Based on these clinical, radiological and therapeutic findings we propose that SUNCT and SUNA are considered a single clinical entity under the name SUNA, a term that highlights the occurrence of a broad array of cranial autonomic features besides

conjunctival injection and lacrimation. A new set of diagnostic criteria have also been proposed for this unified entity.

7.2. SUNA and trigeminal neuralgia: separate entities or a continuum of the same disorder?

The striking clinical similarities between SUNCT/SUNA (labelled as SUNA according to our data from hereon in) and TN, have instigated a wide still unresolved debate on whether these disorders constitute different entities or whether they constitute a continuum of the same disorder. Several reviews and editorials have supported one or the other hypothesis, basing their assumptions on indirect comparison of clinical studies (Lambru , et al., 2014; VanderPluym , et al., 2015; Benoliel , et al., 2017; Wöber , 2017; Uniyal , et al., 2017). The main clinical arguments supporting the hypothesis that SUNA and TN are distinct disorders include pain location, predominantly in V1 in SUNA and V2-V3 in TN; the longer duration of attacks in SUNA compared to TN; the presence of associated cranial autonomic symptoms in SUNA and their absence in TN and the absence vs presence of a refractory period respectively in SUNA and TN. However, what clearly transpires from looking at the differential diagnosis between SUNA and TN and between SUNA and the other TACs, is that the latter association shares only few common clinical domains, namely the association of pain with cranial autonomic features, the occurrence of multiple attacks/day and the predilection for the V1 trigeminal distribution of the headache. Clinical features such as circadian and circannual periodicity, predilection for awakening-attacks and restless behaviour during attacks and triggerability by alcohol, which are some of the cornerstone clinical features of CH and to some extend of the other TACs, are very seldom encountered in SUNA patients. Conversely, the comparison between SUNA and TN abounds with shared clinical domains that constitute their clinical framework. These include: the neuralgiform quality of the painful paroxysms, the very short duration of the attacks, the multitude of daily attacks, the triggerability of attacks by innocuous cutaneous stimulation and the concept of a refractory period. The discrepancy in cranial autonomic activation between SUNA and TN have been claimed as one of the main clinical differences between the two disorders. Despite the presence of some degree of autonomic symptoms in TN, the prominent degree and consistency of occurrence with

most attacks seen in SUNA have been suggested to reflect a different pathophysiological substrate compared to TN, namely a hypothalamic dysfunction (Goadsby , et al., 2001). To date, no studies have addressed the presence of a hypothalamic derangement in TN. A case series of five patients with V1-2-3 TN and multiple sclerosis treated with hypothalamic stimulation, showed that the therapy was able to control the V1 pain, but not the V2-V3 pain for which, patients required other treatments (Cordella, et al., 2009). Although this group of patients did not have classical TN, the study results may suggest that the hypothalamus may not play a key role in V2-V3 trigeminal neuralgiform pain disorders.

However, it could be postulated that at least in cases of TN transforming into SUNA and coexistence of TN and SUNA in the same individual, shared pathophysiological mechanisms known to be involved in TN and SUNA, namely an impairment of posterior hypothalamic circuits and trigeminal neurovascular conflict may be implicated. Although the issue of the role of the hypothalamus in TN cannot be currently resolved, our findings nonetheless support the aetiological link between severe trigeminal neurovascular conflict and SUNA in a proportion of patients which is remarkably similar to TN one (Maarbjerg , et al., 2014). Furthermore, the efficacy of trigeminal MVD showed in our study together with the results of a previously published case series, support the pathophysiological role of trigeminal neurovascular conflict at least in a consistent subgroup of SUNA patients (Williams , et al., 2010). For the remaining patients, other pathophysiological mechanisms may play a role. The efficacy of sodium channels blockers displayed in our SUNA cohorts suggests another possible common denominator in the pathogenesis of SUNA and TN, with sodium channels dysfunction being an attractive hypothesis (Lambru , et al., 2012). A sodium channelopathy may be one of the pathophysiological substrates in those cases where a trigeminal neurovascular conflict is not found or where the degree of contact is mild. Although the presence of abnormal hypothalamic activation in SUNA remains the main pathophysiological link between SUNA and the other TACs, the lack of any association with trigeminal neurovascular conflict along with the lack of efficacy to sodium channel blockers in the other TACs may render the pathophysiological link between SUNA and the other TACs less robust.

Based on our studies' findings, we challenge the traditional view that consider SUNCT, SUNA and TN separate disorders and propose the concept of a broader nosological

entity, named “Short-lasting trigeminal neuralgiform attacks” that represents a clinical continuum between SUNA and TN. The clinical framework of this entity is based on fundamental clinical domains including: the unilateral trigeminal distribution of the pain episodes; the neuralgiform paroxysmal quality of the pain; the short-lasting duration of painful paroxysms (1 seconds to 600 seconds); the association of pain with a variable degree of cranial autonomic features; the triggerability of paroxysms by cutaneous/intraoral innocuous stimulation; and the refractory period. Variations within these clinical domains lead to a SUNA or a TN phenotype. Hybrid cases that present clinical features of SUNA and TN but that do not fulfil their diagnostic criteria are encountered in clinical practice (Authors’ clinical experience) and more research is needed to further characterised these cases. In Chapter 6 we identified clinical predictors for SUNA rather than TN that include: pain in V1, paroxysms duration >5 minutes, entirely spontaneous attacks, absence of a refractory period and chronic pattern of occurrence. Conversely, clinical predictors for a TN phenotype rather than SUNA include: short duration of paroxysms (<1 minute), entirely triggered attacks, presence of a refractory period and episodic pattern of occurrence. Based on these findings, we proposed a new set of diagnostic criteria for TN that aim to clarify the differential diagnosis with SUNA. The presence of cranial autonomic features varies across the spectrum, with SUNA patients reporting multiple and prominent cranial autonomic symptoms on one end and patients with TN with no autonomic features on the opposite end of the spectrum. This unified clinical entity may reflect a unifying pathophysiological model, characterized by different degrees of interaction of more peripheral and central mechanisms, namely focal demyelination of the trigeminal sensory root, a sodium channelopathy and posterior hypothalamic dysfunction. These mechanisms could account for the phenotypic variability within this clinical continuum. Central mechanisms may be more pronounced in patients with cranial autonomic symptoms and less pronounced in patients with one or no autonomic symptoms. Additionally, it is possible that within the group of sodium channel blockers with reported efficacy in these conditions, the presence of certain clinical features, such as cranial autonomic symptoms or the presence of a background interictal pain, imply the involvement of more central mechanisms rather than peripheral ones, which may explain the different level of efficacy of certain drugs in SUNA and TN. For this reason, it is important to carefully phenotype patients with these disorders and obtain MRI

scans with specific trigeminal sequences, aiming to stratify them in order to offer them more effective medical and surgical treatments.

7.3. SUNA: a trigeminal autonomic cephalalgia or a cranial neuralgia?

This unifying hypothesis carries important nosological implications on whether SUNA should belong to the TACs or the cranial neuralgias group. Based on the findings of these studies, we proposed a novel clinical entity called "Short-lasting trigeminal neuralgiform attacks", which encompasses SUNA and TN. This entity may be classified amongst the cranial neuralgias rather than trigeminal autonomic cephalalgias. The recognition of this entity may foster further research aiming to shed light on the complex neurobiology of the clinical variants of this continuum and advance the field of neuralgiform headache and facial pain disorders, ultimately leading to more specific and effective treatments for these patients.

7.4. Future research directions

The findings of this study may inspire several future research avenues in the field of short-lasting neuralgiform headache disorders. The similarities and differences between SUNA and TN including pain location, duration of attacks, triggerability, refractory periods and headache pattern (chronic vs episodic) may suggest that the hypothalamus may play a different role in these disorders, perhaps more relevant in the conditions with V1 pain, longer attacks and associated cranial autonomic features and less relevant in conditions where the pain is in V2-V3, attacks are very short and cranial autonomic symptoms are absent or sparse. A fMRI study assessing the presence of an abnormal hypothalamic activation across the spectrum of SUNA and TN would probably clarify the central pathophysiological mechanisms of these conditions. On the other end of the spectrum SUNA shares some clinical features with CH and the other TACs but it clearly lacks of one of the cornerstone features of CH, which is the circadian and circannual attacks periodicity, which is thought to be driven in CH by an abnormal functioning of the suprachiasmatic nucleus. However during SUNA attacks, abnormal hypothalamic activity has been detected and DBS of the VTA seems to be an effective treatment for

this condition, similarly to CH. Hence it would be important for future research to establish whether hypothalamic dysfunction is a fundamental hallmark of SUNA or whether is it only a marker of unilateral short-lasting headache attacks with predominantly V1 pain accompanied by cranial autonomic symptoms.

Our preliminary data on the prevalence of trigeminal NVC in SUNA should be confirmed in larger studies. Such findings along with the long-term outcomes of trigeminal MVD in SUNA patients will clarify the pathophysiological relevance of trigeminal NVC in SUNA.

Furthermore, the response to sodium channel blockers may suggest a disfunction of these ion channels in SUNA and TN. Genetic studies perhaps using exome sequencing technique in these conditions may shed more light upon the contribution of ion channels dysfunction in these disorders and offer new more specific therapeutic targets for the treatment of these conditions.

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Appendix A.

To be filled by clinician

Date	/ /

SECTION 1: PERSONAL DETAILS

Surname		Date of Birth	/ /
First Name		Age	
Hospital Number			
Sex		Male ☐ Female ☐	
Handedness		Right ☐ Left ☐ Ambidextrous ☐	
Marital status		Single ☐ Married ☐ Divorced/Separated ☐ Living with Partner ☐ Widowed ☐	
Occupation • If disabled or retired, describe what you did before you stopped working?			
Occupation		Student ☐ Unemployed ☐ Retired ☐ ❑ Work full time for pay ❑ Work part time for pay ❑ Work as a volunteer ❑ Going to school or training for a new occupation ❑ Homemaker ❑ Care for a child, elder or sick person ❑ Long-term disability due to facial pain ❑ Long-term disability due to other reason	

SECTION 2: HEADACHE/ FACIAL PAIN

Please repeat this section for each different type of headache/ facial pain

A.Onset

1. Age of onset of pain	
2. Duration (years)	
3. Was there any initial trigger?	Yes ☐ No ☐
4. Precipitant triggers	☐ Head injury ☐ Facial injury ☐ Neck injury ☐ Operation – face , cosmetic ☐ Back trauma ☐ Viral infection ☐ Illness ☐ Oral surgery-extractions, root canal ☐ Episode of extreme stress ☐ Airplane flight ☐ Pregnancy

	☐Stress ❑Other ……..
4. If the answer to Question 3 was 'Yes' then describe the trigger and state the time of onset of the trigger in relation to the onset of the headache attacks	Trigger: …… …….. Onset of Trigger: …….. ……..

B.Side and site (EXACERBATIONS)

1.	On which side of the head do you experience the attacks?	Right …….%		☐
		Left …….%		☐
		Alternates …….%		☐
		Bilateral …….%		☐
2.	If the attacks have occurred on both sides, then has the pain shifted sides during an attack, in different attacks but in the same bout or in different bouts?	Side shifted during a single attack		☐
		Side shifted in different attacks during same bout		☐
		Side shifted in different bouts		☐
		No		☐
3.	Tick the regions over which the pain is felt	Peri-orbital	☐ Palate	☐
		Retro-orbital	☐ Floor of mouth	☐
		Frontal	☐ Jaw	☐
		Temple	☐ Ear	☐
		Parietal	☐ Chin	☐
		Occipital	☐ Neck	☐
		Vertex	☐ V2	☐
		Nasal	☐ V3	☐
		Cheek	☐ Shoulder	☐
		Upper teeth	☐ Other (describe below)	☐
		Lower teeth	☐ …….	

RL **R** **L**

C.Severity and characteristics of pain

1.	Usual severity of the pain	VRS:		
2.	Intensity range (Min-Max)	VRS:		
3.	Which of these descriptions of pain apply to your attacks?	Aching	☐ Stabbing	☐
		Boring	☐ Tearing	☐
		Shooting	☐ Tightening	☐
		Electric	☐ Throbbing	☐
		Burning	☐ Sharp	☐
		Pins and needls	☐ Sudden	☐
		Dull	☐ Gradual	☐
		Pressure feeling	☐ Suffocating	☐
		Pressing	☐ Fearful	☐
		Pulling	☐ Wretching	☐
		Tingling	☐ Annoying	☐
		Tender	☐ Piercing	☐

	Tiring	☐	Cold	☐
	Agonising	☐	Others (describe below)	☐
			.....	

D. Duration and frequency

1.	How long does the ***average*** attack last for?	Seconds/mins/hours:
2.	Duration range of an attack (Min-Max)	Seconds/mins/hours:
3a	What is the ***average*** number of headache attacks that occur per day? (For trigeminal autonomic cephalalgias/cranial neuralgias and hemicranias continua)	
3b	What is the ***average*** number of headache attacks that occur per month? (migraine)	
4.	Frequency range of attacks (Min-Max)	Day/week/month:

E.Timing

1.	Are the attacks more likely to occur when awake or during sleep? (Tick one only)	Awake ☐ Sleep ☐ Both ☐
2.	Which is the average percentage?	Awake: …… % Sleep: ……%
3.	Do the attacks occur at a predictable time or randomly?	Predictable ☐ Random ☐ If predictable, specify the times …….
4.	Is there any time in which the attacks get **worse**?	Waking up ☐ Mid-morning ☐ Mid-day ☐ Afternoon ☐ Evening ☐ Overnight ☐ No difference ☐ ☐

H. Associated symptoms

1.	**CRANIAL AUTONOMIC FEATURES**	Redness of the eye ☐ Same side ☐ Opposite side ☐ Both sides ☐ Watering of the eye ☐ Same side ☐ Opposite side ☐ Both sides ☐ Drooping of the eyelid ☐ Same side ☐ Opposite side ☐ Both sides ☐ Miosis ☐ Same side ☐ Opposite side ☐ Both sides ☐ Swelling of the eyelid ☐ Same side ☐ Opposite side ☐ Both sides ☐ Blockage of the nose ☐ Same side ☐ Opposite side ☐ Both sides ☐ Running of the nose ☐ Same side ☐ Opposite side ☐ Both sides ☐ Facial sweating ☐ Same side ☐ Opposite side ☐ Both sides ☐ Flushing of the face ☐ Same side ☐ Opposite side ☐ Both sides ☐ Fullness in the ears ☐ Same side ☐ Opposite side ☐ Both sides ☐ Swelling of mouth/face ☐ Same side ☐ Opposite side ☐ Both sides ☐ Hypersalivation Yes ☐ No ☐ **Behaviour during attacks** Restless ☐ Still ☐
2.	**MIGRAINOUS FEATURES**	Nausea (feel sick) ☐ Everytime ☐ Sometimes ☐ Vomiting ☐ Everytime ☐ Sometimes ☐ Sensitivity to light ☐ Same side ☐ Opposite side ☐ Both sides ☐ Sensitivity to sounds ☐ Same side ☐ Opposite side ☐ Both sides ☐ Sensitivity to smells ☐ Same side ☐ Opposite side ☐ Both sides ☐ Motion sensivity ☐ Everytime ☐ Sometimes ☐ Vertigo ☐ Everytime ☐ Sometimes ☐
3.	**AURA** **- ≥5 min and ≤60 min** **-Gradual onset and offset**	**YES** ☐ **NO** ☐ VISUAL SYMPTOMS such as blurred vision, flashing lights, zig-zag lines dark spots in one visual field ☐ SENSORY SYMPTOMS such as tingling or numbness ☐ SPEECH SYMPTOMS (dysphasia/dysarthria) ☐ WEAKNESS in one or more limbs ☐ BASILAR: (diplopia, vertigo, tinnitus, ataxia bilateral paraesthesia, decreased level of consciousness) ☐ Total number of attacks with headache/month or year ..... Total number of attacks without headache/month or year ..... Duration of aura (minutes): .....
8.	**ALLODYNIA**: areas of hyperalgesia	**YES** ☐ **NO** ☐ Ipsilateral ☐ Contralateral ☐

	Bilateral	☐

I . Trigger and relieving factors (if only spontaneous, don't tick the provoking)

	FACTORS	PROVOKING	RELIEVING
1.	Light touch	☐	☐
2.	Pressure on the face	☐	☐
3.	Squeezing eyelids	☐	☐
4.	Prolonged chewing/ eating	☐	☐
5.	Start of chewing/ drinking	☐	☐
6.	Swallowing	☐	☐
7.	Wind	☐	☐
8.	Washing face	☐	☐
9.	Brushing teeth	☐	☐
10	Moving / vibration	☐	☐
11	Talking	☐	☐
12	Opening wide/yawning	☐	☐
13	Washing or brushing hair	☐	☐
14	Exercise	☐	☐
15	Light	☐	☐
16	Shower	☐	☐
17	Shaving	☐	☐
18	Blowing nose	☐	☐
19	Neck rotation towards symptomatic side	☐	☐
20	Neck extension/ flexion	☐	☐

1	Alcohol (within 30 minutes)	☐	☐
2	Strong smells (eg perfumes, petrol fumes)	☐	☐
3	Warm environment	☐	☐
4	Heavy physical effort	☐	☐
5	Relaxation from stress	☐	☐

1	Smoking	☐	☐
2	Caffeine	☐	☐
3	Change in weather	☐	☐
4	Heat	☐	☐
5	Cold	☐	☐
6	Stress	☐	☐
7	Relaxation from stress	☐	☐
8	Tiredness	☐	☐
9	Sleep deprivation	☐	☐

10	Sleep excess	☐	☐
11	Recreation	☐	☐
12	Menstruation	☐	☐
13	Hunger/ meal skipping	☐	☐
14	Dehydration	☐	☐
15	Bright lights	☐	☐
16	Loud sounds	☐	☐
17	Foods (chocolate, cheese)	☐	☐

1	Cough and/or sneeze	☐	☐
2	Bending over	☐	☐
3	Change in posture (lying down/sitting up)	☐	☐

	Others (Please specify below)	☐	☐
	None	☐	☐

J. Characteristics of the attacks

1.	**TRIGGERED/SPONTANEOUS** attacks	Only cutaneous triggered ☐ Only spontaneous ☐ Both ☐ Non cutaneous triggers ☐
2.	If you have **both**, please quantify the percentage of each	Triggered …….. **%** Spontaneous …… **%**
3	Relation between cutaneous triggers and side of pain	Ipsilateral triggers ☐ Other triggers ☐ Contralateral triggers ☐ Bilateral triggers ☐ Extra-trigeminal triggers ☐

K. Refractory period (for SUNCT/SUNA and cranial nerualgias)

1.	Could you have a triggered attack immediately after cessation of the previous one?	No (refractory period) ☐ Yes (no refractory period) ☐ No triggers ☐ Not sure ☐
2.	If not, which is the duration of the refractory period?	Seconds/minutes:

L. Features immediately after a headache/ facial pain attack

1.	Do you get any of the following **symptoms immediately after the headache/facial pain** attack is over?	Irritability/ moody ☐ Feeling of being energetic/ well-being ☐ Feeling hungry ☐ Loss of appetite ☐ Passing urine frequently ☐ Diarrhoea ☐ Constipation ☐ Tiredness ☐ Yawning ☐ None of the above ☐ Go to section 3 if you get **none** of the above symptoms		Drowsiness ☐ Difficulty concentrating ☐ Abnormal sensations: burning, numbness, tingling or tenderness ☐ Other (describe below) ☐	
2.	Duration of these symptoms				
3.	Do you get these symptoms after each or most headache attacks?	Each ☐	Most ☐	Seldom ☐	

M. Trigeminal autonomic cephalalgias pattern

1.	Number of attacks per bout		
2.	***Average*** duration of bouts		
3.	Range of duration of a bout (Min-Max)		
4.	Number of bouts per year		
5.	When was the last bout?		
6.	Are your bouts more likely to occur in any particular month/ months?	☐ Yes ☐ No	
7.	If the answer to Question 6 is yes, then during which months are the bouts most likely to occur?	☐ January ☐ February ☐ March ☐ April ☐ May ☐ June	☐ July ☐ August ☐ September ☐ October ☐ November ☐ December
8.	Over the last 12 months, have you had a pain free period lasting more than one continuous month? **(Remission period)**	☐ Yes ☐ No	
9.	***Average*** duration of remission period		
10.	Range of duration of remission period (Min-Max)		

N. Natural history

1	EPISODIC	☐
2	EPISODIC to CHRONIC	☐ Age at chronification ……
3	CHRONIC from onset	☐
4	CHRONIC from onset to REMISSION	☐

	Duration of the remission period …… …..
5 CHRONIC to EPISODIC	☐
6 EPISODIC to CHRONIC to EPISODIC	☐
7 CHRONIC to EPISODIC to CHRONIC	☐

SECTION 3: INTERICTAL PAIN

Have you got any background pain between the headache/facial pain attacks?

YES ☐ NO ☐ (please continue to Section 4)

A. Onset

1. Age of onset of interictal pain	
2. Temporal GAP between the main pain onset and interictal pain onset:	Weeks/ Months/ Years:
3. Was there any interictal pain initial trigger?	Yes ☐ No ☐
4. Precipitant triggers	☐ Head injury ☐ Facial injury ☐ Neck injury ☐ Operation ☐ Back trauma ☐ Viral infection ☐ Illness ☐ Oral surgery ☐ Episode of extreme stress ☐ Airplane flight ☐ Pregnancy ☐ Prophylactic medication ☐ Medication overuse ☐ Other ……..
5. If the answer to Question 3 was 'Yes' then describe the trigger and state the time of onset of the trigger in relation to the onset of the interictal pain	Trigger: …… …….. Onset of Trigger: …….. ……..

B. Side and site

1. Side relation between the interictal pain and the headache/ facial pain	Ipsilateral	☐		
	Contralateral	☐		
	Bilateral	☐		
2. Tick the regions over which the pain is felt	Peri orbital	☐	Palate	☐
	Retro orbital	☐	Floor of mouth	☐
	Front	☐	Jaw	☐
	Temple	☐	Ear	☐
	Parietal	☐	Chin	☐
	Vertex	☐	Neck	☐
	Occipital	☐	Shoulder	☐

	Nose	☐	Same side of the exacerbations	☐
	Cheek	☐		
	Upper teeth	☐		
	Lower teeth	☐		

RL R L

C. Severity and characteristics of the pain

1.	The **usual** severity of interictal pain	VRS:			
2.	Severity range (Min-Max)	VRS:			
3.	Which of these **descriptions of pain** apply to your interictal pain? (You can tick more than one choice).	Aching	☐	Stabbing	☐
		Boring	☐	Tearing	☐
		Shooting	☐	Tightening	☐
		Electric	☐	Throbbing	☐
		Burning	☐	Sharp	☐
		Pins and needls	☐		
		Burning	☐		
		Dull	☐		
		Pressure feeling	☐		
		Others (describe below)	☐		

D. Duration and frequency

1.	***Average*** duration of the pain per day		
2.	Range of duration per day (Min-Max)		
3.	Constant all the time	Yes ☐	No ☐
4.	Background pain only after an attack	Yes ☐	No ☐
5.	**Number of days** of interictal pain **per month**		
6.	**Number of months** of interictal pain **per year**		

E. Associated symptoms

NO ☐

YES ☐ If yes, please specify:

.....
.....
.....
.....
.....

F. Trigger and relieving factors

	FACTORS	PROVOKING	RELIEVING
1	Headache/ facial pain attacks	☐	
2	Stress	☐	☐

3	Neck movements	☐	☐
4	Fasting (missing meals)	☐	☐
5	Alcohol	☐	☐
6	Smoking	☐	☐
7	Sleep deprivation/ excess	☐	☐
8	Coffee	☐	☐
9	Tiredness	☐	☐
10	Change in weather	☐	☐
11	Cough and/or sneeze	☐	☐
12	Loud sounds	☐	☐
13	Strong smells (eg perfumes, petrol fumes)	☐	☐
14	Menstruation	☐	☐
15	Physical exertion	☐	☐
16	Relaxation from stress	☐	☐
17	Sleep	☐	☐
18	Recreation (Taking your mind off it)	☐	☐
19	Others (Please specify below)	☐	☐
20	None ☐		

SECTION 4: LIFESTYLE FACTORS

A.Past medical history

1.	Have you had any of the following illnesses (underline the illness that you have or have had)	Depression, Anxiety, Mental disorders, Stroke, Epilepsy, Heart murmurs, High blood pressure, Angina, Heart attack, Rheumatic fever, Asthma, Bronchitis, Emphysema, Pneumonia, Tuberculosis, Jaundice, Hepatitis, Gall stones, Persistent diarrhoea, Rectal bleeding, Colitis, Kidney stones, Urinary tract infection, Arthritis, Diabetes, Thyroid disorders, Blood disorders, Cancer,Chronic pain elsewhere , ME fibromylgia , MS
2.	Do you have any other illness not already mentioned above? (Please specify)	…… …… …… …… …… …… ……
3.	List the operations that you have had for any conditions other than cluster headaches or TN	…… …… …… …… …… ……

B.Family history

1.	Does any member of your family have your type of headache?	Yes ☐ No ☐
2.	Does any member of your family have migraine?	Yes ☐ No ☐
3.	Does any member of your family have any other headaches?	Yes ☐ No ☐
4.	**Family history for other diseases? Depression ,chronic pain**	Yes ☐ No ☐

C.Developmental migraine markers

Have you ever had any of the following?	☐ Motion sickness ☐ Recurrent abdominal pain ☐ Cycling vomiting ☐ Vertigo ☐ Hangovers

D.Social history

i. Alcohol intake

1.	Do you drink alcohol?	Yes ☐ No ☐
2.	Age of onset	
3.	What is you average alcohol consumption per week? (1 UNIT= 1/2 pint, 1 glass of wine, 1 measure of spirit)	Pints of beer …… Measures of spirits …… Glasses of wine ……
4.	Did you stop drinking alcohol?	Yes ☐ No ☐ Year:
5.	Did you stop drinking alcohol due to your headaches?	Yes ☐ No ☐
6.	Any relation between alcohol intake and the pain?	

ii. Smoking habits

1.	Do you smoke cigarettes/cigars/tobacco?	Yes ☐ No ☐
2.	Age of onset	
3.	Number of cigarettes per day	
4.	If ex-smoker, when did you give up smoking?	…… Not given up ☐
5.	Did you stop smoking due to your headaches?	Yes ☐ No ☐ Not given up ☐

6. Any relation between smoke and the pain?	

SECTION 5: EXAMINATION AND INVESTIGATIONS

A. Examination

1 Neurological examination performed	Yes ☐ Date (/ /) No ☐
2 Result	

B. Neuroimaging/ pituitary profile

INVESTIGATION		DATE	RESULT
CT Scan	☐		
MRI Scan	☐		☐ Normal ☐ Pituitary abnormality • Type: ☐ Abnormal vascular loop: • Artery: ..... • Vein: ..... ☐ Ipsilateral ☐ Contralateral ☐ Bilateral ☐ Other posterior fossa abnormalities • Type: ☐ Other findings
Follow-up MRI Scan	☐		
Cerebral angiography	☐		
Pituitary blood profile	☐		☐ Normal ☐ Abnormality detected : .....

SECTION 6: TREATMENTS

RESPONSE SCALE:

No response (0): any change in headache frequency or severity

Mild (1): < 50%: Mild reduction in headache frequency and/or severity.

Good (2): 50-90%: marked reduction in headache frequency and/or severity.

Excellent (3): 91-100%: The pain is completely or almost completely gone.

Worsen the headache/facial pain (5).

A. Medications to date

	MEDICATION		Dose	Year tried	Duration of the trial	Effects	Side effects	Stopped due to side effects
	ABORTIVES							
Triptans	Sumatriptan tablets (Imigran)	☐						
	Sumatriptan nasal spray (Imigran nasal spray)	☐						
	Sumatriptan injections (Imigran injections)	☐						
	Rizatriptan (Maxalt)	☐						
	Zolmitriptan tablets (Zomig)	☐						
	Zolmitriptan nasal spray (Zomig)	☐						
	Other triptans	☐						
Ergots	Ergotamine tablets (Cafergot, Ligraine, Migril)	☐						
	Ergotamine suppository (Cafergot)	☐						
	Dihydroergotamine nasal spray (Migranal)	☐						
Non-opioids	Aspirin	☐						
	Paracetamol	☐						
	Caffeine	☐						
Opiods	Codeine	☐						
	Dihydrocodeine	☐						
	Morphine	☐						
	Oxycodone	☐						
	Tramadol							
NSAIDs	Ibuprofen	☐						
	Diclofenac (Voltarol)	☐						
	Celecoxib (Celebrex)	☐						
	Indomethacin	☐						
	Mefenamic acid (Ponstan)	☐						
	Naproxen	☐						
Anti-emetics	Promethazine (Avomine, Phenergan)	☐						
	Prochlorperazine (Stemetil, Buccastern)	☐						
	Metoclopramide (Maxalon, Reglan)	☐						
	Domperidone (Motilium)	☐						

Others	Oxygen (give flow rate and duration taken during attack)	☐						
	Lignocaine nasal spray / topical cream (Lidocaine, Xylocaine)	☐						
	Steroids (Prednisolone)	☐						
		☐						
PREVENTIVES								
Antiepileptics	Gabapentin (Neurontin)	☐						
	Pregabalin (Lyrica)	☐						
	Valproate (Epilim)	☐						
	Carbamazepine (Tegretol, Carbagen)	☐						
	Oxcarbazepine (Trileptal)	☐						
	Topiramate (Topamax)	☐						
	Lamotrigine (Lamictal)	☐						
	Phenytoin							
	Lacosamide	☐						
TCA	Amitryptiline (Triptafen)	☐						
	Nortryptiline (Allegron, Motival)	☐						
	Dothiepin (Dosulepin)	☐						
	Imipramine (Tofranil)	☐						
Beta blockers	Propanolol (Inderal)	☐						
	Atenolol (Tenormin)	☐						
	Metoprolol (Lopressor, Betaloc)	☐						
CCB	Verapamil	☐						
	Flunarizine	☐						
NSAIDs	Indomethacin	☐						
	Rofecoxib (Vioxx)	☐						
	Celecoxib (Celebrex)	☐						
	Naproxen	☐						
Other	Lithium	☐						
	Pizotifen (Sandomigran)	☐						
	Methysergide (Deseril)	☐						
	Theophylline	☐						
	Melatonin	☐						
	Mexilitine	☐						
	Baclofen	☐						
	Duloxetine	☐						
	Fluoxetine	☐						
	Steroids (prednisolone)	☐						
	Other drugs	☐						
	Escitalopram	☐						

	Diazepam Clonazepam							
TRANSITIONAL TREATMENTS								
	GON block	☐						
	Multiple cranial nerve blocks	☐						
	Botolinum toxin injection	☐						
	IV DHE	☐						
	IV Lignocaine	☐						
	IV Steroids	☐						
	IV Caffeine	☐						

B. Medication overuse

No ☐

1	Intake of **ANALGESIC** drugs for ≥15 days/month on a regular basis for >3 months	Yes ☐ No ☐
2	Intake of **TRIPTANS** for ≥10 days/month on a regular basis for >3 months	Yes ☐ No ☐
3	Intake of any **OPIOIDS (Codein, Tramadol, Morphine)** for ≥10 days/month on a regular basis for >3 months	Yes ☐ No ☐
4	Intake of **ERGOTAMINE** for ≥10 days/month on a regular basis for >3 months	Yes ☐ No ☐
5	Intake of **COMBINATION drugs** for ≥10 days/month on a regular basis for >3 months	Yes ☐ No ☐
6	Year of overuse	

C. Surgical procedures

Please repeat this section for each different type of surgical procedure done

1.	Have you had any operations or surgical procedures for your headache/ facial pain?	Yes ☐ No ☐
2.	If yes, please list the operations or procedures (including the year of the procedure)	…… …… ……
3	Effect of procedure	**Improvement** ☐ %: After how long: For how long: Reduction of: number of attacks, intensity, duration Background pain:

	Worsening ☐ After how long: For how long: Increase of: number of attacks, intensity, duration: Background pain: **No change** ☐ **Adverse events** related to the procedure: Length of follow-up:

D. Alternative treatments

None ☐

Type of treatment		Year tried	Effects (0-4)	Duration of the effects
Acupuncture	☐			
Chiropractic	☐			
Herbal treatments	☐			
Homeopathy	☐			
Hypnosis	☐			
Osteopathy	☐			
Reflexology	☐			
Spiritual healing	☐			
Other (please specify) Pain managment program Physiotherapist	☐			

SECTION 6: DIAGNOSIS

1.	How long after the onset of these headaches was the diagnosis made?				
2.	Who made the diagnosis of these headaches?				
3.	Please indicate which of the following doctors you have saw **BEFORE** the diagnosis was made	PRACTITIONER	NUMBER SEEN	DIAGNOSIS OFFERRED	TREATMENT GIVEN
		GP ☐			

		Neurologist ☐ Dentist ☐ ENT Specialist ☐ Optician ☐ Ophthalmologist ☐ Others (Please specify) ☐ Maxillofacial surgeon/oral surgeon ☐ Pain specialist Oral physician ☐ ☐			

SECTION 7: PAIN DISABILITY SCORES

Type of measure	**Score**
Headache impact test (HIT-6)	
Migraine disability assessment score (MIDAS)	
Brief pain inventory	
Short form-36 (SF-36)	
Hospital anxiety and depression (HAD) scale	
Pain catastrophising questionnaire (PCS)	
Chronic graded pain scale	
Adverse events questionnaire	