

Chronic cluster-like headache secondary to prolactinoma responsive to cabergoline: a case report and review of the literature

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Introduction: Chronic cluster-like headache was seldom reported in association with prolactinoma [1]. We report a case of cluster headache in a patient with prolactinoma, responding dramatically to cabergoline.

Case history: A 61 year-old man experienced, since the age of 45 years, nocturnal attacks of severe, right orbital and frontal pain, lasting 60–180 min and occurring once a day. The attacks were associated with ipsilateral conjunctival injection, lacrimation, nasal congestion and rhinorrhoea. Cluster periods usually lasted 15–40 days, with remission periods of months. Since the age of 59 years, the attacks' frequency progressively increased to one or more episodes per day, without any temporal pattern, with remission periods lasting less than 15 days. Verapamil, methysergide, topiramate and valproate were ineffective. 1.5 T brain magnetic resonance imaging (MRI) was normal. For the persistence of pain, a 3 T brain MRI was performed, showing a right-side adenoma. Prolactin level was 469.4 ng/mL. The patient was given cabergoline 0.5 mg on alternate day, with complete remission of pain after 2 months.

Conclusion: Few cases of cluster-like headache with pituitary adenomas have been reported [2], and six of them were associated with prolactinoma. Symptomatic cluster headache should be suspected when the clinical features of headache are atypical (absence of the typical periodicity or duration, a persistent headache between attacks, poor response to recognized treatments and the presence of atypical neurological signs or symptoms). Dopaminergic drugs, as cabergoline, may improve or exacerbate headache; this observation is probably related to a complex interaction of the physical effects of the tumor and the central action of dopamine agonists.

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Inpatient withdrawal treatment for chronic migraine with medication overuse and follow-up

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Objective: To investigate a group of CM with medication overuse patients before and after inpatient withdrawal pharmacological program and after a long-term follow-up.

Methods: We hospitalized 114 CM patients with medication overuse (11M, 103F, mean age 48.6 ± 14.5) at our Headache and Pain Unit for 15 days and re-contacted them after discharging. We collected data at baseline (T0) and followed-up after 3 (T3), 6 (T6), 12 (T12), 18 (T18), 24 (T24), 36 (T36), 48 months (T48). Inpatients were treated by discontinuation of the overused drugs and with a therapeutic protocol including i. v. dexamethasone, hydration, anxiolytic and antidepressant therapy. Patients started prophylactic drugs and underwent to psychological and behavioural therapy to identify triggers and promote healthy life style. Once a day cranium-sacral and hydrokinesis therapy was applied as coadjuvant approach. Migraine disability was assessed by MIDAS, depression with Beck Depression Inventory (BDI) and anxiety with State Trait Anxiety Inventory (STAI-1, STAI-2) questionnaires. Quality of life was assessed using Short Form-36 Healthy Survey (SF-36).

Results: A comparison of MIDAS total scores between baseline (120.2 ± 71.5) and other timelines showed a significant reduction at T3 (56.5 ± 59.9 $p < 0.001$) and it was not lost at the others timelines of follow-up (T6: 56.4 ± 60.9 $p < 0.001$; T12: 61.9 ± 68.8 , $p < 0.001$; T18: 71.2 ± 64.8 , $p < 0.002$; T24: 65.6 ± 64.8 $p < 0.001$; T36: 63.5 ± 64.3 $p < 0.001$; T 48: 72 ± 64.9 $p < 0.002$). Days of headache were T0: 63.2 ± 25.7 ; T3: 28.1 ± 24.3 ($p < 0.001$); T6: 26 ± 22.6 ($p < 0.001$); T12: 28.1 ± 23.1 ($p < 0.001$); T18 30.7 ± 25.9 ($p < 0.001$); T24: 30.5 ± 23.5 ($p < 0.001$); T36 38.5 ± 31.7 ($p < 0.001$); T48: 41.7 ± 33.4 ($p < 0.002$). STAI 1 score did not differ at any time, STAI-2 and BDI scores significantly reduced at T3 and maintained the increment at other times. Physical pain, social activity and mental health of SF-36 significantly improved at any timelines of follow-up.

Conclusions: Different factors can contribute to the development and perpetuation of medication overuse in chronic migraine. Withdrawal in hospital setting is considered the first step for helping these patients to stop medication overuse.

Triptans in migraine therapy: incomplete revolution?

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The evaluating patterns of specific acute migraine treatment obtained through the analysis of prescriptions in the population is a main step towards assessing the quality of migraine care. Data from many countries shows today a very low percentage of migraine patients treated with triptans and a low frequency of utilization. We have reviewed data on triptan turnover, that is the percentage of those starting triptans and of those who interrupt triptan treatment. A high percentage of new users (over 50 %) and lapsed users (40–50 %) was reported [Table]. A lower percentage of discontinuation (25–28 %) was found in some studies, but these include only subjects with a long history of migraine or with severe migraine. Confirming previous data, a recent large US study shows that in new triptan users discontinuing the index triptan, only a small percentage (7.4 %) switched to a different triptan, while 67 % switched to a non triptan medication. A better management of migraine in primary can ameliorate the use of triptans in migraine treatment. Until now, however, the so called “triptan revolution” initiated with sumatriptan development remains to be completed.

Study	Triptan users (no)	Study period (months)	%
New users			
Biagi (2011)	34,915	12	48
Panconesi (2010)	1,022	12	52
Lugardon (2007)	13,860	6	63
Sondergaard (2006)	2,463	3	25
Etemad (2005)	8,488	12	63
Lapsed users			
Katic (2011)	40,892	24	46
Golden (2010)	6,625	24	54
Panconesi (2010)	921	12	46
Etemad (2005)	5,294	12	39
Savani (2004)	3,196	15	55
Cady (2009)	785	12	25
Bigal (2010)	1,392	12	28

Chronic headache and body mass index: a case–control study

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Introduction and aim: In recent years clinical research has focused on the possible role played by obesity as a risk factor for headache chronification. The aim of this case–control, hospital-based study was

to evaluate: the prevalence of overweight and obesity in subjects with chronic migraine (CM) and chronic tension-type headache (CTTH); and the possible correlations between body mass index (BMI) and both headache types.

Materials and methods: We studied 79 patients, 46 with CM and 33 with CTTH, consecutively referred to the Adult Headache Centre of the University of Palermo (A.H. Study) between 2007 and 2009, and 316 controls without headache (each patient was matched by sex and age to four controls). The headache diagnosis was established according to the ICHD-II criteria. BMI classes were defined according to WHO guidelines.

Results: Mean age was 47.6 years (± 17.8 years) for the 79 patients with chronic headache (66 F, 13 M) and 47.6 years (± 17.8 years) for the 316 controls (264 F, 52 M). The BMI status did not differ between groups (mean BMI was 27.7 ± 4.8 in chronic headache patients and 27.3 ± 5.1 in controls). In the chronic headache group, 32.9 % were obese, 40.5 % pre-obese and 26.6 % overweight. In the control group, 26.0 % were obese, 40.3 % pre-obese and 33.7 % overweight. Following multiple logistic regression analysis, the presence of obesity and pre-obesity was not associated with chronic headache (obesity: OR = 1.4, 95 % CI 0.7–2.9; pre-obesity: OR = 1.6, 95 % CI 0.5–2.2).

Conclusion: Our data suggest that BMI abnormalities are not associated with CDH. However, considering previous reports of an association of obesity and migraine in population-based studies, we cannot exclude a selection bias.

Anxiety disorder, depression and chronic daily headache: a case–control study

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Introduction and aim: Chronic headache cause high disability in sufferers and high social cost. Data regarding possible comorbid diseases, mainly depression and anxiety, are still few and conflicting. The aim of this case–control, hospital-based study was: to evaluate the prevalence of depression and anxiety in subjects with chronic migraine (CM) and chronic tension-type headache (CTTH); and to compare the results with those found in a control group without headache.

Materials and methods: We studied 79 patients, 46 with CM and 33 with CTTH, consecutively referred to the Adult Headache Centre of the University of Palermo (A.H. Study) between 2007 and 2009, and 316 controls without headache (each patient was matched by sex and age to four controls). The headache diagnosis was established according to the ICHD-II criteria. Anxiety and depressive symptoms were assessed using the Hospital Anxiety and Depression Scale (HAD).

Results: Mean age was 47.6 years (± 17.8 years) for the 79 patients with chronic headache (66 F, 13 M) and 47.6 years (± 17.8 years) for the 316 controls (264 F, 52 M). The mean HAD-D score was 8.6 ± 4.3 in the chronic headache group and 7.0 ± 3.5 in the control group; ($p = 0.00$). The mean HAD-A score was 11.2 ± 4.5 in the chronic headache group versus 9.0 ± 3.7 in the control group. Following multiple logistic regression analysis, the presence of depression and anxiety was associated with chronic headache

(depression: OR = 2.2, 95 % CI 1.2–4.1; anxiety: OR = 2.4, 95 % CI 1.3–4.3).

Conclusion: According to our data, anxiety and depressive symptoms are more prevalent in chronic headache, and correlate to an increased risk of chronic headache.

Nutraceutical administration in childhood migraine prophylaxis: effect on disability

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Background: In developmental age migraine is a very common neurological disorder, but very few drugs are disposable.

Aim of study is comparing the middle term effect of two nutraceutical complexes on frequency, disability grade and intensity of migraine in a paediatric sample.

Materials and methods: One complex composed by Ginkgolide B/Coenzyme Q10/Riboflavin/Magnesium (complex A) was oral administered as prophylactic therapy twice a day for 6 months to 187 school-aged patients and other one composed by the association of L-tryptophan/5hydroxytryptophan (*Griffonia simplicifolia*)/vitamin PP/vitamin B6 (complex B) to other 187 children with MoA, matched for age ($p = 0.575$) and sex distribution ($p = 0.918$). Each patient kept a journal to record: number and intensity of attacks and concomitant symptoms. To assess the intensity, disability grade and behavioural variations linked to migraine a visual analogue scale (VAS), the PedMIDAS scale and a behavioural scale were administered at the beginning and at the end of treatment.

Results: Our results show that the two nutraceutical complexes can reduce all the disabilities aspects of migraine in our samples and the effects of Complex A after 6 months of treatment seem to have more efficacy than Complex B ((Delta% frequency $p < 0.001$, Delta% duration $p < 0.001$, Delta% PedMIDAS $p < 0.001$, Delta% VAS $p \leq 0.001$), also for the behavioural aspects (Delta% Behaviour $p \leq 0.001$), that are very important for the dynamics within the family of migraineurs patients, suggesting its improved therapeutic effect in the middle-long term.

Conclusion: Our findings also suggest that in childhood headache management, the use of alternative treatments could be considered as soft therapy without adverse reactions even in the middle-long term treatment.

Pregnancy after a cryptogenic stroke in migraine sufferers. Outcome in four cases

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Stroke tends to be a catastrophic event at whichever age it occurs, but this is especially true, albeit rare, in young adults, particularly pregnant women, as both the mother and the foetus could suffer the consequences. Most young strokes are eventually ascribed to so-called cryptogenic stroke (CS), i.e., no identifiable cause can be found even after extensive examination. There does, however, appear to be

an association with a history of migraine; indeed, the risk of ischaemic stroke is doubled in migraine with aura (MwA), but not in migraine without aura (MwoA) sufferers [1]. Furthermore, the presence of patent foramen ovale, frequently associated with MwA, as well as smoking and oral contraceptive use increases the risk of stroke, as well as that of recurrence in pregnancy and puerperium, two well-documented pre-thrombotic conditions [2]. This raises the issue of what kind of thromboprophylaxis strategy to adopt, if any. Unfortunately, however, available data pertaining to prevention of stroke in pregnant women at risk of recurrence is scarce, and evidence of the efficacy and safety of antithrombotic treatment during pregnancy has not yet been well established [3].

We report four cases of women with a history of both CS and migraine (two MwoA and two MwA), who undertook a planned pregnancy. No adverse maternal and foetal events were registered during either pregnancy, caesarean delivery or puerperium in the three patients treated with antithrombotic agents, while a minor stroke occurred at the 28th week in the untreated patient. In our experience, pregnancy and delivery in patients with a history of CS are safe if treated with anti-thrombotic agents throughout gestation and soon as possible post-partum. Therefore, a previous history of CS should not be considered an absolute contraindication for pregnancy in young adult women with an associated history of migraine.

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Stroke risk factors in migraine sufferers. Results of the ERICe study

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Although migraine is one of the most common and disabling neurological disorders in western countries (1), and has been recently reported (2) as an independent stroke risk factor, it still remains widely under-diagnosed and under-treated (3). Thus the objective of the present survey was to assess the prevalence of migraine and cardiovascular factors risk in a sample of residents of the Aosta municipality. A structured questionnaire was therefore mailed to 850 female and 860 male 20–54 year-old residents representative of the study area population, as part of the ERICe project, an information campaign promoted by the regional Association against Stroke (ALICe). The ultimate aim of the campaign was to increase awareness of stroke risk in the local general population and migraine, but herein we focus on the prevalence of cardiovascular risk factors in the migraineurs. **Results** Of the 387 respondents, a total of 144 (37.2 %) reported suffering some form of headache, and according to the ICHD-II criteria (4), 18 % (70/387) were diagnosed with migraine. The prevalence of stroke risk factors in the migraine group was: hypertension 7.2 %, diabetes mellitus 0 %, smoking 31 %, oral contraceptive use 3.6 %, alcohol use 36 %, low fruit and vegetable consumption 28 % and obesity 22 %. No significant differences were found in any of these factors, except for current smoking in migraineurs ($p < 0.001$) and hypertension ($p < 0.05$) in headache sufferers. **Conclusion** Although the study was undoubtedly limited by a small sample population and non-response bias, it did reveal associations

between stroke risk factors and migraine/headaches. Although this association was fairly weak, considering the worldwide prevalence of the conditions in question, it does merit assessment on a larger scale. Indeed, a larger study is already being planned; should it confirm the present findings, it will highlight the need not only to identify headache and migraine sufferers in general, but also to assess known patients for stroke risk factors, particularly in migraine with aura. Indeed, if our results are borne out, it may well ultimately transpire that treating the former conditions has the potential to prevent or at least reduce the risk of the latter in a significant number of people.

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Clinical presentation, course, neuroimaging findings and response to treatment in three suspected cases of Tolosa-Hunt syndrome

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Tolosa-Hunt syndrome (THS) is a rare cranial neuralgia caused by idiopathic inflammation of, generally one but occasionally both, cavernous sinuses and less frequently the superior orbital fissure and/or orbital apex. Although THS usually resolves either spontaneously or after treatment, it can persist or relapse and remit in some cases.

The four IHS criteria (1) describe the course and features of THS as: “episode(s) of unilateral orbital pain for an average of 8 weeks if left untreated; association with paralysis of one or more of the third, fourth, and/or sixth cranial nerves, which may coincide with onset of pain or follow it by a period of up to 2 weeks; pain is relieved within 72 h of steroid therapy initiation; and exclusion of other conditions by neuroimaging and (not compulsory) angiography”. In this context, magnetic resonance imaging (MRI) without contrast agents can reveal enlargement of the cavernous sinus, narrowing of the intracranial internal carotid artery and/or infiltration of orbital structures by abnormal tissue, which appears isointense with grey matter in T1, and isohypointense in T2-weighted images, and whose signal intensity markedly increases after contrast injection (2). These findings, if present, are typical of THS but not specific, as they can also be found in other progressive intracranial diseases such as neoplasms and inflammatory conditions. Herein we report three cases, two females and one male, recently examined due to unilateral painful ophthalmoparesis (and associated reduction in visual acuity in one case) similar to that described for THS.

MRI and CT scan showed findings typical of THS in two cases. One patient experienced progressive spontaneous remission of the pain and partial ophthalmoparesis. The other two cases were both treated with oral prednisone, resulting in complete cessation of pain, in one case very rapidly, but only partial resolution of the ophthalmoparesis.

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Medical conditions associated to chronic daily headache: SPARTACUS sub-study

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Background: Chronic daily headache (CDH) is defined as headache occurring ≥ 15 days per month for at least 3 months. Many medical conditions have been reported to be associated with CDH. To date, there are no population based studies in Italy.

Objectives: To identify medical conditions associated with development of medication overuse in chronic headache sufferers.

Methods: 435 of the 636 CDH sufferers identified using a validated questionnaire in the SPARTACUS-study population, underwent a semi-structured interview by their GPs about current and past associated medical conditions. Patients were divided into two diagnostic groups: CDH with medication overuse ($n = 127$, mean age 49 ± 14) and CDH without medication overuse ($n = 308$, mean age 53 ± 17). We use descriptive statistics and Chi-square test.

Results: CDH patients complained cardiovascular (31.5 %), gastrointestinal (20.5 %), respiratory (10.3 %), thyroid (14.5 %), immunological (6.2 %), musculoskeletal (23.2 %), neurological (5.5 %), psychiatric (20 %), genitourinary (6.2 %), other (5.3 %) diseases and trauma history (3.2 %). Comparing CDH patients with and without medication overuse, we observed significant difference only concerning cardiovascular disease prevalence (22.8 % vs 35.1 %, $P = 0.017$). In particular, patients with CDH without medication overuse showed a high prevalence of hypertension with respect to those with medication overuse (28.6 % vs 17.3 %, $P = 0.019$).

Conclusions: Our study revealed an high prevalence of medical disease among CDH patients. Unexpectedly hypertension, and cardiovascular diseases in general, are more frequent in CDH without medication overuse, probably due to the older age of non-overusers.

Treatment of withdrawal headache in patients with medication overuse headache (MOH): a randomized, single-blinded, placebo controlled study

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Introduction: Withdrawal headache in MOH is a therapeutic challenge.

Objectives: we performed a randomized, single-blinded, placebo controlled trial for the evaluation of the efficacy of methylprednisolone or paracetamol in the treatment of withdrawal headache in patients with MOH.

Materials and methods: MOH patients, unresponsive to the prophylaxis in the run-in period, underwent withdrawal therapy on an inpatient basis. Overused medications were suddenly stopped and methylprednisolone 500 mg i. v. (A) or paracetamol 4 g i. v. (B) or placebo i. v. (C) were given daily for 5 days. Severity of headache

and of autonomic symptoms was reported in a daily diary. Metoclopramide and/or lorazepam were allowed as rescue medications. Chi-square test and Student's *t* test were used.

Results: 38 consecutive patients (34 F, 4 M; mean age 44.7 ± 9.1) were enrolled: 13 in A, 15 patients in B and 10 in C. Overused medications included triptans (50 %), simple analgesics (5.3 %), combination analgesics (7.9 %); 42.1 % of patients overused two or more drugs' categories. No differences about the overused drugs, the time of overuse, the days of headache and the days of overuse per month were found. Withdrawal headache on the 5th day was absent in 2 patients (15.4 %) of A, in 3 patients (20 %) of B and none of C ($p \geq 0.5$). 2 patients of C dropped on the 2nd day of withdrawal. Mean headache intensity was significantly lower in A and B versus C on the 1st day ($p \leq 0.04$), and in A versus C on the 2nd day ($p 0.007$) of withdrawal. The three groups did not show differences about the mean number of days with autonomic symptoms. The mean intensity of autonomic symptoms was significantly lower in A and B versus C on the 1st day of withdrawal ($p < 0.0009$). The mean number of rescue medications taken during the 5 days of withdrawal was significantly lower in the A (3.5 ± 2.2) and B (2.1 ± 1.5) versus C (7.7 ± 5.7 ; $p \leq 0.02$).

Conclusion: our preliminary data suggest that methylprednisolone and paracetamol are superior to placebo in reducing the intensity of rebound headache and of autonomic symptoms on the first day of withdrawal, and in reducing the consumption of rescue drugs in MOH patients. Methylprednisolone resulted superior to placebo in reducing headache intensity also on the 2nd day of withdrawal.

PACE study: past-year prevalence of tension-type headache in Parma's adult general population

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Introduction: Primary headache prevalence and features in the Italian general population have been little studied so far. The PACE study (PARma CEfalea, or "Headache in Parma") is an observational study aimed at detecting the prevalence and clinical features of primary headaches in the city of Parma's adult general population.

Objectives: To evaluate in a sample representative of Parma's adult general population the past-year prevalence of (a) infrequent, (b) frequent, and (c) chronic tension type headache (TTH).

Materials and methods: The initial study sample ($n = 1,270$) consisted of all residents registered with a general practitioner (LB) in downtown Parma. The study population can be considered representative of the Italian adult general population for age/gender distribution. Using a specially developed, previously validated 13-section questionnaire, four physicians of the Parma Headache Centre administered face-to-face interviews to 904 responders (71.2 % of the sample) aged ≥ 18 years between September 2007 and February 2009. The responders included 508 women (56.2 %; mean age 55.9 years, SD 17.2 years, max. 92 years) and 396 men (43.8 %; mean age 55.0 years, SD 18.2 years, max. 91 years). Headache diagnosis was made according to the International Classification of Headache Disorders 2nd Edition (ICHD-II).

Results: A total of 175 subjects (19.4 %, 95 %CI 16.8–21.9) had a diagnosis of TTH, 20.1 % women (95 %CI 16.6–23.6) and 18.4 % men (95 %CI 14.6–22.3), the F:M ratio being 1.1:1. The subjects who suffered from TTH were distributed as follows: (a) 81 subjects (9 %, 95 %CI 7.1–10.8) had infrequent TTH, including 45 women

(8.9 %, 95 %CI 6.4–11.3) and 36 men (9.1 %, 95 %CI 6.3–11.9). (b) A diagnosis of frequent TTH was made in 89 subjects (9.8 %, 95 %CI 7.9–11.8); 54 women (10.6 %, 95 %CI 7.9–13.3) and 35 men (8.8 %, 95 %CI 6–11.6). (c) The crude prevalence of chronic TTH was 0.6 %, 95 %CI 0.1–1 (F 0.6 %, 95 %CI 0–1.3; M 0.5 %, 95 %CI 0–1.2).

Conclusion: Our study results indicate past-year prevalence of TTH that are lower than those found in the epidemiological population-based studies in Western countries. No differences are observed in sex distribution.

"Headache frequency and characteristics in chronic cocaine users: a cross sectional study"

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Background: The association between headache and cocaine use has been investigated only with retrospective studies so far.

Aims: (1) to evaluate the prevalence of headache and its characteristics in chronic cocaine users in a cross sectional study. (2) to assess any temporal correlation between the onset of cocaine use and the onset of headache.

Methods: Cross sectional study on consecutive subjects with chronic cocaine use attending a Drug Addiction Service from 1/8/10 to 31/12/11. Subjects were visited and interviewed by a psychiatrist (VO) who gathered detailed information on cocaine use, concomitant psychiatric disorders/treatments and other comorbidities, and by a neurologist (LF) who assessed the presence of lifetime headache and/or current headache and gathered information on headache characteristics and its correlation cocaine use. Subjects were divided in 3 groups: no headache (group 0), current headache and positive history of pre-existing headache (group 1) and current "de novo" headache (individuals who developed headache after the onset of cocaine use) (group 2).

Results: Eighty subjects (mean age 37.8 ± 9.4 ; 16 F:64 M) were enrolled. Seventy-two (90 %) had current headache. Of these, 29 (40.2 %) had a pre-existing history of headache [MWOA = 15, probable MWOA = 6, TTH = 4, CM = 2, other = 2, while 43 (59.7 %) developed "de novo" headache following the onset of cocaine use [cocaine-induced headache = 2, MWOA = 17, probable MWOA = 8, TTH = 9, CM = 1, other = 6]). Seven subjects had medication overuse (4 in group 1 and 3 in group 2).

There were no differences between the 3 groups as regards socio-demographic characteristics.

Group 1 patients showed a longer duration of headache history ($p = 0.002$), more severe headache intensity ($p = 0.001$) and nausea ($p = 0.041$) during the attack and more frequent analgesics assumption ($p = 0.04$) compared to group 2 (one-way ANOVA analysis). Group 2 patients revealed a better response to analgesics than group 1 ($p = 0.047$) (one-way ANOVA analysis).

In group 2, Pearson's analysis evidenced a linear correlation between the age of headache onset and the age of first use of cocaine ($p = 0.008$, $r = 0.401$) and between the age of headache onset and the age of continuous use of cocaine ($p = 0.016$, $r = 0.367$). A multiple regression analysis showed that the age of

headache onset was predicted in the group 2 by the age of first use of cocaine and the age of continuous cocaine use with a value of R^2 of 18 %.

Discussion and conclusions: Headache is extremely frequent (90 %) but cocaine-induced headache (ICHD-II: 8.1.66) is extremely rare (2.5 %) in chronic cocaine users. Migraine without aura and probable migraine without aura were the most frequent types of headache in both group. Almost 60 % of chronic cocaine users develops headache after the onset of cocaine use. The combination of cocaine with cannabis or alcohol does not influence the presence and characteristics of headache. Usually, headache starts >2 h following cocaine use. Headache onset shows a linear correlation with duration of cocaine use, but is not correlated to the doses, ways of assumption and frequency of cocaine use. In the de novo headache group (group 2), the age of headache onset could be predicted by the age of first use of cocaine and the age of continuous use of cocaine.

The sporadic hemiplegic migraine (SHM) pathogenesis: the role of SCN1A gene

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Sporadic Hemiplegic Migraine (SHM), whose etiology is still unknown, is a paroxysmal disorder characterized by motor aura and headache. Three studies of SHM patients demonstrated CACNA1A mutations essentially in patients with cerebellar signs, permanent cerebellar ataxia or cerebellar atrophy on CT scan. In 2008 Thomsen studied 105 SHM patients, without permanent signs, and the found mutations were only in CACNA1A and ATP1A2 genes. Moreover, two authors confirmed the absence of mutations in SCN1A gene in all the screened SHM patients. Results from genetic and functional studies indicate that neuronal hyperexcitability has a pivotal role in the pathogenesis of hemiplegic migraine and multimodal neuroimaging (MRI, DWI, MRS, SPET) in prolonged attacks supports evidence for a primary neuronal dysfunction. In this review we have focalized the pathogenesis of the sporadic form and we have tried to understand if the absence of mutations in SCN1A gene suggests that SHM is a distinct form from FHM.

Botulinum A toxin for treatment of chronic migraine

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Introduction: Chronic migraine is a common and debilitating headache syndrome. Botulinum neurotoxin (BoNT), a potent toxin produced by the anaerobic bacterium clostridium botulinum, used largely for treatment of disorders associated with increased muscle tone and hyperhidrosis, has been recently used for patients suffering from chronic migraine.

Aim: As the significant population of chronic migraine patients, refractory to common therapeutic prophylaxis, BoNT has been used

in our clinical experience for treating patients referring to our headache centre and suffering from chronic migraine with medication overuse.

Method: Ten patients have been submitted to a withdrawal treatment from medications in a day hospital setting and after that, they have been treated by BoNT A injection in multiple sites according to the protocol of the PREEMPT study at the dosage of 150 U for 31 sites. Every session of local injection (150 U per 31 sites) has been repeated every 3 months for a period of almost 1 year. The clinical indexes were recorded by using an headache daily diary, with the number of medication intake per month and the days of headache per month. MIDAS questionnaire was given for recording the disability levels pre and during treatment period.

Patients were followed for 1 year.

Results: Days of headache/month decreased during the period of treatment (pre 21.4 + 7.9 post 13.8 + 10.9 $p < 0.01$). Also medication intake decreased (pre 19.6 + 8 post 11.7 + 9.5 $p < 0.01$).

At the same time the disability level decreased as evidenced from the MIDAS total score (pre 86.7 ± 73 post 74.9 + 91.1)

Discussion: Although these results are preliminary they led to intense efforts to evaluate the analgesic properties of BoNT A and to assess their clinical applicability.

The pharmacological profile of BoNT A makes it a good candidate for migraine prevention. Its long duration of action (3 months) makes it particularly attractive for patients who are not compliant with the daily use of preventive medications, or if they cannot tolerate it or when they are refractory to preventive medications.

Day hospital withdrawal for chronic migraine with medication overuse: results at 3 years follow-up

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Background: patients with chronic headache and medication overuse are particularly difficult to treat, with no one approach being universally accepted. Some type of withdrawal program, however, is typically implemented before beginning a pharmacological prophylaxis treatment. Different withdrawal modalities have been performed for managing these patients: at first step, in-patient withdrawal has been confirmed effective in preceding clinical experiences. In recent years new modalities for withdrawal have been developed as day-hospital setting withdrawal.

Objective: Purpose of this study was to determine the clinical course of a sample of chronic migraine patients with medication overuse 3 years after day hospital withdrawal.

Methods: A group of 202 patients were treated. Patients were suffering from chronic migraine with medication overuse according with HIS criteria. All patients were submitted to a day hospital withdrawal and then they were followed with meetings every 3 months until the first year and then every 6 months until the last follow-up 3 years after withdrawal.

Results: Eighty patients achieved the last follow-up meeting 3 years after withdrawal. Patients clinically improved: days of headache per month decreased significantly from 22.8 (SD 5.8), at baseline to 7.8 (SD 4.9); consumption of medications per month decreased significantly too from 26.7 (SD 19.9) to 7.4 (SD 5.0) at the last follow-up.

Conclusions: From these results the day hospital setting for withdrawal, followed by periodic clinical meetings, seems to be effective for this category of patients to improve significantly at long-term headache frequency and analgesics intake.

Abnormalities of immune parameters in chronic migraine with medication overuse

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Background: It has been postulated in the past that migraine and chronic forms in particular, has been connected to immunologic disturbances. Moreover the psychiatric comorbidity is often responsible of chronification of migraine but also of developing of particular immune function alterations.

Aim: Of our study was to evaluate 2 groups of subjects: first group of patients suffering from chronic migraine with medication overuse before a withdrawal procedure; second group control subjects of same age and general characteristics. Blood samples were collected from both of groups

Methods: Peripheral Blood samples from 25 patients suffering from chronic migraine with medication overuse and 25 controls were collected. Samples were collected in the morning, and the following analysis were performed: lymphocytes and subsets, CD3, CD4, CD8, CD 19, T reg.

Patients were also submitted to the MIDAS questionnaire for evaluating the disability level induced from their headache status

Patients were studied before an intervention of withdrawal in a day hospital setting.

Results: From the analysis of samples we obtained the following results: CD4 were significantly higher in patients than in controls ($1,102.24 \pm 464.28$ vs. 790.52 ± 206.11 $p < 0.007$). CD19 increased significantly too in patients (385.68 ± 175.89 vs. 193.72 ± 72.07 $P < 2.46E-06$); also CD8 and CD 3 increased significantly in patients than in controls (respectively CD8: 747.93 ± 271.09 $p < 0.0006$; CD3 1949.42 ± 642.08 vs. 1356.62 ± 288.1 $p < 0.0001$). Other analysis did not show any significant abnormality.

Discussion: The alterations reported, although limited to particular parameters, may indicate a inflammatory state in patients suffering from chronic form of migraine with medication overuse, similar to those showed from preceding literature.

More studies will be necessary to confirm these preliminary results and to explain the clinical implications of these abnormalities.

Occipital nerve stimulation in the treatment of chronic medically intractable SUNCT and SUNA syndromes: a long term follow-up study in nine patients

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Objective: To report on the outcome and follow-up of nine chronic medically intractable SUNCT (Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing) and SUNA (Short-lasting Unilateral headache attacks with Autonomics symptoms) patients treated with occipital nerve stimulation (ONS).

Background: SUNCT and SUNA are primary headaches characterized by repeated attacks of very severe headaches in association with cranial autonomic features that usually occur several times daily.

They can be medically intractable, in which case neurally destructive or cranially invasive treatments can be offered. ONS offers a non-destructive and relatively low-risk surgical alternative.

Methods: Nine medically intractable patients (6 SUNCT, 3 SUNA) had bilateral ONS implants. Data was collected retrospectively for demographics, diagnosis and previous treatments. Data about frequency, intensity and duration of attacks were collected from headache diaries at baseline and after the implant, to assess the objective improvement of the headache. Disability, anxiety and depression scales were administered at baseline and during the follow-up.

Results: At a median follow-up of 31 months (range 16–48 months), all but one patient showed substantial improvements: four patients became pain free, two, almost pain free (≥ 95 % improvement), and two had a remarkable reduction in attack frequency and severity (≥ 80 % improvement). Five patients were able to discontinue preventive medications, whereas two, to reduce them. After a rapid initial improvement, the maximum benefits of ONS were attained over few months. Battery failure or voluntary stimulator switch-off were followed by recurrence or worsening of the attacks within few days in most of patients. Adverse events included new-onset hemi-*crania continua*, lead migration, exposition of the electrode and muscle pain over the leads.

Conclusion: ONS seems to be an effective and safe treatment for medically intractable SUNCT and SUNA syndromes. Given the poor and controversial results on the surgical management of these conditions, ONS might be considered the surgical treatment of choice for medically intractable SUNCT and SUNA.

Impact of migraine and chronic migraine on disability and reduced productivity: a cross-sectional study

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Migraine is a common disease that, in association with specific lifestyle and life events, may undergo a chronification process, often associated to medication overuse. Chronic Migraine with Medication Overuse (CM-MO) is a condition characterised by more frequent attacks that are likely to impact on patients’ disability and productivity, with relevant consequences in terms of disease cost (445€/year/patient for migraine; 1,875€ for CM-MO). Aim of this paper is to assess differences between patients with episodic and chronic migraine with regard to disability and reduced productivity.

Patients with migraine (MIG) and CM-MO in the productive age and employed, were consecutively enrolled and administered the MIDAS and the WHO-DAS-2. Independent-sample *t* test was performed to assess group differences; $P < 0.05$ was set for statistical significance. In total, 178 patients were enrolled (80 with MIG, 98 with CM-MO; 144 females), with no group differences for age (40.9 for MIG; 41.4 for CM-MO), years of formal education and number of worked hours per week. Significant differences were instead found at MIDAS (25.3, 95 % CI 20.3–30.4 for MIG; 85.5, 95 % CI 71.9–99.1 for CM-MO) and WHO-DAS-2 global disability (20.1, 95 % C.I. 16.9–23.3 for MIG; 29.4, 95 % CI 26.8–32.0 for CM-MO). Considering the items related to difficulties with remunerative job, significant differences were found too, both in terms of number of workdays lost (1.8, 95 % CI 1.2–2.5 for MIG; 4.1, 95 % CI 2.8–5.3 for CM-MO), and in terms of difficulties in dealing with work duties as measured with

WHO-DAS-2 Work/school activities scale (28.9, 95 % CI 24.4–33.4 for MIG; 35.6, 95 % CI 31.1–40.0 for CM-MO).

Recent estimates show that the cost of CM-MO is approximately four times higher: the difference is relevant for direct healthcare costs (86€ for MIG; 267€ for CM-MO) and even more for indirect costs (359€ for MIG; 1,608 for CM-MO). Our results are consistent with the cost estimate and we recommend that longitudinal studies be performed to assess the effectiveness of treatment not only for reducing headaches frequency and intensity, but also to reduce disability and increase patients ability to be productive in the workplace.

Search for possible predictive factors of the course of migraine without aura during pregnancy

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As is known from the literature, attacks of migraine without aura (MO) are generally reduced and sometimes even disappear altogether during pregnancy. Unfortunately, however, in a minority of cases this improvement will not occur.

In order to evaluate the possible existence of clinical features that can predict the course of MO during pregnancy, we reviewed the clinical records of 121 MO patients seen on a consecutive basis at the University of Parma Headache Centre who had at least one pregnancy after their MO onset.

The women were divided into two groups: Group A with 94 patients showing a favourable MO evolution, and Group B with 30 patients showing an unfavourable MO evolution.

The two groups were compared using statistical tests (Student's *t* test, Wilcoxon-Mann-Whitney test, Chi-square test, Fisher's test) to evaluate the following aspects: age at MO onset; family history of migraine; age at menarche and possibly menarche-related MO onset; evolution of attacks related to menstruation and the possible use of oral contraceptive; pain site; associated symptoms; unhealthy personal habits; and possible MO association with migraine with aura and/or tension-type headache.

Statistical significant differences were found between the two groups in the predominant pain site and in the MO association with tension-type headache: pain was less consistently unilateral and association with tension-type headache was present in the women who did not have MO improvement during pregnancy.

Other differences in the clinical variables considered were not statistically significant but nonetheless showed a tendency that is worth studying through a review of broader case series: the women with MO that did not improve during pregnancy had a younger age at onset, an older age at menarche, and a less unfavourable course of their migraine when using oral contraceptives.

Oxidative balance in migraine: an open study by d-ROMs test and BAP test on 50 patients

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Introduction: Migraine is the most common neurological disorder, but the molecular basis is still not completely understood. An impairment of mitochondrial oxidative metabolism might play a role in the pathophysiology. Moreover there is strong evidence associating migraine with a variety of comorbid disorders, including cardiovascular disease and stroke, in which oxidative stress seems to be an important underlying mechanism. However, data are in part controversial and the possible underlying mechanism remain elusive to date and the data regarding the interictal state in migraineurs is limited.

Aim: To evaluate the oxidative balance in a sample of patients with migraine by means of routine specific serum tests, such as d-ROMs test and BAP test.

Methods: 50 outpatients, (32 F, 18 M) mean age 34.8 years (SD 10.9), range 18–58 years, suffering from migraine without aura (ICDH-II 2004 criteria) were enrolled. The mean duration of disease was 1.4 (SD 0.7) years, range 1–3 years. Serum total oxidant capacity was determined by performing the d-ROMs test (2), which chemical principle is based on the ability of a biological sample to oxidize *N,N*-diethylparaphenylenediamine (normal range 250–300 CARR U, where 1 CARR U is equivalent to 0.8 mg/L H₂O₂), while serum total antioxidant capacity was assessed by means of BAP test, which measures the ability of a serum sample to reduce iron from the ferric to the ferrous ionic form (optimal value >2,200 μmol/L reduced iron).

Results: Mean values of d-ROMs tests were 385.2 CARR U (SD 119.8) while mean values of BAP test were 1,705.4 μmol/L reduced iron (SD 438.9).

Discussion and conclusions: According to herein reported data, enrolled patients were found to be in a classical condition of oxidative stress. In fact compared to the normal range, oxidant capacity, as measured by means of d-ROMs test, was increased (>300 CARR U) and biological antioxidant potential (as measured by means of BAP test) was decreased (<2,200 μmol/L reduced iron). Although preliminary our study confirm that migraine without aura is associated to oxidative stress and suggests that d-ROMs test and BAP test can be useful to identify an oxidative unbalance in clinical routine of patients suffering from this frequent disease. Our data suggest that oxidative stress may represent a key event in the pathophysiology of migraine and a suitable therapeutic target. Further knowledge about this issue may contribute the cause and complications of migraine and may be essential for development of treatment approaches.

Migraine and food intolerance

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Background: Several factors can trigger migraine; among them, dietary factors play a very important role in the onset of migraine attacks. The aim of our study was to evaluate the incidence of food intolerances in a group of migraineurs, by using the Cytotoxic test.

Materials and methods: 80 consecutive patients suffering from migraine and coming to the Headache Centre of S. Luca Hospital, Vallo della Lucania (SA) were examined. 58 were females (F), whose mean age was 33.8 years, range 18–46 years, 22 were males (M), whose mean age was 42.5 years, range 24–56 years. The Cytotoxic test is capable of identifying the presence of specific food intolerances by observing the appearance, the size, the shape or the integrity of leukocytes exposed to extracted food antigens or other materials derived from specific foods.

Results: We found that: 31 F (53.4 %) and 10 M (45.4 %) were intolerant to tyramine. 9 F (15.5 %) and 3 M (13.6 %) were intolerant to milk, 11 F (18.9 %) and 3 M (13.6 %) were intolerant to yeast. 9 F (15.5 %) and 2 M (9.9 %) were intolerant to Solanaceae. 12 F (20.6 %) and no M were (0 %) intolerant to coffee. 13 F (22.4 %) and 1 M (4.5 %) were intolerant to cocoa. 4 F (6.89 %) and no M (0 %) were intolerant to tea. 3 F (5.2 %) and 2 M (9.9 %) were intolerant eggs. 2 F (3.4 %) and 1 M (4.5 %) were intolerant to pork. 3 F (5.2 %) and 1 M (4.5 %) were intolerant to sugar.

Conclusions: Our study showed a high incidence of food intolerance in migraineurs (in females more than in males). The dietary factors which gave more significant results were tyramine, yeast, solanaceae, coffee and cocoa. These results are in agree with those of other studies found in literature, proposing tyramine, coffee and cocoa as very important migraine-precipitating factors. Few are, on the contrary, the evidences of a comorbidity between migraine and intolerance to solanaceae. For this reason, further studies are requested to confirm this hypothesis.

Prophylaxis therapy of pediatric migraine: an open study with L-tryptophan, Griffonia simplicifolia, vitamin PP and vitamin B6

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Aim: To evaluate the efficacy and tolerability of L-tryptophan, griffonia simplicifolia, vitamin PP and vitamin B6 in prophylaxis therapy of pediatric migraine.

Methods and materials: 18 outpatients, (11 F, 7 M) mean age 10.1 years (SD 4.1), range 4–18 years, suffering from migraine without aura (ICDH'04 criteria) were enrolled. The mean duration of disease was 2.3 (SD 1.2) years, range 1–4 years. At baseline the mean frequency of attacks was 7.2/month (SD 2.2), range 4–12; the mean number of drugs intaking for acute attacks was 6.3 tablets/month (SD

1.4). During the 6 month evaluation period L-tryptophan, griffonia simplicifolia, vitamin PP and vitamin B6 was administered (at dose 100, 480, 18 and 1 mg/die respectively). All patients filled a headache-diary card during the evaluation.

Results: The basal frequency of attack was 7.2 (SD 2.2) and 4.2 (SD 1.9), 3.4 (SD 1.8), 2.5 (SD 2.2), after 1, 3 and 6 months respectively [$P < 0.0001$; $P < 0.0001$; $P < 0.0001$]. The basal value of intaking drugs for acute attacks was 6.3 (SD 1.4) and 3.8 (SD 1.6), 2.9 (SD 1.6), 1.9 (SD 1.8) after 1, 3 and 6 months respectively [$P = 0.002$; $P < 0.0001$; $P < 0.0001$] (T test analysis). L-tryptophan, griffonia simplicifolia, vitamin PP and vitamin B6 was well tolerated (7 patients complained somnolence, diarrhoea and gastralgia but none patient withdrew the study).

Conclusions: These data showed a good efficacy in reduction of frequency and intensity of headache attack, a good tolerability and a very good reduction of drugs intaking for acute attacks. Our study suggests that L-tryptophan, griffonia simplicifolia, vitamin PP and vitamin B6 could be an alternative therapy for pediatric migraine prophylaxis.

Migraine and Shiatsu: a preliminary results

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Purpose: Several studies showed that complementary and alternative medicine (CAM) therapies, like Shiatsu, are widely used among primary headache patients, despite few scientific evidence of their benefits. Our aim was to evaluate the effectiveness of Shiatsu versus Amitriptyline in the prophylactic treatment of migraine.

Methods: Patients diagnosed as affected by migraine, and who failed at least one prophylactic drug other than Amitriptyline, were randomly assigned to Shiatsu treatment (group A) or to orally Amitriptyline (group B). Patients in group A underwent weekly sessions for 3 consecutive months in an outpatient neurological setting; orally 10 mg of Amitriptyline daily for 3 consecutive months was administered to patients in group B. The number of days with headache and pain killers per month, as well as the Visual Analogic Scale (VAS) for pain severity, were recorded by means of patient diaries during the 1 month scheduled interviews in the 3 months before the study enrolment and up to 3 month follow-up period. The occurrence of side effects or adverse events were also recorded.

Results: A total of 20 female patients with a mean (\pm SD) age of 40 ± 15 years, affected by migraine without aura, were enrolled. Each group accounted for 10 patients with similar clinical features. Two patients in the group B reported a mild drowsiness as side effect. After the 3 month follow-up period there was a significant reduction in the mean number of days with headache per month in both group A ($p = 0.05$) and B ($p = 0.04$). The mean number of pain killers per month also decreased in both group A ($p = 0.04$) and B ($p = 0.05$). The VAS score improvement is maintained in group B ($p = 0.04$), but not in A ($p = 0.12$).

Conclusion: Our extended study results suggest that Shiatsu might represent a safe, well tolerated and effective alternative prophylaxis treatment for migraine.

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Survey about headaches in patients with obstructive sleep night apneas

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Introduction: We subjected to study 254 subjects, 173 men and 81 women, average age, suffering from 56.8 ± 15.0 syndrome of obstructive sleep night apneas to evaluate the prevalence of headache and put in place a series of preventive measures also in view of preventing complications.

Materials and methods: The subjects were recruited within the Department of Pneumology Teramo Hospital. Apneas are graded as mild (AHI between 5 and 10), moderate (AHI between 11 and 20),

severe (AHI > 20). Headaches were classified according to the criteria of HIS. 20 persons (8.1 %) referred to a history of primary headache: 3 affected by Migraine (1.2 %) and 17 (6.9 %) headache. 180 (70.9 %) had headache on awakening, with a greater frequency of breathing pauses during sleep, insomnia central type and episodes of sweating. All were subjected to an interview with a standardised questionnaire on sleep features on related conditions on the type of headache and on risk factors for headache.

Results: At the end of the study, after 2 years, we can say that the severity of obstructive night underlies the morning headache frequency (frequency greater than patients with insomnia), assuming an important role regarding the hypercapnia consequential vasomotor phenomena.

Conclusions: Ultimately, we can say it is appropriate to subject all morning to headache sufferers screening for sleep disturbance related to diseases of the breath, for a correct diagnostic-therapeutic approach in preventive and key.