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Trigeminal neuralgia in multiple sclerosis: prevalence and association with demyelination

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Abstract

Objectives: The association of trigeminal neuralgia (TN) with multiple sclerosis (MS) is still widely unaddressed in larger, systematical clinical series. In this study, a cohort of Finnish MS patients was assessed regarding the incidence and prevalence of TN, as well as the presence of demyelinating lesions near the trigeminal ganglion, thus searching for a causative role of MS plaques in TN onset.

Materials & Methods: All consecutive patients treated and followed up for MS (ICD-code G35) in Helsinki University Hospital during 2004 – 2017 were identified from the Finnish MS register. A hospital administrative database search was used to identify all patients treated and followed up for TN during the same period. Among the MS patients, head MRI scans available from the diagnostic phase of TN or thereafter were analysed.

Results: We identified a total of 2575 patients with MS and 2008 patients with TN. Both diagnoses could be verified for 55 patients, giving a prevalence of 2.1% for TN in MS. The incidence of TN in MS patients was 149/ 100 000 person-years (95% CI 108–190). In the general outpatient population of our neurological department, the incidence of TN was 9.9/ 100 000 person-years (95% CI 9.5–10.3). A demyelinating lesion in the proximity of the trigeminal ganglia was seen for 63% of the 41 patients with relevant MRI data available.

Conclusions: Incidence of TN among MS patients was 15-fold higher than in the general neurological outpatient population, thus in favor of a strong association between MS and TN.

Keywords

Multiple Sclerosis; Trigeminal neuralgia; Neuroimaging

Introduction

Multiple sclerosis (MS) is the most common chronic autoimmune disease attacking the brain and spinal cord. The prevalence of MS in Finland is one of the highest in the world, with a crude estimate of 247 / 100 000 (1). Disease course is relapsing remitting (RRMS) in approximately 85% of patients, where a new demyelinating lesion or lesions may cause a new symptomatic period. Demyelinating lesions of the brain stem can present with symptoms of the cranial nerves, such as sudden sensorineural hearing loss (2), abnormal eye movements (3) or facial motor paresis (4), in addition to painful trigeminal neuralgia (TN).

TN is a pain disorder where recurrent unilateral sharp pain attacks, often triggered by innocuous stimuli, occur in the area of the face and jaw innervated by the branches of the trigeminal nerve, and the pain. The causative process behind TN remains unidentified in most patients, but the most common finding is vascular compression and subsequent morphological change in the nerve root. Tumours and other inflammatory or infectious processes may also be etiological factors (5). Demyelinating MS lesions damaging intrapontine trigeminal primary afferents (6, 7) or the spinal trigeminal nucleus and tract (7) have been found in patients diagnosed with TN. Histological sections of trigeminal nerve root have shown demyelination, gliosis and inflammation in MS patients suffering from TN (8).

The prevalence of TN in the general population is between 0.03 and 0.3% (9, 10). There is a clear association of TN with MS, as the prevalence of TN in MS patients has been reported to vary between 1.1 and 6.3% (11–16). A survey-based study estimated the prevalence of TN in MS patients to be as high as 9.7% (17), but there are limitations to the reliability of this study approach. An even larger variation is seen in the results of studies on the etiology of TN in MS patients, reflecting their paucity and small size with fewer than ten patients, where an associated demyelinating lesion of the pons has been identified with a highly variable portion in 14 to 100% of patients (18, 19). A recent report with an initial study cohort of 1628 MS patients identified a total of 28 patients with TN, 26 of whom (93%) had a pontine demyelinating plaque ipsilateral to the TN symptoms (12). That study also found a relevant neurovascular compression site for more than half of the patients. This finding is a reminder not to neglect evaluations for surgically treatable cases in MS patients with TN. This was also highlighted in a recent review of the treatment options for MS-associated TN (20).

The objective of the present study was to determine the prevalence and incidence of TN in a large single-centre cohort. We used the national Finnish MS register to identify patients, and to ascertain a substantial study population with good coverage. Our secondary objective was to assess the presence of demyelinating plaques in the proximity of the trigeminal ganglia in these patients, and thus gain further understanding on the causative role of MS plaques in TN onset.

Materials and Methods

This is a single-centre retrospective study, where all patients treated and followed up for MS (ICD-code G35) in the Helsinki University Hospital neurology outpatient clinic during 2004 – 2017 were identified from the Finnish MS register (21). The hospital's administrative database was used to identify all patients treated and followed up for TN (ICD-code G50.0) in the Helsinki University Hospital neurology outpatient clinic during the same period. This general TN cohort was not characterized in more detail, because it was collected for crosschecking the data. Finally, data on MS patients with a diagnosis of TN was collected in more detail using the MS register and electronic hospital patient records.

After the identification of the patients with concomitant diagnoses of MS and TN, the patient records were reviewed to retrieve the dates for setting the MS and TN diagnoses, as well as medications used for these conditions and surgical treatments for TN. Two experienced neuroradiologists (GK and JM) reviewed the head MRI images available from the diagnostic phase of TN or thereafter, searching for demyelinating plaques in the proximity of the trigeminal ganglia. The MRI field strength ranged from 1.5T to 3T, and the MRI protocol used in analysis was T2-weighted axial sequence for all cases and axial flair, axial T1-weighted Gadolinium (Gd) -enhanced and/or diffusion weighted imaging (DWI) sequences for those with data available.

Statistical analyses were performed using the SPSS software. The incidence of TN in patients diagnosed with MS and in the general neurological outpatient population were calculated using Poisson's regression analysis. Mean ages at diagnosis and mean follow-up times with standard deviation were calculated.

This study was approved by the institutional review board of Helsinki University Hospital. According to Finnish law, approval of the ethical committee was not required because the study was based on administrative register data and included no contact with patients.

Results

Prevalence and incidence of TN in the MS patient cohort and neurological outpatient cohort

We identified a total of 2575 patients with MS and 2008 patients with a diagnosis of TN, followed-up in Helsinki University Hospital. A combination of the two diagnoses could be verified in 55 patients (Figure 1), which gives a prevalence of 2.1% for TN in MS patients. The incidence of TN in MS patients was 149/ 100 000 person-years (95% CI 108–190). For the general neurological outpatient population of Helsinki University Hospital, the incidence of TN was 9.9/ 100 000 person-years (95% CI 9.5–10.3).

Among patients with a diagnosis of MS (n=2575), 71% were female, and the mean age at the time of analysis was 49.7 years (SD 12.9). The mean age for diagnosis of MS was 35.5 years (SD 10.9), giving a follow-up time of 14.0 years (SD 9.8). Disease modifying treatment (DMT) was used by 55% of the MS patient cohort.

Of the 55 patients with both MS and TN, MRI data at the time or after the TN diagnosis was available for 41 patients (75%; Figure 1). Clinical data and the presence of demyelinating plaques in the proximity of the trigeminal ganglia were analysed in this subcohort.

Demographics of patients with concurrent MS and TN

Of the patients with diagnoses of both MS and TN (n=55), 41 (75%) were women. The precise time of onset of TN could be retrieved for 54 patients. Of these patients, 40 (74%) had a diagnosis of RRMS, eight (15%) had a diagnosis of primary progressive MS (PPMS), and six (11%) had a diagnosis of secondary progressive MS (SPMS) at the time of onset of TN.

Treatment for MS was used by 31 of the 55 patients (64%), of whom 25 (81%) had a DMT regarded as a first-line therapy for MS. Six patients (19%) had azathioprine for MS, a drug often prescribed for SPMS. Temporal association of MS with TN is shown in Figure 2.

Demyelinating lesions in the proximity of the trigeminal ganglia in MRIs of MS patients with TN

Out of the 55 patients with both MS and TN diagnoses, there were 41 patients with MRI data available. The MRI images were reviewed for demyelinating plaques of the pons, close to the site of the trigeminal neural ganglia. Twenty-six out of the 41 patients (63%) had such a demyelinating lesion, and in 23 patients (88% of those with lesion,

56% of all MS patients with MRI data available) a lesion ipsilateral to the TN symptoms was found. The majority of the lesions, 17 (65%), were found using 1.5T MRI and 9 with 3T MRI. The detection rate with 3T MRI appeared to be a little higher, with 82% (9 out of 11) of imaging studies detecting a demyelinating lesion compared to 57% with 1.5T. The MRI was taken median 2.5 years (range 0.1–18.4 years, n=40) after the onset of TN symptoms. In the subgroup of patients that had a demyelinating lesion in the pons (n=26), the MRI was taken median 3.0 years (range 0.1–14.8 years) after the onset of TN symptoms. Nine patients had the MRI taken within 6 months of the onset of TN symptoms, and of these 9 patients, four (44%) had a demyelinating lesion in the pons.

To assess the number of acute lesions, the number of Gd-enhancing lesions and lesions visible on DWI sequences were calculated. Thirty-six patients had available data on Gd-enhanced T1-weighted sequences, and one patient showed Gd-enhancement, suggesting that the lesion was acute. In addition, one patient that did not show Gd-enhancement had a lesion visible in DWI sequence, suggesting that also this lesion was acute. Figure 3 demonstrates a demyelinating pontine lesion in a patient with TN.

We also evaluated the patient records for other brain stem derived newly onset symptoms at the time of TN onset. Forty-five patients (82%) out of the total of 55 patients with MS-associated TN had a documented contact with a neurologist at the time of TN onset. Of these patients, only four (9%) presented with other symptoms possibly associated with brain stem lesions, such as dysarthria or vertigo. Interestingly, two patients had optic neuritis, verified by an ophthalmologist, coinciding with the onset of TN.

Symptomatic medication use and surgical treatment of TN

Thirty-four patients were on TN medication (Table 1). The most common medications for TN were first-line therapies such as carbamazepine (22%) and oxcarbazepine (33%). Others included medications for neuropathic pain, i.e. gabapentinoids (20%), lamotrigine (2%), topiramate (2%), and opioids (2%). One patient received misoprostole for TN relief. Most patients were on monotherapy. Seven patients had undergone surgical treatment (Table 1).

Discussion

The prevalence of TN was 2.1% for MS patients in our cohort, which is in line with previous studies reporting prevalences between 1.1 and 6.3% (11–16). In our study, the incidence of TN in MS patients was 15-fold higher compared to the general neurological outpatient population. MS was diagnosed at a mean age of 36.4 years in our cohort, which does not differ from the usual age of MS onset (22). The age of onset of TN symptoms, mean 46.6 years in our study, is comparable to the age of TN onset in other studies on MS patients (12, 17). Although our TN cohort is hospital-based, the symptoms of TN are often so severe that referral to a neurological outpatient clinic is likely, making the incidence estimation more reliable. The coverage of our referral-based TN population is strengthened also by the reimbursement policy for TN treatments in Finland, requiring a statement from a neurologist or neurosurgeon. The incidence of TN in the Western countries has been reported to be 12.6–28.9/ 100 000 person-years (23), and comparing this to our data, an incidence of 9.9/ 100 000 person-years in the general neurological outpatient population, it is likely that there are TN patients in our hospital district treated by private sector neurologists and therefore unreached by our study. MS is however almost exclusively diagnosed and treated in Finland by neurologists working in public health care, further supporting the study approach.

The association of TN with a demyelinating plaque in the proximity of the trigeminal ganglia was seen in 26 (63%) of the 41 patients with a concomitant MS diagnosis and with MRI available. In 23 (88%) the lesion was ipsilateral to the TN symptoms. In a recent study that screened 1628 consecutive MS patients, the rate was slightly higher, as ipsilateral demyelinating lesions of the trigeminal root entry zone were seen in 26 of 28 patients with concomitant diagnoses of MS and TN in this cohort (12). There is a risk of false negatives in our study, as the MRI was taken median 2.5 years after the onset of TN symptoms, and therefore prior, smaller lesions may have escaped detection. Both 1.5 and 3.0 Tesla MRI were used in our data set. For infratentorial lesions, the detection rate for demyelinating lesions has been reported as equivalent for the two field strengths (24). In our study, however, the detection rate with 3.0 Tesla appeared to be somewhat higher, 82% vs 57% detection rate in comparing 3T with 1.5T MRI. It has also been suggested that supratentorial demyelinating plaques, especially of the insular region, could associate with TN (25) and these sites were not assessed in the present study.

Optic neuritis (ON) is by far the most common cranial nerve symptom in MS, with a prevalence of almost 50% during the course of the disease. The reason for an increased incidence of ON in MS has been speculated to be connected with the histological features of cranial nerves (2). Myelin sheath encircling the optic nerve is produced by oligodendroglial cells, whereas in other cranial nerves from the third nerve onwards the myelin is mainly produced by Schwann cells. Similarly, the root entry zone myelin of the trigeminal nerve is made by oligodendroglial cells, and this could enhance an autoimmune attack leading to TN in MS patients, comparable with the biological reaction in ON. However, neurovascular compression may act as a concurring mechanism leading to the focal demyelination of

primary afferents near the entry of the trigeminal root into the pons (20). Thus, these etiologies may be hard to separate, even histologically. Neurovascular compression could also be the causative factor among patients in our cohort without ipsilateral pontine lesions.

The severity of TN symptoms did not appear to be particularly high in MS patients, with 38% of the patients having no need for medication, and the majority receiving monotherapy. Surgical treatment had been performed for only 13% of the patients, whereas a recent Danish study reported a surgery rate of 25% for the general TN population (26). This may reflect hesitancy for surgical referral, or it could be related to reports that surgical procedures are less successful in MS patients with TN than in the general population (27). Other approaches, such as stereotactic radiosurgery, have been more promising (28). Our findings suggest that there is a substantial proportion of MS patients with TN who do not have an associated demyelinating lesion. Therefore, vascular compression should be sought similarly as in non-MS patients and surgical treatment subsequently considered equally among MS patients. Unfortunately, we did not have magnetic resonance angiography (MRA) data available due to the retrospective nature of our study.

The majority of the patients, 85%, had MS diagnosed many years before the onset of TN symptoms: 12.9 years on average. If the symptoms of TN preceded the diagnosis of MS, the follow-up interval between the two diagnoses was clearly shorter (3.9 years on average). These findings, along with the significantly higher incidence of TN in MS patients, suggest a causative role for MS-derived pontine inflammation in TN onset. The onset of TN is not usually regarded as a relapse in MS patients, and this study supports this consensus since a third of the patients did not show evidence of pontine demyelination in a follow-up MRI. To detect an active enhancing causative demyelinating lesion, an MRI within 2 months of symptom onset is warranted. If such a lesion in close proximity of the trigeminal nerve is detected, this could however be considered a relapse of MS, as the causative mechanism is the same as in other relapses.

As discussed by Cruccu et al. (29), MRI is a valuable diagnostic tool only if preceded by an evaluation of symptoms and signs that indicate probable TN. A recent meta-analysis reported neurovascular contact in 89% of symptomatic trigeminal nerves and in 36% of asymptomatic nerves, indicating high sensitivity but poor specificity for MRI performed with MRA (30). Further prospective studies are needed that search for causative demyelinating lesions as well as neurovascular compression immediately after TN onset. The MRI protocol should include high resolution (preferably 3T) MRA in addition to contrast enhancement imaging to cover the concurring mechanisms of demyelination, compression and inflammation (31).

To conclude, a 15-fold higher incidence of TN among MS patients compared to the general neurological outpatient population was seen in our cohort. Our results support considering a contrast enhanced MRI together with MRA

diagnostics to evaluate both demyelinating lesions and neurovascular compression as etiological factors. However, the benefit of such an approach for treatment needs to be studied prospectively.

Conflict of interest

S M L: Fee for lecture Merck; congress expenses Roche, Merck

O H: No disclosures.

G K: No disclosures.

J M: Lecture honoraria Santen

T S: Grants Orion Corporation (Finland), TEVA Pharmaceutical Industries Ltd., Allergan plc; personal fees Boehringer Ingelheim Inc., outside the submitted work.

S A: Fees for lectures Merck, Roche, Santen; congress expenses Biogen, Sanofi Genzyme, Merck, Orion, Pfizer; advisory boards Biogen, Sanofi Genzyme, Merck, Pfizer, Roche.

Data Availability Statement

The data that support the findings of this study is available from the corresponding author upon reasonable request.

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Tables

Table 1. Treatments for trigeminal neuralgia (TN).

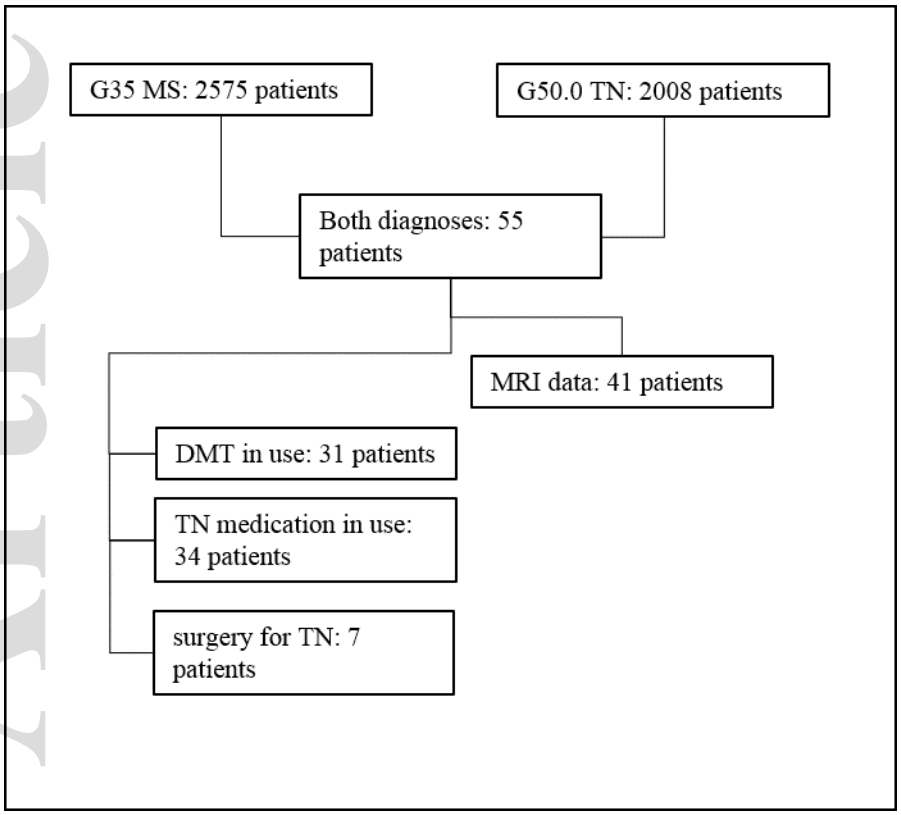
Treatment	Number of patients (%, n=55)
Medication for TN	34 (62%)
monotherapy	23 (42%)
two or more medications	11 (20%)
Surgery for TN performed	7 (13%)
electrocoagulation	7 (13%) once, 6 patients ≥ 2 times (11%)
microdecompression	1 (2%)

Figure legends

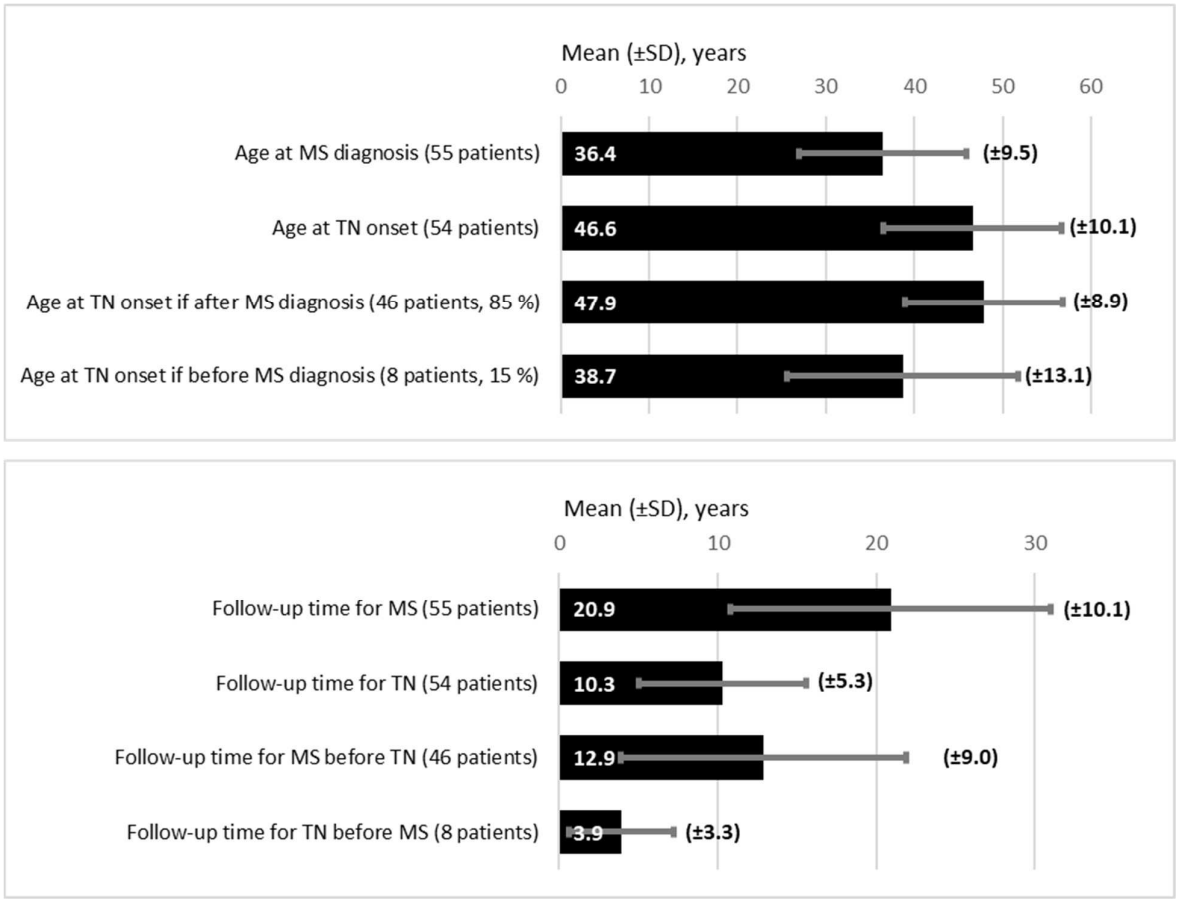
Figure 1. Patient cohorts with MS, TN, concomitant MS and TN diagnoses, and available head MRI. The flow chart demonstrates the patient cohorts, medication use and surgery for TN.

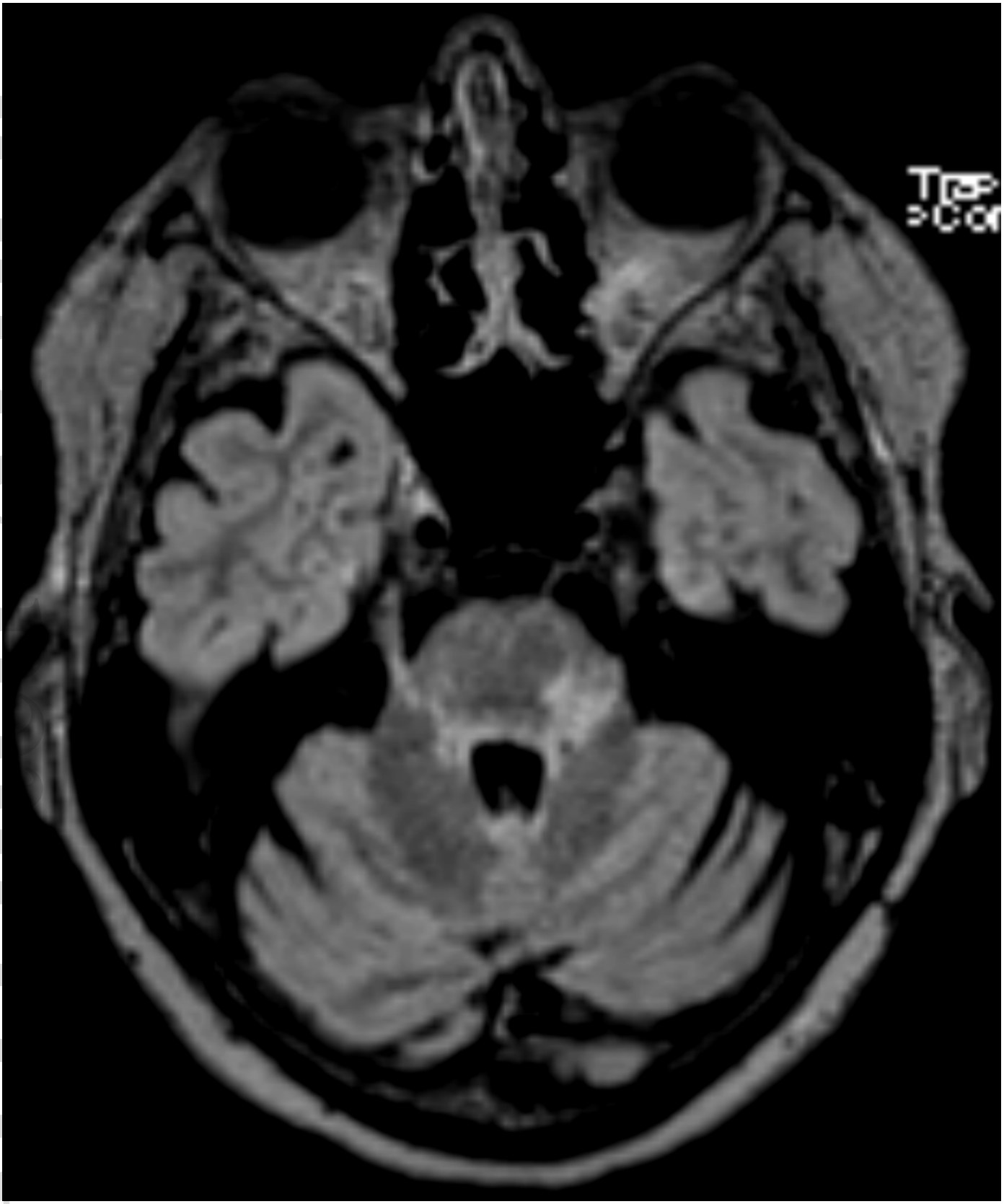
Figure 2. Temporal association of MS and TN in the cohort with concomitant diagnoses of MS and TN (n=55). The upper graph presents the mean age of patients at the time of MS and TN diagnoses, and the lower graph the follow-up time for MS and TN in the cohort, whichever came first. The precise time of onset of TN could be retrieved for 54 patients.

Figure 3. A representative MRI scan showing a demyelinating lesion near the trigeminal ganglion. A 52-year-old female patient with MS had the onset of left-sided TN at the age of 40 years. An MRI taken 10 years later, when the TN was clinically very active, showed a relatively large demyelinating lesion on the left in the pons, near the trigeminal ganglion. MRI field strength was 1.5T (T2 flair sequence).



Footnote to figure 1. TN trigeminal neuralgia; MS multiple sclerosis; MRI magnetic resonance imaging; DMT disease modifying treatment.





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