



Original article

Characteristics and treatment of Multiple Sclerosis-related trigeminal neuralgia: An Italian multi-centre study



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ARTICLE INFO

Keywords:

Trigeminal neuralgia

Multiple Sclerosis

Pain

Disability

ABSTRACT

Background: The prevalence of trigeminal neuralgia (TN) in Multiple Sclerosis (MS) patients is higher than in the general population and its management can be particularly challenging. Our aim is to describe the characteristics, treatment and prognostic factors of MS-related TN in a retrospective multicentre study.

Methods: Neurologists members of the RIREMS group (Rising Researchers in MS) enrolled MS patients with a TN diagnosis and filled out a spreadsheet comprising their clinical data.

Results: Population consisted of 298 patients. First-choice preventive treatments were carbamazepine and oxcarbazepine. A surgical procedure was performed in 81 (30%) patients, most commonly gamma knife stereotactic radiosurgery (37%), followed by microvascular decompression (22%) and radiofrequency thermo-coagulation (21%); one third of patients underwent at least two procedures. Surgery was associated with higher disability, male sex and longer interval between MS and TN onset. Patients (77%) who stayed on at least one

Abbreviations: ICHD-3, International Classification of Headache Disorders; TN, trigeminal neuralgia; MS, Multiple Sclerosis; RIREMS, Rising Researchers in MS; EDSS, Expanding Disability Status Scale; NSAIDs, nonsteroidal anti-inflammatory drugs; IQR, interquartile range; OR, odds ratio; VAS, visual analogic scale

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<https://doi.org/10.1016/j.msard.2019.101461>

Received 5 July 2019; Received in revised form 7 October 2019; Accepted 18 October 2019

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preventive medication at most recent follow-up, after a mean period of 8 years, had a higher disability compared to the untreated group. Furthermore, patients with higher disability at TN onset were less likely to discontinue their first preventive medication due to pain remission, had bilateral TN more frequently and underwent surgical interventions earlier.

Conclusion: MS patients with a higher disability at TN onset and with a longer interval between MS and TN onset had differing clinical features and outcomes: pain was more frequently bilateral, surgery was more frequent and anticipated, and preventive medication discontinuation due to pain remission was less common.

1. Introduction

According to the third edition of the International Classification of Headache Disorders (ICHD-3) (“Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition,” 2018), trigeminal neuralgia (TN) is a disorder characterized by recurrent unilateral brief electric shock-like pain, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve and triggered by innocuous stimuli. TN is divided into either classic (when there is demonstration of neurovascular compression), idiopathic or secondary TN caused by several pathologic conditions such as space-occupying lesions or Multiple Sclerosis (MS), in which case TN is caused by a MS plaque or plaques in the pons or trigeminal nerve root entry zone, and is associated with other symptoms and/or clinical signs or laboratory findings of MS. As per recent European guidelines on TN (Bendtsen et al., 2019), classic and idiopathic TN are, hereafter, grouped under the term “primary” TN. The incidence of TN in the general population is variably reported between studies, with a range from 4.3 to 27 new cases per 100,000 people per year and a lifetime prevalence of 0.16–0.3% in population-based studies (Katusic et al., 1990; MacDonald et al., 2000; Mueller et al., 2011). Overall, 2%–8% of TN patients have MS, which is 20-fold higher than in the general population. Conversely, the prevalence of TN in the MS population has been reported to be between 1% and 6.3% (Maarbjerg et al., 2017; O’Connor et al., 2008; Putzki et al., 2009; Solaro et al., 2004). Although the exact pathophysiology of TN in MS patients is unclear, proposed mechanisms include peripheral demyelination, central plaques, and a mixed peripheral–central mechanism (e.g., dual pathology of inflammatory demyelination resulting from MS plus mechanical demyelination caused by vascular compression). Indeed, a prospective clinical and neuroimaging study revealed a significant association between neurovascular compression and TN secondary to MS (Truini et al., 2016), suggesting that neurovascular compression may act as a concurrent mechanism that leads to the focal demyelination of primary afferents near the entry of the trigeminal root in the pons. Patients with MS-related TN are generally commenced on medical therapy first. Medications used are the same as for primary TN (sodium channel-blockers as first-line treatment choice) (Cruccu et al., 2008). Surgical approaches are considered eventually and include percutaneous balloon compression, gamma knife surgery, microvascular decompression and percutaneous radiofrequency rhizotomy. However, an analysis of surgical treatments of MS-related TN failed to show any differences in the short-term results of the various procedures (Montano et al., 2013). Overall, outcomes of treatment in MS-related TN suggest higher recurrence rates and lower pain-free responses compared with primary TN, regardless of treatment modality, with up to 70% of MS patients requiring multiple procedures compared with only 44% of non-MS patients (Martin et al., 2015; Mohammad-Mohammadi et al., 2013).

Aim of this retrospective, multicentre study was (1) to collect information on the characteristics of MS-related TN and on the frequency and type of medical/surgical treatments, also in relation to patient disability (EDSS) and disease duration at TN onset and (2) to identify prognostic demographic/clinical factors associated with surgical treatment, repeat surgical treatment and with a medication-free status at follow-up, as an indicator of long-term pain remission.

2. Methods

2.1. Patients and data collection

During an ad-hoc meeting of the RIREMS group (Rising Researchers in MS—see <http://www.rirems.it>), comprised by a group of Italian neurologists with expertise in the diagnosis and management of MS, following an in-depth discussion, a consensus was reached regarding which patient selection criteria to apply and which data to collect. It was agreed on that MS patients who had received a diagnosis of TN at any time (either before or after the MS diagnosis), out of those seen throughout a 2-year period by RIREMS members, would be included in the study, prior verification, during a routine clinical visit, of the following inclusion/exclusion criteria: (a) recurrent, unilateral, brief electric shock-like pain, limited to the distribution of one or more divisions of the trigeminal nerve, (b) absence of constant pain and (c) absence of other possible causes of secondary TN (e.g. cerebellopontine angle tumours). The above-said neurologists also examined clinical records and filled out a spreadsheet comprising selected patients’ clinical data, information on prior and current medical treatments, and on type/timing of surgical procedures, if carried out. The following medications were considered “symptomatic” as they were used for acute pain relief: intravenous/oral steroids, opioids, paracetamol or NSAIDs; all other medical treatments (mainly antiepileptic drugs) were considered “preventive” as they were used for the long-term treatment of TN. Area Vasta Emilia Nord Ethics Committee approval was obtained for this study (protocol nr. 1010/2018).

2.2. Statistical analyses

Comparisons between groups were made using the chi-square test for categorical variables, and the Mann–Whitney and Kruskal–Wallis test for continuous variables. Logistic regression analysis was used to search for an association between baseline clinical variables and surgical/long-term outcomes. Data were analyzed using STATA 11 (StataCorp, Texas, USA).

3. Results

3.1. Population

Patient population consisted of 298 patients. Table 1 summarizes TN and MS patients’ characteristics.

TN onset preceded MS diagnosis in 29 cases (10%) by 5 ± 3 years (range: 1–15). TN occurred after a median period of 8 years from MS onset, with an interquartile range (IQR) of 1–15 years. Patients were, thus, divided in three groups: an early-onset group (TN onset which preceded or occurred within 1 year from MS onset), an intermediate-onset group (TN onset 1–15 years from MS onset) and a late-onset group (TN onset > 15 years from MS onset). Late-onset TN patients were significantly older and more disabled (Table 2).

First-choice preventive treatments significantly differed between patient groups ($p = 0.003$) (Fig. 1).

Patients were also divided in three groups based on median (4) and IQR ranges (2–6) of EDSS at TN onset. As significant results: in patients with an EDSS ≥ 6 at TN onset, TN was more frequently bilateral (9/90

Table 1
TN and MS patients' characteristics.

Variable	
Sex (M/F)	119/179
Age, years ^a	57.6 ± 11.3
Age at TN onset, years ^a	48 ± 11
Time between MS and TN onset, years ^b	8 [1–15]
EDSS at TN onset ^b	4 [2–6]
Follow-up duration, years ^b	5 [2–12]
EDSS at last follow-up ^b	5 [3–6.5]
TN site, n/total (%)	
Right	140/297 (47)
Left	145/297 (49)
Bilateral	12/297 (4)
TN branch involved, n/total (%)	
First	83/288 (29%)
Second	77/288 (27%)
Third	62/288 (22%)
First + second	27/288 (9%)
Second + third	15/288 (5%)
First + second + third	15/288 (5%)
Other	9/288 (3%)

^a Mean ± standard deviation.^b Median [interquartile range].

versus 3/207; $p = 0.001$) and surgical intervention was anticipated (time between TN onset and surgery: 3.07 ± 4.1 years versus 5.6 ± 5.6 years in the other patients, $p = 0.04$).

3.2. Pharmacological treatment

First-choice symptomatic medications were intravenous steroids in 95/218 patients (44%), and NSAIDs (20%), followed by opioids (17%), oral steroids (9%) and combination therapy (e.g. paracetamol + codeine) (4%). Table 3 summarizes prescribed first and second-choice preventive treatments. The first-choice treatment was discontinued in 131 (47%) of patients, mostly due to inefficacy (48%) or to adverse events/tolerability issues (40%), with only 12% of patients discontinuing it due to pain remission. At the time of the most recent follow-up visit, the majority of patients (77%) were still being treated with preventive medications, 19% requiring a combination of at least two medications.

3.3. Surgical treatment

Table 3 shows surgical procedures carried out. A second surgical procedure was carried out in 32% of these (26/81), and a third procedure in 10%. In relation to the temporal distribution of the different types of surgical interventions, microvascular decompression was the most frequent procedure between 1995 and 2010 (9/19), while gamma-knife and was the most frequent procedure after 2010 (27/62).

3.4. Comparisons between groups

We compared collected variables between patients who had

Table 2
Comparison of characteristics and treatment of patients based on timing of TN onset.

Variable	Early-onset TN (nr = 76)	Intermediate-onset TN (nr = 151)	Late-onset TN (nr = 71)	p-value
Sex (M/F)	35/41	56/95	28/43	ns
Age, years ^a	55 ± 13	56 ± 11	59 ± 9	ns
Age at TN onset, years ^a	43 ± 13	48 ± 10	53 ± 9	0.001
EDSS at onset ^a	2.7 ± 1.8	4 ± 2	5.2 ± 2	0.001
EDSS at last follow-up ^a	3.9 ± 2.1	4.8 ± 2	5.8 ± 2.2	0.001
Bilateral TN site, n (%)	1 (1.3)	6 (4.1)	5 (7.7)	ns
Surgical treatment carried out, n (%)	15 (19.7)	40 (26)	26 (37)	ns

^a Standard deviation.

undergone at least one surgical procedure with those who had not (Table 4).

Patients who underwent a surgical procedure were most often male, with a higher disability both at TN onset and at last follow-up and with a longer interval between MS and TN onset.

Collected variables were also compared between patients who, at the most recent follow-up visit, were still being treated with at least one preventive medication and untreated patients, showing a significantly higher EDSS at last follow-up in treated patients (5 ± 2.2 versus 4.3 ± 2.3 , $p = 0.039$). There was also a significant difference at Kruskal–Wallis analysis ($p = 0.016$), showing that patients who underwent percutaneous balloon compression and radiofrequency thermocoagulation were less frequently untreated at last follow-up (4/7 and 9/17, respectively) compared to those treated with microvascular decompression (13/18), gamma-knife stereotactic radiosurgery (26/30) and glycerol rhizotomy (8/9).

3.5. Logistic regression

We could not identify any predictor of the need for a repeat surgical procedure considering age, sex, EDSS, TN site, timing of TN onset in relation to MS onset, timing of surgical intervention in relation to TN onset, number of failed preventive treatments or type of surgical treatment as independent variables (data not shown). The type of surgical procedure, however, influenced the odds of being medication-free at long-term follow-up (OR: 0.72, 95%CI: 0.52–0.98; $p = 0.039$): a higher proportion of patients treated with rhizotomy (88%), gamma-knife (86%) and microvascular decompression (72%) were medication-free compared to those treated with percutaneous balloon compression (57%) and radiofrequency thermocoagulation (52%).

4. Discussion

In summary, we investigated characteristics and prognostic factors of MS-related TN in a sample of 298 patients from different Italian centres of the RIREMS group. Surgical approaches were associated with higher disability, male sex and a longer interval between MS and TN onset. In MS patients with a higher disability and with a longer interval between MS and TN onset, pain was more frequently bilateral, surgery was more frequent and anticipated, and preventive medication discontinuation due to pain remission was less common.

Case series of MS patients with TN mainly consist of single-centre or small multicentre experiences, involving less than 100 patients. Xu et al. (2019) described a group of 232 patients, but, as in many previously published papers, their work was focused on the efficacy of a single surgical procedure (namely, stereotactic radiosurgery). The present real-life/observational study includes an appraisal of both medical and surgical treatments in the largest ever described group of MS patients with TN. Limitations of our work are clearly related to its retrospective nature: complete information on clinical characteristics or treatment was unavailable in some cases and there was no objective assessment (i.e. VAS scores, questionnaires) on the outcomes of medical and surgical approaches.

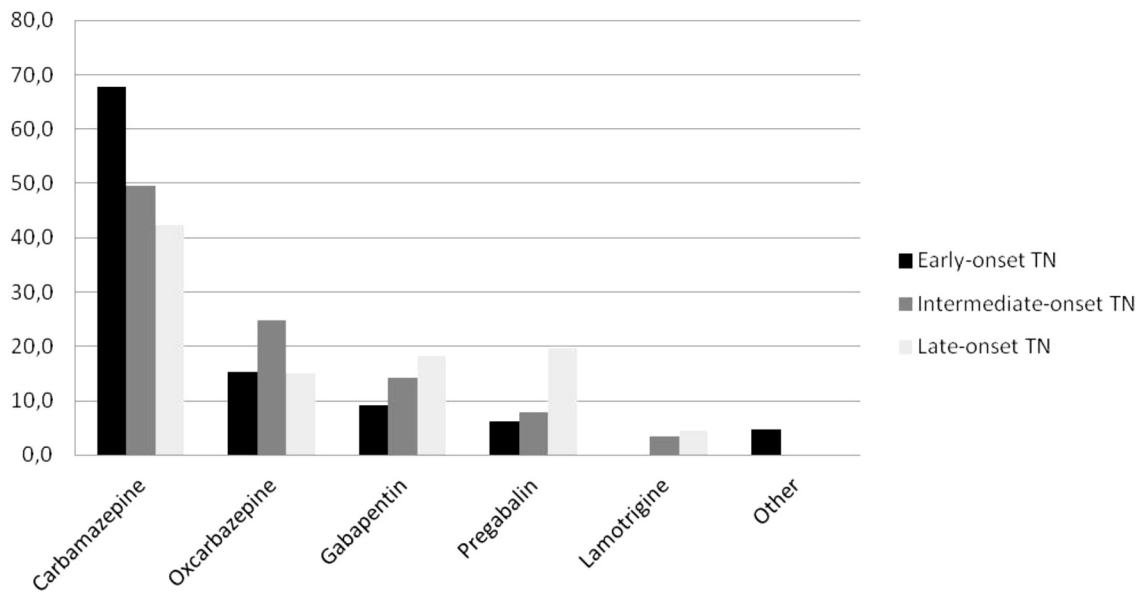


Fig. 1. Preventive treatment. Figure shows which medications are prescribed as a first-choice (%) in patients with early, intermediate and late-onset TN.

Table 3
Medical and surgical treatments.

First preventive medication taken, n/total (%)	
Carbamazepine	142/298 (47.7)
Oxcarbazepine	55/298 (18.5)
Gabapentin	38/298 (12.8)
Pregabalin	28/298 (9.3)
Lamotrigine	8/298 (2.7)
Clonazepam	2/298 (0.7)
Phenytoin	1/298 (0.3)
None	24/298 (8.0)
Second preventive medication taken, n/total(%)	
Carbamazepine	30/127 (23.6)
Oxcarbazepine	28/127 (22.0)
Gabapentin	27/127 (21.3)
Pregabalin	24/127 (18.9)
Lamotrigine	17/127 (13.4)
Phenytoin	1/127 (0.8)
First surgical procedure carried out, n/total (%)	
Gamma Knife stereotactic radiosurgery	30/81 (37)
Microvascular decompression	18/81 (22)
Radiofrequency thermocoagulation	17/81 (21)
Glycerol rhizotomy	9/81 (11)
Percutaneous balloon compression	7/81 (9)
Second surgical procedure carried out, n/total (%)	
Gamma knife stereotactic radiosurgery	11/25 (44)
Percutaneous balloon compression	5/25 (20)
Microvascular decompression	3/25 (12)
Glycerol rhizotomy	3/25 (12)
Radiofrequency thermocoagulation	3/25 (12)

Bearing in mind the above-described limitations, this study gives an overview of TN in MS patients and of its management across multiple Italian MS centres, also in relation to the interval between MS and TN onset and patient disability. As previously described (Fallata et al., 2017), TN may often be the first symptom of MS: in our cohort, “early-onset” TN preceded MS onset (9.7%), coincided with MS onset (9.6%) or occurred during the first year of the disease (6%) in one quarter of cases. Patients with “late-onset” TN had a higher disability at TN onset and underwent surgical treatments more frequently. Furthermore, in patients with an EDSS ≥ 6.0 at TN onset, TN was more frequently bilateral and surgical intervention was anticipated, perhaps suggesting that in patients with a longer disease history and greater demyelinating damage, pathological processes leading to TN might be more profound and less reversible. The degree of disability in MS patients is also known

Table 4
Comparison between patients who underwent at least one surgical procedure versus the remaining patients.

Variable	At least one surgical procedure (nr = 81)	No surgical procedure (nr = 217)	p-value
Sex, n (%)			
Males	41(51)	78 (36)	0.021
Females	40 (49)	139 (64)	
Age, years ^a	58 \pm 10	56 \pm 12	ns
Age at TN onset, years ^a	47 \pm 10	48 \pm 10	ns
MS to TN onset, years ^a	11 \pm 10	8 \pm 10	0.048
EDSS at onset ^a	4.3 \pm 2.1	3.8 \pm 2.1	0.04
EDSS at last follow-up ^a	5.2 \pm 2.2	4.6 \pm 2.2	0.043
TN site, n (%)			
Right	32 (40)	108 (50)	ns
Left	44 (54)	101 (47)	
Bilateral	5 (6)	7 (3)	

^a Standard deviation.

to be associated with frequency and/or severity of chronic neuropathic pain (Ferraro et al., 2018; Heitmann et al., 2016; Solaro et al., 2004; Truini et al., 2012). Another hypothesis involves the bio-psycho-social aspect of pain and its relation with disability and depression (Alschuler et al., 2013; Solaro et al., 2016): TN may be less tolerable when it starts at later stages of MS. Further investigations correlating lesional site/load, TN and clinical characteristics, focusing also on depression and coping strategies, may help confirm these hypotheses.

In accordance with European guidelines (Bendtsen et al., 2019; Cruccu et al., 2008), oxcarbazepine and carbamazepine were, overall, the most frequently first-line prescribed preventive treatments, whilst pregabalin and gabapentin were most frequently prescribed as second-line agents. Treatment drop-out rates for tolerability issues (20%) were similar to the reported ones in both idiopathic and symptomatic TN (Di Stefano et al., 2018). The vast majority (77%) of all patients were still on preventive medications at follow-up, after a mean period of 8 years, suggesting that complete and long-lasting pain remission is uncommon. This data is line with other studies indicating that MS-related TN is refractory to treatment (Bendtsen et al., 2019; Martin et al., 2015; Mohammad-Mohammadi et al., 2013) and that its management is particularly challenging. Indeed, only 16 patients discontinued their

first preventive medication due to pain remission. Interestingly, only two of these had EDSS values > 6.0 at TN onset (2/52 versus 14/78 with EDSS > 6.0, $p = 0.016$), implying that TN onset in earlier stages of disability may be more likely to recede. We may speculate that this may be because symptoms are more linked to inflammatory/reversible mechanisms, as opposed to degenerative/irreversible ones.

One third of our patients were referred to surgery. Need for a second surgical intervention was more frequent (66% of the cases) in patients treated with balloon compression compared to all other approaches, in which re-treatment ranged from 14.6% (glycerol rhizotomy) to 41% (radiofrequency thermocoagulation), but this result was not statistically significant and we could not identify any other predictors of re-intervention. However, if we consider preventive drug discontinuation as a surrogate marker of surgery effectiveness, there was a significantly higher benefit in patients treated with rhizotomy and gamma-knife compared to other approaches. Future studies aimed at correlating clinical and neuroimaging data on trigeminal anatomical abnormalities (including the presence of concurrent vascular compression) with surgical procedure outcomes are warranted in order to guide future decision-making and patient information.

The definition of distinct patient subgroups, in relation to the timing of TN onset, leads to observations on the differing pain management. From a pharmacological point of view, even though oxcarbazepine and carbamazepine were the most frequent first-line drugs in both groups, they were less extensively used in late-onset TN, in favour of gabapentin and pregabalin. This may be due, in the case of pregabalin, to its more recent introduction (and late-onset TN patients have developed TN more recently), but in part it may also be due to concerns on tolerability (side effects affecting balance) and drug interactions (Solaro et al., 2005).

5. Conclusions

The present real-life/observational multicentre study, although limited by its retrospective nature, provides an overview of TN features and its medical and surgical management in people with MS in Italy and highlights differing clinical features, outcomes and therapeutic management in patients with late-onset TN and a higher disability at TN onset. These preliminary data may set the stage for further investigations on this topic, both from a pathophysiological and therapeutic point of view.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

Authors report no conflicts of interest in relation to the study.

Acknowledgements

RIREMS group is supported unconditionally by Merck.

We thank Daniela Primerano for support in data management.

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