Trigeminal neuralgia : comparison of characteristics and impact in patients with or without multiple sclerosis.

Kimia Godazandeh [1], Santiago Martinez Sosa [2], Jianhua Wu[3], Joanna M Zakrzewska [4]

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Comments to reviewer 2, second resubmission

TABLES ARE STILL TOO EXTENSIVE -WE DO NOT NEED ALL THE STATISTICALLY NEGATIVE DATA IN DETAIL IN A TABLE - ABBREVIATE IN TEXT. WE NEED TABLE & FIGURE LEGENDS (ABBREVIATIONS), DESCRIPTION IN METHODS OF SCALES USED AND REFERENCES; LEVELS/ SCORES OF HADS REGARDED AS ABNORMAL etc.

Thank you for the additional comments. We have reduced many of the tables and put them in as supplemental. There remains controversy as to whether the phenotype of TN is different in patients with MS. This small study suggests it is the same and hence the need for negative result. We are also planning on publishing data on further long term data on both these cohorts and it will be important to see if these baseline negative findings change and that greater differences are seen between the cohorts when they are managed using the same internationally agreed guidelines. Providing this data is important as we are being increasingly asked to be more transparent and report negative data. We are not prepared to cut down the number of tables and put more data into the text as it is easier to assimilated when in a table.

In order to cut down on references and length of paper we have not provided the references for all the measures we used but these are to be found in reference 8 which we quote in the methods. These had not been requested previously. On table 3 we have added the normal and abnormal values for HAD and provided the abbreviations.

***Highlights (for review)**

Highlights: Trigeminal neuralgia: comparison of characteristics and impact in patients with or without multiple sclerosis.

- Trigeminal neuralgia (TN) is more severe in patients with multiple sclerosis
- TNMS patients are more likely to have had surgery prior to referral
- TNMS exhibits reduced lengths of remissions and fewer identifiable triggers
- TNMS is associated with sleep disturbances and higher chronic pain scores
- Both TNMS and primary TN impact on activities of daily living, anxiety and depression

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ABSTRACT

Objectives The commonest secondary cause for trigeminal neuralgia (TN) is multiple sclerosis (MS) and little is known about this group of patients in terms of their presentation and treatments. We compared patients with TN and MS (pwTNMS) with a cohort of patients with primary TN, who had been referred to the same specialist unit, both in terms of characteristics and impact on quality of life at the time of their first assessment.

Methods Using a prospective patient database we extracted key clinical data and results from psychometrically tested questionnaires of 26 pwTNMS and compared them to an age and gender-matched set of 68 patients with primary TN.

Results Our findings suggest that pwTNMS exhibit a more severe clinical phenotype than primary TN. Prior to referral, pwTNMS are more likely to have used more healthcare services and undergone more neurosurgical interventions. Strikingly, pwTNMS exhibit reduced lengths and duration of remission periods and fewer identifiable triggers. Furthermore, pwTNMS report significant impact on quality of life comparable to those in primary TN, scoring highly in measures of anxiety, depression, and catastrophizing, but also report greater sleep disturbance, and overall interference in activities of daily living.

Conclusions: pwTNMS have a more intractable TN, one which may necessitate a more complex approach to treatment, earlier referral to secondary care and an extensive assessment of mental health. Quality of life in pwTNMS is severely affected by both their MS and their TN, suggesting management should occur in specialist centres with access to a multidisciplinary team.

Key words: trigeminal neuralgia, multiple sclerosis, case control

BACKGROUND

Trigeminal Neuralgia (TN) is a chronic, and severe pain syndrome characterised by unilateral episodic facial pain. It is a debilitating condition whose aetiology remains poorly understood. Most cases of TN are idiopathic or due to compression of the trigeminal nerve by vessels in the posterior fossa (classical TN)[1], collectively referred to as primary TN. A minority are attributable to known pathologies, including external compression of the nerve by tumours or vascular malformations, pontine infarcts and inflammatory conditions like multiple sclerosis. Multiple sclerosis (MS) is a degenerative neurological condition characterised by widespread cerebral inflammation and progressive demyelination of the central nervous system. MS is associated with a 20-fold higher prevalence of TN. A recent review of the literature shows that up to 4% of MS patients are likely to have TN. The TN in the majority appears after MS but up to 10% report TN as the first sign of MS and it can predate a second MS episode by up to 10 years[2]. In these patients, the clinical presentation of TN is grossly similar as for the primary form, although more prolonged background pain and atypical features are reported[3-4], more women are affected, and the age of onset appears to be lower (45 years as compared to 50-60 years). Only De Simone et al [3] have compared clinical characteristics, and only between 15 patients with TN and MS (pwTNMS) and 13 patients with TN only. While other reported case series exist Rushton & Olafson[5] - 35 cases, Jensen et al[6]- 22 cases, Hooge & Redekop[7] – 35, these provide no details regarding the impact of TN on quality of life nor its management.

As the TN of MS may arises from different pathological mechanisms than the primary form, its management might need to reflect this. However, a recent systematic review on the management of patients pwTNMS found that there is insufficient and poor-quality evidence to advise how this specific sub-population of TN should be managed. The review concluded that no specific pharmacological treatment can currently be advised, and that pwTNMS should therefore be managed in the same manner as non-MS TN[2].

This study aims to describe the clinical, psychological, pharmacological and surgical profiles of a cohort of pwTNMS and compare them to a cohort of primary TN patients to determine if there are significant differences in initial presentation to a specialist facial pain unit.

METHOD

Participants

All patients included in the study were diagnosed with TN after their first visit to a specialist facial pain unit in a London teaching hospital and were previously diagnosed with MS (by a neurologist using MRI and CSF for confirmation).

Data collection

Data for these patients were extracted from a prospective cohort of TN collected between 2007-2016. Data on the non-MS cohort has been published and was used to match the patient cohort by age and gender[8]. All patients were seen by the same

clinician, JZ. Data collection was performed by two medical students and a senior investigator and any differences during data extraction where discussed by the team.

Measures

Data was derived from patient notes, letters and self-report questionnaires completed at the first visit.

Duration of MS was calculated as the number of years from year of diagnosis of MS to first visit date. The same method was applied for calculating duration of TN. The same questionnaires used for the non-MS cohort to gauge information regarding pain were used here, including the Graded Chronic Pain Scale, Pain Catastrophizing Scale, Brief Pain Inventory, Hospital Anxiety and Depression scale and McGill Pain Questionnaire details to be found in a previous publication [8]. The maximum daily dosage of current and previous medication taken for the patients' TN symptoms as well as previous surgery for TN were also recorded. Patient information for the MS clinic was used when required. The data was entered on an Excel spreadsheet using the same format as for the non-MS data. Control data was taken from the previous non-MS cohort matched for age and gender to the pwTNMS cohort[8]. Multiple controls might be matched for one pwTNMS.

Statistical analysis

Descriptive statistics were used to summarize the pwTNMS and TN respectively. Mean and standard deviation were used for continuous variables if they were normally distributed, otherwise median and interquartile range were used. Frequency and percentage were used for categorical variables.

Two-sample T-test or Mann-Whitney U test were used to compare the difference for continuous variables between pwTNMS and TN, and Fisher Exact Test or Chi-square test were used to compare the difference for categorical variables. Significance level was set at 5%. All analyses were performed in R version 3.4.1 (http://cran.r-project.org/).

RESULTS

The database of patients registered between 2007-2016 contained 279 patients with classical TN, TN and concomitant pain, and TN with autonomic features. Of these, 33 patients were reported as having TN and MS. Seven patients were excluded as three did not have confirmed MS, three had neuropathic facial pain but not TN, and one was too severely affected by MS to give a history or complete questionnaires. This left 26 patients.

Nine pwTNMS had previously undergone surgery (three of them more than once), with mixed results. Only two achieved complete pain relief for any period of time: one after microvascular decompression (one-year pain relief) and one after glycerol rhizotomy (two years pain relief; however, repeating the surgery yielded no relief). One patient underwent three glycerol rhizotomies, which were only partially successful, while another received Gamma knife surgery, which afforded no pain relief. Radiofrequency thermocoagulation provided some pain relief for three patients, one of whom had a repeat procedure which provided no further relief. In one patient, pulsed radiofrequency performed by a pain specialist was ineffective.

The final patient had peripheral surgery, cryosurgery, performed by an oral surgeon with only partial pain relief.

Table 1 summarises the basic characteristics of our TN patient cohorts. While grossly similar, there exist some significant differences between the two. PwTNMS were more likely than TN patients to have had previous contact with GP services (100% pwTNMS vs. 80.9% TN; p = 0.039), and neurologists (53.8% vs. 29.4%; p = 0.049), as well as to have already had other procedures at presentation to our clinic (38.5 % vs. 13.2%; p = 0.015). There were also significant differences in the socioeconomic status of the two cohorts, specifically their deprivation index scores (p = 0.047) and employment status (p = 0.002). Extra data in supplemental table 1

Table 1 Characteristics for patients with TNMS and TN.

Characteristic	**pw TNMS n = 26 (%)**	**TN n = 68 (%)**	**P-value**
Age in years, mean (SD)	61.35 (8.60)	61.50 (5.88)	0.921
Age at first attack, median [IQR]	53.00 [48.50, 59.00]	57.00 [50.75, 62.00]	0.239
Duration of TN in years, median [IQR]	5.00 [3.25, 9.50]	4.00 [2.00, 7.00]	0.214
Duration of MS years	15.5 [11.25, 24.75]	-	
Interval between MS and TN [IQR] years	9.0 [3.50, 19.50]	-	
Type of MS			
Benign MS	3 (11.5)	-	
Primary progressive	8 (30.8)	-	
Secondary progressive	7 (26.9)	-	
Relapsing-remitting	8 (30.8)	-	
Female	20 (76.9)	54 (79.4)	1.000
Index of multiple deprivation			
1 (least deprived)	3 (12.0)	18 (26.5)	0.047
2	10 (40.0)	10 (14.7)	
3	3 (12.0)	20 (29.4)	
4	6 (24.0)	13 (19.1)	
5(most deprived)	3 (12.0)	7 (10.3)	
Missing	1 (5.6)	-	

Note: values are presented as frequency (%); P-value represents comparison between two groups; missing values are not included.

While the characteristics of the pain were broadly comparable between the two cohorts, there were also some significant differences, as shown in Table 2. Most notably, the pwTNMS exhibited significantly reduced lengths of remission (p = 0.008), with 46.2% of this group reporting “no remission”, as compared to only 5.2% of the TN group. Despite having fewer remissions, pwTNMS reported fewer instances of prolonged pain after an acute attack, as compared with TN patients (11.5% vs. 47.5%; p = 0.011).

The anatomical distribution of the pain was similar, with both cohorts experiencing third division distribution as the major focus of pain. Of these, ten reported only lower mandibular area with no extension above the ear. Just under half of pwTNMS have pain in only one division, similar to primary TN, and neither group had only first

division pain. However, pwTNMS reported more bilateral pain, but this did not meet statistical significance.

Table 2 Clinical features stratified by type of TN

Pain characteristic	Group 1 MSTN n = 26	Group 2 TN n = 68	P-trend
V1 only	0 (0.0)	0 (0.0)	-
V2 only	3 (11.5)	15 (22.1)	0.263
V3 only	10 (38.5)	21 (30.9)	0.622
V1 + V2	2 (7.7)	6 (8.8)	1.0
V2 + V3	8 (30.8)	22 (32.4)	1.0
V1 + V2 + V3	3 (11.5)	3 (4.4)	0.428
Right	10 (38.5)	43 (63.2)	0.053
Left	14 (53.8)	24 (35.3)	0.160
Bilateral	2 (7.7)	1 (1.5)	0.379
Intra oral pain	26 (100)	58 (85.3)	0.090
Extra oral pain	17 (65.4)	54 (100.0)	0.025
Predominant type of attack			
Single stab	12 (46.2)	28 (41.2)	0.539
Series of stabs	5 (19.2)	23 (33.8)	
Saw tooth	4 (15.4)	9 (13.2)	
Single stab + Series of stabs	5 (19.2)	8 (11.8)	
Circumstances			
Acute onset	6 (23.1)	19 (32.2)	0.682
Memorable onset	11 (42.3)	25 (42.4)	
Slow to develop	6 (23.1)	11 (18.6)	
Cannot remember onset	3 (11.5)	4 (6.8)	
Frequency of pain attack			
Daily	16 (88.9)	48 (90.6)	1.000
Duration of attacks			
Seconds	20 (76.9)	40 (59.7)	0.089
Minutes	3 (11.5)	23 (34.3)	
1-4 hours	3 (11.5)	4 (6.0)	
Pain after main attack	3 (11.5)	29 (47.5)	0.011
Length of remission			
None	9 (34.6)	3 (5.2)	0.013
Days	0 (0.0)	6 (10.3)	
Weeks	4 (15.4)	8 (13.8)	
Months	10 (38.5)	33 (56.9)	
Years	2 (9.5)	8 (13.8)	
Missing (but in remission)	1 (3.85)		
Remission period change (% of participants who have had remission)	n= 17	n= 55/59	

No change	1 (6.25)	15 (25.4)	0.753
Shorter remission	12 (75.0)	40 (67.8)	
Longer remission	2 (12.5)	4 (6.8)	
Missing	1 (6.25)	-	
Provoking factors			
Provoked by ≥1 light touch stimuli	24 (92.3)	66 (97.1)	0.998
Intraoral triggers (eating and/or brushing teeth)	25 (96.1)	63 (92.6)	0.241
Provoked by other factors			
Cold wind/weather	9 (34.6)	26 (38.2)	0.931
Bodily movement	8 (30.8)	29 (42.6)	0.413
Noise or light	1 (3.8)	0 (0.0)	0.616
McGill pain questionnaire			
Number of words chosen (mean ± sd)	10.6 (4.0)	10.9 (3.8)	0.672
Sensory groups	Stabbing (21)	Stabbing (27)	
	Shooting (19)	Shooting (51)	
	Sharp (14)	Sharp (43)	
Affective	Terrifying (12)	Fearful (17)	
	Vicious (9)	Vicious (23)	
Evaluative	Unbearable (17)	Unbearable (24)	
Miscellaneous	Piercing (18)	Piercing (23)	

Note: values are presented as frequency (%); P-value represents comparison between two groups; missing values are not included. V = fifth trigeminal nerve , 1 ophthalmic division , 2= maxillary division, 3 = mandibular division

The medical histories were broadly similar between the two groups, with the major difference being that pwTNMS were much more likely to have had surgery prior to referral (53.8% vs.10.3%; $p < 0.001$) and were much more likely to report disturbances to their sleep (50% vs. 14.9%; $p = 0.001$). Other differences included an increased incidence of migraines and tension-type headaches, cardiovascular disease, neck pain, dental problems and disturbed salivation amongst pwTNMS. Autonomic features were also seen noted in some pwTNMS. See supplemental table 2 .

Both pwTNMS and TN patients similarly reported that their pain has a considerable impact on activities of daily living and their psychosocial wellbeing, with many patients scoring high on assessments of both anxiety and depression (table 3).

Table 3 Impact of trigeminal neuralgia on quality of life

Scale	pw TNMS	TN	P-value

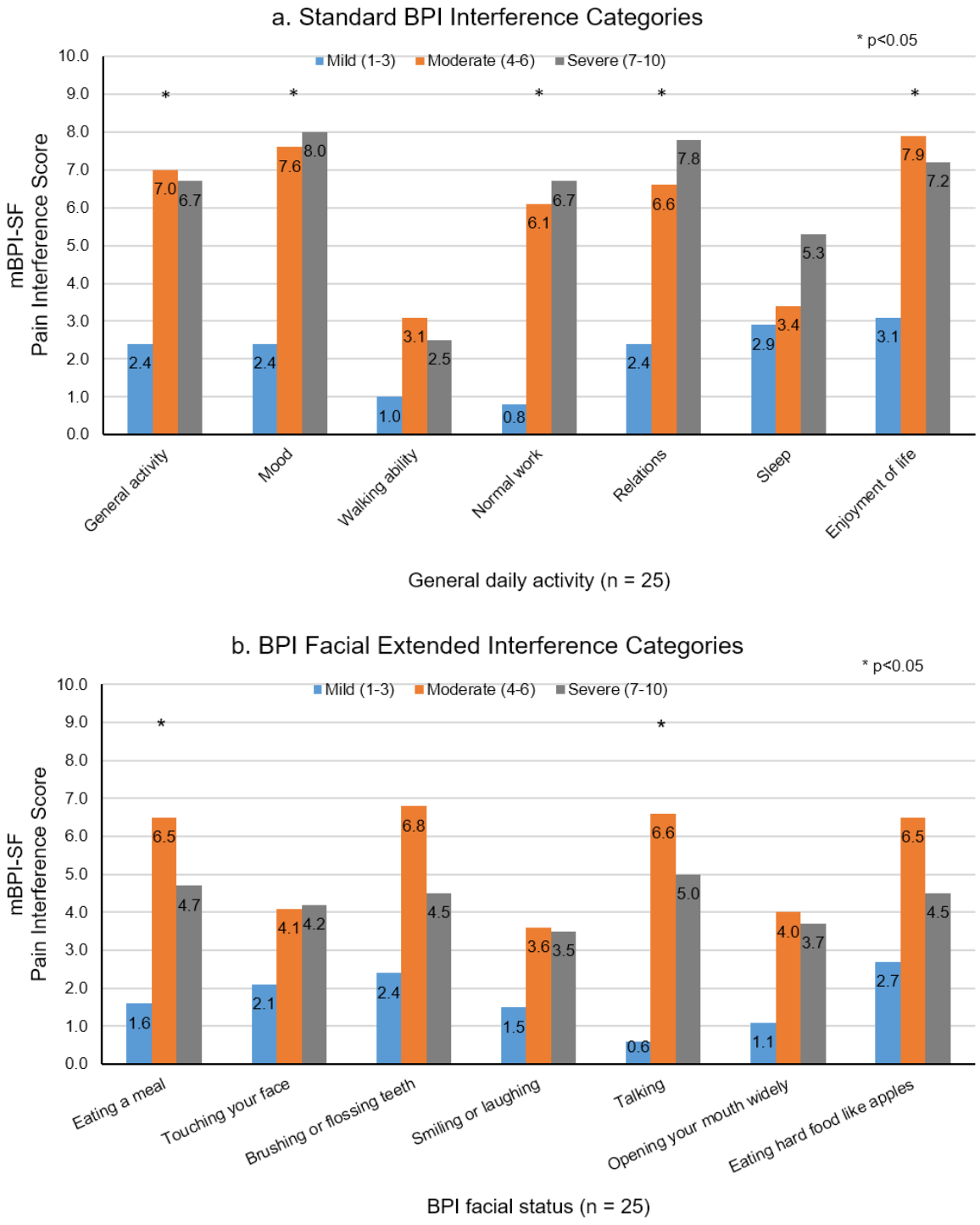
Chronic graded pain scale	**n=24**	**n=54**	
Grade 1 low impact	4 (16.7)	8 (14.8)	0.024
Grade 2	2 (8.3)	22 (40.7)	
Grade 3	6 (25.0)	7 (13.0)	
Grade 4 – high impact	12 (50.0)	17 (31.5)	
Days off normal activities	**n=23**	**n=59**	
0-6	5 (21.7)	25 (42.4)	0.154
7-14	3 (13.0)	9 (15.3)	
15-30	4 (17.4)	16 (27.1)	
31+	11 (47.8)	9 (15.3)	
Pain catastrophizing score	**n=20**	**n=55**	
Total score, median (IQR)	41.5 [33.5,47.5]	30 [17, 42]	0.201
Score over 20 significant	17 (85.0%)	36 (65.5)	0.532
HAD-Anxiety	**n=25**	**n=60**	
Nil score 0-7	11 (46.2)	22 (36.7)	0.151
Mild score 8-10	6 (23.1)	26 (43.3)	
Severe score 11-21	8 (30.8)	12 (20.0)	
HAD-Depression	**n=26**	**n=60**	
Nil score 0-7	11 (44.0)	40 (66.7)	0.136
Mild score 8-10	4 (16.0)	9 (15.0)	
Severe score 11-21	10 (40.0)	11 (18.3)	
Brief pain inventory, median [IQR] score 0-10	**n=25**	**n=68**	
Pain severity average index	3.67 [2.33, 6.67]	3.75 [1.81, 5.69]	0.718
Pain interference- general daily life	4.71 [1.43, 6.71]	2.29 [0.57, 5.00]	0.266
Pain interference- facial status	5.64 [2.82, 7.93]	4.71 [1.21, 8.00]	0.356

Note: values are presented as frequency (%); P-value represents comparison between two groups; missing values are not included.HAD Hospital anxiety and depression scale

Scores over 20 on the Pain Catastrophizing Score indicate significant negative thoughts and the majority of patients in both cohorts exhibited this (85% and 65.5%; p = 0.201). The major difference between the two groups was on the Chronic Graded Pain Scale (p=0.024), where pwTNMS scored more frequently in grades 3/4 (high-disability) while TN patients were more frequently grades 1/2 (low-disability).

Figure 1a and b shows the results from the Brief Pain Inventory including the more specific facial extended one and highlights the significant impact on quality of life especially in facial activities and is similar to the TN group as shown in previous publication[8].

Figure 1a and b HERE Brief Pain Inventory in patients with TNMS



Both cohorts of patients have trialed a wide variety of drugs, as seen in Table 4. The majority of patients have used carbamazepine (pwTNMS 21 vs. TN 53), which represents the most commonly used drug. Following carbamazepine use is gabapentin (pwTNMS 13 vs.TN 20) and then pregabalin (pwTNMS 5 vs TN 9) and

oxcarbazepine (pwTNMS 5 vs. TN 8). Other drugs included Tizanidine and prednisolone.

Table 4 Drugs used prior to referral

	pwTNMS (n = 26)	**TN (n = 68)**	**P-value**
No of anticonvulsants			
0	1 (3.8)	4 (5.9)	0.241
1	6 (23.1)	19 (27.9)	
2	13 (50.0)	21 (30.9)	
3	3 (11.5)	12 (17.6)	
4+	3 (11.5)	12 (17.6)	
Opioids	4 (15.4)	9 (13.2)	0.749
OTC + analgesics	5 (19.2)	18 (26.5)	0.595
Muscle relaxant baclofen	7 (26.9)	16 (23.5)	
Antidepressants any	12 (46.2)	4 (5.9)	<0.001
Antibiotics	1 (3.8)	19 (27.9)	0.011
Other	2 (7.7)	1 (1.5)	0.184

Note: values are presented as frequency (%); P-value represents comparison between two groups; missing values are not included. OTC- over the counter medications

DISCUSSION

To our knowledge, this is the first study to document the impact of TN on patients with MS and to compare this group to those with primary TN. While the two groups share many similarities, as outlined above, we have found several domains in which they differ, differences which suggest that pwTNMS exhibit a more severe phenotype than TN. The severity of pwTNMS is shown by their increased use of healthcare services, the features of the pain, and the secondary impact of that pain on their physical and mental wellbeing.

PwTNMS may require and rely on healthcare services more than their TN counterparts. At presentation to our clinic, every single one of our pwTNMS reported having used GP services to attempt to manage their pain, while this was true for a majority, but not the entirety of our TN cohort who may come through the dental route due to the frequent presentation in the lower mandibular area. This cohort had comparatively higher rates of interventions prior to presentation, and, specifically, higher rates of neurosurgery than TN patients. Notably, neurosurgery provided relief only to a minority of patients, and even then only for limited amounts of time, in accordance with a recent systematic review of the management of pwTNMS[2].

With regards to the clinical features of pwTNMS, the most striking difference was the reduced length and duration of remissions that these patients suffered from. A majority of pwTNMS reported either no remissions (46.2%) or only weeks of remission (11.5%), despite the majority of TN patients reporting months to years of

remission. Moreover, pwTNMS exhibited fewer identifiable triggers to acute attacks, complicating preventative measures. This is likely reflective of the underlying disease process of MS, which is characterized by often unpredictable flare ups. Like TN patients, pwTNMS also tend to trial many types of drugs, reflecting the common difficulty in achieving pharmacological control of symptoms.

There exists limited literature on the impact of TN on wellbeing, but these few published papers highlight a notable impact on anxiety, depression and sleep[8]-[10]. This study shows that a comparable level of disability is noted in pwTNMS. Significant disruptions to activities of daily living are noted for all TN patients but these appear higher in pwTNMS, especially with regards to disturbances to sleep. On the Chronic Graded Pain Scale pwTNMS suffered greater interference in activities of daily living due to pain than TN patients. However, this conclusion is complicated by the difficulty in distinguishing pain due to TN from other pain that commonly occurs in MS patient, the prevalence and course of which is poorly described[11]. We did not ascertain their status on the Expanded Disability Status Scale (EDSS), which may have provided further information.

At first presentation, our TNMS cohort was similar in age to patients with primary TN, in keeping with other studies[2]. On average, symptoms first occurred in the 5th decade of life, although this is in contrast to De simone et al[3] who found the mean age of onset to be 43 years, albeit in a smaller cohort of 15 pwTNMS. In this cohort, all patients first presented with MS, but a review of the literature based on 950 patients has shown that 10.5% have TN before MS, and the gap between the diagnosis of MS and TN could be 10 years. Cruccu et al[4] suggests that MS starts later in those who develop TN, but we could not validate this in our dataset .

From this baseline data it appears that pwTNMS have a more intractable TN, one which may necessitate a more complex approach to treatment, earlier referral to secondary care and a thorough assessment of mental health. Heinskou et al[12] have previously suggested that this cohort needs a multidisciplinary approach, and our findings support this. This should potentially include psychological support on how to manage fear, isolation and the unpredictability of flare ups. For example, a recent review by Simpson et al[13] has shown that mindfulness-based interventions may benefit patients with MS in terms of quality of life and mental health.

Limitations

This is an observational design study and is based largely on subjective reports of pain, depression, anxiety and impact on well-being. While these reports are useful, prospective and interventional studies on these patient groups will help elucidate the extent of these differences. For example, do the two groups differ in their response to interventions due to this purported difference in pain phenotype?

This study was carried out in patients referred to a specialist facial pain centre. By definition, the symptoms of such patients were of great enough severity to warrant referral, and may not be representative of all TN cases, many of which may be successfully managed in the community. As such, the results should be interpreted with caution in a primary care setting. Nevertheless, this limitation does impact the

comparison between the two groups (TN vs. TNMS), as both patient populations were drawn from the same centre. As such, it can still be concluded that, in patients referred to a specialist pain clinic, TNMS patients exhibit a more severe disease phenotype than TN patients. It would be reasonable to expect a similar trend in primary care patients, but this must be verified with further research.

Findings of greater sleep disturbances and impact of chronic pain on activities of daily living in patients with TNMS is confounded by their underlying MS. The MS itself may be directly contributing to a worsening of these measures by mechanisms unrelated to the TN, for example due to mobility or bladder issues or pain elsewhere. This represents a true confounder. Nevertheless, MS may also impact these measures by a TN-dependent effect. MS may heighten the perception of TN pain, and MS lesions on the trigeminal nerve may be biologically more painful, although we did not ascertain this in our study.

Cruccu et al[4] suggest that abnormal blink reflexes show good specificity and sensitivity in differentiating between TN and pwTNMS, but these were not carried out with this group. This series, while larger than previous studies, remains small, therefore limiting the strength of the conclusions we have drawn. Moreover, detailed data on imaging was not available, which may be important as diffusivity studies (Diffusion MRI tractography) begin to differentiate the microstructure of MSTN[14]. Truini et al[15] also highlight that in pwTNMS both demyelination and compression can be present. We have not been able to link disease progression with MS progression or drug usage as the numbers are too small.

Future

Larger series will need to be studied. Registries such as those held by the MS Society UK show that up to 15% of their patients (1,800) report having TN, providing a potential pool of data. Enlarging the database and collecting longitudinal data would make it possible to determine if the TNMS care-pathway needs to be different from those of TN, with particular emphasis on how different treatments impact on quality of life and mental health. Currently there is no data to determine if management of MS impacts in any way with long term TN outcomes. Data from Scandinavian countries suggests that overall MS patients have a shortened life expectancy although it is now improving[16] and many live with 20 years moderate and 30 years severe disability[17] and TN can add to this burden.

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Patient consent obtained
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Supplemental tables

Supplemental Table 1 Referral pathways and previous treatments for TN patients

Referrer to specialist clinic			
Dentist	3 (12.0)	13 (19.1)	0.302
GP	11 (44.0)	33 (48.5)	
Specialist	1 (4.0)	0 (0.0)	
Missing	11 (42.3)	-	
Family history of TN	2 (7.7)	4 (5.9)	0.620
Previous services used multiple times			
GP	26 (100.0)	55 (80.9)	0.039
Dentist	14 (53.8)	50 (73.5)	0.113
Dental Service			
Dental Specialist	2 (7.7)	11 (16.2)	0.464
Oral Surgeon (cryosurgery procedures)	3 (11.5)	16 (23.5)	0.314
Dental Procedures	4 (15.4)	3 (4.4)	0.170
Medical Service			
ENT surgeon	0 (0.0)	6 (8.8)	0.274
Neurosurgeon	8 (30.8)	11 (16.2)	0.633
Neurologist	14 (53.8)	20 (29.4)	0.049
Physician	0 (0.0)	5 (7.4)	0.364
Psychiatrist	0 (0.0)	1 (1.5)	1.000
Psychologist	2 (7.7)	0 (0.0)	0.130
Pain Specialist	5 (19.2)	6 (8.8)	0.296
Other medical procedures	10 (38.5)	9 (13.2)	0.015
No. of secondary dental or medical services for TN			
For all			0.651
0	3 (11.5)	15 (22.1)	
1	15 (57.7)	34 (50.0)	
2	7 (26.9)	15 (22.1)	
3+	1 (3.8)	4 (5.9)	

Supplemental Table 2 Associated factors and medical history in TN patients

Associate factors and medical history	**Group 1 MS TN n = 26**	**Group 2 TN n = 68**	**P-trend**
Altered sensation or numbness	9 (34.6)	15 (22.4)	0.344
Disturbed salivation	9 (34.6)	7 (10.6)	0.015
Dental problem	7 (26.9)	3 (4.5)	0.006
Affects sleep	13 (50.0)	10 (14.9)	0.001
Any autonomics unilateral	16 (61.5)	50 (73.5)	0.376

Swelling face	3 (11.5)	9 (13.4)	1.000
Redness of the face	4 (15.4)	7 (10.4)	0.712
Nasal stuffiness/runny	5 (19.2)	16 (23.9)	0.838
Eye redness	5 (19.2)	5 (7.5)	0.204
Eye tearing	7 (26.9)	14 (20.9)	0.728
Oedema eyelid	2 (7.7)	1 (1.5)	0.387
Earache	4 (15.4)	7 (10.4)	0.761
Ringing ears	5 (19.2)	9 (13.4)	0.705
Fullness ears	3 (11.5)	6 (9.0)	1.000
Headaches			
Migraines	6 (23.1)	11 (16.7)	0.678
Migraines + TTH	5 (19.2)	2 (2.9)	0.024
Bruxism	11 (42.3)	17 (26.2)	0.209
Medical history			
Hypertension	7 (26.9)	25 (36.8)	0.766
CVS	5 (19.2)	3 (4.4)	0.035
Diabetes	0 (0.0)	3 (4.4)	0.665
Deafness	4 (15.4)	4 (6.0)	0.298
Other chronic pain	9 (34.6)	16 (23.5)	0.408
Neck pain	8 (30.8)	6 (9.2)	0.024
Back pain	5 (19.2)	11 (16.7)	1.000
Previous surgery TN	14 (53.8)	7 (10.3)	<0.001

Note: values are presented as frequency (%); P-value represents comparison between two groups; missing values are not included. CVS- cardiovascular problems; TTH- Tension type headaches

Trigeminal neuralgia : comparison of characteristics and impact in patients with or without multiple sclerosis.

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ABSTRACT

Objectives The commonest secondary cause for trigeminal neuralgia (TN) is multiple sclerosis (MS) and little is known about this group of patients in terms of their presentation and treatments. We compared patients with TN and MS (pwTNMS) with a cohort of patients with primary TN, who had been referred to the same specialist unit, both in terms of characteristics and impact on quality of life at the time of their first assessment.

Methods Using a prospective patient database we extracted key clinical data and results from psychometrically tested questionnaires of 26 pwTNMS and compared them to an age and gender-matched set of 68 patients with primary TN.

Results Our findings suggest that pwTNMS exhibit a more severe clinical phenotype than primary TN. Prior to referral, pwTNMS are more likely to have used more healthcare services and undergone more neurosurgical interventions. Strikingly, pwTNMS exhibit reduced lengths and duration of remission periods and fewer identifiable triggers. Furthermore, pwTNMS report significant impact on quality of life comparable to those in primary TN, scoring highly in measures of anxiety, depression, and catastrophizing, but also report greater sleep disturbance, and overall interference in activities of daily living.

Conclusions: pwTNMS have a more intractable TN, one which may necessitate a more complex approach to treatment, earlier referral to secondary care and an extensive assessment of mental health. Quality of life in pwTNMS is severely affected by both their MS and their TN, suggesting management should occur in specialist centres with access to a multidisciplinary team.

Key words: trigeminal neuralgia, multiple sclerosis, case control

BACKGROUND

Trigeminal Neuralgia (TN) is a chronic, and severe pain syndrome characterised by unilateral episodic facial pain. It is a debilitating condition whose aetiology remains poorly understood. Most cases of TN are idiopathic or due to compression of the trigeminal nerve by vessels in the posterior fossa (classical TN)[1], collectively referred to as primary TN. A minority are attributable to known pathologies, including external compression of the nerve by tumours or vascular malformations, pontine infarcts and inflammatory conditions like multiple sclerosis. Multiple sclerosis (MS) is a degenerative neurological condition characterised by widespread cerebral inflammation and progressive demyelination of the central nervous system. MS is associated with a 20-fold higher prevalence of TN. A recent review of the literature shows that up to 4% of MS patients are likely to have TN. The TN in the majority appears after MS but up to 10% report TN as the first sign of MS and it can predate a second MS episode by up to 10 years[2]. In these patients, the clinical presentation of TN is grossly similar as for the primary form, although more prolonged background pain and atypical features are reported[3-4], more women are affected, and the age of onset appears to be lower (45 years as compared to 50-60 years). Only De Simone et al [3] have compared clinical characteristics, and only between 15 patients with TN and MS (pwTNMS) and 13 patients with TN only. While other reported case series exist Rushton & Olafson[5] - 35 cases, Jensen et al[6]- 22 cases, Hooge & Redekop[7] – 35, these provide no details regarding the impact of TN on quality of life nor its management.

As the TN of MS may arises from different pathological mechanisms than the primary form, its management might need to reflect this. However, a recent systematic review on the management of patients pwTNMS found that there is insufficient and poor-quality evidence to advise how this specific sub-population of TN should be managed. The review concluded that no specific pharmacological treatment can currently be advised, and that pwTNMS should therefore be managed in the same manner as non-MS TN[2].

This study aims to describe the clinical, psychological, pharmacological and surgical profiles of a cohort of pwTNMS and compare them to a cohort of primary TN patients to determine if there are significant differences in initial presentation to a specialist facial pain unit.

METHOD

Participants

All patients included in the study were diagnosed with TN after their first visit to a specialist facial pain unit in a London teaching hospital and were previously diagnosed with MS (by a neurologist using MRI and CSF for confirmation).

Data collection

Data for these patients were extracted from a prospective cohort of TN collected between 2007-2016. Data on the non-MS cohort has been published and was used to match the patient cohort by age and gender[8]. All patients were seen by the same

clinician, JZ. Data collection was performed by two medical students and a senior investigator and any differences during data extraction where discussed by the team.

Measures

Data was derived from patient notes, letters and self-report questionnaires completed at the first visit.

Duration of MS was calculated as the number of years from year of diagnosis of MS to first visit date. The same method was applied for calculating duration of TN. The same questionnaires used for the non-MS cohort to gauge information regarding pain were used here, including the Graded Chronic Pain Scale, Pain Catastrophizing Scale, Brief Pain Inventory, Hospital Anxiety and Depression scale and McGill Pain Questionnaire details to be found in a previous publication [8]. The maximum daily dosage of current and previous medication taken for the patients' TN symptoms as well as previous surgery for TN were also recorded. Patient information for the MS clinic was used when required. The data was entered on an Excel spreadsheet using the same format as for the non-MS data. Control data was taken from the previous non-MS cohort matched for age and gender to the pwTNMS cohort[8]. Multiple controls might be matched for one pwTNMS.

Statistical analysis

Descriptive statistics were used to summarize the pwTNMS and TN respectively. Mean and standard deviation were used for continuous variables if they were normally distributed, otherwise median and interquartile range were used. Frequency and percentage were used for categorical variables.

Two-sample T-test or Mann-Whitney U test were used to compare the difference for continuous variables between pwTNMS and TN, and Fisher Exact Test or Chi-square test were used to compare the difference for categorical variables. Significance level was set at 5%. All analyses were performed in R version 3.4.1 (http://cran.r-project.org/).

RESULTS

The database of patients registered between 2007-2016 contained 279 patients with classical TN, TN and concomitant pain, and TN with autonomic features. Of these, 33 patients were reported as having TN and MS. Seven patients were excluded as three did not have confirmed MS, three had neuropathic facial pain but not TN, and one was too severely affected by MS to give a history or complete questionnaires. This left 26 patients.

Nine pwTNMS had previously undergone surgery (three of them more than once), with mixed results. Only two achieved complete pain relief for any period of time: one after microvascular decompression (one-year pain relief) and one after glycerol rhizotomy (two years pain relief; however, repeating the surgery yielded no relief). One patient underwent three glycerol rhizotomies, which were only partially successful, while another received Gamma knife surgery, which afforded no pain relief. Radiofrequency thermocoagulation provided some pain relief for three patients, one of whom had a repeat procedure which provided no further relief. In one patient, pulsed radiofrequency performed by a pain specialist was ineffective.

The final patient had peripheral surgery, cryosurgery, performed by an oral surgeon with only partial pain relief.

Table 1 summarises the basic characteristics of our TN patient cohorts. While grossly similar, there exist some significant differences between the two. PwTNMS were more likely than TN patients to have had previous contact with GP services (100% pwTNMS vs. 80.9% TN; p = 0.039), and neurologists (53.8% vs. 29.4%; p = 0.049), as well as to have already had other procedures at presentation to our clinic (38.5 % vs. 13.2%; p = 0.015). There were also significant differences in the socioeconomic status of the two cohorts, specifically their deprivation index scores (p = 0.047) and employment status (p = 0.002). Extra data in supplemental table 1

Table 1 Characteristics for patients with TNMS and TN.

Characteristic	**pw TNMS n = 26 (%)**	**TN n = 68 (%)**	**P-value**
Age in years, mean (SD)	61.35 (8.60)	61.50 (5.88)	0.921
Age at first attack, median [IQR]	53.00 [48.50, 59.00]	57.00 [50.75, 62.00]	0.239
Duration of TN in years, median [IQR]	5.00 [3.25, 9.50]	4.00 [2.00, 7.00]	0.214
Duration of MS years	15.5 [11.25, 24.75]	-	
Interval between MS and TN [IQR] years	9.0 [3.50, 19.50]	-	
Type of MS			
Benign MS	3 (11.5)	-	
Primary progressive	8 (30.8)	-	
Secondary progressive	7 (26.9)	-	
Relapsing-remitting	8 (30.8)	-	
Female	20 (76.9)	54 (79.4)	1.000
Index of multiple deprivation			
1 (least deprived)	3 (12.0)	18 (26.5)	0.047
2	10 (40.0)	10 (14.7)	
3	3 (12.0)	20 (29.4)	
4	6 (24.0)	13 (19.1)	
5(most deprived)	3 (12.0)	7 (10.3)	
Missing	1 (5.6)	-	

Note: values are presented as frequency (%); P-value represents comparison between two groups; missing values are not included.

While the characteristics of the pain were broadly comparable between the two cohorts, there were also some significant differences, as shown in Table 2. Most notably, the pwTNMS exhibited significantly reduced lengths of remission (p = 0.008), with 46.2% of this group reporting “no remission”, as compared to only 5.2% of the TN group. Despite having fewer remissions, pwTNMS reported fewer instances of prolonged pain after an acute attack, as compared with TN patients (11.5% vs. 47.5%; p = 0.011).

The anatomical distribution of the pain was similar, with both cohorts experiencing third division distribution as the major focus of pain. Of these, ten reported only lower mandibular area with no extension above the ear. Just under half of pwTNMS have pain in only one division, similar to primary TN, and neither group had only first

division pain. However, pwTNMS reported more bilateral pain, but this did not meet statistical significance.

Table 2 Clinical features stratified by type of TN

Pain characteristic	**Group 1 MSTN n = 26**	**Group 2 TN n = 68**	**P-trend**
V1 only	0 (0.0)	0 (0.0)	-
V2 only	3 (11.5)	15 (22.1)	0.263
V3 only	10 (38.5)	21 (30.9)	0.622
V1 + V2	2 (7.7)	6 (8.8)	1.0
V2 + V3	8 (30.8)	22 (32.4)	1.0
V1 + V2 + V3	3 (11.5)	3 (4.4)	0.428
Right	10 (38.5)	43 (63.2)	0.053
Left	14 (53.8)	24 (35.3)	0.160
Bilateral	2 (7.7)	1 (1.5)	0.379
Intra oral pain	26 (100)	58 (85.3)	0.090
Extra oral pain	17 (65.4)	54 (100.0)	0.025
Predominant type of attack			
Single stab	12 (46.2)	28 (41.2)	0.539
Series of stabs	5 (19.2)	23 (33.8)	
Saw tooth	4 (15.4)	9 (13.2)	
Single stab + Series of stabs	5 (19.2)	8 (11.8)	
Circumstances			
Acute onset	6 (23.1)	19 (32.2)	0.682
Memorable onset	11 (42.3)	25 (42.4)	
Slow to develop	6 (23.1)	11 (18.6)	
Cannot remember onset	3 (11.5)	4 (6.8)	
Frequency of pain attack			
Daily	16 (88.9)	48 (90.6)	1.000
Duration of attacks			
Seconds	20 (76.9)	40 (59.7)	0.089
Minutes	3 (11.5)	23 (34.3)	
1-4 hours	3 (11.5)	4 (6.0)	
Pain after main attack	3 (11.5)	29 (47.5)	0.011
Length of remission			
None	9 (34.6)	3 (5.2)	0.013
Days	0 (0.0)	6 (10.3)	
Weeks	4 (15.4)	8 (13.8)	
Months	10 (38.5)	33 (56.9)	
Years	2 (9.5)	8 (13.8)	
Missing (but in remission)	1 (3.85)		
Remission period change (% of participants who have had remission)	n= 17	n= 55/59	

No change	1 (6.25)	15 (25.4)	0.753
Shorter remission	12 (75.0)	40 (67.8)	
Longer remission	2 (12.5)	4 (6.8)	
Missing	1 (6.25)	-	
Provoking factors			
Provoked by ≥1 light touch stimuli	24 (92.3)	66 (97.1)	0.998
Intraoral triggers (eating and/or brushing teeth)	25 (96.1)	63 (92.6)	0.241
Provoked by other factors			
Cold wind/weather	9 (34.6)	26 (38.2)	0.931
Bodily movement	8 (30.8)	29 (42.6)	0.413
Noise or light	1 (3.8)	0 (0.0)	0.616
McGill pain questionnaire			
Number of words chosen (mean ± sd)	10.6 (4.0)	10.9 (3.8)	0.672
Sensory groups	Stabbing (21)	Stabbing (27)	
	Shooting (19)	Shooting (51)	
	Sharp (14)	Sharp (43)	
Affective	Terrifying (12)	Fearful (17)	
	Vicious (9)	Vicious (23)	
Evaluative	Unbearable (17)	Unbearable (24)	
Miscellaneous	Piercing (18)	Piercing (23)	

Note: values are presented as frequency (%); P-value represents comparison between two groups; missing values are not included. V = fifth trigeminal nerve , 1 ophthalmic division , 2= maxillary division, 3 = mandibular division

The medical histories were broadly similar between the two groups, with the major difference being that pwTNMS were much more likely to have had surgery prior to referral (53.8% vs.10.3%; $p < 0.001$) and were much more likely to report disturbances to their sleep (50% vs. 14.9%; $p = 0.001$). Other differences included an increased incidence of migraines and tension-type headaches, cardiovascular disease, neck pain, dental problems and disturbed salivation amongst pwTNMS. Autonomic features were also seen noted in some pwTNMS. See supplemental table 2 .

Both pwTNMS and TN patients similarly reported that their pain has a considerable impact on activities of daily living and their psychosocial wellbeing, with many patients scoring high on assessments of both anxiety and depression (table 3).

Table 3 Impact of trigeminal neuralgia on quality of life

Scale	pw TNMS	TN	P-value

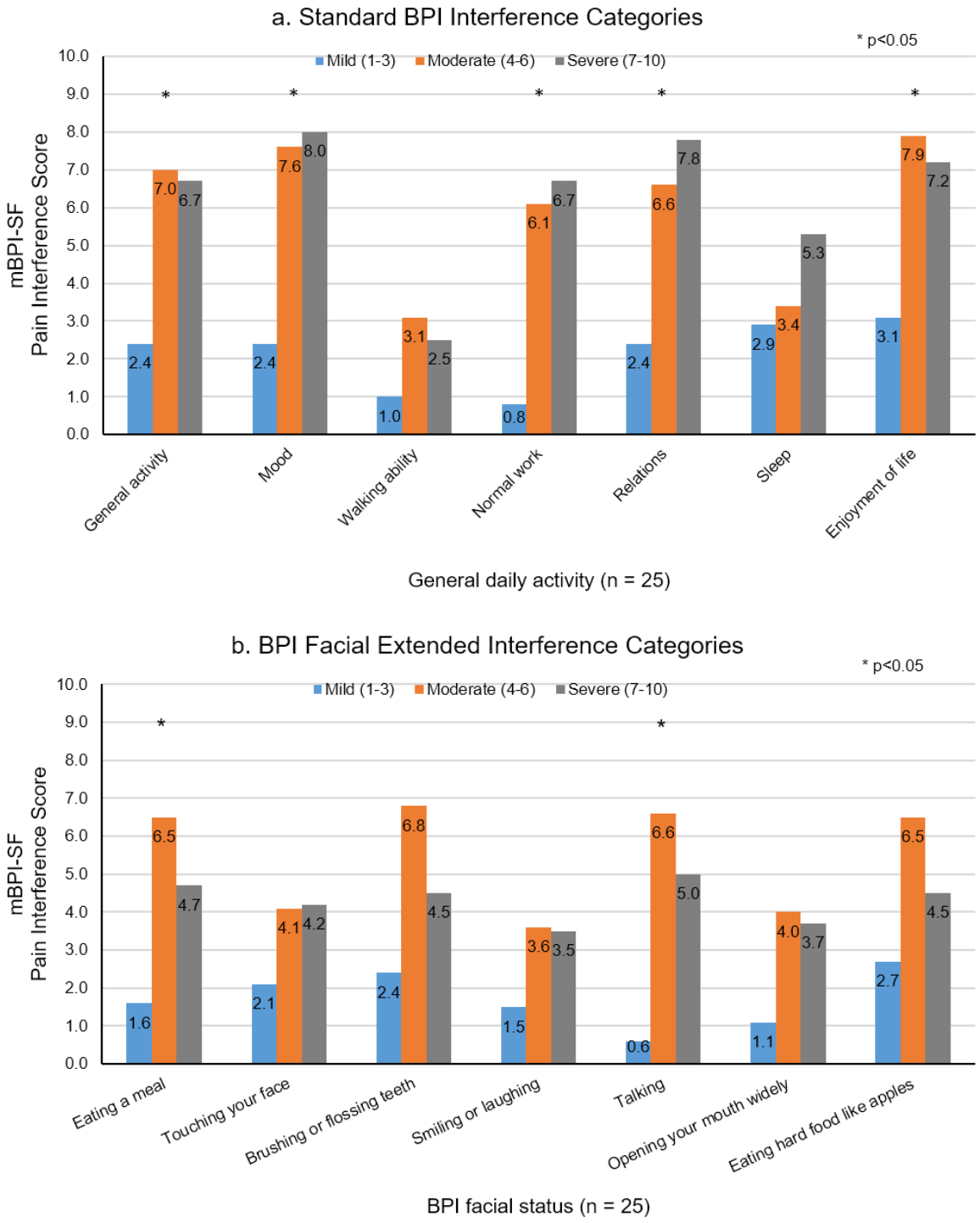
Chronic graded pain scale	**n=24**	**n=54**	
Grade 1 low impact	4 (16.7)	8 (14.8)	0.024
Grade 2	2 (8.3)	22 (40.7)	
Grade 3	6 (25.0)	7 (13.0)	
Grade 4 – high impact	12 (50.0)	17 (31.5)	
Days off normal activities	**n=23**	**n=59**	
0-6	5 (21.7)	25 (42.4)	0.154
7-14	3 (13.0)	9 (15.3)	
15-30	4 (17.4)	16 (27.1)	
31+	11 (47.8)	9 (15.3)	
Pain catastrophizing score	**n=20**	**n=55**	
Total score, median (IQR)	41.5 [33.5,47.5]	30 [17, 42]	0.201
Score over 20 significant	17 (85.0%)	36 (65.5)	0.532
HAD-Anxiety	**n=25**	**n=60**	
Nil score 0-7	11 (46.2)	22 (36.7)	0.151
Mild score 8-10	6 (23.1)	26 (43.3)	
Severe score 11-21	8 (30.8)	12 (20.0)	
HAD-Depression	**n=26**	**n=60**	
Nil score 0-7	11 (44.0)	40 (66.7)	0.136
Mild score 8-10	4 (16.0)	9 (15.0)	
Severe score 11-21	10 (40.0)	11 (18.3)	
Brief pain inventory, median [IQR] score 0-10	**n=25**	**n=68**	
Pain severity average index	3.67 [2.33, 6.67]	3.75 [1.81, 5.69]	0.718
Pain interference- general daily life	4.71 [1.43, 6.71]	2.29 [0.57, 5.00]	0.266
Pain interference- facial status	5.64 [2.82, 7.93]	4.71 [1.21, 8.00]	0.356

Note: values are presented as frequency (%); P-value represents comparison between two groups; missing values are not included.HAD Hospital anxiety and depression scale

Scores over 20 on the Pain Catastrophizing Score indicate significant negative thoughts and the majority of patients in both cohorts exhibited this (85% and 65.5%; p = 0.201). The major difference between the two groups was on the Chronic Graded Pain Scale (p=0.024), where pwTNMS scored more frequently in grades 3/4 (high-disability) while TN patients were more frequently grades 1/2 (low-disability).

Figure 1a and b shows the results from the Brief Pain Inventory including the more specific facial extended one and highlights the significant impact on quality of life especially in facial activities and is similar to the TN group as shown in previous publication[8].

Figure 1a and b HERE Brief Pain Inventory in patients with TNMS



Both cohorts of patients have trialed a wide variety of drugs, as seen in Table 4. The majority of patients have used carbamazepine (pwTNMS 21 vs. TN 53), which represents the most commonly used drug. Following carbamazepine use is gabapentin (pwTNMS 13 vs.TN 20) and then pregabalin (pwTNMS 5 vs TN 9) and

oxcarbazepine (pwTNMS 5 vs. TN 8). Other drugs included Tizanidine and prednisolone.

Table 4 Drugs used prior to referral

	pwTNMS (n = 26)	**TN (n = 68)**	**P-value**
No of anticonvulsants			
0	1 (3.8)	4 (5.9)	0.241
1	6 (23.1)	19 (27.9)	
2	13 (50.0)	21 (30.9)	
3	3 (11.5)	12 (17.6)	
4+	3 (11.5)	12 (17.6)	
Opioids	4 (15.4)	9 (13.2)	0.749
OTC + analgesics	5 (19.2)	18 (26.5)	0.595
Muscle relaxant baclofen	7 (26.9)	16 (23.5)	
Antidepressants any	12 (46.2)	4 (5.9)	<0.001
Antibiotics	1 (3.8)	19 (27.9)	0.011
Other	2 (7.7)	1 (1.5)	0.184

Note: values are presented as frequency (%); P-value represents comparison between two groups; missing values are not included. OTC- over the counter medications

DISCUSSION

To our knowledge, this is the first study to document the impact of TN on patients with MS and to compare this group to those with primary TN. While the two groups share many similarities, as outlined above, we have found several domains in which they differ, differences which suggest that pwTNMS exhibit a more severe phenotype than TN. The severity of pwTNMS is shown by their increased use of healthcare services, the features of the pain, and the secondary impact of that pain on their physical and mental wellbeing.

PwTNMS may require and rely on healthcare services more than their TN counterparts. At presentation to our clinic, every single one of our pwTNMS reported having used GP services to attempt to manage their pain, while this was true for a majority, but not the entirety of our TN cohort who may come through the dental route due to the frequent presentation in the lower mandibular area. This cohort had comparatively higher rates of interventions prior to presentation, and, specifically, higher rates of neurosurgery than TN patients. Notably, neurosurgery provided relief only to a minority of patients, and even then only for limited amounts of time, in accordance with a recent systematic review of the management of pwTNMS[2].

With regards to the clinical features of pwTNMS, the most striking difference was the reduced length and duration of remissions that these patients suffered from. A majority of pwTNMS reported either no remissions (46.2%) or only weeks of remission (11.5%), despite the majority of TN patients reporting months to years of

remission. Moreover, pwTNMS exhibited fewer identifiable triggers to acute attacks, complicating preventative measures. This is likely reflective of the underlying disease process of MS, which is characterized by often unpredictable flare ups. Like TN patients, pwTNMS also tend to trial many types of drugs, reflecting the common difficulty in achieving pharmacological control of symptoms.

There exists limited literature on the impact of TN on wellbeing, but these few published papers highlight a notable impact on anxiety, depression and sleep[8]-[10]. This study shows that a comparable level of disability is noted in pwTNMS. Significant disruptions to activities of daily living are noted for all TN patients but these appear higher in pwTNMS, especially with regards to disturbances to sleep. On the Chronic Graded Pain Scale pwTNMS suffered greater interference in activities of daily living due to pain than TN patients. However, this conclusion is complicated by the difficulty in distinguishing pain due to TN from other pain that commonly occurs in MS patient, the prevalence and course of which is poorly described[11]. We did not ascertain their status on the Expanded Disability Status Scale (EDSS), which may have provided further information.

At first presentation, our TNMS cohort was similar in age to patients with primary TN, in keeping with other studies[2]. On average, symptoms first occurred in the 5th decade of life, although this is in contrast to De simone et al[3] who found the mean age of onset to be 43 years, albeit in a smaller cohort of 15 pwTNMS. In this cohort, all patients first presented with MS, but a review of the literature based on 950 patients has shown that 10.5% have TN before MS, and the gap between the diagnosis of MS and TN could be 10 years. Cruccu et al[4] suggests that MS starts later in those who develop TN, but we could not validate this in our dataset .

From this baseline data it appears that pwTNMS have a more intractable TN, one which may necessitate a more complex approach to treatment, earlier referral to secondary care and a thorough assessment of mental health. Heinskou et al[12] have previously suggested that this cohort needs a multidisciplinary approach, and our findings support this. This should potentially include psychological support on how to manage fear, isolation and the unpredictability of flare ups. For example, a recent review by Simpson et al[13] has shown that mindfulness-based interventions may benefit patients with MS in terms of quality of life and mental health.

Limitations

This is an observational design study and is based largely on subjective reports of pain, depression, anxiety and impact on well-being. While these reports are useful, prospective and interventional studies on these patient groups will help elucidate the extent of these differences. For example, do the two groups differ in their response to interventions due to this purported difference in pain phenotype?

This study was carried out in patients referred to a specialist facial pain centre. By definition, the symptoms of such patients were of great enough severity to warrant referral, and may not be representative of all TN cases, many of which may be successfully managed in the community. As such, the results should be interpreted with caution in a primary care setting. Nevertheless, this limitation does impact the

comparison between the two groups (TN vs. TNMS), as both patient populations were drawn from the same centre. As such, it can still be concluded that, in patients referred to a specialist pain clinic, TNMS patients exhibit a more severe disease phenotype than TN patients. It would be reasonable to expect a similar trend in primary care patients, but this must be verified with further research.

Findings of greater sleep disturbances and impact of chronic pain on activities of daily living in patients with TNMS is confounded by their underlying MS. The MS itself may be directly contributing to a worsening of these measures by mechanisms unrelated to the TN, for example due to mobility or bladder issues or pain elsewhere. This represents a true confounder. Nevertheless, MS may also impact these measures by a TN-dependent effect. MS may heighten the perception of TN pain, and MS lesions on the trigeminal nerve may be biologically more painful, although we did not ascertain this in our study.

Cruccu et al[4] suggest that abnormal blink reflexes show good specificity and sensitivity in differentiating between TN and pwTNMS, but these were not carried out with this group. This series, while larger than previous studies, remains small, therefore limiting the strength of the conclusions we have drawn. Moreover, detailed data on imaging was not available, which may be important as diffusivity studies (Diffusion MRI tractography) begin to differentiate the microstructure of MSTN[14]. Truini et al[15] also highlight that in pwTNMS both demyelination and compression can be present. We have not been able to link disease progression with MS progression or drug usage as the numbers are too small.

Future

Larger series will need to be studied. Registries such as those held by the MS Society UK show that up to 15% of their patients (1,800) report having TN, providing a potential pool of data. Enlarging the database and collecting longitudinal data would make it possible to determine if the TNMS care-pathway needs to be different from those of TN, with particular emphasis on how different treatments impact on quality of life and mental health. Currently there is no data to determine if management of MS impacts in any way with long term TN outcomes. Data from Scandinavian countries suggests that overall MS patients have a shortened life expectancy although it is now improving[16] and many live with 20 years moderate and 30 years severe disability[17] and TN can add to this burden.

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Contributors: JZ was responsible for the study concept and monitored all the patients clinically. KG and MS inputted all the data and wrote the first draft of the paper. JW performed the statistical analysis. All contributed and approved the final draft

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Supplemental tables

Supplemental Table 1 Referral pathways and previous treatments for TN patients

Referrer to specialist clinic			
Dentist	3 (12.0)	13 (19.1)	0.302
GP	11 (44.0)	33 (48.5)	
Specialist	1 (4.0)	0 (0.0)	
Missing	11 (42.3)	-	
Family history of TN	2 (7.7)	4 (5.9)	0.620
Previous services used multiple times			
GP	26 (100.0)	55 (80.9)	0.039
Dentist	14 (53.8)	50 (73.5)	0.113
Dental Service			
Dental Specialist	2 (7.7)	11 (16.2)	0.464
Oral Surgeon (cryosurgery procedures)	3 (11.5)	16 (23.5)	0.314
Dental Procedures	4 (15.4)	3 (4.4)	0.170
Medical Service			
ENT surgeon	0 (0.0)	6 (8.8)	0.274
Neurosurgeon	8 (30.8)	11 (16.2)	0.633
Neurologist	14 (53.8)	20 (29.4)	0.049
Physician	0 (0.0)	5 (7.4)	0.364
Psychiatrist	0 (0.0)	1 (1.5)	1.000
Psychologist	2 (7.7)	0 (0.0)	0.130
Pain Specialist	5 (19.2)	6 (8.8)	0.296
Other medical procedures	10 (38.5)	9 (13.2)	0.015
No. of secondary dental or medical services for TN			
For all			0.651
0	3 (11.5)	15 (22.1)	
1	15 (57.7)	34 (50.0)	
2	7 (26.9)	15 (22.1)	
3+	1 (3.8)	4 (5.9)	

Supplemental Table 2 Associated factors and medical history in TN patients

Associate factors and medical history	**Group 1 MS TN n = 26**	**Group 2 TN n = 68**	**P-trend**
Altered sensation or numbness	9 (34.6)	15 (22.4)	0.344
Disturbed salivation	9 (34.6)	7 (10.6)	0.015
Dental problem	7 (26.9)	3 (4.5)	0.006
Affects sleep	13 (50.0)	10 (14.9)	0.001
Any autonomics unilateral	16 (61.5)	50 (73.5)	0.376

Swelling face	3 (11.5)	9 (13.4)	1.000
Redness of the face	4 (15.4)	7 (10.4)	0.712
Nasal stuffiness/runny	5 (19.2)	16 (23.9)	0.838
Eye redness	5 (19.2)	5 (7.5)	0.204
Eye tearing	7 (26.9)	14 (20.9)	0.728
Oedema eyelid	2 (7.7)	1 (1.5)	0.387
Earache	4 (15.4)	7 (10.4)	0.761
Ringing ears	5 (19.2)	9 (13.4)	0.705
Fullness ears	3 (11.5)	6 (9.0)	1.000
Headaches			
Migraines	6 (23.1)	11 (16.7)	0.678
Migraines + TTH	5 (19.2)	2 (2.9)	0.024
Bruxism	11 (42.3)	17 (26.2)	0.209
Medical history			
Hypertension	7 (26.9)	25 (36.8)	0.766
CVS	5 (19.2)	3 (4.4)	0.035
Diabetes	0 (0.0)	3 (4.4)	0.665
Deafness	4 (15.4)	4 (6.0)	0.298
Other chronic pain	9 (34.6)	16 (23.5)	0.408
Neck pain	8 (30.8)	6 (9.2)	0.024
Back pain	5 (19.2)	11 (16.7)	1.000
Previous surgery TN	14 (53.8)	7 (10.3)	<0.001

Note: values are presented as frequency (%); P-value represents comparison between two groups; missing values are not included. CVS- cardiovascular problems; TTH- Tension type headaches

***Conflict of Interest/ Role of Funding Source**

Trigeminal neuralgia : comparison of characteristics and impact in patients with or without multiple sclerosis.

Kimia Godazandeh [1], Santiago Martinez Sosa [2], Jianhua Wu[3], Joanna M Zakrzewska [4]

Funders: JZ undertook the work at UCL/UCLHT who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centre funding scheme.

Conflict of interest - nil

Table

Trigeminal neuralgia : comparison of characteristics and impact in patients with or without multiple sclerosis.

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Supplemental tables

Supplemental tables

Supplemental Table 1 Referral pathways and previous treatments for TN patients

Index of multiple deprivation			
1 (least deprived)	3 (12.0)	18 (26.5)	0.047
2	10 (40.0)	10 (14.7)	
3	3 (12.0)	20 (29.4)	
4	6 (24.0)	13 (19.1)	
5(most deprived)	3 (12.0)	7 (10.3)	
Missing	1 (5.6)	-	
Referrer to specialist clinic			
Dentist	3 (12.0)	13 (19.1)	0.302
GP	11 (44.0)	33 (48.5)	
Specialist	1 (4.0)	0 (0.0)	
Missing	11 (42.3)	-	
Family history of TN	2 (7.7)	4 (5.9)	0.620
Previous services used multiple times			
GP	26 (100.0)	55 (80.9)	0.039
Dentist	14 (53.8)	50 (73.5)	0.113
Dental Service			
Dental Specialist	2 (7.7)	11 (16.2)	0.464
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Pain Specialist	5 (19.2)	6 (8.8)	0.296
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No. of secondary dental or medical services for TN			
For all			0.651
0	3 (11.5)	15 (22.1)	

1	15 (57.7)	34 (50.0)
2	7 (26.9)	15 (22.1)
3+	1 (3.8)	4 (5.9)

There are significant differences in the socioeconomic status of the two cohorts, specifically their deprivation index scores ($p = 0.047$) and employment status ($p = 0.002$).

Supplemental Table 2 Associated factors and medical history in TN patients

Predominant type of attack	**Group 1 MS TN n = 26**	**Group 2 TN n = 68**	**P-trend**
Single stab	12 (46.2)	28 (41.2)	0.539
Series of stabs	5 (19.2)	23 (33.8)	
Saw tooth	4 (15.4)	9 (13.2)	
Single stab + Series of stabs	5 (19.2)	8 (11.8)	
Circumstances			
Acute onset	6 (23.1)	19 (32.2)	0.682
Memorable onset	11 (42.3)	25 (42.4)	
Slow to develop	6 (23.1)	11 (18.6)	
Cannot remember onset	3 (11.5)	4 (6.8)	
Frequency of pain attack			
Daily	16 (88.9)	48 (90.6)	1.000
Duration of attacks			
Seconds	20 (76.9)	40 (59.7)	0.089
Minutes	3 (11.5)	23 (34.3)	
1-4 hours	3 (11.5)	4 (6.0)	
Pain after main attack	3 (11.5)	29 (47.5)	0.011
Provoking factors			
Provoked by ≥1 light touch stimuli	24 (92.3)	66 (97.1)	0.998
Intraoral triggers (eating and/or brushing teeth)	25 (96.1)	63 (92.6)	0.241
Provoked by other factors			
Cold wind/weather	9 (34.6)	26 (38.2)	0.931
Bodily movement	8 (30.8)	29 (42.6)	0.413
Noise or light	1 (3.8)	0 (0.0)	0.616
Associate factors and medical history			
Altered sensation or numbness	9 (34.6)	15 (22.4)	0.344
Disturbed salivation	9 (34.6)	7 (10.6)	0.015
Dental problem	7 (26.9)	3 (4.5)	0.006
Affects sleep	13 (50.0)	10 (14.9)	0.001
Any autonomics unilateral	16 (61.5)	50 (73.5)	0.376
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