TRIGEMINAL NEURALGIA IN MULTIPLE SCLEROSIS PATIENTS: A CLINICAL COMPARISON OF TRIGEMINAL NEURALGIA IN PATIENTS WITH AND WITHOUT UNDERLYING MULTIPLE SCLEROSIS

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ABSTRACT

Background: The prevalence of trigeminal neuralgia (TN) is higher in multiple sclerosis (MS) as compared in the general population. Clinical and treatment responses of MS patients compared with non-MS patients are in debate.
Objective: To evaluate clinical differences in trigeminal pain presentation and pharmacological treatment response in patients with and without underlying MS.
Material and methods: A retrospective study of 10 MS patients that had TN as a first symptom or in the MS course (from the total 545 MS patients). Data regarding MS (sex, age at MS onset, type, symptomatology, number and site of lesions on brain MRI, treatment) and TN (clinical characteristics of facial pain, treatment), period from TN as a clinically isolated syndrome to defined MS or period from MS onset to TN beginning were analyzed. Clinical, demographical and treatment response were compared with corresponding data of 10 consecutive patients hospitalized for idiopathic TN.
Results: The only difference between MS and non-MS patients was the age of onset of TN (41.8 ±6.12 in MS vs 52.7±16.5 in non –MS patients, p=0.07, unpaired Student's t-test). There are no differences in trigeminal pain characteristics between MS and non-MS patients.
Conclusions: TN among MS patients has an onset at younger age but share the same pain characteristics and treatment respons with TN in the general population. TN in MS has multiple mechanisms of aetiopathogenesis and surgical treatment must be held in mind in selected cases.

Keywords: multiple sclerosis, trigeminal neuralgia

INTRODUCTION

Firstly, H Oppenheim in 1911 recognized that trigeminal neuralgia (TN) is a symptom of multiple sclerosis (MS). Since then, TN is probably the most widely recognized neuropathic syndrome in MS (1).

Approximately 2% of people with TN have MS and 1% of individuals with MS will have TN. As compared to the prevalence in the general population (15/100000), the percentage of TN in MS patients is higher (2).

The nature of facial pain in MS patients is usually indistinguishable from idiopathic TN except in being more often bilateral and less frequently triggered. Also, the age at onset is on average 5 years earlier than in the idiopathic form of TN and only rarely is the first MS symptom (1-4).

TN is clinically characterized by paroxysmal, episodic, triggered facial pain that occurs in the trigeminal area. The pain is described as stabbing, electric shock-like, in the maxillary or mandibular branches of the trigeminal nerve and is triggered by non-noxious stimuli when applied to the involved area of the face. There is little if any sensory loss. The pain paroxysms often are evoked by trivial stimulation, such as light touch or vibration, to ex-

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traoral or intraoral triggered areas. Spontaneous remissions lasting months or years occur in some patients; however, TN usually is progressive and the pain attacks become more frequent and severe (1-5).

The aetiology of TN is multifactorial, but is becoming increasingly recognized that most of so called "idiopathic" cases are due to vascular compression of the nerve by a looping blood vessel where the nerve enters the pons. The variable aetiology of TN is present in patients with coexistent neurological conditions such as MS. In MS patients, TN is caused not solely by pontine demyelinating plaques but also by vascular compression or cerebellopontine tumors (6).

Conventional opinion is that TN in MS patients is due to demyelinating plaque affecting the trigeminal nociceptive pathway. Demyelination is frequently found at the trigeminal nerve root entry zone on the symptomatic side.

The pathophysiological processes underlying TN are still in debate. A peripheral hypothesis, central hypothesis and theories trying to reconcile central and peripheral hypothesis about TN have been evoked. It is known that compression, distortion or stretching of the trigeminal nerve by a slow growing tumor, aberrant vessels or vascular malformations can cause typical TN. Intrinsic brain lesions such as MS, syringobulbia, brain stem infarcts, may also cause TN. The most plausible hypothesis regarding pathophysiology, which explains the fact that both extrinsic and intrinsic brain lesions may produce typical TN as well as the paroxysmal nature of the pain is that TN has a peripheral cause and a central pathogenesis. Chronic irritation of the peripheral nerve leads both to ectopic action potentials within the nerve and failure of segmental inhibition in the trigeminal nucleus.

A central neuromodulatory role of impulses coming from the area of cross compression explains the possibility that a long lasting alteration of discharge modalities of the trigeminal root can cause lowering of the pain threshold. This explains how a demyelinating plaque leads to increase activity within the trigeminal nucleus by generating ectopic action potentials in the trigeminal nerve. The episodic activation of the trigeminal neurons may result in paroxysms of pain whenever these bursts of activity exceed the threshold for activation of pain neurons in the trigeminothalamic tract. Moreover, demyelination promotes ephaptic neural transmission, development of abnormal contacts between adjacent nerve axons, which results in inappropriate spread of action potentials and activation of one nerve. Such inappropriate spread of action potentials may underlie the generation of pain by innocuous stimulation.

In MS patients, the underlying hyperexcitability in the trigeminal nucleus secondary to demyelination might elucidate that vascular compression is more likely to cause TN in a higher percentage than in general population. This same argument may explain the higher incidence of bilateral occurrence of TN in patients with MS and perhaps also the earlier onset. In a patient with one central nervous system abnormality and coexistent TN, it seems reasonable to attribute both to the same underlying process (5-7). Nakashima et al have described TN in patients with MS that is associated with magnetic resonance imaging (MRI) lesions situated in pons: along the trigeminal nerve root, large lesions near the cerebellopontine angle, intramedullary trigeminal root lesions which extends from the root entry zone to the fourth ventricle. Gass et al, in all six patients with MS and TN, found on conventional T2-wheighted MRI lesions in positions expected to involve trigeminal fibers, particularly the entry zone of sensory fibers. Other authors found on IRM, in some of the MS cases, vascular compression of the nerve by an artery at the root entry zone on the symptomatic side or an epidermoid tumour (5-9).

MRI and MR angiography, with special sequences and oriented sections, by showing the vascular relationships of the trigeminal nerve may identify neurovascular conflict(s) that might need microvascular decompression (13).

Sensory and motor trigeminal evoked potentials are used only to localize the position of trigeminal electrodes prior to thermocoagulation during percutaneous treatment for TN. Trigeminal evoked potentials are simple to record, noninvasive and inexpensive and might be used also in predicting the presence of trigeminal nerve compression (11,14).

Treatment contains two approaches, pharmacological and surgical procedures.Pharmacological therapy is the first line treatment for TN and its' goal is the reduction of neuronal hyperexcitability in the peripheral and central nervous system. Antiepileptic drugs are used: carbamazepine, oxcarbazepine, lamotrigine, phenitoin, gabapentine, pregabaline, etc. Carbamazepine has been found effective and is the mainstay of therapy in TN. The most common adverse effects include sedation, fatigue, dizziness, blurred vision, nausea, vomiting and allergic skin reactions. Periodic, the patient needs monitoring tests: complete blood cell count, liver tests. The dosage used in MS is often lower than the 600-1600mg/day used in essential TN. If adverse reactions occur other antiepileptic drugs

might be used. Often, drug combinations are used to maximize benefit and minimize adverse effects. Misoprostol, a prostaglandin E analogue that acts on immune cells such as macrophages which inhibit proinflammatory cytokines, may suppress inflammation in MS plaques. It was used with good results on a small group of patients resistant to conventional therapies. In some cases, corticotherapy administered for a MS relapse, might ameliorate trigeminal pain for a certain period of time (3,5,7, 10).

Surgical procedures are indicated for patients who neither become refractory to pharmacological treatment nor cannot tolerate its adverse effects. Surgical techniques used for TN treatment are peripheral surgery, percutaneous ablative procedures, stereotactic radiosurgery and microvascular decompression (3, 5, 7, 12).

OBJECTIVE

In the present study we evaluate clinical differences in trigeminal pain presentation and pharmacological treatment response in patients with and without underlying MS.

MATERIAL AND METHODS

We performed a retrospective study of the medical documents of a series of 545 MS patients hospitalized and followed for 3 years (jan 2007- jan 2010) in our neurological department. The MS patients that had TN as a first symptom or in the MS course were analyzed data regarding MS (sex, age at MS onset, type, symptomatology, number and site of lesions on brain MRI, treatment) and TN (clinical characteristics of facial pain, treatment), period from TN as a clinically isolated syndrome to defined MS or period from MS onset to TN beginning. Also they underwent a new brain MRI performed with a General Electric equipment of an 1T induction.

The diagnosis of MS was based on revised McDonald criteria (15).

Clinical, demographical and treatment response were compared with corresponding data of 10 consecutive patients hospitalized for idiopathic TN in a three years period. This second group performed a brain MRI to exclude a tumoral or vascular etiology of facial pain.

TN had clinical characteristics of facial pain according to the '' Headache Classification Subcommittee of the International Headache Society'', diagnosed as ''Classical trigeminal neuralgia''. Clinical intensity of pain was classified according to the Barrow Neurological Institute (BNI) score: grade I (pain free, no use of medication), grade II (occasional pain but off medication), grade IIIa (no pain and continued use of medication required), grade IIIb (some pain, controlled with medication), grade IV (pain improved but not adequately controlled on medication) and grade V (no pain relief whatsoever) (16).

RESULTS

The results of clinical characteristics of both groups of patients are marked in table 1 and 2.

Regarding the MS patients the results are as follows.

From the total 545 MS patients, 10 had TN (1.83%). Mean age of TN onset was 41.8 years (SD 6.12).In 6 patients, MS has started with TN, and in the rest of patients, TN appeared in the course of MS at a mean time of 16.5 years.

A number of 3 patients had involvement of 2 trigeminal branches, the rest had only one branch affected. The most frequent branch affected was the second division of trigeminal nerve.

The intensity of facial pain was severe in 6 patients (grade IIIb and IV), in which the medical treatment did not stop completely the neuralgic pain.

All patients had trigger areas, but interestingly, half of patients had trigeminal hypoesthesia at the neurological examination suggesting the presence of a demyelinating lesion involving the trigeminal nucleus in the brain stem or a demyelination of the trigeminal entry root in the pons (fig.1). This was not provable in all patients by brain MRI. Lesions in the brain stem were found in 4 patients, half of them having asymptomatic lesions.

The majority of the cases had a relapsing remitting course of MS. The patients with CIS had MRI lesions that fulfilled the Barkhof criteria for MS.

Not all patients treated with Carbamazepine responded well but they remained on the therapy as they did not tolerate or responded worse to other antiepileptics. Four patients did not require therapy for TN.

All patients had brain MRI with demyelinating plaques having the usual localization, shape and size for MS. Seven of these patients had brain stem lesions that could involve the trigeminal paths. From these 7 cases, 4 had trigeminal hypoesthesia, but not statistical correlation could be found between these 2 variables.

The patients without MS had a higher age (mean 52.7/SD 16.5) at TN onset than the MS group (p

Table1. *Clinical characteristics of trigeminal pain in MS patients.*

Clinical characteristics	MS1	MS2	MS3	MS4	MS5	MS6	MS7	MS8	MS9	MS10
Age of onset of TN±SD	44	39	42	35	39	49	39	55	36	40
Side Left		X		X	X	X			X	X
Right	X		X				X	X		
Time from MS to TN onset (years)	0	0	0	0	15	16	0	32	3	0
Trigeminal branches involved I			X						X	
II		X	X	X	X	X		X		X
III	X				X		X	X		
Intensity of facial pain	IIIb	IIIb	I	I	IV	IV	IIIb	IIIb	II	II
Trigger areas	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Trigeminal hypoesthesia	No	No	Yes	Yes	No	Yes	No	Yes	No	Yes
Type of MS	CIS	RR	PP	CIS	SP	SP	RR	RR	RR	RR
Treatment received for MS	Cld	Nab	ø	Cld	Rb	Bf	Bf	Bf	Bf	Bf
Treatment received for TN	Pg	Gp	ø	ø	Cbz	Cbz	Cbz	Cbz	ø	ø

Abbreviations: Bf- Betaferon, Cbz- Carbamazepine, CIS- Clinically Isolated Syndrome, Cld- Cladribine, Gp- Gabapentine, Nab- Natalizumab, Pg- Pregabaline, PP- Primary Progressive, RR- Recurrent Remitting, SP- Secondary Progressive.

Table 2. *Clinical characteristics of trigeminal pain in non-MS patients*

Clinical characteristics	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Age of TN onset	72	55	45	72	61	17	63	40	54	48
Side Left			X		X	X		X	X	X
Right	X	X		X			X			
Trigeminal branches involved I		X			X	X				
II			X	X	X		X	X		X
III	X				X				X	
Intensity of facial pain	IIIa	II	II	IIIb	IV	IIIb	IIIa	IIIa	I	IIIb
Trigger areas	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Trigeminal hypoesthesia	No	No	No	No	No	No	No	No	No	No
Comorbidities	Pk	ø	ø	Asc	I St	ø	HT	ø	NeoU	ø
Treatment received for TN	Cbz	Gp	Pg	Cbz	Pg	Gb	Pg	Pg	Cbz	Pg

Abbreviations: Asc- Atherosclerosis, Cbz- Carbamazepine, Gp- Gabapentine, HT- Hypertension, I St- Ischaemic Stroke, NeoU- uterine neoplasia, Pg- Pregabaline, Pk- Parkinson disease

0.07). We could not observe any differences for affected side, branches involved or intensity of pain. Patients in the second group had no trigeminal hypoesthesia associated, the diagnosis of "essential" TN implying no neurological signs between the attacks.

Table no.3 compares the two groups of patients. Statistical significance was not found but a clear trend toward the age of onset and trigeminal hypoesthesia.

DISCUSSIONS

Our percentage (1.82%) of MS patients with TN was in the same trend with other authors, TN being 20 times more frequent than in the general population (5, 6, 12).

There was a trend for a difference for the age at onset, that was lower in the MS group. We explain this partially due to the high standard deviation (16.5) in the nonMS group. Patients reported typi-

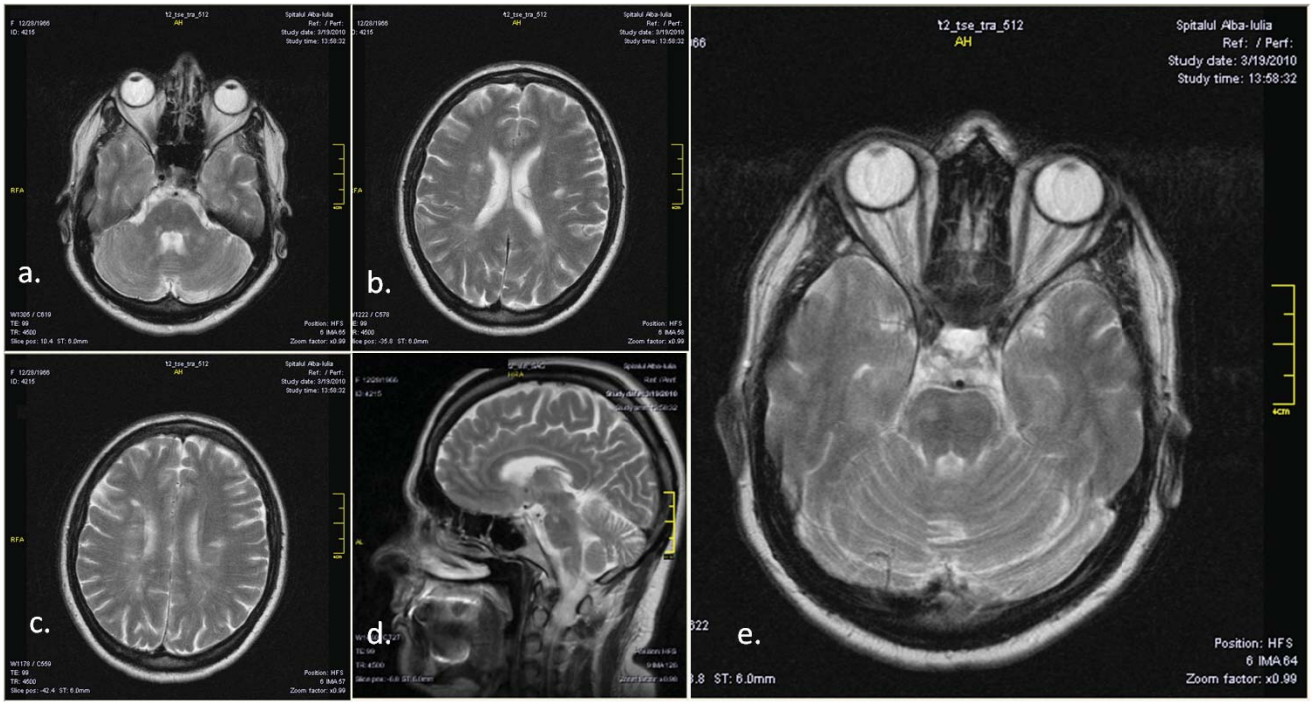

Figure 1. *(MS patient 3): (a) Axial T2 showing multiple demyelinating plaques in pons, middle cerebellar peduncle. (b) and (c) Axial T2 showing multiple demielinating plaques in periventricular, subcortical white matter.(d) Sagittal T2 showing demyelinating plaques in corpus callosum, upper pons. (e) Axial T2 showing the same upper right pons lesion as in image (d) that probable caused right V1 and V2 hipoaesthesia.*

Table 3. *Comparison of clinical characteristics of trigeminal pain in MS patients vs. non-MS patients*

Clinical characteristics	MS +	MS -	P
Age of onset±SD	41.8 (SD 6.12)	52.7 (SD 16.48)	0.07
Side Left	6 (60%)	6 (60%)	Ns
Right	4 (40%)	4 (40%)	Ns
Trigeminal branches involved (alone or in combination) I	2/13 (15.4%)	3/12 (25%)	Ns
II	7/13 (53.8%)	6/12 (50%)	Ns
III	4/13 (30.8%)	3/12 (25%)	Ns
Pain quality stereotyped			
Trigger areas	10 (100%)	10 (100%)	Ns
Trigeminal hypoaesthesia	5 (50%)	ø	

cal intermittent paroxysmal pain that may be related to demyelination of the central trigeminal pathways or root-entry zone in the pons. There are no differences in trigeminal pain characteristics between MS and non-MS patients. These findings were found also by other authors, suggesting the view of a common pathogenic mechanism underlying TN in the two groups (2).

None of our patients had bilateral TN. This finding is different from the literature were percentages up to 18% from MS patients had a bilateral TN (12, 17).

MRI is useful for demonstrating and monitoring demyelinatied lesions of the brain in patients with MS. Meany et al stressed the importance of MRI in MS patients having TN, as they found other coexistent neurological conditions such as vascular compression or tumors (6). We did not find any shape differences among brain stem lesions but Nakashima et al found linear pontine trigeminal root lesions in 5 MS cases with various facial sensory manifestations, suggesting a different mechanism of such lesions that may be related to herpes simplex infection (8). We can presume that antigens against my-

elin might affect both central and peripheral nervous system, explaining why the brain MRI doesn't reveal hypersignals in brain stem. Peripheral and central myelin have different protein composition, but share one common protein antigen. Specifically, peripheral myelin P1 protein is identical to central myelin basic protein and there is an indication that immunological response could spread from one to the other (18, 19).

More than half of patients from both groups were not well controlled by medical therapy. Some of these cases could be candidates for percutaneous rhizotomy or for gamma knife radiosurgery that is the most minimally invasive with the lowest morbidity of the surgical treatment options (7, 12).

CONCLUSIONS

TN among MS patients has an onset at younger age but share the same pain characteristics with TN in the general population. TN in MS has multiple mechanisms of aetiopathogenesis and surgical treatment must be held in mind in selected cases.

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