Research Article

Tractography innovative knowledge of multiple sclerosis and trigeminal neuralgia

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Abstract

In Multiple Sclerosis (MS) pathophysiology, a detailed history is known to be the most innovative tool for clarifying the trigeminal nerve (TGN) and predicting its possible interaction. TGN is one of the largest and most engaged cranial nerves (CN) in MS pathology, which probably has received limited attention so far. In addition, it has a very active peripheral ascending and descending neural transport. Patients with classic trigeminal neuralgia (TN) will be used as a proxy to obtain additional information on MS pathology when symptoms are unilateral, with magnetic resonance imaging (MRI) showing bilateral pathology, and neurophysiological result supporting the MRI findings. Using MRI was found to raise the level of information on the microstructure and neural interconnection of TGN, for example, using the T2 and diffusion tensor imaging (DTI) with tractography can improve our understanding in this regard. Microvascular information with retrograde reflux of TGN venous contact can also be followed to the central venous branches in the corpus callosum and read out from the neurosurgical report. In this study, a sign of common demographical factors, such as predominantly female, younger ages, and side specific, white matter (WM) lesions when reviewing diffusion MRI data of naïve TN, and MS-TN was found. Other findings included anatomical differences, e.g., smaller diameter, volume, and greater atrophy, when looking through findings on female associated diffusion MRI. A tractographical comparison between TN patients without MS and TN patients with MS has facilitated a better understanding about the possible role of TGN in MS pathology.

Keywords: Multiple Sclerosis , MRI, trigeminal neuralgia, TGN

Introduction

Multiple Sclerosis (MS) is a chronic inflammatory disease of myelin, mostly affecting patients between 20 and 50 years of age. MS is reported to occur at least twice as often in females as in males[1] and accompanies a variety of signs and symptoms.[2] Its etiology is unknown and the pathology is characterized by a multifactorial, immune-mediated disease caused by complex gene–environmental interactions and plaque burden of the central nerve system (CNS),[3] including the trigeminal nerve (TGN).[4] Patients with MS-trigeminal neuralgia (MS-TN) frequently suffer from bilateral plaques, but the pain is overwhelmingly unilateral.[5] Therefore, the contribution of plaques to the clinical presentation of pain is not fully understood and is in urgent need of being explored further.

In several MRI studies, trigeminal root entry zone (REZ) abnormality has been reported in patients with MS (PwMS),[6-8] particularly in those with signs and symptoms related to the TGN. Findings suggest that using a 3T MRI scanner might show TGN (Fig. 1), selectively impairs with widespread white matter (WM) lesion, especially in the contralateral hemisphere, which, in turn, may be the hallmark of disease severity in patients with MS and TN (PwMS-TS).[9] The microstructure of the tissue damage may affect the TGN in patients with TN (PwTN), and as a possible consequence, WM microstructural alterations in the CNS.[10] Some evidence also indicates that injury to TGN may include trauma, neuroinflammation, and edema.[11] Affection on the TGN can also be visualized by an immunohistochemical method which shows focal CNS demyelination.[12] The REZ is regarded as a highly important area of pathophysiological exchanges between the peripheral part (PNS) of the TGN and the CNS.[7, 13] Especially, TGN demyelination[14] and WM lesions may be explained by performing a bilateral representation of the transcallosal pathways or the trigeminothalamic system.[15] Further, specific lesions in MS, such as Dowson's fingers might probably manifest.[16]

Recent theories concerning the nature and role of TGN in CNS pathogenesis have been studied to use the TGN as a proxy or a measurable mechanism to identify pathways for spreading pathogens from peripheral fibers of the TGN to the central sensory radiators.[5, 17, 18] In addition to the fact that the focus is on pain per se, the vascular consequences are also of interest, given that it acts like a venous angioma at the REZ of TGN which retrogradely gives raised pressure to the CNS venous system inclusive of the central vein in Corpus Callosum (CC), which has been shown having a pathognomonic role in MS radially.[19] Some evidence attributed to reversible splenial lesions of the CC in various clinical conditions has also been reported[20] and it could lead to widespread abnormalities in the microstructure of WM tracts related to sensory, motor, cognitive, and pain functions, including a focal area of the CC[21]. Comparing findings by performing tractography can help to find some common parameters to emphasize the common affection in PwTN and PwMS-TN with a view to better understanding the peripheral etiology in MS.

Herein, we describe the tractographical patient studies, which compared the association of TGNs role with non-MS controls with and without TN. Also, more detailed studies of TN to enhance the understanding of TGN in general would help provide more information about TGN in MS.

Materials and Methods

A "targeted" review of the scientific literature within the PubMed, EMBASE, and the Cochrane Database of Systematic Reviews and Google Scholar was carried out. Publications up to December 1, 2019, were included. We extracted all parameters using the following keywords: multiple sclerosis and tractography combined with/or trigeminal neuralgia, facial pain or numbness, microstructure, WM, diffusion-MRI (dMRI), MRI, Tesla, Gadolinium, slice thickness, neurophysiology, and pathology. Using the bibliographies of the publications retrieved, the primary search was supplemented by secondary tracking details. Only full- length, original communications were valid, and the search was primarily confined to English language publications or, in some cases, other languages (Danish, Swedish, Norwegian, and German) if indicated. The animal model studies were only used to support clinical context if no human study was available.

Results

This search yielded a total of approximately 586 hits, which were reviewed by title and abstract for potential relevance to this topic; the body-text itself was reviewed in case the abstract was found lacking relevance search information. After excluding duplicates, malignancy, tumor, bleeding, and hereditary cause, reviews, animal, migraine, and headache studies (flow diagram), 60 studies were included in the final review (PRISMA Flow Diagram).

PRISMA Flow Diagram
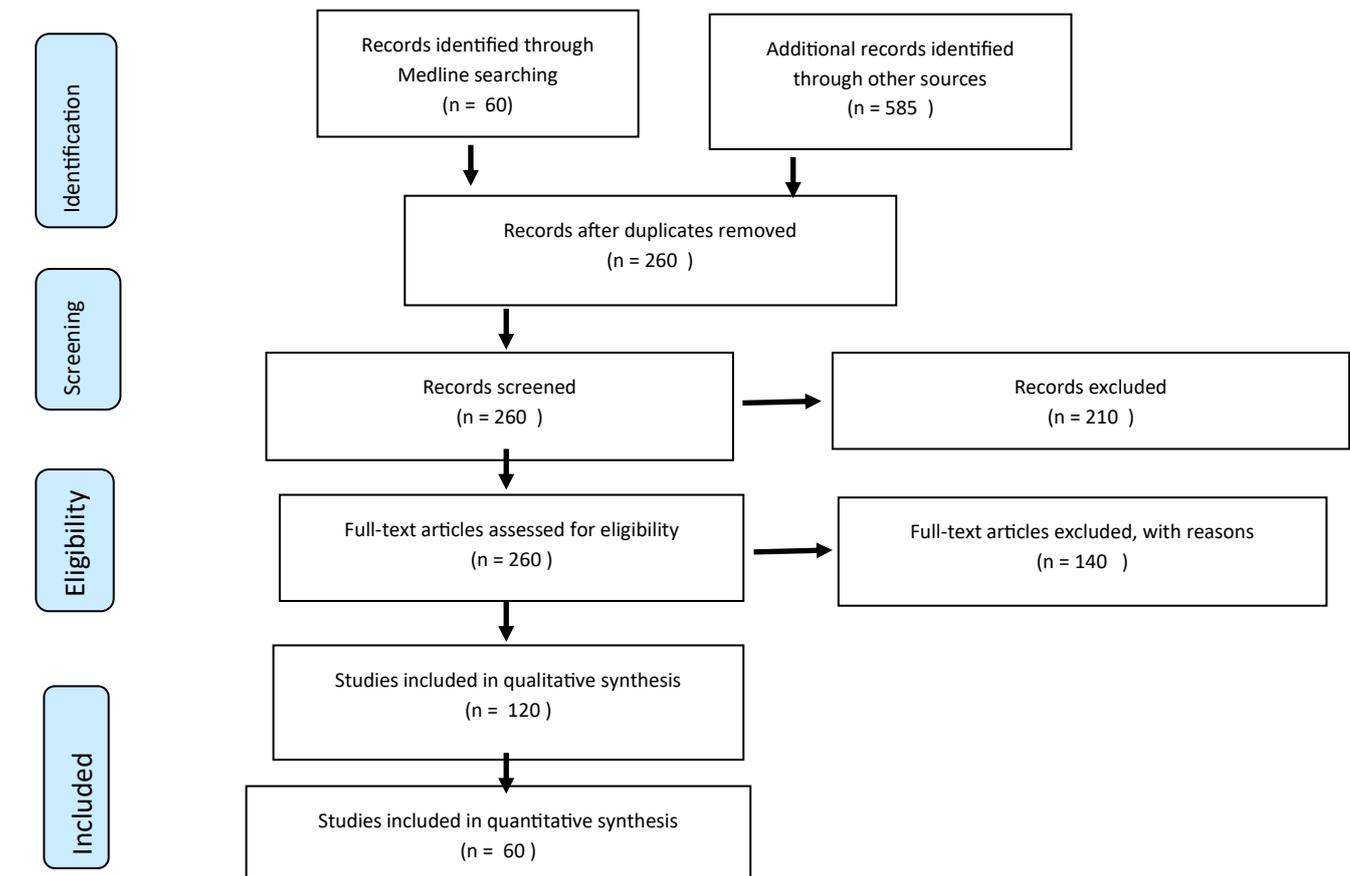
The background of TGN

TGN is a mixed nerve that primarily encompasses sensory neurons, albeit with embryological origin from the lymph node.[22] Three divisions of neurons converge the trigeminal ganglion (TG): the ophthalmic nerve (V1), the maxillary nerve (V2), and the mandibular nerve (V3), which also carries components of descending motoric fibers that leave the CNS to innervate different facial muscles.[23] The sensory neurons build up the Gasser ganglion, i.e. a diverse population of cells, that can be classified according to cellular morphology, neurochemistry, and functional characteristics.[22, 24, 25] In this regard, it is pertinent to note that the peripheral and CNS connection of TGN has been studied tractographically.[26] In analyzes of myelinated axons[27] and nerve volumes,[28] gender differences have been found, e.g. lower values in females.[29] Further, comparisons of the diameter of the TGN's cisternal portion using a 3.0 T MRI, reveals significantly smaller in left TGN volumes in females as compared to corresponding findings in males (p<0.0001). [30] Previous studies using 1.5T MRI have pointed out that even in general, the diameter of the left-sided mean volume of TGN is smaller, with the dimensions of right-sided nerves being 0.093 cm3 (0.055–0.147 cm3) and that of left-sided nerves being 0.091 cm3 (0.057–0.142 cm3).[31] Further, heart rate alterations due to stimulations of the TGN have been elucidated with significant gender differences.[32]

Trigeminal free nerve endings, which are sensitive to mechanical and thermal stimuli, appear to primarily respond to noxious and potentially harmful levels of chemical stimulation, CO_2 included.[33] Peripheral temperature sensing cell bodies located in TGN mediating primarily two classes of neurons activated by innocuous warmth: (34 - 42°C) or cold (14 -30°C).[34] Further, it has been shown that TGN activation depends on the sex hormone.[35] The role of TGN in cardiovascular alterations, diving, and temperature reflex is specialized for each branch of TGN and sex-dependent.[32, 36, 37] The thermoregulatory system shifted to hypometabolism could cause obesity, which again is more frequent among females.[38]

The imaging technology has grown successfully over the last few decades.[39] With advancements in MRI technology, it has become possible to visualize 1 (51.2%), 2 (37.5%), or even 3 (11.2%) small motor roots typically emerging from the pons anterosuperomedially to the entry point of the large sensory root.[40, 41] However, detailed pathways for sensory, motoric, and autonomic is more complex[42] and may need high field MRI as 11.75 T for the purpose of visualization. Further, it is also essential to verify that detected damages of the optic and TGN appeared before lesions in CC occurred as a result of CNS malaria that had been triggered in mice.[43]

Definitions and epidemiology

With an annual incidence of ~4.5 per 100 000, TN is characterized by a recurrent, unilateral, brief, electric shock-like pain, abrupt in onset and termination, as well as with lancinating jerk localized to small areas of the face. Pain is limited to the distribution of one or more divisions (V1, V2, or V3) of the TGN and intensely triggered by innocuous stimuli. In addition, there may be concomitant continuous pain of moderate-intensity within the distribution(s) of the affected nerve branches; either idiopathic or in conflict with arteries or veins.[44] Secondary TN occurs in up to 37%[45] of PwTN and the diagnosis is made in the presence of a structural abnormality, other than vascular compression, albeit including MS plaques, tumors, and abnormalities of the skull base, that affects the TGN. Previously lesions could be detected using low field MRI, but only in 15%[46] MS plaques are the most commonly identified secondary abnormalities in TN.[47] Patients with MS have a 20-fold increased risk of developing TN[47] and according to current information, 1.9 - 4.9% of these patients have an increased risk of suffering from TN without differences between MS-courses, relapsing-remitting (RRMS), secondary (SPMS) and primary progressive (PPMS). Conversely, MS is detected in 2%-14% of PwTN, and 10% of patients with PwMS have a higher risk of bilateral TN.[48] Also, the reasons why both facial pains including TN and non-painful facial sensory disturbances are a common phenomenon in PwMS are not fully known. Painful facial attacks determined in patients under the age of 50 are most likely to have MS etiology. In patients, with late-onset of MS at even higher ages, these attacks may occur with a more aggressive disability impact.[49] Agreeing with these similarities in PwTN, the histopathologic findings show large demyelinated axons, loss of axon quantity, and abnormal remyelination in the nerve specimens.[14, 50]

dMRI, DTI and Tractography

The dMRI is one of the basic approaches of investigating the WM of the human brain. Tractography is a postprocessing method that can help derive further information of the WM microstructure by visualizing WM pathways, for example, the TGN, as 3D reconstructed tracts.[51-53]. In deterministic tractography, the algorithm uses the diffusion tensor (DT) to point out the diffusion direction from seeding points, proceeding stepwise from voxel to voxel along with the voxel-wise calculated DT. In probabilistic tractography (Fig 1), the algorithm performs a probability distribution of the diffusion directions.[51, 54] It is notable that other imaging-based approaches used to identify the TGN traditionally rely on T2-weighted MR images, which provide localization of the cisternal portion of the TGN, where the contrast between nerve and cerebrospinal fluid (CSF) is high enough to allow differentiation.[55]

The use of DTI-MRI can add information about WM microstructure and evaluation of the diffusional measures, together with visual reviews and other measures. This increases the possibilities to perform clinical diagnostics with higher accuracy.[56]
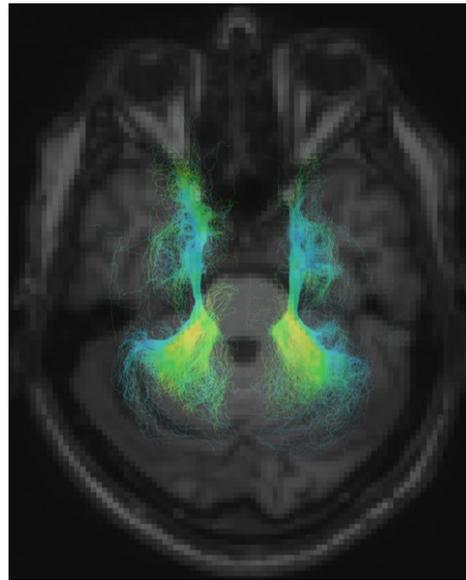

Fig 1. Probabilistic tractography of the TGN bilaterally in a healthy control. Image acquisition was performed at Philips Achieva 3.0T MR scanner (Philips Achieva, Best, the Netherlands) using a DTI sequence, measured in 48 directions with b values 0 and 1000.

DTI in TN

A reconstruction of four WM pathways within the TGN region can be enabled with the utilization of DTI: the REZ, the spinal trigeminal tract (TGT), as well as the ipsilateral and contralateral ventral trigeminothalamic tracts, which can be illustrated in figure 2[57]. In a previous MR study performed at 3.0T, variances of fractional anisotropy (FA) in affected regions of TGN in PwTN were observed to be significantly higher in comparison to the corresponding values of TGN in healthy controls (HC). In addition, a significant positive correlation between FA and contralateral values of TGN was obtained.[58] In an investigation of TGN in PwTN without MS performed at a 7T MR scanner, affected parts of TGN had significantly lower FA values (0.31 ± 0.09) than unaffected parts of TGN (0.43 ± 0.10).[15]
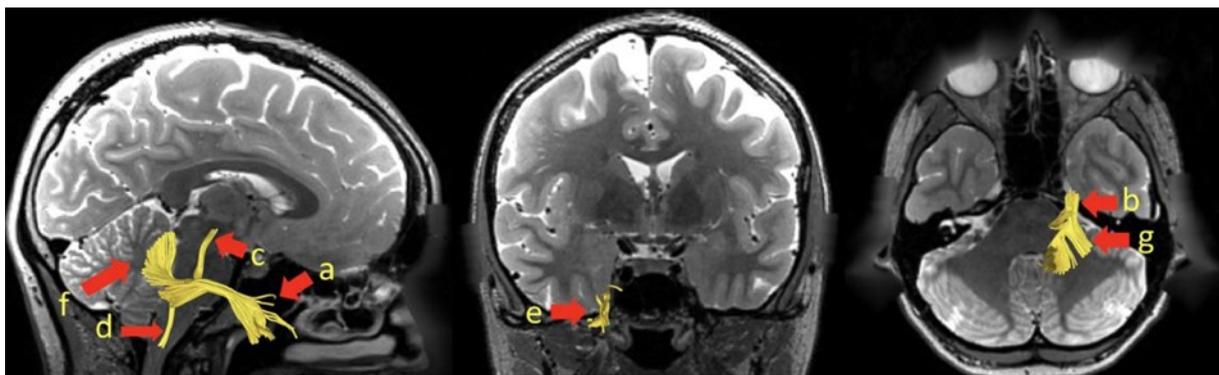

Fig 2. The above pictures were borrowed from Guoqiang et al. This illustrates the normal anatomical assessment criteria of the TGN for expert evaluation. Sagittal, coronal, and axial views of an example TGN (yellow) are overlaid on T2-weighted MRI. Criteria include: (a) presence (or absence) of branch-like structure, (b) quality of cisternal portion and T2 overlap, (c) presence (or absence) of the mesencephalic trigeminal tract, (d) presence (or absence) of spinal cord tract of the TGN, (e) avoiding entering (or entering) into the temporal lobe, (f) avoiding (or entering) inferior cerebellar peduncle, and (g) avoiding (or entering) middle cerebellar peduncle.[26]

Volume

Investigation of volume may help to identify some common parameters to emphasize the associated affection in PwTN and PwMS-TN. In this regard, Leal et al determined that the mean volume (V) of the TGN ipsilateral to pain (64.75 ± 14.12 mm3; Confidence Interval (CI), 53.22 to 76.28) and the volume was significantly smaller than contralateral (p < 0.05).[29] Decreased TGN volume has been detected in primary TN in comparison to controls. Additionally, volume reduction has been detected for grey matter (GM) in several regions associated with pain in primary TGN subjects, including the insula, secondary somatosensory cortex, hippocampus, dorsal anterior cingulate cortex, precuneus, and several areas of the temporal lobe.[15, 59] Across all patients, thalamus volume was reduced ipsilateral compared to contralateral to the side of pain. Between responders and non-responders, the latter exhibited larger contralateral TGN volume, and larger ipsilateral and contralateral hippocampus volume.[60]

MRI at higher field strengths allow for improved visualization of the brain and increases the possibility of detecting microstructural changes of the WM in PwTN.[15, 61] Significant differences in fractional anisotropy of TN can be measured in the rostral and caudal pathway of TGN in the first part[15] and then posteromedially into the pons before turning and descending caudally into the spinal TGT.[61] Compared with control subjects, TN subjects exhibit significant ipsilateral reductions in grey matter volume (GMV).[62] Further, higher field of imaging was performed at MRI 7.0T, and the volumes were significantly smaller in the affected TGN (33.83 ± 23.12 mm3) than in the unaffected (47.76 ± 32.48 mm3; p = 0.008).[63]

The trigeminovagal complex in humans was investigated post-mortem by performing imaging at 11.7 T MRI, and the results gave a very new insight to the spinal cord nerves and nuclei, thus contributing to the investigation of pain and other CNS diseases.[64] Also, the existence of a bifurcation of the TGT into a ventral trigeminothalamic tract and dorsal trigeminothalamic tract could be described when performing 11.7 T MRI scans of the human brainstem.[65]

Microstructural Changes

The orientation of WM pathways can be reconstructed successfully to characterize the microstructure changes of the TGN along with its divisions at the skull base by using deterministic and probabilistic tractography algorithms at 3.0 and 7.0 T MRI. The microvascular changes are confined with or without vascular conflict and TN respectively.[15, 50] Tractography was applied to the thalamic-somatosensory tract (TST) ipsilateral to the site of neurovascular compression and the FA values were reduced in patients with TN in comparison to side-matched healthy controls, (mean 0.43) versus (mean 0.47, p = 0.01) (ref). The finding of these WM pathways' reduced FA may provide credible evidence of microstructural alteration at the level of the thalamus and S1, thus deepening the understanding of TN neurobiology. [66]

Correspondingly, images with 7.0T MRI study revealed ipsilateral reduced microstructural integrity of TST which, when found at the site of neurovascular compression in patients with TN and the altered structure, is followed to the cortex. [67] After removal of the compression on classic TGN, the loss of FA remained, probably indicating altered microstructural arrangement. However, after decompression surgery was performed, some part of damages improved in conduction sensitivity and reduction of edema in the REZ.[68]

Further, when using multiple DTI metrics, microstructural abnormalities of CN V in patients with TN due to NVC was found. Compared with the unaffected side, the affected side exhibited significantly decreased FA, increased ADC and RD, and no significant change of AD. [69]

Atrophic changes

Examinations of PwTN with ultra-high field MRI at 7.0 T have shown volumes and structure looseness [15, 61], an affection expressed with nerve atrophy.[68] Scans at 7.0 T MRI allow identifications of the grade of atrophy and diffusion abnormalities of the trigeminal nerves in PwTN, f.e. FA, as well as quality assurance (QA) values of the cisternal segment, which were found to be significantly lower in affected TGN than in unaffected ones.[63] In addition, a sign of atrophy detected at an earlier timepoint during the study, even with low field MRI technique, without other relevant findings, correlated to the side of symptoms.[70] The mean diameter of the TGN on the symptomatic side was found to be significantly smaller than the mean diameter on the asymptomatic side in 30 of 31 patients (2.11 mm ± 0.40 [standard deviation] and 2.62 mm ± 0.56, P < .001, 95% CI: −0.35 to −0.67 mm). Similarly, the cross-sectional area on the symptomatic side was found to be significantly smaller than the area on the asymptomatic side in 27 of 31 patients (4.50 mm2 ± 1.75 and 6.28 mm2 ± 2.19, P < .001, 95% CI: −2.41 to −1.16 mm2).

The results indicate that TGN atrophy can be depicted noninvasively in patients with TN.[71] Right-sided TN patients are described with significant volumetric reductions in ipsilateral cornu ammo- 1 (CA1), CA4, dentate gyrus, molecular layer, and hippocampus-amygdala transition area, resulting in decreased whole ipsilateral hippocampal volume, in comparison to healthy controls.[72] In addition, another study revealed GMV atrophy in the multiple temporal subregions in primary TN patients, including the bilateral temporal pole, right inferior temporal gyrus, and left middle temporal gyrus.[73]

Those studies with a focus on TN, which have confirmed significant association with TN and central WM lesions (when compared with healthy subjects) are depicted in Table 1.

Table 1: Trigeminal nerve in non-MS conditions

Author/	Study design	Number of subjects (exposed-unexposed)	MRI/Gd acquired	Significant
Leal et al, 2011[29]	RCT	10	3.0/+	TN affected 23% and 25% smaller than painless TGN
Marinković et al, 2009 [12]	Autopsy	12-2		Demyelination of central myelin and glia
Moayedi et al, 2012 [21]	Case-Control	17-17		white matter lesions
DeSouza et al, 2014 [10]	Case-Control	18-18	1.5	white matter lesions & CC
Tian et al, 2016[17]	Case-Control	20-22		white matter lesions
Liu et al, 2018[9]	Case-Control	29-35	3.0 T/	white matter lesions
Moon et al, 2018[15]	Case-Series	14	7.0 T MR	Ansiotrophy at affected TGN was significantly higher than for compared unaffected TGN
Lee et al, 2019[63]	Case-Series	16	7.0T/+	Tract volume reduction
Chai et al, 2019[112]	Case-Control	34	3.0	Revisable changes in the trigeminal nerve
Docampo et al, 2015 [84]	Case-Control	30-50	3.0	30% veins making contact with TGN

CC: Corpus Callosum, **RCT:** Randomized Clinical Trial

MRI in MS

The number of visual lesions in or related to different segments of TGN has changed during the increased access to advanced analysis methods as well as the use of higher field strengths at MRI. Previous studies using MRI at lower field strengths and with large slice thickness suggested that the prevalence of this lesion was between 3% and 7%,[7, 74] and with bilateral enhancement found in 55-75% MS subjects with TGN lesion.[75] However, the use of 3D MRI at a higher resolution (3.0 T) with thinner slice thickness (1 mm), showed that the prevalence increased up to 23%.[75] Studies have shown that TGN lesions can be already present in MS patient's initial attack[75] and that demyelination may occur in younger ages at MS onset.[76] These radiological findings however, were not associated with TN, despite a subgroup (37.5%) with painless paraesthesia of the V3 innervation territory of TGN. When studies explore the neuro-anatomical and diagnostic benefits of MRI at 7.0 T, information that could not be obtained from MRI at lower field strengths may now compensate with better accuracies.[77] Clinically, TN is shown headed to the diagnosis of MS in 15% and more likely to be female[78] while a recent revision to MS criteria complete palsy of the right III nerve have been included in MS attack.[79]

In addition to the intrapontine tract, the TGN, the pontine ERZ, the cisternal segment, and the trigeminal nuclei are characteristic sites of MS lesions. TGN lesions can be shown with a frequency of 12%-38% at 3.0 T MRI.[75] Thickened TGN have been elucidated in MS patients and should be recognized as a rare feature of this disease and, in cases, more frequent in right-sided CNS lesions[80] and even more aggressive right-sided TGN lesion.[81] This was in correspondence to MRI tractography findings at 3.0 T that was more frequent left hemisphere lesions in the clinically isolated course of MS.[82] In agreement with this finding, another study with MRI at 3.0T showed a demyelinating plaque in the pontine and trigeminal REZ on the affected side. The frequency of the neurovascular compression and its association with the pontine demyelinating plaque were higher on the affected side than on the unaffected side (54% vs 0%; p = 0.0001).[4] The MS-TN plaque distribution was ruled out with the coalescence of plaques bilaterally along the intrapontine TGN pathway at the proximal pontine segment (PPS). Brainstem plaques at the PPS appear to affect the laterality of MS-TN pain. The distribution of plaques indicates that 11 patients (61%) had bilateral plaques and 4 patients (22%) had unilateral plaques near the PPS fibers; however, the remaining 3 did not reveal any radiologic mark of plaques along the intrapontine TGN.[83]

Vol*ume changes in PwMS-TN*

In PwTN without MS, the diagnosis is shown as in MS with predominantly female manifestation. This gender difference can be followed by the volume of the normal cisternal TGN measured on 3.0 T MRI in vivo, which shows 77.4–78 mm3 in male and 66.1–66.4 mm3 in female,[30, 84] implying a difference between 11.3 mm3 to 11.6 mm3.

In non-MS TN, the posterior fossa volume in males was found to be larger than the posterior fossa volume in females [85]. In the TN group, females were found to be younger than males and less likely to have neurovascular compression. [86] In a case-report of females with the clinical sign as MS investigated with MRI, revisable contrast was found with enhancement in REZ.[87] When compared to the general population, patients with MS have a 20-fold higher risk of TN, regardless of the type of MS.[47] The risk of getting diagnosed with MS-TN is most frequent in females.[78] MS-TN behaves like classical and idiopathic TN and is known to be more common in females than in males, affecting the right side more frequently than the left side[47] and showing significantly increase d serum levels of IL-1β, IL-6, IL-8 and TNF-α in comparison to healthy volunteers.[88]

In agreement with these findings regarding the TN, TN-MS studies of T2-hyperintense lesions within the pontine trigeminal pathway found evidence that FA was significantly lower and ADC higher, within the affected TGN and the non-affected TGN in patients with MS, when compared to patients with idiopathic TN or healthy controls (p < 0.001) .[89] Patients with a higher field of MRI examination could show significantly lowered FA and QA values in affected-side cisternal segments of TGN than in unaffected-side cisternal segments of TGN. However, this affection in other studies is mostly seen as volume reduction.[63]

Most importantly, 89% of patients in TN-group were found to have abnormal trigeminal reflexes, when the neurophysiological test was used and showed that stimulation were strongly delayed on the affected side.[90] Also, tongue somatosensory-evoked potentials (tSSEPs) performed on MS patients has indicated 90% prolonged; even the MRI showed brainstem lesions in only 50% of 10 cases.[91] Furthermore, the significantly altered tSSEP score was a predictor for the presence of midbrain lesions in CIS patients.[92] Further trigeminal SSEPs, as well as facial nerve conduction studies performed in MS patients with RRMS course, showed abnormalities in all included patients in this study.[93]

Microstructural changes:

The findings of FA and ADC values enables assessment of microstructural changes within the TGN in patients with demyelination.

The existence of microstructural changes have been obtained from DTI within the TGN as well as in-NVC-related PwTN. [94] The MS in comparison to a group with TN only, TNG group showed lower FA in the ipsilateral peri-lesional segments, thus suggesting differential microstructural changes along with the CN V in MS patients.[95] In another study, 17 of 18 patients were non- responders to surgical treatment. The lesions were uniformly located along the affected trigeminal pontine pathway, where the site of maximum overlap across patients was in the area of the trigeminal nucleus (TGNC). These microstructural abnormalities in WM were characterized by lower FA values and higher mean diffusivities when compared to the unaffected side. The microstructure of the brainstem TGN within a lesion highlighted the difference between solitary pontine lesion (SPL) of TN and MS plaques. In conclusion, although SPL-TN patients have identical clinical features to TN, their single pontine lesion does not even fulfill criteria of MS, and are refractory to surgical management.[83]

MS-TN with atrophy

Previous studies showed that neurovascular compression, i.e. with morphological changes of the TGN such as atrophy, dislocation, indentation, or flattening, was strongly associated with the symptomatic side in PwMS-TN.[4, 47] With or without neurovascular conflict, constructive interference demonstrates TGN atrophy[4]; with lesions in the typical, periventricular, and brain stem distribution, including the pontine trigeminal pathway on the affected side.[89]

The comparison of PwMS-TN and the none-MS subject has been outlined as in Table 2.

Table 2: Trigeminal nerve in MS

Study	Study design	Number of subjects (MS-Non-MS)	MRI/Gd acquired	Significant
Meaney et al, 1995[113]	Case-Series	7	1.5 T/+	One case demyelination of TGN
van der Meijs et al, 2002 [114]	Case-Series	851	0.5-1.5 T/	Enhancement of TGN (3%) clinically silent, the incidence of trigeminal nerve demyelination
Silva et al, 2005[74]	Case-Series	275	1.0 T/+	TRE
Cruccu et al, 2008[90]	Case-Control	80-50	Vaxalbased	TGN lesion
Shor et al, 2016[79]	Case report	1	1.5 T/+	showed enhancement and thickening of the cisternal right III nerve
Zhu et al, 2012[115]	Case-report	1	1.5T/-	demyelination in the right pons at the TRE and Dawsons Fingers
Mills et al, 2010[75]	Case-Control	47-2	3.0/-	TGN lesion
Sugiyama et al, 2015	Case-Control	128-46	1.5 T/-	TRE lesion
Fallata, et al, 2017[78]	survey	8590	NA	15% TN before MS diagnosis
Danyluk et al, 2019[60]	Case-Series	34	1.5T	TGN volumetry
Truini et al, 2016[4]	Case-Series	28	3.0 T	demyelinating plaque in the pontine trigeminal root entry zone

TRE=Trigeminal Root Entry, **Gd**=Gadulinium, **TGN**=Trigeminal Nerve

Discussion

There is a clinical need to improve the visualization of CNs within the nasal cavity, particularly in the context of pathology, and to enable detailed analysis of the affected nerves' microstructure when studying MS pathophysiology. The prospect of obtaining 7.0 T MR imaging in the routine clinical setting should improve the ability to reliably visualize the larger CNs such as the TGN. In this regard, knowledge of the exact neuroanatomy of the TGTs will contribute to a deeper understanding of its role in MS pathology. As shown in this review, the management of TN has revealed a new pathway in order to better understand the role of TGN in MS; this nerve has the capability to transmit or mediate the peripheral injuries to CNS and improve the knowledge of pathophysiology in MS with or without MRI pathognomonic lesions.

In this study, we have found a sign of common demographical factors such as predominantly female, younger ages, and side specific WM lesions when reviewing diffusion MRI data of TN and MS-TN. We have also found anatomical differences, e.g., smaller diameter, volume, and more atrophy, when looking through findings on female associated diffusion MRI. Further, the similarity in microstructural changes in both TN and MS-TN has also been identified, when studying DTI parameters.

However, the pathogenesis of many chronic TGN pain conditions, such as TN, migraine, and temporo-mandibular disorders, is still not clear. When fibers display a wide innervation in CNS, one of the proposed biochemical mechanisms involves calcitonin gene-related peptide (CGRP), which is considered as the most important neuropeptide in the trigeminal system (TS).[96] The higher concentration of intraganglionic of CGRP can modulate the neuronal transmission of pain signals. Expression of CGRP in the cerebral cortex and TG one week post-injury is altered when compared to uninjured control animals.[97] Further, there is evidence that peripheral inflammatory reaction in the area of trigeminal nociceptors cascades increases expression of CGRP and brain-derived neurotrophic factor gene in TG.[98] In various animal models of TGN-associated disorders, the concentration of CGRP was observed to increase in TG. In most of these models, pathological changes in the TGN are accompanied by inflammation within peripheral neuronal endings of TGN, and as shown in other studies, with a significant sex depended difference in CGRP expression in female mice.[99, 100] This finding could probably be suggesting some association with the anatomically smaller volume of TGN in females. [101]

The studies with proton density-weighted image show a classic MS "ovoid lesion" with the long axis perpendicular to the lateral ventricle[102] MS is known to commonly surround the subependymal veins that drain perpendicular to the ventricles, named "Dawson's fingers" signs at MRI and pathological preparation.[103-105] According to studies, the proton density can detect the cortical changes in only 21 years females with suddenly aggressive dementia as the first symptom in MS cases.[105] The sagittal proton density-weighted image turned out with multiple WM lesions with Dawson's finger signs.[105] This method, in conjunction with diffusion MRI and tractography, would help to better understand GM connectivity in the brain.

An animal study could by studying cortical spreading depolarization (CSD) carry out pathological phenomenon with proven relevance to functional outcome from traumatic brain injuries (TBI). The effects of TGN stimulation in targeting CSDs to completely terminate CSDs in the injured rat's brain exhibited significantly decreased numbers of the CSD from 60% to 49%. The finding supports the intimate connection between TGN and cerebral and meningeal blood vessels, referred to as the trigemino-cerebrovascular system (TCVS).[106] The TCVS are also capable of activating the so called 'diving reflex', where the primary role is to conserve oxygen for the sensitive brain and heart tissue.[106] This reflex has different outcomes in females than in males.[32] This connection can probably explain the increased stroke risk in MS and regardless to course of MS,[107] and beyond the effect of surveillance bias.

The ophthalmic branch of the trigeminal nerve seems to be commonly affected in MS.[108] This division of TGN has the highest amount of myelinated and unmyelinated nerve branches on the cornea, sinus cavities, as well as internal and external nasal environment. All these surfaces can make a specifically route via epithelium transportation, as nano-peptide research has shown a direct connection between the nerve ending and CNS.[109, 110] Further, TGN exhibited higher concentrations of tested nanocarrier than any other sampled CNS tissues.[111] This finding can contribute to developing a better understanding of the possibility of peripheral pathogens into CNS.

Limitations

Despite the clear advantages of using comorbidity like TN and strengthening pathophysiological understanding in MS, there are potential limitations of each procedure. There is a possibility of selection bias in each of those studies that sought to use patient with pain caused by TN. Another limitation that could have been hidden in those included studies was the pharmacological treatment effect and hormonal impact which have not been exclusively described in any of the included studies. Therefore, factors relating to the female sex, such as differences in sex hormone levels, may be risk factors in TN and MS and should be included in future studies, even when ruling out the confounder effect of MS therapies.

Conclusion

The authors reiterate the importance of evaluating TGN impact in MS through the inclusion of DT-MRI and tractography and an emphasis on the fact that the knowledge in classical TN and MS-TN may be pivotal in pointing out TGN as the suggested main port of MS pathology. A series of studies can be carried out to further discuss the TGNs in different genetic and environmental risk associations.

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Citation: Homayoun Roshanisefat. "Tractography innovative knowledge of multiple sclerosis and trigeminal neuralgia". SVOA Neurology 1:1(2020) 24-38.