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Diffusion tensor imaging of the trigeminal nerve in patients with trigeminal neuralgia due to multiple sclerosis

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Abstract
Introduction Neurovascular compression (NVC) is the most common cause of trigeminal neuralgia (TN), leading to microstructural changes in the affected nerve detectable using diffusion tensor imaging (DTI). But TN may also emerge as a symptom of multiple sclerosis (MS). The aim of this study was to evaluate if patients with MS-related TN feature the same DTI characteristics as patients with TN caused by NVC.
Methods Twelve patients with MS-related TN, 12 age-matched patients with NVC-related TN, and 12 healthy controls were included. Using 3T-DTI, mean fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values were calculated for each affected and contralateral trigeminal nerve in patients with MS and NVC-related TN as well as healthy controls. Furthermore, presence of NVC was evaluated for patients with TN.
Results There was no significant difference concerning FA or ADC when comparing the affected and the non-affected sides in patients with MS. FA was significantly lower and ADC higher in patients with MS on the TN affected as well as on the non-affected side compared to the non-affected side of patients with idiopathic TN or healthy controls. Likewise, FA was significantly lower on the affected side compared to the non-affected side in patients with idiopathic TN or healthy controls. NVC was evident in 41.7/0 % on the affected/contralateral side in MS patients and 100/8 % in the patients with NVC-related TN.
Conclusion In patients with MS-related TN, DTI reveals microstructural changes within the trigeminal nerve not only on the affected side but also on the clinically non-affected side.

Keywords Trigeminal neuralgia · Multiple sclerosis · MS · Neurovascular compression · DTI

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Introduction

Trigeminal neuralgia (TN) is characterized by recurrent episodes of sudden, severe, electric shock-like stabbing pain localized in the sensory supply areas of the trigeminal nerve. The most frequent cause of TN is a mechanical irritation of the nerve caused by neurovascular compression (NVC) at the vulnerable site of the nerve, the so-called root entry or exit zone, where the myelination changes from central to peripheral [1]. However, as TN can also emerge as a symptom in a variety of other diseases of the central nervous system (CNS), such causes of TN have to be excluded in patients presenting with typical symptoms. Multiple sclerosis (MS) represents one of the most important of these secondary causes of TN. Neuralgic pain syndromes in general are a well-known symptom in MS patients [2–4], and TN occurs in approximately 4 % of patients, regardless of the type of disease [3, 5].

The pathophysiological mechanism of TN, especially in patients with MS, is not entirely resolved yet. In patients with MS-related TN, demyelination of the proximal and secondary

trigeminal pathways has been demonstrated [1]. MS-associated, T2-hyperintense brainstem lesions as cause of demyelination in the pontine trigeminal pathways only moderately correlate with the clinical presentation of MS-related TN [1, 6–9].

Magnetic resonance imaging (MRI) with high spatial resolution is the imaging modality of choice in patients with TN to detect a neurovascular contact and to detect or exclude second causes of TN. Diffusion tensor imaging (DTI) has recently been shown to be a useful tool for examining the trigeminal system in great detail [10–12]. Clinical studies using DTI have identified tissue abnormalities, including decreased fractional anisotropy (FA), in the affected trigeminal nerve in TN patients with NVC stating measurable microstructural alterations [10–12]. DTI studies investigating the trigeminal nerve in patients with MS and TN are lacking to date.

Thus, the aims of our study were to evaluate DTI characteristics of the trigeminal nerves in patients with MS and TN and to compare these findings to those in patients with TN due to purely mechanical NVC and to those in a healthy control group.

Methods

Study populations

We declare that this study was approved by our institutional review board and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We declare that all patients and controls gave informed consent prior to inclusion in this study.

Since February 2010, we prospectively identify all patients that present with TN in our institution. Diagnosis is verified by an experienced neurosurgeon (with 10 years of experience in functional neurosurgery), and MRI with a standardized imaging protocol is routinely acquired. From this group, all patients with MS and TN, 12 patients in total (3 male, and 9 female, mean age: 50.9 years; age range: 42–65 years), were identified and included in this study. Type of MS, duration of disease, and duration of TN were noted (Table 1).

Out of the remaining patient group, 12 age-matched patients with an unequivocal neurovascular contact on MRI, which was verified during surgery (6 male, 6 female mean age 50.1 years; age range 41–66 years), were identified (Table 2).

Furthermore, we included a healthy control group of again 12 approximately age-matched individuals (5 male, 7 female mean age 47.9 years; age range 33–67 years), without any history of facial pain.

Image acquisition

MRI was performed on a 3.0T MR scanner (Signa HDxt 3.0T; GE Healthcare, Milwaukee, WI, USA) with an eight-channel head coil. For TN patients, identical imaging protocol as in our previous investigation on NVC-related TN [10] was used, including axial FLAIR, T2-weighted, 3D T1-weighted imaging before and after intravenous contrast, as well as a 3D fast imaging employing steady state (FIESTA), a contrast-enhanced MRA (ceMRA), and a spin-echo single-shot echo-planar diffusion tensor imaging sequence. Imaging parameters are summarized in Table 3. For healthy controls, the same imaging protocol was adopted, granted that a non-contrast time-of-flight MRA was acquired instead of a ceMRA, and contrast-enhanced T1-weighted imaging was left out to spare intravenous contrast in healthy volunteers.

For DTI in patients and controls, diffusion gradients were applied in 15 spatial directions, as described by Pierpaoli and Basser [13]. The maximal b value was 1000 sec/mm^2, and 32 axial sections were acquired. Therefore, ten measurements were obtained and averaged. The 3D FIESTA images and DTI were angulated exactly parallel to the cisternal segment of the trigeminal nerve.

Data analysis

Image analysis of the MR data sets of both patient populations (MS-related TN and NVC-related TN) and control group was performed by two experienced neuroradiologists (with ten and 6 years of experience, respectively) in consensus, which were not aware of the clinical data or the affected side.

Axial T2-weighted sequences were evaluated regarding pontine T2-hyperintense lesions. Lesions in the lateral and/or dorsal pons along the pontine trigeminal pathway [6] were categorized as MS lesions, whereas T2-hyperintensities in the central pons were not assessed in this investigation as T2-hyperintesities in the central pons are at times hardly distinguishable from microangiopathic pontine lesions.

FIESTA images and ceMRA were used to assess the right and left trigeminal nerve separately for the presence of a neurovascular conflict. If applicable, the respective vessel was identified on the ceMRA.

DTI data sets were analyzed by using FuncTool software, release AW4.3_07 (GE Healthcare, Buc, France) at a commercially available workstation (AW 4.2; GE Healthcare, Buc, France). First, diffusion tensor trace images were generated by averaging all 15 diffusion-weighted images. Then, a motion correction algorithm was applied to correct for head motion and image distortion due to eddy current artifacts. From these images, ADC and FA values in each voxel and color-coded maps (orientation encoding) were automatically calculated and displayed.

Table 1 Clinical and imaging characteristics of patients with MS-related TN

Pat.	Sex	Age	TN-affected		Durat. of TN (month)	Type of MS	Durat. of MS (month)	Pontine lesion		NVC		
			Side	Branch (V)				Aff. side	Nonaff. side	Aff. side	Vessel	Nonaff. side
1	f	62	*r*>l	2,3	132	p. p.	276	+	+	−	−	−
2	f	52	l	2,3	60	i. d.	i. d.	+	+	+	BA	−
3	f	49	l	2	17	i. d.	i. d.	+	−	−	−	−
4	f	46	r	1,2,3	37	r. r.	24	−	−	+	SCA	−
5	m	51	l	2,3	84	i. d.	i. d.	+	−	+	SCA	−
6	f	41	l	1,2	120	i. d.	i. d.	+	−	−	−	−
7	f	56	r	1,2,3	51	p.p.	180	+	+	−	−	−
8	f	65	r	1,2	48	p.p.	168	+	+	−	−	−
9	m	42	l	1,2,3,	10	i. d.	i. d.	+	−	−	−	−
10	f	43	r	3	36	r. r.	108	+	−	+	SCA	−
11	m	51	r	3	8	r. r.	312	+	+	−	−	−
12	m	53	r	2	6	r. r.	372	+	−	+	SCA	−

TN trigeminal neuralgia, *MS* multiple sclerosis, *Durat*. duration, *Aff*. affected, *Nonaff*. non-affected, *f* female, *m* male, *r* right, *l* left, *p. p*. primary progressive, *r. r*. relapsing remitting, *i. d*. initial diagnosis, + evident, − nonevident, *BA* basilar artery, *SCA* superior cerebellar artery

Data fusion and region of interest analysis

Calculated FA and ADC maps were matched with the FIESTA images and visualized both alone and as fused images. For quantitative analysis, a standard region of interest of approximately 6 mm^2 (range 4–6 mm^2) was positioned in the root entry or exit zone of each trigeminal nerve on the fused images to measure local ADC and FA values (Figs. 1 and 2). Region of interest was manually placed within the trigeminal nerve extending to the very edge of the nerve, if needed with magnification tools to precisely define the borders of the nerve. If NVC was evident, region of interest was always placed proximal to the artery. Mean values and standard deviation of these DTI indices were calculated.

Statistical analysis

Statistical analysis was performed with PASW Statistics 18, Release Version 18.0.2 (SPSS, Chicago, IL, USA, www.spss.com). Data were initially assessed for normality by visual inspection of their histograms. On the basis of these results, means and standard deviation as well as median values

Table 2 Clinical and imaging characteristics of patients with NVC-related TN

Pat.	Sex	age	TN-affected		Durat. of TN (month)	NVC			
			Side	Branch (V)		Aff. side	Vessel	Nonaff. side	Vessel
1	f	60	l	1,2,3	24	+	SCA	−	−
2	f	48	r	2,3	60	+	SCA	−	−
3	f	47	l	1,2,3	60	+	SCA	+	SCA
4	f	47	l	2,3	60	+	SCA	−	−
5	m	51	l	2,3	120	+	SCA	−	−
6	m	41	r	2,3	36	+	SCA	−	−
7	f	53	r	2,3	8	+	SCA	−	−
8	f	66	r	1,2	60	+	SCA	−	−
9	m	41	r	2,3	24	+	SCA	−	−
10	m	43	r	2,3	132	+	SCA	−	−
11	m	50	l	2,3	84	+	AICA	−	−
12	m	54	r	1,2	96	+	SCA	−	−

Durat. duration, *Aff*. affected, *Nonaff*. non-affected, *f* female, *m* male, *r* right, *l* left, + evident, − not evident, *SCA* superior cerebellar artery, *AICA* anterior inferior cerebellar artery

Table 3 Imaging parameter

	FIESTA	ceMRA[a]	FLAIR	T2 PROPELLER	ceFSPGR	DTI
TR (ms)	4.5	6.6	85	51	3.2	10.5
TE (ms)	1.8	2.3	1.2	7.5	7.9	6.5
FOV (mm)	160	180	220	200	220	220
Matrix (mm×mm)	256×256	450×450	512×512	480×480	256×256	128×128
Slice thickness (mm)	0.6	0.8	5.0	3.0	1.0	2.0
NEX (*n*)	2.0	1.0	1.0	1.5	1.0	4.0
Resolution (mm)	0.6×0.6×0.6	0.4×0.4×0.6	0.69×0.69×5	0.4×0.4×0.3	1.0×1.0×1.0	1.7×1.7×2.0
Duration (min:s)	7:15	8:15	3:49	1:59	3:42	11:55

[a] ceMRA was performed first and started 30 s after application of 0.1 mmol/kg (0.2 ml/kg) gadobenate dimeglumine (MultiHance®, Bracco)

FIESTA fast imaging employing steady state acquisition, *ce* contrast enhanced, *MRA* magnetic resonance angiography, *FLAIR* fluid-attenuated inversion recovery, *PROPELLER* periodically rotated overlapping parallel lines with enhanced reconstruction, *FSPGR* fast spoiled gradient-recalled pulse, *DTI* diffusion tensor imaging, *TR* repetition time, *TE* echo time, *FOV* field of view, *NEX* number of excitations

and 25 and 75 % percentiles were calculated for the DTI data as FA and ADC. Wilcoxon rank sum tests were used to compare the affected and the non-affected sides within patients. Mann–Whitney *U* tests were used to compare the FA and ADC values of the affected versus the non-affected sides in patients with MS and in patients with NVC-related TN. Furthermore, the FA and ADC values of the affected and the non-affected sides of patients with MS- as well as NVC-related TN were compared to both sides of the healthy control group respectively. The p value <0.05 was considered to indicate a significant difference. For the variables age and duration of the disease mean and standard deviation were calculated for both patient populations.

Results

Clinical findings

Of the 12 patients in the MS group, five patients (41.7 %) presented with a relapsing remitting type of MS and two patients (16.7 %) with primary progressive MS. In patients with definite MS, mean time between diagnosis of MS and MRI within this investigation was 206 months (range 24–372 months). In another five patients, TN was the only clinical symptom at the time of MRI for this investigation. In three of these patients MRI, cerebrospinal fluid examination as well as visual and somatosensory evoked potentials were pathologic,

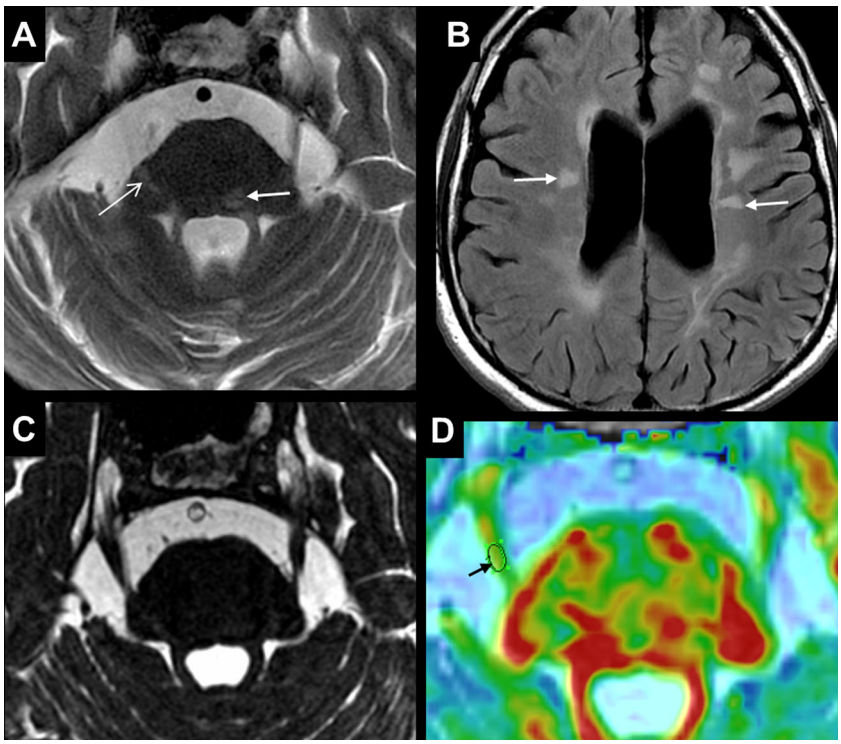

Fig. 1 Axial T2w (**a**), FLAIR (**b**), FIESTA (**c**), and FIESTA fused with FA images (**d**) of a 52-year-old male with relapsing remitting MS and TN concerning the V3 segment on the right side. T2-hyperintense lesions were demonstrated in the typical, periventricular, and brain stem distribution (*closed white arrows*), including the pontine trigeminal pathway on the affected side (*open white arrow*). Neurovascular contact was not evident on the affected side (**c**). FIESTA fused with FA images (**d**) show the region of interest drawn on the right trigeminal nerve (*black arrow*)

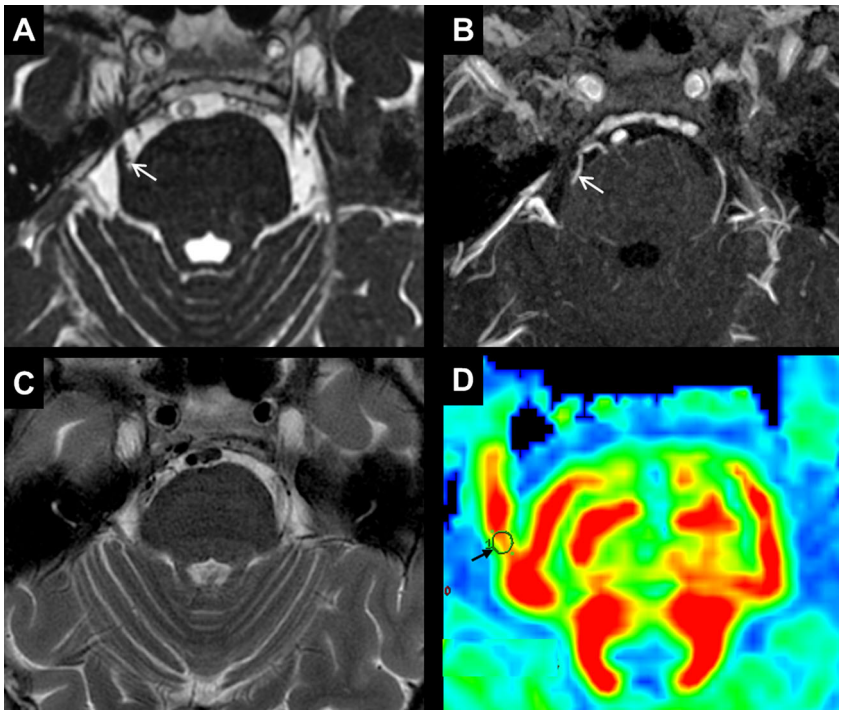

Fig. 2 Axial FIESTA (**a**), ceMRA MIPs (**b**), T2w (**c**), and FIESTA fused with FA images (**d**) of a 66 year old female with idiopathic TN concerning the V1 and V2 segments on the right side. FIESTA and ceMRA (A+B) show neurovascular conflict within the root entry zone of the right trigeminal nerve and a loop of the SCA on the affected side (*white arrows*). Inflammatory brainstem lesions are not evident on T2w (**c**). FIESTA fused with FA images (**d**) show region of interest drawn on the right trigeminal nerve (*black arrow*)

suggestive for MS, at the time of the MRI examination. In the remaining two patients, diagnosis of MS was confirmed by the 12 attending physicians, respectively, 36 months after the MRI examination evaluated in this investigation. TN affected the right side in six cases and the left side in five patients with MS. One MS patient suffered from bilateral TN, with the right side being more severely clinically affected than the left side.

In patients with TN due to NVC, the right side was affected in seven patients and the left side in six cases. Mean duration of TN was 51 months (range 6–132 months) in patients with MS and 64 months (range 8–132 months) in patients with NVC-related TN. Patient characteristics and clinical presentation of both patient groups (MS-related and NVC-related TN) are summarized in Tables 1 and 2.

Imaging findings

In MS patients, T2-hyperintense lesions within the pontine trigeminal pathway were evident in 11 patients (91.7 %) on the affected side and in 4 cases (33.3 %) on the contralateral side (Fig. 1).

FIESTA and ceMRA revealed a neurovascular contact at the root entry/exit zone of the trigeminal nerve in five patients (41.7 %) on the affected side and in 0 cases (0 %) of the non-affected side in patients with MS. In patients with NVC-related TN, a neurovascular contact at the root entry zone of the trigeminal nerve was found in all 12 patients on the affected side and in 1 case (8 %) also on the non-affected side (Fig. 2). The superior cerebellar artery (SCA) was the offending vessel in most cases in both patient groups (for details, see Tables 1 and 2).

Diffusion tensor imaging

Mean (standard deviation) for FA/ADC values was 0.31 (0.59)/2.21 (0.27) for the affected side and 0.32 (0.06) for the non-affected side in patients with MS-related TN; 0.32 (0.09)/2.2 (0.32) for the affected side and 0.38 (0.11) for the non-affected side in patients with NVC-related TN; and 0.42 (0.05)/1.85 (0.32) for the right and the left side taken together in healthy controls. Medians and interquartile ranges are summarized in Fig. 3.

FA was significantly lower on the affected ($p=0.01$) and the non-affected ($p=0.03$) sides of MS patients as well as on the affected side of patients with NVC-related TN ($p=0.002$) when comparing to the non-affected side of patients with NVC-related TN. Furthermore, FA was significantly lower on the affected ($p<0.001$) and the non-affected ($p<0.001$) sides of MS patients as well as on the affected ($p<0.001$) and non-affected ($p=0.02$) sides of patients with NVC-related TN when comparing to healthy controls.

ADC was significantly higher on the affected ($p=0.02$) and the non-affected ($p=0.02$) sides of MS patients as well as on the affected side of patients with NVC-related TN ($p=0.007$) when comparing to the non-affected side of patients with NVC-related TN. Furthermore, ADC was significantly higher on the affected ($p=0.002$) and the non-affected ($p=0.001$) sides of MS patients as well as on the affected ($p=0.005$) side of patients with NVC-related TN when comparing to healthy

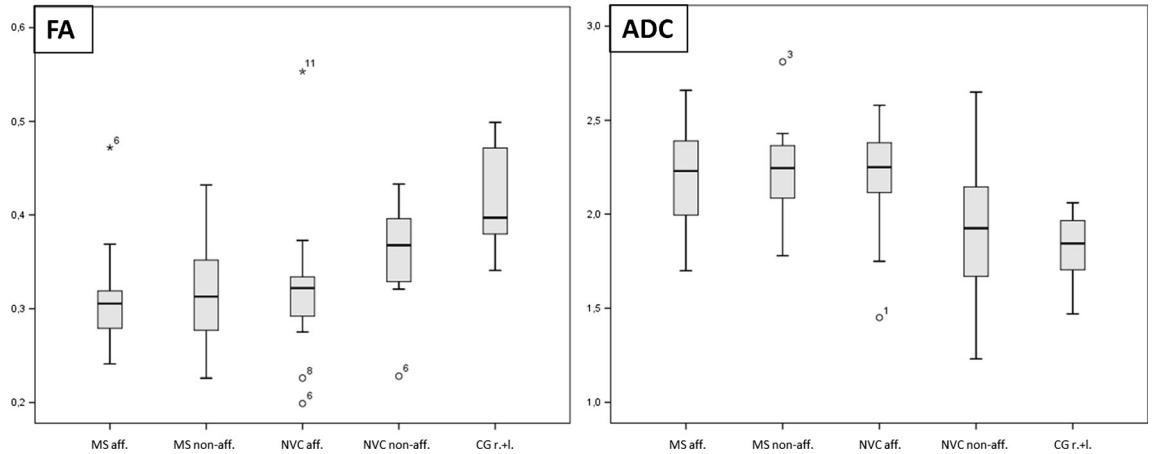

Fig. 3 Box-and-whisker plots demonstrating medians and interquartile ranges (25–75 %) of FA (*left image*) and ADC (*right image*) values for the affected (*aff.*) and non-affected (*nonaff.*) trigeminal nerve of patients with multiple sclerosis (*MS*)- and neurovascular compression (*NVC*)-related trigeminal neuralgia, as well as the right plus left trigeminal nerve of a healthy control group (*CG*). Outliers are marked by * and ° respectively

controls. There was no significant difference when comparing the ADC between the non-affected side of patients with NVC-related TN and healthy controls (p=0.54).

Furthermore, there were no statistically significant differences for both FA/ADC values when comparing the affected to the non-affected side of MS patients (p=0.75/0.81) nor when comparing the affected side of patients with NVC-related TN to the affected (p=0.32/p=0.93) or non-affected side of MS patients (p=0.8/0.98), respectively.

Discussion

According to previous studies, we found significant DTI alterations as a sign of anisotropic microstructural changes on the affected side of patients with TN due to NVC compared to the non-affected side as well as compared to healthy controls. In patients with MS-related TN, analog differences between the affected and the non-affected sides were not evident in this investigation. However, compared to the non-affected side of patients with NVC-related TN as well as compared to a healthy control group, DTI measurements of the trigeminal nerves in patients with MS-related TN were pathologic on both sides.

The most frequent cause of TN is a mechanical irritation of the nerve caused by NVC at the root entry zone. Overtime, the nerve–vessel contact results in damage in the form of a focal myelin loss and somehow inadequate remyelination, which was thought to disrupt normal nociceptive transmission [14–16].

Besides TN due to NVC, there are other known causes for symptomatic TN, e.g., multiple sclerosis [6, 9, 17]. MS is a chronic inflammatory disease of the central nervous system characterized by demyelination, axonal dysfunction, and neuronal loss [18]. Neuropathic pain syndromes, TN the most frequent among others, are a common comorbidity in these patients [2–4]. Although still controversial, numerous retrospective studies have noted that MS-related TN tends to present at younger ages compared with NVC-related TN (48 versus 57 years, respectively) [19, 20], is more often bilateral (11 versus 32 %), may have trigeminal sensory deficits in 13 to 37 %, and has more frequently (30 %) atypical constant pain between single TN attacks [19]. The average time between MS onset and TN was reported to be between 5 and 12 years [5, 19]. Although the diagnosis of MS usually precedes the development of TN symptoms, TN can be the first clinical manifestation of MS [19]. In our series, TN was the first manifestation of MS in five patients (42 %). This percentage is very high due to the bias of patient selection based on clinical symptoms of TN.

The pathophysiology of MS-related TN is not entirely understood to date. A neurovascular contact as a primary and unique cause of MS-related TN is considered unlikely [6]. Published data on neurovascular contact in patients with MS-related TN are rare to date. Meaney et al. [8] found a neurovascular contact in five of seven patients (71.4 %) with TN and MS. In our investigation, five of 12 patients (42 %) demonstrated a neurovascular contact regarding the TN-affected nerve in MS patients. To support that MS-related TN is not solely due to neurovascular contact, previous studies have shown that trigeminal reflexes are significantly more often abnormal in patients with MS-related TN than in patients with pure NVC-related TN [21]. The most commonly accepted theory regarding TN and MS is that TN arises as the result of an inflammatory process causing demyelination along the proximal trigeminal nerve or secondary trigeminal pathways in the pons [1, 7]. This theory is substantiated by the finding of demyelination in histopathologic specimens of the central portion of the trigeminal nerve at surgery [22] and in

the pons at autopsy [23] in patients with MS-related TN. However, these T2-hyperintense brainstem lesions on MRI are a frequent but not consistent finding in patients with MS and TN. In the literature data range from 23 [9] to 100 % [7], we found MS-related brainstem lesions in 92 % of our study cohort. Besides, there is a suspicion that inflammation can be present all over the CNS, even in the absence of visible T2-weighted MRI lesions [24]. Therefore, it has been hypothesized that a dual mechanism involving inflammation and NVC could account for the clinical presentation in some patients [6]. Both mechanisms would act on the same primary axons and can lead to demyelination [1, 6, 15].

In patients with NVC-related TN, high spatial resolution MRI is performed preoperatively to confirm a neurovascular conflict and to rule out other possible causes of TN [25]. But neurovascular contact alone does not define TN, as contact is likewise a frequent finding in healthy subjects [26]. The aim is to demonstrate microstructural damages of the trigeminal nerve, such as axonal loss and demyelination as an underlying pathogenesis of TN [10, 15], especially using DTI. DTI has already proven to be a valuable tool in assessing the axonal architecture of white matter tracts in vivo by quantifying the amount of nonrandom water diffusion within nerve tissues [27]. FA and ADC values represent the two diffusion tensor imaging indices that are most widely used to investigate white matter changes because these measurements reliably indicate the presence or absence of abnormalities in white matter tracts, independent of their cause [28]. The degeneration of white matter tracts results in a reduction of FA due to the loss of the directionality of diffusion and an increase of ADC due to diffusivity being averaged in all spatial directions as a result of the loss of myelin and axonal membranes [28].

Several studies using DTI have identified microstructural abnormalities, including decreased FA, in the affected root entry zone of the trigeminal nerve in patients with TN and NVC [10–12]. In accordance to previous results, FA of the affected nerve was decreased compared to the contralateral side in patients with NVC-related TN in this investigation. To emphasize these findings, significant differences were also evident regarding the ADC with higher ADC in the TN-affected nerve compared to the non-affected nerve. In previous DTI studies, a comparison of DTI indices was made between the affected nerve and the unaffected contralateral side in patients with unilateral NVC-related TN [10]. However, previous studies on patients with TN have shown that anatomical (volumetric) changes can be detected not only on the affected, but also on the non-affected side [29]. For this reason, we further included a healthy control group without any history of facial pain. Comparing DTI indices of the affected side of patients with NVC-related TN to healthy controls, FA and ADC were significantly pathologic in the patient group, supporting previous data [10–12]. But also regarding the non-affected side of patients with NVC-related TN, FA was significantly decreased in patients compared to that in healthy controls in this investigation, whereas ADC values did not differ significantly. These findings are in line with previous studies, indicating that FA might be more sensitive and detect more subtle anisotropic nerve changes compared to ADC [10, 30].

To the best of our knowledge, this is the first study evaluating DTI changes of the trigeminal nerves in patients with symptomatic, MS-related TN. In our population of patients with MS-related TN, comparison of the affected and non-affected sides yielded no significant differences regarding FA, nor ADC, indicating another underlying pathomechanism as in patients with NVC-related TN. When comparing to the affected side of patients with NVC-related TN, no significant difference was found for the affected as well as the non-affected side of MS patients. Compared to the non-affected side of patients with NVC-related TN and also compared to healthy controls, significant microstructural changes of the trigeminal nerve were identified in patients with MS.

Moreover, the interest of this investigation was to evaluate possible differences of anisotropic changes caused either by compression or inflammation. Our results further support the assumption that there is an etiologic difference between idiopathic and symptomatic (i.e., MS-related) TN [1, 6] although patients usually present with the same symptoms and demyelination apparently seems to play the key role in the genesis of TN in general. In a small series, Love et al. (2001) found a somewhat different pattern of histopathologic changes in patients with MS-related TN compared to patients with NVC-related TN, in which vascular compression causes the loss of tissue structure in the root of the trigeminal nerve [1]. Furthermore, our results show that microstructural changes are detectable not only in the affected trigeminal nerve but also in the clinically non-affected nerve in patients with symptomatic, MS-related TN. Generally, DTI has proven a very sensitive technique for the detection of microarchitectural white matter disorganization in patients with MS [31, 32]. MS lesions typically demonstrate decreased FA compared with contralateral normal-appearing white matter [24]. Because of the high sensitivity of DTI, decreased FA values can also be detected in white matter of patients with MS that appears to be normal on conventional MRI when comparing to control subjects without MS. These findings ought to represent microarchitectural changes that are not resolved on conventional MR sequences including demyelination and axonal disruption [32].

Overall, DTI has shown to be a valuable tool for the identification of microstructural changes of the trigeminal nerve in TN patients independent of the causing mechanism. An altered anisotropy, measured by DTI in a patient with clinical TN, needs further workup, as in looking for a neurovascular contact or signs of demyelination. Further evaluation or even classification of these microstructural changes is not feasible at present using this technique. Continuing

studies including a larger series and histopathologic correlation are needed to shed more light on the different underlying mechanisms of demyelination.

As the limitations of this study, the small patient population must be considered as the most relevant constraint. Further studies with high spatial resolution MRI and DTI are needed to confirm our data in a larger patient cohort. Furthermore, lack of histopathologic correlation is another limiting factor. It would be favorable to correlate DTI parameters with histologic specimen or at least surgical findings, but this is difficult as patients with MS-related TN rarely undergo "open", microsurgical procedures at the trigeminal nerve.

Conclusion

In patients with MS-related TN, diffusion tensor imaging reveals microstructural changes within the trigeminal nerve not only on the affected side but also on the clinically non-affected side, indicating the fact that MS is a general demyelinating disease. Our data exhibit further evidence that the pathomechanism of symptomatic, inflammation-related TN in MS patients must be different from the mechanism underlying NVC-related TN.

Ethical standards and patient consent We declare that this study was approved by our Institutional Review Board and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We declare that all patients gave informed consent prior to inclusion in this study.

Conflict of interest We declare that we have no conflict of interest.

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