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Abnormal trigeminal nerve microstructure and brain white matter in idiopathic trigeminal neuralgia

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ABSTRACT

Idiopathic trigeminal neuralgia (TN) is classically associated with neurovascular compression (NVC) of the trigeminal nerve at the root entry zone (REZ), but NVC-induced structural alterations are not always apparent on conventional imaging. Previous studies report lower fractional anisotropy (FA) in the affected trigeminal nerves of TN patients using diffusion tensor imaging (DTI). However, it is not known if TN patients have trigeminal nerve abnormalities of mean, radial, or axial diffusivity (MD, RD, AD – metrics linked to neuroinflammation and edema) or brain white matter (WM) abnormalities. DTI scans in 18 right-sided TN patients and 18 healthy controls were retrospectively analyzed to extract FA, RD, AD, and MD from the trigeminal nerve REZ, and Tract-Based Spatial Statistics (TBSS) was used to assess brain WM. In patients, the affected trigeminal nerve had lower FA, and higher RD, AD, and MD was found bilaterally compared to controls. Group TBSS ($P < 0.05$, corrected) showed patients had lower FA and increased RD, MD, and AD in brain WM connecting areas involved in the sensory and cognitive-affective dimensions of pain, attention, and motor functions, including the corpus callosum, cingulum, posterior corona radiata, and superior longitudinal fasciculus. These data indicate that TN patients have abnormal tissue microstructure in their affected trigeminal nerves, and as a possible consequence, WM microstructural alterations in the brain. These findings suggest that trigeminal nerve structural abnormalities occur in TN, even if not apparent on gross imaging. Furthermore, MD and RD findings suggest that neuroinflammation and edema may contribute to TN pathophysiology.

1. Introduction

Idiopathic trigeminal neuralgia (TN) is a severe neuropathic pain disorder affecting the trigeminal nerve. It is characterized by intense, lancinating attacks of facial pain, typically triggered by normally nonpainful stimuli or movements. Unlike many other neuropathic pains, TN patients usually do not exhibit major sensory loss, and are pain-free between pain attacks [40,41]. As the disorder progresses, pain attacks may become more frequent and the pain more sustained [34].

Previous research on TN has mainly focused on gross trigeminal nerve abnormalities, but little is known about the nature of such presumed nerve damage. The most prevalent theory is that TN is associated with neurovascular compression (NVC) of the trigeminal nerve at the root entry zone (REZ) [28,40]. The REZ is a transition zone between central and peripheral nervous system myelin and where the trigeminal nerve is believed to be the most vulnerable to vascular compression [55]. Over time, the nerve–vessel contact results in damage or focal myelin loss [18,24,35,37], which can disrupt normal nociceptive transmission. Although gross NVC is not always apparent with standard imaging, magnetic resonance imaging (MRI)-based diffusion tensor imaging (DTI) has been shown to be a useful tool for examining the trigeminal system in great detail [25,53]. Clinical studies using DTI have identified microstructural abnormalities, including decreased fractional anisotropy (FA), in the affected REZ of TN patients with NVC [23,33,36]. Although FA is often used as a quantitative biomarker of white matter (WM) "integrity," other DTI metrics provide insight into factors underlying WM microstructure and pathology.

Previous studies have shown WM abnormalities in the brain following peripheral nerve injury and in chronic pain [16,41]. Importantly, many of these patients also had other significant sen-

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sory abnormalities, including numbness. It is not understood how TN, without major sensory loss, impacts brain WM. Therefore, we examined WM abnormalities in TN to provide insight into the mechanisms involved in neuropathic pain, without the confounding of other sensory abnormalities. Our study aim was to examine both trigeminal nerve and brain WM using multiple DTI-derived metrics to test the hypothesis that TN is associated with both nerve and brain WM abnormalities.

2. Materials and methods

2.1. Participants

Under the University Health Network Research Ethics Board approval, retrospective MR analyses were carried out in 18 patients with right-sided TN, seen at the Toronto Western Hospital, and 18 healthy control participants. All healthy control participants provided written informed consent (note that our Research Ethics Board does not require this for retrospective analyses of patient data as were analyzed here). For each patient, demographic and clinical details were obtained via retrospective chart reviews. Inclusion criteria were: unilateral (right-sided) pain in the distribution of one or more peripheral branches of the trigeminal nerve; intense, sharp, superficial, or stabbing paroxysmal pain precipitated from trigger areas or by trigger factors; stereotyped attacks for each patient; no clinically evident neurological or sensory deficit or not attributed to another disorder [22]; and no previous surgical procedures for TN.

2.2. Image acquisition

Using a 3T GE MRI system with an 8-channel phased-array head coil (GE Healthcare, WI, USA), 60-direction diffusion-weighted images were acquired with a spin echo echo planar sequence ($0.94 \times 0.94 \times 3$ mm voxels; TE = 86.6 ms; TR = 12,000 ms; 1 B_0; b = 1000 s/mm^2; matrix = 128×128; 1 excitation; ASSET. T1-weighted 3D FSPGR axial images were also obtained ($0.9 \times 0.9 \times 1$ mm^3 voxels, 256×256 matrix, FOV = 24 cm (controls), 22 cm (patients), TE = 5 ms, TR = 12 ms, TI = 300 ms).

2.3. DTI-derived metrics

DTI techniques use diffusion-weighted imaging scans, which are sensitized to the diffusion of water molecules [29], to characterize WM microstructure. This property is useful because in healthy WM, diffusion is more restricted across an axon than along it due to structural barriers such as myelin, axonal membranes, microtubules, and neurofilaments [7]. A mathematical model, typically a tensor/ellipsoid, characterized by its 3 orthogonal eigenvectors and their associated eigenvalues (λ_1, λ_2, λ_3), can be applied to each brain voxel to provide information about the 3-dimensional character of the water molecules' diffusion [29]. The most commonly used DTI-derived metric is FA [4], which ranges from 0 (completely isotropic), meaning water molecules can diffuse equally in all directions (eg, cerebrospinal fluid), to 1 (completely anisotropic), meaning the diffusion of water is hindered (eg, along axons in WM). Other metrics, highlighted in

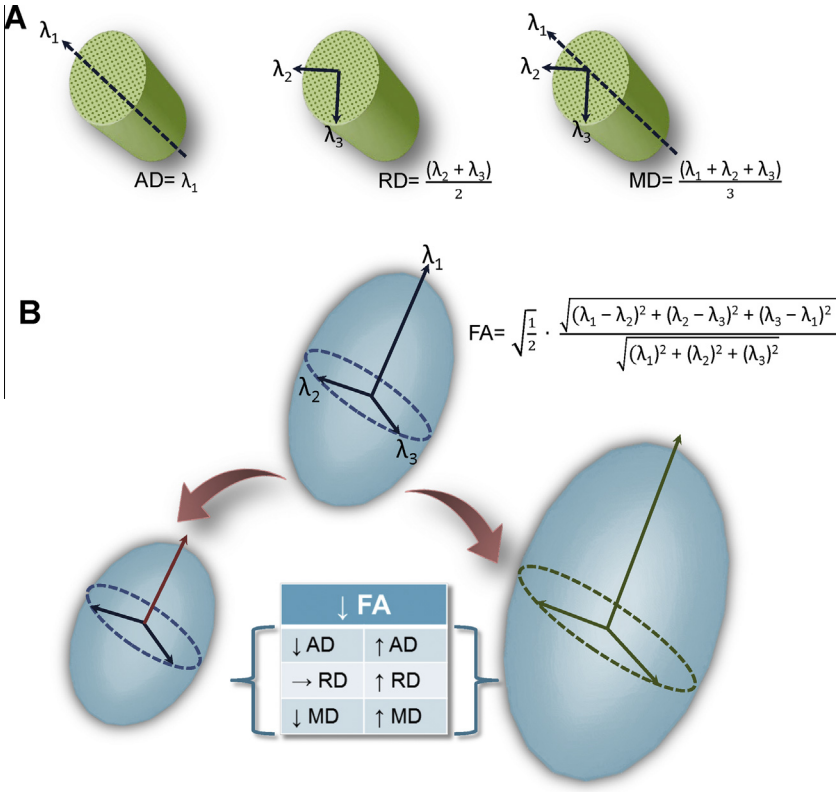

Fig. 1. Schematic representation of diffusion tensor imaging (DTI)-derived metrics and tensor changes that can occur with lower FA. Four DTI-derived metrics derived from the eigenvalues of the tensor model were examined. Schematic representations of how these metrics were calculated and their formulas are shown in panel (A), with AD being diffusion along the length of the axon (λ_1) (left), RD being diffusion perpendicular to the length of the axon (average of λ_2 and λ_3) (center), and MD being the magnitude of diffusion regardless of direction (average of λ_1, λ_2, and λ_3) (right). Panel (B) shows the tensor model and the formula for FA (top). Also illustrated are 2 scenarios where FA has decreased, but the shape of the tensors are different due to differences in the other 3 DTI-derived metrics (shown in chart). The first scenario is when FA, AD, and MD decrease, but RD remains stable (bottom left); and the second is when FA decreases, but AD, RD, and MD increase (bottom right). For additional potential scenarios of changes to the tensor, see reference [1]. Abbreviations: FA, fractional anisotropy; RD, radial diffusivity; MD, mean diffusivity; AD, axial diffusivity.