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SHORT COMMUNICATION

Quantitative magnetic resonance evaluation of the trigeminal nerve in familial dysautonomia

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Abstract

Purpose Familial dysautonomia (FD) is a rare autosomal recessive disease that affects the development of sensory and autonomic neurons, including those in the cranial nerves. We aimed to determine whether conventional brain magnetic resonance imaging (MRI) could detect morphologic changes in the trigeminal nerves of these patients.

Methods Cross-sectional analysis of brain MRI of patients with genetically confirmed FD and age- and sex-matched controls. High-resolution 3D gradient-echo T1-weighted sequences were used to obtain measurements of the cisternal segment of the trigeminal nerves. Measurements were obtained using a two-reader consensus.

Results Twenty pairs of trigeminal nerves were assessed in ten patients with FD and ten matched controls. The median (interquartile range) cross-sectional area of the trigeminal nerves in patients with FD was 3.5 (2.1) mm^2, compared to 5.9 (2.0) mm^2 in controls ($P < 0.001$). No association between trigeminal nerve area and age was found in patients or controls.

Conclusions Using conventional MRI, the caliber of the trigeminal nerves was significantly reduced bilaterally in patients with FD compared to controls, a finding that appears to be highly characteristic of this disorder. The lack of correlation between age and trigeminal nerve size supports arrested neuronal development rather than progressive atrophy.

Keywords Hereditary sensory autonomic neuropathy · Neuroimaging · Autonomic dysfunction · Riley–Day syndrome · Neuroimaging · Trigeminal nerve

Introduction

Familial dysautonomia (FD), also known as Riley–Day syndrome or hereditary sensory and autonomic neuropathy type III, is a rare autosomal recessive disease caused by a founder mutation of the *IKBKAP* gene on chromosome 9q31, which encodes for the elongator-1 protein (ELP-1, also known as IκB kinase-associated protein or IKAP) [17]. The deficiency in ELP-1 during embryogenesis affects the development of autonomic and sensory neurons with cell bodies in the dorsal root and cranial nerve ganglia [6, 9, 22].

Hallmark features of the disease are reduced pain and temperature perception, absent corneal reflexes [7, 12], reduced basal lacrimation [16], and neurogenic dysphagia [2, 5, 18, 19]. These are all functions that rely on sensory feedback from trigeminal nerve afferents, and activities such as chewing [15], swallowing [13, 19], and speech [8] remain abnormal throughout life in these patients. Moreover, reduced facial sensation can result in oral and facial trauma and self-mutilation [14].

Postmortem neuropathological studies in patients with FD reveal marked reduction in the size and number of sensory neurons arising from the Gasserian ganglion as well as absence of myelin sheaths along the mesencephalic tract [3, 20]. There is, however, limited literature on in vivo neuroimaging evaluation of patients with FD. Focusing on a major afferent pathway involved in FD, we used MRI to assess whether the caliber of trigeminal nerves was reduced compared to age- and sex-matched controls. We hypothesized

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that the caliber of the trigeminal nerve would be reduced in these patients compared to controls. Small trigeminal nerves could potentially constitute a novel neuroimaging marker of this disorder.

Methods

Design and participant selection

This was a single-center cross-sectional study including patients with genetically confirmed FD who underwent a neurological clinical assessment and brain MR imaging at our institution over an 8-year period (2003–2011). A comprehensive review of their clinical charts was performed, with attention to clinical features of trigeminal dysfunction, including decreased corneal sensation, decreased lacrimation, and neurogenic dysphagia. Age- and sex-matched control patients were identified by searching consecutively performed brain MRI exams of subjects undergoing routine evaluation for the indication of "headache" who were found to have normal MRI examination. All MRI images were anonymized and randomized for review. The New York University Institutional Review Board approved this study.

Neuroimaging

The cross-sectional area of the cisternal portion of the trigeminal nerves was measured bilaterally in all subjects using standard T1-weighted magnetization-prepared rapid-acquisition gradient-echo (MPRAGE) images acquired in the axial plane [Siemens MAGNETOM Sonata 1.5-Tesla, inversion time (TI) 1100, repetition time (TR) 2100, echo time (TE) 3.67, flip angle (FA) 7, field of view (FoV) 220×220, matrix size 256×218]. Source data centered at the level of the cisternal trigeminal nerve were used to prescribe 1-mm double-oblique reconstructions oriented perpendicular to the long axis of the nerve (Fig. 1). Region-of-interest (ROI) measurement was done on the cisternal slice demonstrating the largest nerve cross-sectional area and placed by two-reviewer consensus, blinded to subject group.

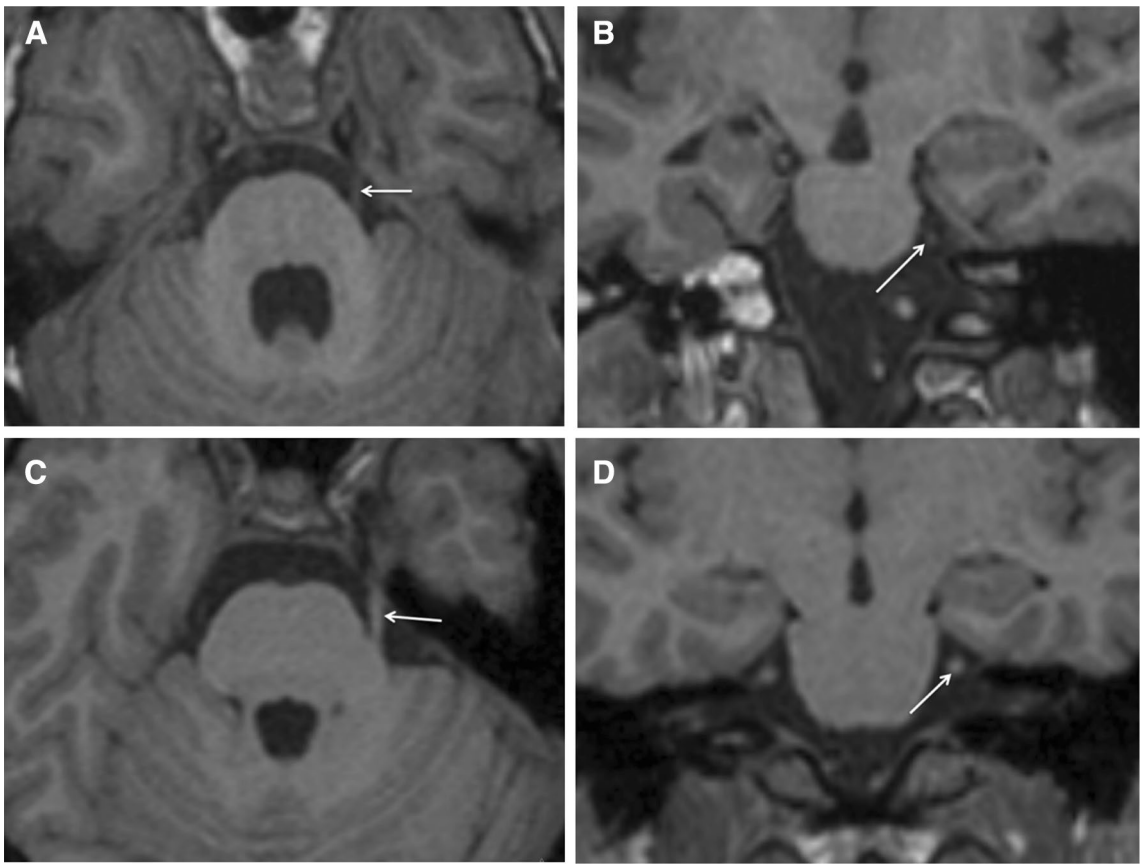

Fig. 1 Trigeminal nerve neuroimaging in familial dysautonomia and controls. Double-oblique orthogonal reconstructions from 3D MPRAGE images through the cisternal left trigeminal nerve in a 27-year old patient with familial dysautonomia (**a**, **b**) and an age- and sex-matched control (**c**, **d**). Note the considerably smaller caliber of the left trigeminal nerve (arrows) in the patient with familial dysautonomia

Statistics

A nonparametric Wilcoxon signed-rank test was used to compare the subject groups in terms of nerve caliber on the left and right sides and the within-subject average over sides. Partial Spearman rank correlation characterized the association between nerve caliber and age while controlling for study group. In an attempt to study the association between trigeminal nerve caliber and clinical severity, we quantified the degree of neurotrophic keratopathy (the corneal afferent information is conveyed by the trigeminal nerve) using the Mackie classification ranging from 0 (no corneal damage) to 3 (severe corneal ulcers) [11].

Receiver operating characteristic (ROC) curves for the mean, minimum, and maximum measurements of left and right trigeminal nerves were calculated to identify cutoff values for trigeminal caliber in order to distinguish between patients with FD and controls. All statistical tests were conducted at the two-sided 5% significance level using MedCalc version 17.9.7 software (MedCalc Software, Ostend, Belgium).

Results

Twenty pairs of nerves from ten patients with FD (seven women, aged 8–61 years) and ten age- and sex-matched controls were studied. The body mass index at the time of neuroimaging acquisition was similar in FD and controls (23.3 ± 2.8 in FD vs. 25.1 ± 4.5 kg/m^2 in controls; $P = 0.28$). All patients with FD had clinical evidence of impaired afferent trigeminal function including diminished corneal reflexes with keratopathy, reduced basal lacrimation, and neurogenic dysphagia. The cross-sectional area of the trigeminal nerve in patients with FD was 3.5 ± 2.1 mm^2 vs. 5.9 ± 2.0 mm^2 in the control group (median ± interquartile range, $P = 0.002$) (Fig. 1) Significant differences were also seen between patients and controls when analyzing the left and right nerve subgroups separately: on the left, 3.0 ± 2.1 mm^2 compared to 6.0 ± 1.6 mm^2 (FD vs. controls, $P = 0.0059$), and on the right, 4.2 ± 1.4 mm^2 vs. 5.8 ± 3.4 mm^2 (FD vs. controls, $P = 0.0039$), respectively (Fig. 2). There was no association between trigeminal caliber and age while controlling for study cohort ($\rho = 0.09$, $P = 0.72$).

The neurotrophic keratitis stage of patients with FD ranged from 1 to 3. Higher scores were significantly associated with smaller areas of the right side ($\rho = -0.72$, $P = 0.017$) and the average ($\rho = -0.72$, $P = 0.018$) trigeminal nerve. Higher scores tended to be associated with smaller areas of the left trigeminal nerve, although this did not reach statistical significance ($\rho = -0.48$, $P = 0.15$).

ROC curves for the mean, minimum, and maximum trigeminal cross-sectional areas had an area under the curve (AUC) value of 0.99 [95% confidence interval (CI) 0.81–1.0], 0.97 (95% CI 0.78–1.0), and 0.97 (95% CI 0.78–1.0), respectively. A cross-sectional area ≤ 4.85 mm^2 had 100% sensitivity and 90% specificity, and area ≤ 4.42 mm^2 had 90% sensitivity and 100% specificity to distinguish between FD and controls.

Discussion

This study shows that the cross-sectional area of the cisternal trigeminal nerve as measured on routine MRI was significantly smaller bilaterally in patients with FD compared to age- and sex-matched normal controls. Bilateral reduction in trigeminal caliber appears to be a highly characteristic finding in FD, although validation in larger samples might be required. This is not surprising, as the disorder is characterized by impaired development of sensory (afferent) neurons, resulting in sensory and autonomic deficits. Our results provide objective in vivo evidence supporting

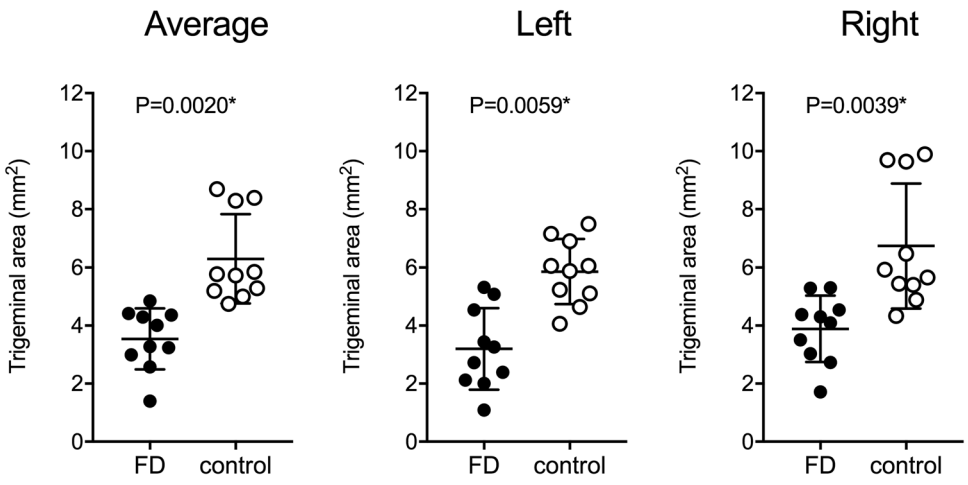

Fig. 2 Trigeminal nerve area in familial dysautonomia and controls. Patients with familial dysautonomia had significantly reduced area in both right and left trigeminal nerves, as well as the average of both sides. Asterisks denote statistical significance

neuropathological findings of a reduced number of sensory neurons in the trigeminal ganglia in a few patients with FD [3, 20, 21].

Trigeminal nerve atrophy follows trigeminal nerve injury, compression, or denervation, but the findings in these scenarios are typically unilateral. Here, we found reduced caliber on both sides, an imaging finding which may be highly characteristic of FD.

The lack of correlation between age and nerve size argues against progressive atrophy and instead supports the theory of arrested afferent neural development of the trigeminal nerve, in keeping with current thinking regarding the pathophysiology of the disorder. This suggests that trigeminal imaging might not be a suitable outcome measure for clinical trials of disease modification in FD. The association between higher degree of corneal damage and lower trigeminal area in the right and the average support the hypothesis that lack of trigeminal afferences contribute to a lack of corneal sensitivity in patients with FD. There was a similar trend with the left trigeminal area, although the lack of statistical significance might be due to the small sample size.

Limitations of the study include its retrospective nature and small sample size. However, FD is an extremely rare disease, with an incidence among Ashkenazi Jews estimated at 1 in 10,000 in North America [4] and 1 in 3700 in Israel [10]. Moreover, there is only one previous neuroimaging study in patients with FD, which enrolled seven patients [1]. Our cohort of ten well-characterized, genetically confirmed patients with FD with imaging data is a sizable group for this uncommon disorder and showed a strong statistically significant difference compared to controls. Further studies should quantify the diameter of other cranial nerves with predominantly motor function (e.g., cranial nerves III, IV, VI, or XII). Normal caliber of motor cranial nerves would support the notion of FD as a disorder predominantly affecting the development of sensory (afferent) nerves. Advanced cranial nerve evaluation requires specific MR sequences not typically used in standard protocols [23].

In conclusion, the trigeminal nerve is significantly smaller in patients with FD compared to age- and sex-matched controls. The findings are consistent with clinical neurological deficits as well as neuropathology studies showing a reduced number of trigeminal ganglion neurons in patients with FD [3, 7, 20, 21].

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Compliance with ethical standards

Conflict of interest Dr. Palma receives funding support from the Familial Dysautonomia Foundation and is Managing Editor of *Clinical Autonomic Research*. Dr. Norcliffe-Kaufmann receives funding support from the Familial Dysautonomia Foundation. Dr. Kaufmann receives funding support from the Familial Dysautonomia Foundation and is Editor-in-Chief of *Clinical Autonomic Research*.

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