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Relationship between the corpus callosum and neurocognitive disabilities in children with NF-1: diffusion tensor imaging features☆

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ABSTRACT

Purpose: Mild neurocognitive disabilities are commonly observed in children with neurofibromatosis type 1 (NF-1). Enlargement of the corpus callosum (CC) is one of the findings in NF-1, but the pathogenesis has not yet been clarified. In this study, we investigated whether diffusion tensor imaging (DTI) features of CC differed between children with NF-1 and healthy control subjects, and we tried to evaluate the association between the microstructural integrity of CC and neurocognitive disabilities, based on apparent diffusion coefficient (ADC) and fractional anisotropy (FA) values.
Materials and methods: The study population consisted of 37 children with NF-1 and 31 healthy controls. Midsagittal CC surface area measurements were obtained from volumetric sagittal T1-weighted turbo spin echo images. FA and ADC values were obtained from the genu and splenium of CC. The results were compared to that of controls. The correlations between neurocognitive test results and measurements of ADC, FA, and surface areas of midsagittal CC in NF-1 patients were investigated.
Results: Total CC area in children with NF-1 was significantly larger than healthy controls. ADC values obtained from the genu of CC were significantly higher in NF-1 children. A negative correlation was observed between the ADC values of the genu of the CC and the arithmetic and digit span scores and between the FA values of the genu and coding scores in children with NF-1.
Conclusion: The DTI changes in the genu of CC in children with NF-1 may indicate subtle structural damage, although conventional MRI is normal. ADC and FA changes in the genu may be due to loss of axonal integrity and vasogenic-like edema in the axons responsible for some intellectual functions. DTI may help clarify the underlying pathophysiology of CC changes in relation to neurocognitive function disorders in children with NF1.

1. Introduction

Neurofibromatosis type 1 (NF-1) is an autosomal dominant neurocutaneous syndrome that results from a mutation on chromosome 17. Its intracranial manifestations have been well demonstrated with MRI. These findings include macrocephaly, corpus callosum (CC) enlargement, optic pathway and parenchymal gliomas, and nontumorous deep gray and white matter changes [1–3]. The latter lesions, so-called unidentified bright objects, are nonexpansile and nonenhanced T2 hyperintense foci that commonly disappear before the age of 20 years. At least half of children with NF-1 present with these focal parenchymal lesions that frequently affect the putamen, globus pallidus, thalamus, cerebellum, and brainstem [4–6]. Abnormal or delayed myelination and spongiform and vacuolar changes due to intramyelinic edema are suggested in the pathogenesis of these lesions [4,7–9]. The pathogenesis of CC enlargement in NF-1 patients has not yet been clarified. CC enlargement is in excess of macrocephaly [3]. The relationship between neurocognitive dysfunction and CC area is controversial. To our knowledge, only a few studies have focused on this relationship. The most widely accepted opinion is that there is a negative correlation between CC area and intelligence quality (IQ) in children with NF-1 [3,10,11].

Diffusion tensor imaging (DTI) is a newly developed MR technique that is used to obtain fractional anisotropy (FA) maps of white matter tracts. DTI findings demonstrate the relationship between white matter structures and neural functions. Both apparent diffusion coefficient (ADC) and FA values can provide information about microstructural changes in white matter. FA decreases in situations such as axonal degeneration and demyelination. FA increase shows decreased

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axon caliber and increased axonal density [12]. ADC increases with increased tissue water in edema but decreases in the presence of cell proliferation [13].

In this study, we investigated whether DTI features of CC differed between children with NF-1 and healthy control subjects, and we tried to evaluate the association between the microstructural integrity of CC and neurocognitive disabilities, based on ADC and FA values.

2. Materials and methods

2.1. Patients

The ethics committee of our institution approved this prospective study. Written and oral consent were obtained from the patients' parents immediately before MRI. The study population consisted of 37 children with NF-1 and 31 healthy controls. The mean age±standard deviation was 10.12±3.82 years for the children with NF-1 and was 9.83±3.76 years for the control group. Additionally, 40.5% (15) of the NF-1 group and 41.9% (13) of the control group were boys, and 59.5% (22) of the NF-1 group and 58.1% (18) of the control group were girls. The control group consisted of children who were examined by a pediatric neurologist and psychologist for different reasons and found to be neurologically normal. These children had normal brain MRI findings. The children with NF-1 were examined by a neuropsychologist from the Pediatric Neurology Department for neurocognitive testing.

2.2. MRI technique

The children with NF-1 and the healthy group underwent routine MRI. The images were obtained utilizing a dedicated 8-channel head coil with a 1.5-T MR unit (Siemens Avanto, Erlangen, Germany). The MRI protocol included the following: axial T2-weighted [time of repetition (TR) TR/time of echo (TE): 4.280/91 ms; matrix: 384×211; number of signal averages (NSA): 1; slice thickness: 5 mm], axial T1-weighted (TR/TE: 500/87 ms; matrix: 256×125; NSA: 1; slice thickness: 5 mm), axial fluid-attenuated inversion recovery (FLAIR) (TR/TE/TI: 8.000/118/23.687 ms; matrix: 256×140; NSA: 1; slice thickness: 5 mm), coronal FLAIR (TR/TE/TI: 8.000/118/23.695 ms; matrix: 256×144; NSA: 1; slice thickness: 5 mm), and T2-weighted sagittal (TR/TE: 4.810/90; matrix: 320×247; NSA: 1; slice thickness: 5 mm) images, as well as postcontrast axial T1-weighted (TR/TR: 448/87; matrix: 256x134; NSA: 1; slice thickness: 5 mm), coronal T1-weighted (TR/TE: 730/87; matrix: 256x125; NSA: 1; slice thickness: 5 mm), and sagittal 3D T1-weighted (TR/TE: 476/86; matrix: 256×154; NSA: 1; slice thickness: 1 mm) images.

Midsagittal CC surface area measurements were obtained from sagittal T1-weighted turbo spin echo images using the public domain National Institutes of Health image program (available at http://rsb.info.nih.gov/nih-image/). The midsagittal image was defined as the image that clearly demonstrated the pituitary infundibulum, cerebral aqueduct, and CC in a single image (Fig. 1).

The DTI data were acquired in the axial plane. The protocol included spin-echo echo-planar imaging images, TR=6.000 ms, TE=89 ms, 30 gradient directions, b=1000 s/mm^2, a 5-mm slice thickness, a field of view of 230 mm, and a matrix of 128×128. FA and ADC maps were generated on a Leonardo console (software version 2.0; Siemens), and FA and ADC values were measured from the genu and splenium of the CC using regions of interest (ROIs) (Fig. 2). CC area measurements and ROI selections were performed by the same investigator (SA). All ROIs were drawn manually in circular shapes, and ROI size was kept constant.

2.3. Neurocognitive testing

All cognitive assessments were performed by the same neuropsychologist (MF) who remained blinded to the patients' MRI results. Intellectual ability was assessed using Wechsler Intelligence Scales for Children-Revised (WISC-R), which consists of two scales, the Verbal and Performance Scales, each with several subtests. The Verbal Scale measures language expression, comprehension, listening, and the ability to apply these skills to solve problems. Six verbal subtests of the WISC-R were used: Information, Similarities, Arithmetic, Comprehension, Vocabulary, and Digit Span. The Performance Scale assesses nonverbal problem solving, perceptual organization, speed, and visual–motor proficiency. It includes tasks such as puzzles, analysis of pictures, imitating designs with blocks, and copying. We used five performance subtests of the WISC-R: Picture Completion, Picture Arrangement, Block Design, Object Assembly, and Coding.

The Bender Visual–Motor Gestalt Test is a psychological assessment used to evaluate visual–motor functioning, visual perceptual skills, neurological and emotional disturbances, and functions of the nondominant parietal lobe. The Judgment of Line Orientation is an assessment of visual recognition and visual–spatial functioning in subjects aged 3 years and older. It measures the functions of the nondominant cerebral hemisphere, mainly the parietal lobe. The Stroop Color Word Interference Test measures the ability to shift a perceptual set with changing demands, to inhibit a habitual behavior pattern, and to behave unusually, which are mainly the functions of the frontal lobes.

Statistical analyses were performed using IBM SPSS Version 20.0. Following MRI analysis, the total CC area and ADC and FA values from the genu and splenium in the NF-1 and control groups were compared using Student's t test. Spearman's correlation test was used to test associations between CC area, ADC and FA values, and neurocognitive

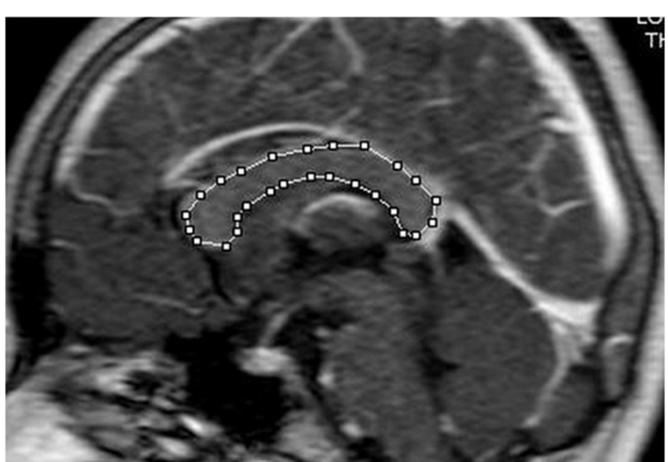

Fig. 1. CC area. Midsagittal T1-weighted image demonstrates the midsagittal surface area measurement of CC.