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The effectiveness of cerebellar lesions on neurocognitive functions in children with neurofibromatosis Type 1: Diffusion tensor imaging features

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Abstract

In children with Neurofibromatosis type 1 (NF1), hamartomatous lesions called FASI (focal areas of signal intensity) on brain MRI are common. The relationship between neurocognitive functions and the presence of cerebellar FASI in NF1 children is a controversial issue. Our aim in this study is to investigate whether there is a difference in fractional anisotropy (FA) and mean diffusivity (MD) values in children with NF1 with and without cerebellum FASI, and to analyze its effect on neurocognitive functions. Twenty-seven patients children were assessed using Diffusion Tensor Imaging (DTI) and MRI. According to MRI features, we classified children with NF1 as group 1 with FASI (n=14) in the cerebellum, group 2 without FASI (n=13). The WISC-R scale (a revised form of the Wechsler intelligence scale for children) was used to analyze cognitive functions. MD and FA values were measured from cerebellar FASI and white matter. The relationship between neurocognitive function test scores and FA and MD values was investigated. There was a significant difference between group 1 and group 2 in terms of MD and FA values of the cerebellum. Verbal and performance test scores were lower in group 1 and group 2. The MD values obtained from the cerebellum were positively correlated with the full-scale intelligence quotient (IQ), Verbal IQ, and Performance IQ. There was a significant difference between group 1 and group 2 in terms of information, vocabulary, digit span, picture arrangement. DTI changes in the cerebellum are associated with demyelination and loss of axonal integrity in the white matter pathways responsible for some neurocognitive functions. We think that the presence of cerebellar FASI in children with NF1 does not contribute to the severity of neurocognitive impairment.

Keywords: Neurofibromatosis type 1, cognitive functions, diffusion tensor imaging, fractional anisotropy, mean diffusivity

Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant inherited genetic disease that is seen 1 in 3000-3.500. Hamartomatous lesions observed as hyperintense in the brain parenchyma on T2-weighted images in NF1 patients are called FASI (focal areas of signal intensity) [1]. It is seen in 55-93% of patients with NF1. The most common locations are the globus pallidum, brainstem, thalamus, cerebellum, and subcortical white matter [1-3]. The physiopathology of how FASI occurs is not clearly understood. Histopathologically, heterotopia, gliosis, atypical glial infiltrates, microcalcification foci, dysplasias, intramyelinic edema, and areas of spongy or vacuolar changes in white matter have been reported in the internal structure of FASI [2, 3]. The relationship between neurocognitive functions and the presence of FASI in NF1 patients is a controversial issue [1-9]. It is thought that there may be an important relationship between specific locations of FASIs such as thalamus, and cerebellum, size, and number and their cognitive functions [1, 2, 5, 10-13]. It has been reported that IQ levels are lower in NF1 patients with FASI in the cerebellum [10]. The most common accompanying neurocognitive disorders in children with NF1 are related to academic difficulties (i.e. reading, writing, spelling or math performance) and school failure [4, 5, 11, 14, 15].

DTI can provide important information to better understand the changes in the cellular level of FASI monitored in NF1 and their relationship with neurocognitive functions [3, 6, 7]. The most important DTI parameters indicating microstructural alterations of FASI in cerebellar white matter are fractional anisotropy (FA) and mean diffusivity (MD). To the best of our knowledge, no DTI studies are investigating the relationship between FASI

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and neurocognitive functions in the cerebellum. We aim is to investigate whether there is a difference in terms of MD and FA values in children with NF1 with and without cerebellum FASI, and to analyze its effect on neurocognitive functions.

Material and Methods

This retrospective study was approved by Institutional Ethics Committee (2021; 03/52). Twenty-seven children with NF1 (11 boys, 16 girls) were included in the study. Those with systemic or cerebrovascular disease or a history of head trauma were excluded from the study.

Neurocognitive Tests

All neurocognitive tests were performed by the same neuropsychologist (M.F). The WISC-R scale (a revised form of the Wechsler intelligence scale for children) was used to analyze cognitive functions. Verbal and performance were evaluated with the WISC-R scale. General information, similarities, comprehension, vocabulary, digit span, and arithmetic tests were applied under the verbal section title. In the performance section, picture completion, picture arrangement, block design, object assembly, coding, and labyrinths were analyzed. After the WISC-R test was completed, the verbal intelligence coefficient, performance intelligence quotient, and the full intelligence quotient (IQ) coefficient were evaluated. The Bender Visual-Motor Gestalt Test (BG) is a psychological assessment used to evaluate visual–motor functioning, visual perceptual skills, neurological and emotional disturbances, and functions. Since neurocognitive tests take a long time in children with NF1, Bakar's study [13] was accepted as a control group to compare test scores.

MRI Protocol

Patients with NF1 and healthy controls were examined using a 1.5T MRI system (Siemens, Avanto, Erlangen, Germany) with a maximum gradient strength of 43 mT/m and an 18-channel head coil. Before performing DTI, the conventional MRI protocol included: axial T2-weighted (TR/TE: 4.280/91 ms, matrix: 384x211) and T1-weighted (TR/TE: 500/87 ms), axial fluid-attenuated inversion-recovery (FLAIR) (TR/TE/TI: 8.000/118/23.687 ms, matrix: 256x140), coronal FLAIR, and T2-weighted sagittal images. According to MRI features, we classified children with NF1 as group 1 with FASI in the cerebellum (n=14) (Figure 1), group 2 without FASI (n=13). DTI is used as a routine component of our MRI protocol in our center. The DTI protocol included SE-EPI images, TR=6.000 ms, TE=89 ms, 30 gradient directions, b=0 s/mm^2 and b=1000s/mm^2, 5-mm slice thickness, FOV of 230 mm, and matrix: 128x128. A semi-automated system was used for DTI analysis. This was not a voxel-based, but the region of interest (ROI) based technique. The MD and color-coded FA maps were reconstructed on a Leonardo console (software version 2.0; Siemens) utilizing the DTI data. Placement of all ROIs on axial color-encoded FA map was performed simultaneously by two experienced radiologists with consensus (D.H.C and A.A). ROIs were placed in FASI in the cerebellum in group 1, and in cerebellar white matter in group 2. ROIs placement and size were standardized.

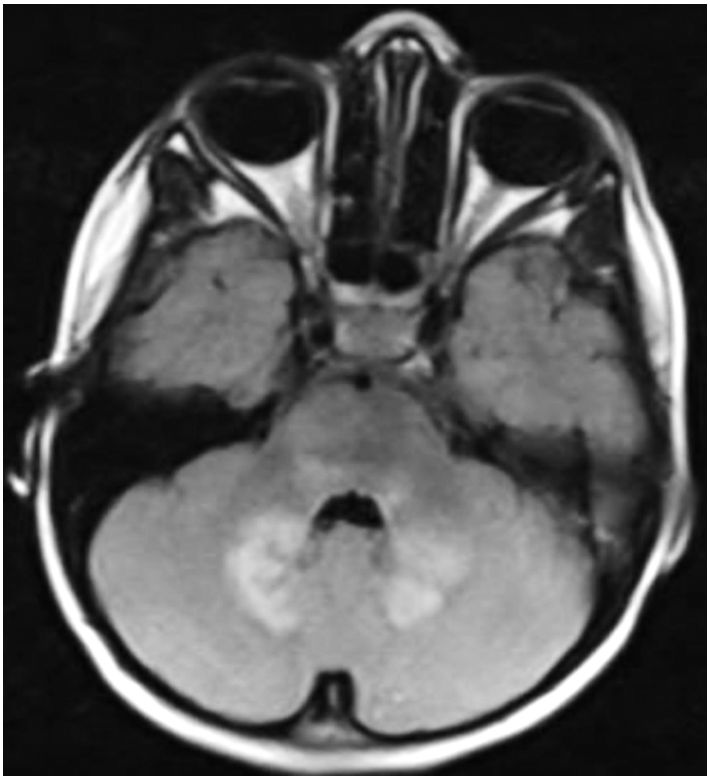

Figure 1a. An 11-year-old male with NF1. Axial FLAIR weighted image show focal areas of abnormal signal intensity (FASI) in the cerebellum

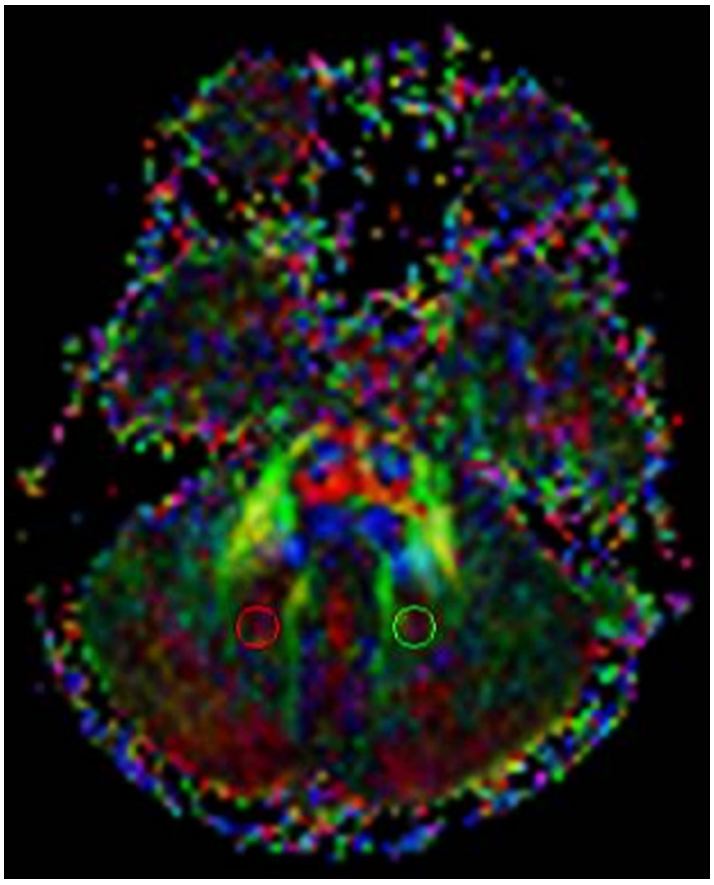

Figure 1 b. The axial color-coded FA

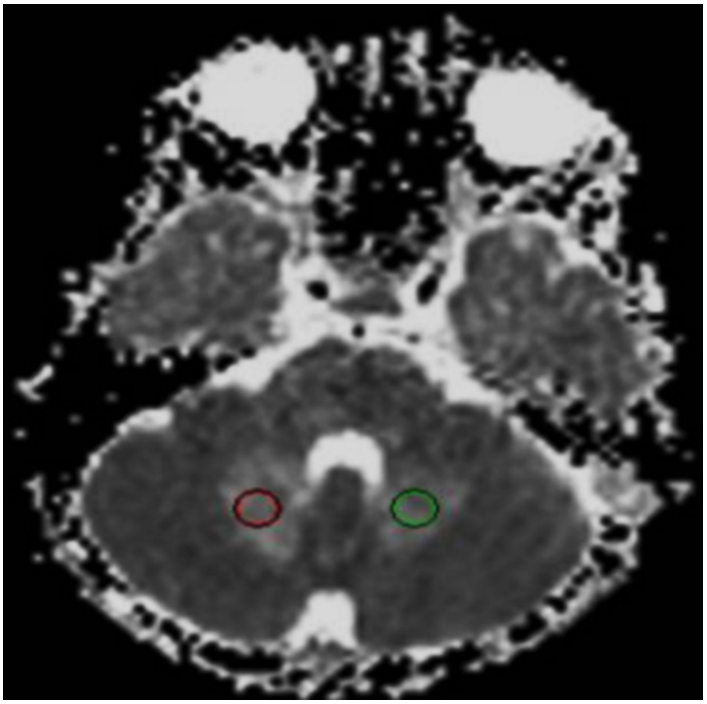

Figure 1 c. MD maps were obtained from a patient with FASI. MD and FA values are measured by placing ROIs (region of interest) in cerebellar FASI.

Statistically Analyses

Statistical evaluations were made by using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). The Kolmogorov Smirnov and Shapiro-Wilks tests were used to determine whether the data corresponded to normal distribution. Since our data did not show normal distribution, the nonparametric test were applied. The comparison between group 1 and group 2 in terms of MD and FA mean values was evaluated using the Mann-Whitney U test. We used Spearman's correlation test to assess the association between MD and FA values and neurocognitive function scores. P values <0.05 were considered statistically significant.

Results

The mean age of 27 children with NF1 was 10.33 ± 3.39 years old.

There was a significant difference between group 1 and group 2 in terms of MD and FA values at the cerebellum (each for; p=0.0001). When compared with group 1 and group 2, decreased FA values and increased MD values were detected. FA and MD values obtained from cerebellum in children with NF1 with/without FASI are shown in Table 1.

Table 1. FA and MD values obtained from cerebellum in children with NF1 with/without FASI are shown in Table 1

Groups	MD ($x10^{-6}mm^2/s$)	FA
Group 1 (n=14)	974.65±0.60	0.262±0.49
Group 2 (n=13)	732.43±0.14	0.468±0.12

Group 1: with FASI in cerebellum, Group 2: without FASI in cerebellum, FA; Fractional anisotropy, MD: mean diffusivity

Table 2. Neurocognitive function test scores are seen in group 1 and group 2

Cognitive Functions (WISC-R scale	Groups		
	Group 1 (n=14)	**Group 2 (n=13)**	**Controls ***
Information	6.89±3.57	4.04±2.80	10.07±1.84
Similarities	8.83±3.94	7.52±2.98	11.71±1.65
Arithmetic	6.82±2.52	6.00±3.20	11.75±1.92
Vocabulary	6.79±3.38	4.39±2.75	-
Comprehension	9.13±2.74	8.21±3.48	10.68±2.14
Digit span	7.55±2.77	6.04±2.05	10.89±1.95
Picture completion	7.79±2.94	7.39±1.90	11.96±1.86
Picture arrangement	9.06±3.49	6.17±3.22	10.86±2.61
Block design	8.44±2.61	7.26±2.39	12.18±2.47
Object Assembly	6.62±2.67	5.87±2.75	12.79±1.75
Coding	8.89±3.59	7.73±4.02	10.86±1.43
Labyrinths	8.55±4.07	7.34±4.68	-
BG	8.24±3.74	10.91±3.82	2.68±1.66
Full scala IQ	84.44±19.51	73.34±15.61	110.50±8.12
Verbal IQ	84.41±19.92	72.87±17.05	107.00±8.28
Performance IQ	86.75±18.51	77.47±13.94	113.50±9.72

*reference 13, Group 1: with FASI in cerebellum, Group 2: without FASI in cerebellum, WISC-R scale (a revised form of the Wechsler intelligence scale for children), BG; Bender Visual–Motor Gestalt Test

In group 1, the mean verbal IQ (VIQ) was 84.41±19.92, the performance IQ (PIQ) mean 86.75±18.51, and the full-scale IQ mean 84.44 ±19.51. The mean VIQ: 72.87±17.05, PIQ:77.47±13.94, and full-scale IQ: 73.34±15.61 were analyzed in group 2 (Table 2).

The MD values obtained from cerebellum were positively correlated with the full-scale IQ (r=.413, p=0.002), VIQ (r=.454, p=0.001) and PIQ (r=.399, p=0.003). No correlation was found between cerebellum FA values and VIQ, PIQ, and full IQ.

Verbal and performance test scores were lower in group 1 and group 2 children with NF1 compared to the normal healthy control group [13]. There was a significant difference between group 1 and group 2 in terms of information (p=0.003), vocabulary (p=0.008), digit span (p=0.021), picture arrangement (p=0.018), verbal IQ (p=0.032), BG test (p=0.019).

There was a negative correlation between the FA values of the cerebellum and information (r=-.295, p=0.03), vocabulary (r=-.348, p=0.01) and digit span scores (r=-.286, p=0.04).

There was a positive correlation between the MD values of the cerebellum and information (r=.534, p=0.0001), similarities (r=.479, p=0.0001), arithmetic (r=.280, p=0.04), vocabulary (r=.428, p=0.002), digit span (r= .389, p=0.004), picture arrangement (r=.472, p=0.0001), block design (r=.358, r=0.009), object assembly (r=.312, p=0.02). Negative correlation was found between BG test scores and cerebellum MD values (r= -.424, p=0.002).

Discussion

School performance in children with NF1 is lower than expected in more than 70% of cases [12]. NF1 cases below 70 of the full IQ level, which is considered to be an intellectual disability, are seen slightly more than the normal population [9, 12]. However, inconsistencies between VIQ and PIQ and changes in BG tests appear to be the most common neuropsychological disorders [13]. In our study, there were 9 cases with full-scale IQ below 70 (33.3%). Only 5/27 (18.51%) NF1 patients was FSIQ >90.

Decreased FA and increased MD values in FASI in children with NF1 may indicate a breakdown of myelin sheaths and/or an axonal disruption. Although the cause of imaging findings is not certain, it is the most widely accepted theory. In our study, increased the cerebellar MD values in group 1 can be explained by myelin sheath irregularity resulting in decreased cellularity or axon number and greater extracellular water mobility/diffusivity. FA decreases in situations such as axonal degeneration and demyelination. In our study, decreased FA values at cerebellum in group 1 compared to group 2 may indicate the presence of a dysmyelination process and/or loss of axonal fibers.

Hayman et al. [4] reported that there was no significant correlation between the presence or absence of FASI and neurocognitive dysfunction. Neurocognitive test scores in children with NF1 with FASI in the cerebellum, corpus callosum, and hemisphere reported that they had low neurocognitive scores very similar to cases with FASI in other localizations [4]. Some researchers claimed that certain positions of FASI do not affects the overall cognitive profile and the relationship between their numbers and IQ is not significant [11, 16]. Contrary to this view, some authors stated that FASI in the thalamic or thalamo-striatal pathway affect general cognitive functions [2, 8, 11, 16-19]. In the study conducted by Piscitelli et al. [10], they found that full IQ and VIQ values were lower in those with FASI in the cerebellum than those without FASI, but they concluded that there was no difference in terms of PIQ values. In our study, both group 1 and group 2 VIQ, PIQ, and full-scale IQ values were lower than the control group. IQ values were lower in patients with NF1 without FASI in the cerebellum. Therefore, we can conclude that the effect of the presence or absence of cerebellar FASI on IQ values is not significant. The positive correlation between MD values at cerebellum and PIQ, VIQ and full-scale IQ support this hypothesis. Although demyelination develops in cerebellar FASIs, it is thought to have little effect on IQ values. The accepted view is that low IQ may not always be related to the clinical severity of the disease [20].

In a study, information, vocabulary, and picture completion test scores of those with cerebellar FASI were found to be lower than those without FASI [10]. In our study, verbal and performance test scores of children with NF1 with and without FASI were lower than the normal healthy control group. In our study, contrary to the study conducted by Piscitelli [10], the information, vocabulary, digit span, and picture arrangement test scores of the group without cerebellar FASI were lower than those with FASI. Verbal IQ was more affected in group 2. We think that verbal IQ is affected in children with NF1, independent of the presence of cerebellar FASI.

In our study, as cerebellum MD values increased, an increase in information, similarities, arithmetic, vocabulary, digit span, picture arrangement, block design, object assembly test scores were detected. As the cerebellar FA values decreased, the scores for information, vocabulary, and digit span increased. A decrease in FA and an increase in MD in cerebellar FASI may indicate a disintegration of myelin sheaths and/or an axonal disruption. We think that the presence of cerebellar FASI in children with NF1 does not add to the severity of the impairment in neurocognitive functions.

Visuospatial deficits in NF1 patients are the best-known feature of neurocognitive functions [12, 13]. Children with NF1 perform significantly worse on visual-perceptual tasks than their siblings [12]. In our study, visual-motor and visual perceptual functions were evaluated with the BG test in children with NF1. Impairment in the listed functions is associated with high scores. BG test scores were higher in group 1 and group 2 compared to the healthy control group. In group 2, BG test scores were higher than group 1. In our study, as the cerebellar MD values increase, the BG test scores decrease. In our study, we can say that visual-motor functioning and visual perception skills are impaired in children with NF1, independent of the presence of cerebellar FASI.

There are some limitations to our study. The most important limitation is the low number of patients with NF1 whose neurocognitive functions are evaluated. Our second limitation is that the control group was not included in the study due to the long duration of neurocognitive function tests. Our third limitation is that the study is retrospective.

Conclusion

The effect of FASI observed in the cerebellum on neurocognitive functions has not been revealed yet. DTI changes in the cerebellum may be associated with demyelination and loss of axonal integrity in the white matter pathways responsible for some neurocognitive functions. We think that the presence of cerebellar FASI in children with NF1 does not contribute to the severity of neurocognitive impairment. More comprehensive studies are needed to reveal the effectiveness of cerebellar FASI on developmental processes of neurocognitive functions in children with NF1.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
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Ethical approval
Bezmialem Vakif University, Institutional Ethics Committee (2021; 03/52).

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