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The evaluation of anterior thalamic radiation with diffusion tensor imaging in children with neurofibromatosis type-1

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Abstract

To determine whether there is a difference in the apparent diffusion coefficient (ADC) and fractional anisotropy (FA) values of the anterior thalamic radiation (ATR), which are involved in the inhibitory control mechanism, in Neurofibromatosis type-1 (NF1) patients with or without Neurofibromatosis bright objects (NBOs), in comparison to the healthy control group. Thirty children diagnosed with NF1 and 17 age-matched children were included in the study. 30 children with NF1 had a mean age of 10.47±5.43, compared to 11.35±5.43 of the control group. NF1 patients were divided into two groups as those with and without NBOs. The comparison was made by measuring ADC and FA values of ATR in patients with NF1 and a healthy control group. There was a significant difference in terms of ADC and FA values of ATR between the patients with NF1 and the control group. While a significant decrease was seen in FA values of ATR, ADC values were increased. There was a significant difference in ATR ADC and FA values between NF1 patients with and without NBOs and the healthy control group. On the other hand, no major difference was displayed between NF1 patients with NBOs and without NBOs in terms of ATR ADC and FA values. The results of increased ADC and decreased FA values may denote the demyelination process in ATR. We speculate that the onset of microstructural damage in the ATR may result in executive function impairment, particularly in the inhibitory control mechanism.

Key words: Neurofibromatosis type 1, diffusion tensor imaging, executive function, anterior thalamic radiation, neurofibromatosis bright objects

Introduction

This article was previously presented as an oral presentation at the 2021 30th Year Annual Meeting of Turkish Society of Neuroradiology with International Participation on 17-21 February, 2021.

Neurofibromatosis type-1 (NF1) is a multisystemic progressive disorder with an autosomal dominant inheritance pattern affecting nearly 1/2500-3000 individuals [1]. As the name of the disorder denotes, mainly the nervous and integumentary system is affected. Along with follow- ups, magnetic resonance imaging (MRI) is crucial for the diagnosis. On MRI, majority of patients display T2-hyperintensities in brainstem, optic tract, thalamus, cerebellum, internal capsule, globus pallidus and subcortical white matter known as Neurofibromatosis bright objects (NBOs) [2]. The exact nature of the NBOs is still unknown [3]. It has been established that the pathophysiology of NBOs is characterized by aberrant or delayed myelination, as well as spongiform and vacuolar changes brought on by intramyelinic edema [4-8].

The NF1 patient group present with high rates of social and cognitive impairment [3,9,10]. Most of these individuals experience learning disabilities, spectrum of symptoms of autism, and attention deficit disorder [3,9,10]. Among the

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cognitive functions; executive dysfunction including working memory, self-control, and cognitive flexibility are important features of this disorder [3,11]. It has been proposed that the presence of NBOs might deteriorate the function of white matter tracts and subsequently cognition [3,12]. Regarding the effects of NBOs, an association between lesion location and the cognitive dysfunction has been revealed but the load of the lesions and their presence has not been linked to any functional abnormalities in the previous studies [3,13].

Diffusion tensor imaging (DTI) is a neuroimaging modality utilized to evaluate the connectivity in the brain. Recent studies have revealed unusual structural connections in NF1 patients. [3,14]. Studies have showed a significant role of frontal-limbic neuronal networks in executive functioning and cognitive processing in NF1. The white matter fiber bundle known as the anterior limb of the internal capsule, or anterior thalamic radiation (ATR), connects the thalamus to the prefrontal cortex. Abnormalities in ATR have shown to be associated with cognitive disorders, especially in inhibitory control mechanisms [3,14].

We purposed to determinate the alterations in Apparent Diffusion Coefficient (ADC) and Fractional Anisotropy (FA) values of ATR in NF1 subjects with or without NBOs compared to healthy control group.

Material and Methods

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The ethical review board of our university gave its approval to this retrospective study (54022451-050.05.04-102717).

Participants

A group of 30 NF1 patients (15 females, 15 males, mean age 10.47±5.43) and 17 age-matched healthy controls (8 females, 9 males, mean age 11.35±5.43) are included in our study. The healthy control group had a similar age and gender distribution with the NF1 patients. The diagnostic criteria established by the National Institutes of Health Consensus Conference are met by all NF1 patients. The control group is selected from the patients without having any neurological abnormalities following the physical examinations of a registered pediatric neurologist. Healthy state of these children is ensured by brain MRI scan. The patients with the history of epilepsy, brain surgery, tumor, trauma, vascular damage were excluded from the study. None of the patients had optic glioma or any comorbidities.

Imaging technique

All participants have undergone MRI scan at our university hospital. 1.5T MRI scanner with a maximum gradient power of 43 mT/m and an 18-channel head coil (Siemens Avanto, Germany) is utilized. The MRI protocol in our study consisted of axial T1 (TR/TE: 500/87 ms), T2 (TR/TE: 4.280/91 ms), fluid-attenuated inversion-recovery (FLAIR; TR/TE/TI: 8.000/118/23.687 ms), MPRAGE 3D T1 (three dimensional magnetization-prepared rapid-acquisition gradient-echo with an isotropic voxel resolution of 1 mm), coronal FLAIR and sagittal T2 images. DTI was applied in every patient using a single-shot, spin-echo, echo-planar sequence with fat suppression technique. 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. DTI analysis was performed using an area of interest (ROI) based technique. Values were calculated by reconstructed ADC and color coded FA maps in the Leonardo console (software version 2.0; Siemens). Region of interests (ROIs) are placed on the ATR. All ROIs are located in the left hemisphere to standardize the measurements. During the placement of the ROIs axial color-coded FA maps are referred. The size of ROIs is 5-10 mm^2. Examining the slices above and below the area helps reduce partial-volume effects by preventing averaging with the cerebrospinal fluid. (Figures 1, 2).

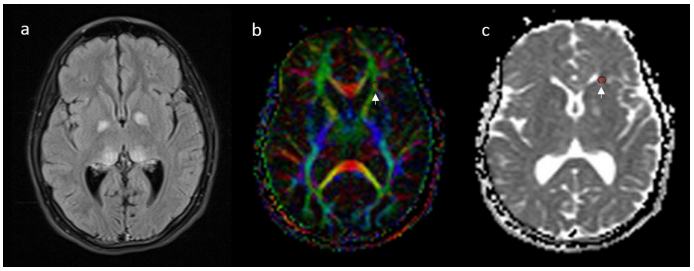

Figure 1. A 13-year-old girl with NF1. Axial FLAIR weighted image show focal NBOs in thalamus and globus pallidum **1a.** The axial color - coded FA **1b** and ADC **1c** maps showing the ROI on the anterior thalamic radiation (ATR) (white arrow)

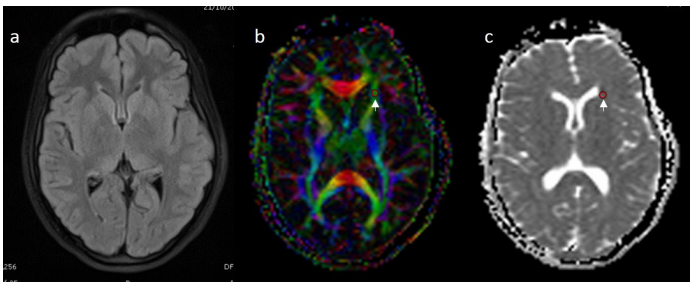

Figure 2. A 16-year-old girl with NF1. Axial FLAIR weighted image show no NBO in the brain **1a.** The axial color - coded FA **1b** and ADC **1c** maps showing the placement of ROI on the anterior thalamic radiation (ATR) (white arrow)

NBOs

T2 and FLAIR images are interpreted by a neuroradiologist (BA, DHC) for detecting NBOs. The NF1 patients are divided into two group as those with (group 1=15 patient) and without (group 2=15 patient) NBOs.

Statistical analysis

SPSS Statistics v28.0 is used for all statistical analysis (IBM, Armonk, NY). The results were shown as mean±standard deviation. The comparison of the ADC and FA values between

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the NF-1 subjects and control group is done with independent sample t test. ANOVA is used to investigate the DTI changes between group 1, group 2 and control group. A p-value of <0.05 is accepted as statistically significant.

Results

There is a statistically significant difference in terms of ADC and FA values of ATR in all patients with NF1 in comparison to healthy controls (p=0.001, p=0.001; respectively). FA values are significantly decreased in the patient group in comparison to healthy subjects. ADC values are significantly increased in NF1 patients compared to control group.

There was a significantly difference between group 1, group 2 and the control group in terms of ATR ADC and FA values (for each; p<0.001). ADC values of ATR are higher in group 1 and group 2 compared to control group. FA values of ATR are significantly lower in in group 1 and group 2 in comparison to control group. There was no significant difference in ADC and FA values measured from ATR between group 1 and group 2.

The FA and ADC values obtained from the ATR in group 1, 2, 3 and the control group are shown in Table 1.

Table 1. The ADC and FA values obtained from Anterior Thalamic Radiation in children with total NF-1 patients (group 3) with (group 1) and without (group 2) NBOs and the control group

	ATR_ADC (x 10^{-3}mm^2/sn)	ATR_FA
Group 1 (n:15)	0.799.77±22.35	0.486.20±48.05
Group 2 (n:15)	0.776.07±48.36	0.474.47±34.03
Group 3 (n:30)	0.787.87±38.91	0.480.33±41.34
Control (n:17)	0.691.12±37.88	0.570.65±44.52

Group 1; NF-1 with NBOs, group 2; NF-1 without NBOs, group 3; NF-1 patients (total), ATR: anterior thalamic radiation, NBOs: neurofibromatosis bright objects

Discussion

NF1 syndrome is the most prevelant single gene disorder with a mutation in the chromosome 17 band q11.2 which encodes neurofibromin protein [12]. Although NF1 is mainly characterized by skin lesions, plexiform and cutaneous neurofibromas, scoliosis, optic pathway gliomas; the most common childhood manifestations are cognitive impairment and learning difficulties [9,12].

The prevalence of NBOs in children with NF1 is 60-80% [12,15]. Cognitive impairments related with NF1 are complicated and not completely understood. Studies show that one or more cognitive function areas, such as language, executive function, attention, and visual perception, are moderately to severely impaired in close to 80% of children [9,12,16]. Previous studies emphasized a link between NBOs and cognitive problems in subjects with NF1 [17,18]. These studies have attempt to link the number, presence or the location of NBOs with the cognitive function. Although the previous studies argue on the correlation between the presence or the load of NBOs and cognitive deterioration, there is evidence suggesting NBOs located in thalamus or thalamostriatal pathway possess a significant risk factor for cognitive dysfunction [11,16]. Some of the studies depicted a decrease in attentions scores and intellectual levels in regards to the presence of thalamic NBOs [8,13,17].

DTI is an useful neuroimaging technique for assessing the integrity of the white matter and visualizing neural connections. By quantifying the direction and amplitude of the diffusion, it makes it possible to diagnose tissue damage at the microstructural level. FA values decrease in axonal degeneration and demyelination. ADC values indicate increased water level, such as in edema or inflammation. Lower levels of ADC values are generally the result of higher cellular densities.

Recent studies emphasize links between NF1's cognitive phenotype and the white matter microstructural alterations. [3,14]. A DTI study found decreased microstructural white matter integrity in NF1 patients, but most notably in the ATR [14]. Their results of reduced FA values in ATR were explained by disorganization of tracts and decreased myelination [14]. Another study demonstrated significantly decreased FA values in ATR in NF1 patients with and without NBOs and depicted strong relationship between white matter microstructural integrity of the ATR and inhibitory control mechanism [3]. Consistent with previous studies, we detected decreased FA values and increased ADC values in ATR independent of the presence of NBOs. A study utilized ADC alone suggested that the increase in ADC values in NF1 may represent increased number or size of the myelin vacuoles which reflects demyelination [14,19]. In demyelinating disease, diminished myelin amount and loss of normal myelin structure causes the enlargement of the extracellular space concluded with the increased ADC values [20]. Ertan et al reported increased ADC values in NBOs and they attributed this finding with the myelin vacuolation and spongiotic alterations due to increased water accumulation. Also, they found decreased FA values in NBOs, which could be explained by the myelin injury and axonal disruption [21]. In addition, a different study showed that NF1 patients with or without NBOs had higher ADC values in the thalamostriatal pathway compared to healthy controls. They attributed these findings to the breakdown of myelin sheath, which causes a reduction in the number of axons and increase in the level of extracellular fluid [8].

ATR is a white matter bundle that runs through the anterior limb of internal capsule and connects the dorsomedial thalamic nucleus to the prefrontal cortex. It is crucial for both the regulation of complex cognitive behaviors and executive functioning. In our study, we recorded increased ADC values of ATR in NF1 subjects with and without NBOs. ADC is a scale based measurement of the total diffusion within a voxel. It is sensitive to cellular density

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and edema. Increased ADC values may reflect decreased number of total axons, increased volume of the extracellular fluid and destruction of the myelin sheath. Increased ADC values may be compatible with the demyelinating process in ATR. Higher FA values may show normal myelination process and physiological axonal structure. The decreased FA values can be interpreted as a quantitative decrease in anisotropic diffusion [22]. This finding may point out white matter disintegration, demyelination and decreased axonal structural integrity in all NF1 subjects independent of NBOs presence.

The data of our study is collected retrospectively. As a result, certain limitations were observed. The primary drawback is the small sample size. Secondary limitation is that only ATR values are evaluated by DTI. The correlation between the cognitive functions and DTI findings are not interpreted. Additionally, manual placement of ROI-based approach is used for DTI measurements. Margining errors are kept minimal by using voxel-based measurement techniques.

Conclusion

DTI findings may demonstrate that ATR is affected in all NF1 subjects' independent of NBOs presence. Increased ADC and decreased FA values may point out to demyelinating process in ATR. We speculate that development of microstructural damages in the ATR may result in executive cognitive dysfunction, through inhibitory control mechanism. Further studies including larger sample size might be better in the understanding of the underlying pathophysiology of cognitive dysfunctions in NF1 patients related to microstructural damage in ATR.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Bezmialem Vakif University Ethics Committee.

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