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ÖZGÜN ARAŞTIRMA/ORIGINAL ARTICLE

Serebral Beyaz Cevherde Diffüzyon Değişiklikleri: Yaş ve Cinsiyetin Etkisi

Diffusion Changes in Cerebral White Matter: The Effect of Age and Gender

Merter Keçeli[1] **Orcid ID: 0000-0002-9412-6733**

[1]Sağlık Bilimleri Üniversitesi Konya Şehir Hastanesi, Konya, Türkiye.

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Yazışma Adresi/Address for Correspondence:
Merter Keçeli
Sağlık Bilimleri Üniversitesi
Konya Şehir Hastanesi,
Adana Çevre Yolu, Akabe
42090 Karataya, Konya.
E-posta: merterkeceli@gmail.com

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Korpus Kallosum
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ÖZ

Amaç: Myelinasyon, doğumdan sonra devam eden dinamik bir süreçtir. MR görüntüleme tekniklerinden biri olan difüzyon ağırlıklı görüntüleme (DAG) ve görünen difüzyon katsayısının (GDK) ölçümü, normal beyin gelişimi için bir kılavuzdur. Bu çalışmanın amacı çocuklarda normal miyelinasyon gelişiminin izlenmesinde DAG ve GDK haritalarının rolünü göstermek ve korpus kallozum (KK) ve temporal bölgelerde (TB) GDK değerlerini belirlemektir.

Gereç ve Yöntem: MR görüntülerinin yeniden değerlendirildiği retrospektif çalışmaya 57'si erkek toplam 112 çocuk (ortalama yaş 98 ± 52,9 ay) dahil edildi. Katılımcılar 0 ile 202 ay arasında dört yaş grubuna ayrıldı. DAG ve GDK haritaları her iki TB'de KK'nın her iki tarafından ve parahipokampal sulkus beyaz cevherinden elde edildi. GDK değerlerinin ortalamaları belirlendi.

Bulgular: Yaş ilerledikçe GDK değerlerinin tüm ölçüm alanlarında düştüğü görüldü ($p< 0,005$). Bu değişiklik TB'nin her iki tarafında ve KK genu ve gövdenin sol yarısında önemliydi. ADC değeri cinsiyete ve ölçülen tarafa göre değişmedi.

Sonuç: GDK değerleri yaş ilerledikçe azalmaktadır. KK ve TB'nin ADC değerleri kullanılarak beyinde normal myelinasyon gelişimi ve ergenliğin neden olduğu değişiklikler diğer patolojilerden ayırt edilebilir.

ABSTRACT

Objective: Myelination is a dynamic process that continues after birth. One of the MR imaging techniques diffusion-weighted imaging (DWI) and measurement of apparent diffusion coefficient (ADC) is a guide for normal brain development. The aim of this study is to show the role of DWI and ADC maps in monitoring the normal development of myelination in children, and to determine ADC values in corpus callosum (CC) and temporal regions (TL).

Material and Method: A total of 112 children (mean age 98 ±52.9 months), 57 of whom were male, were included in the retrospective study in which MRI images were reevaluated. Participants were divided into four age groups between 0 and 202 months. DWI and ADC maps were obtained from both sides of CC and parahippocampal sulcus white matter in both TL. Averages of ADC values were determined.

Results: It was found that ADC values decreased in all measurement areas as the age progressed ($p< 0.005$). This change was significant on both sides of the TL and left half of the CC genu and body. ADC value did not change according to gender and measured side.

Conclusion: ADC values decrease with progressive increase of age. Using ADC values of CC and TL, the development of normal myelination in the brain and changes caused by puberty can be distinguished from other pathologies.

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Introduction

Brain development in children is a dynamic process that involves white matter maturation. This process is characterized by axonal development and myelination (1,2). The microstructural organization of white matter develops under the influence of these two components (3). Myelination is a continuous process and an accessible marker of maturation in the brain of developing infants. Several researchers have documented the changes in magnetic resonance imaging (MRI) corresponding to myelination of the white matter in neonates and infants; a relatively normal adult appearance can be seen at 2 years of age, and all major fiber tracts can be identified by 3 years of age (4,5). With the development of diffusion-weighted imaging (DWI), it has become possible to evaluate these effects.

Myelination begins at around 20 weeks gestational age and continues up to around 2 years of age. As myelination precedes, the water content of the white matter decreases. Changes in the signal of the white matter due to myelination are demonstrated at different ages on MRI (6,7). An important area in the myelination process is the corpus callosum (CC) (8,9). Sex steroid hormone receptor densities are high in the medial part of the cerebral temporal lobes and cortical gray matter (10). It has been shown that puberty-related myelin maturation differs according to gender (11). However, none of the studies conducted have analyzed the developmental changes of these structures together with this area before and after puberty.

MRI measurements of the Brownian motion of water molecules can be illustrated using DWI, apparent diffusion coefficient (ADC) maps, diffusion tensor imaging (DTI), and tractography (5,8,12,13). ADC is a metric of the magnitude of diffusion within cerebral white matter tissue (14). Callosal microstructural integrity is better explored by DWI and ADC maps (15). ADC values have been reported to better reflect white matter maturation in the fiber pathways than fractional anisotropy (FA) measures (13). Both values can be used to evaluate the white matter structure, especially in major psychiatric illnesses (16,17).

In this study, it was aimed to determine the changes before and after puberty by evaluating the DWI and ADC values of the specific white matter region in children and adolescents.

Material and Method

After obtaining ethics committee permission (KTO Karatay University Medical School, 17.05.2020/decision number: 2020/036), cranial MRI images taken between January of 2018 and 2020, obtained via the standard protocol in our imaging department, of 112 participants (57 males, 55 females, mean age of 98±52.9 months), were reevaluated. Attention was paid to the absence of ethnic differences among the participants. Using the information obtained from the hospital information system, cases of normal physical examinations and laboratory examinations were selected and included in the evaluation. The clinical history of each patient was carefully inspected by a pediatrician to rule out developmental abnormalities, chronic headaches, and migraines. No pathological findings were found in the imaging of these cases, which were imaged due to nonspecific complaints, such as headache and dizziness, except for sinusitis and mastoiditis. Children evaluated by the pediatric psychiatry and genetic diseases departments were excluded from the study. To facilitate interpretation, the participants were divided into four age groups, according to their ages calculated from their birth dates, comprising 0-48 months, 49-96 months, 97-144 months, and 145-202 months.

MRI scans were acquired using a Siemens Magnetom Aera 1.5 T (Global Siemens Healthcare, Erlangen, Germany). A standard head coil was used for radiofrequency transmission and reception of the MR signal, and restraining foam pads were utilized to minimize head motion. Axial plane T1-weighted images were first obtained to verify the head position of the participant and image quality. Next, T2-weighted axial and coronal plane images were acquired, according to an axial plane parallel to the anterior-posterior commissures, for clinical neurodiagnostic evaluations. Then, axial plane fluid-attenuated inversion recovery (FLAIR) sequence images were obtained (Figure 1). In our imaging unit, in daily practice, diffusion-weighted imaging is added in addition to standard sequences in cranial MRI examinations. Specifically, three gradients were acquired in three orthogonal directions. ADC map images obtained in the axial plane in our department were reconstructed in the coronal plane using the standard multi-plane imaging technique in order to take measurements from anatomical structures during image archiving and re-evaluation in the communication system (Figure 2).

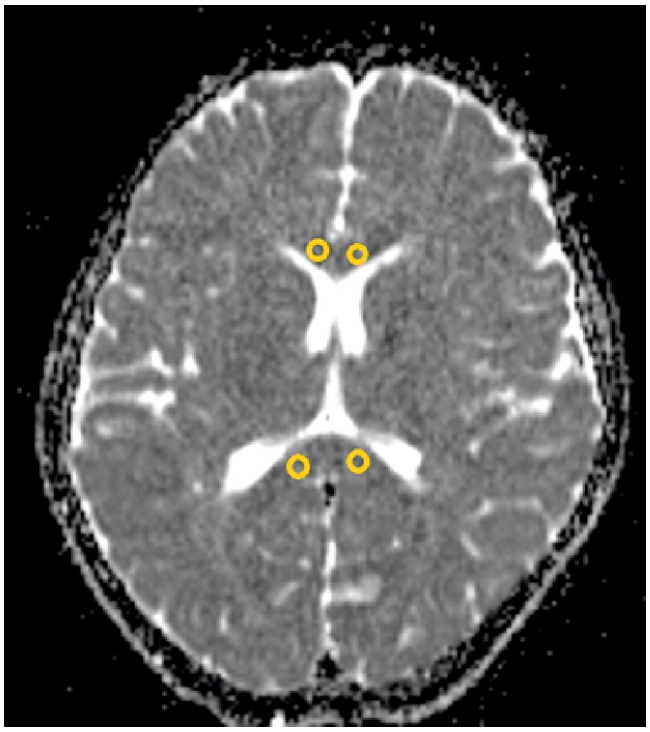

Figure 1. On the ADC map (axial plane) obtained, the regions of interest placed in the corpus callosum genu and splenium.
(RCC head: The head of Corpus Callosum right side,
LCC: The head of Corpus Callosum left side,
RCC bd: The body of Corpus Callosum right side,
LCC bd: The body of Corpus Callosum left side,
RCC spl: The splenium of Corpus Callosum right side,
LCC spl: The splenium of Corpus Callosum left side,
Temp R: Temporal lobe: Cerebral white matter in right parahypocampal sulcus region,
Temp L: Cerebral white matter in left parahypocampal sulcus region.)

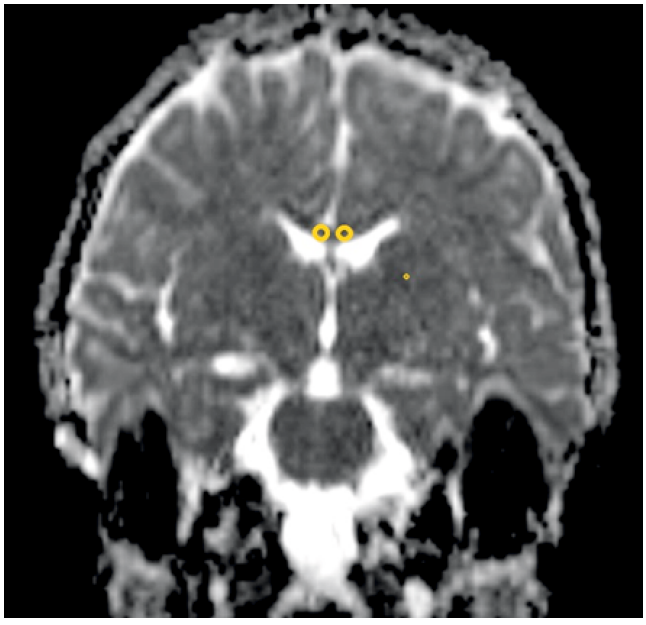

Figure 2. On the ADC map (reconstruction coronal plane) obtained, the regions of interest placed in the corpus callosum genu and splenium.

In our department, imaging of patients in their first year is obtained during physiological sleep after the baby has been fed. Older children who cannot cooperate are left sleepless before the examination and imaged during their physiological sleep. If imaging is not possible under these conditions, sedation is applied. To eliminate the possible effect of sedation on the results, the images to be evaluated were selected from MRI obtained from non-sedated participants. Images with artifacts were not included in the study.

Determination of the cellular density of the tissue, which is one of the advantages of MRI examination, can be made with the ADC map calculated from DWI. Measurements made from areas selected from the ADC map provide diagnostic benefit in the differentiation of many pathologies. With the region of interest (ROI) marking options available to the user, this measurement can be carried out electronically in a safe and simple way. The ADC is used reliably in the differentiation of CNS lymphoma from other malignancies and in the response of CNS tumors to chemotherapy (18). Using this feature of the DWI and ADC map, the corpus callosum and temporal lobe white matter, which have high hormone receptors in puberty development, were used to measure ADC values in the cerebral tissue. Eight ROIs were evaluated for all of the subjects, including the white matter adjacent to the parahippocampal sulcus in the bilateral temporal lobe (TL), bilateral genu, and body and splenium of the CC sections. Landmarks for callosal subregions were adapted from the design reported in the studies of Bonekamp and Prunas (13,16). A round-shaped ROI was placed in these areas on the b=0 DWI and ADC map. Measurement areas were marked manually. Circular ROIs standardized at 5 pixels (corresponding to an area of 0.2 cm2) were placed in the determined regions. In the genu and splenium of the CC, ADC measurements were taken from the axial plane (Figure 1, 3). In the body of the CC, ADC measurements were taken from the reconstructed coronal plane in order to reduce the partial volume artifacts that may occur due to close vicinity with the ventricular system (Figure 2). Since there was no loss of information in the ADC map, which is a mathematical map, with reconstruction algorithms, measurements could be made on these images. In the axial plane, the ADC map was measured from the white matter adjacent to the parahippocampal sulcus adjacent to the temporal horn of the lateral ventricle on both sides (Figure 3). The values obtained from the ADC map were recorded in mm/s2. All of the measurements were performed in all four age groups. The ADC values were compared with the average age in the age group.

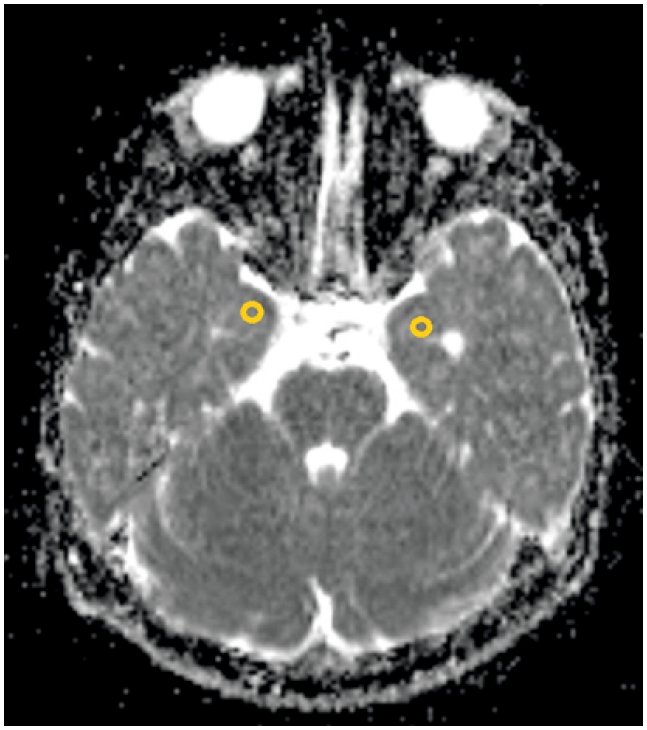

Figure 3. On the ADC map (axial plane) obtained, the regions of interest placed in the parahypocampal region in temporal lobes.

Reevaluation was performed by a single experienced pediatric radiologist who was interested in pediatric neuroradiology. For each participant, each measurement was repeated two times at three-day intervals; the average of the values obtained was recorded. Intrarater reliability was investigated for each measurement.

The sample range of this study was determined by taking the power (strength of the test) for each variable as at least 80% and the type 1 error as 5%. The Kolmogorov-Smirnov (n>50) and skewness-kurtosis tests were employed to determine whether the measurements in the study were normally distributed, and parametric tests were applied after determining that the measurements were normally distributed. Descriptive statistics for continuous variables in this study were as follows: average, standard deviation, minimum, and maximum. For the categorical variables, they were presented as numbers and percentages. The independent t-test and one-way analysis of variance (ANOVA) were applied in comparing the measurements made according to the gender and age groups. The kappa statistical test was used to investigate the reliability of repeated measurements of ADC values made by a single rater. ANOVA was followed by the Duncan multiple range test to determine differences between the different groups. The paired t-test was employed in the comparison of right-left measurements separated in accordance with gender. Pearson correlation coefficients were calculated to determine the relation between the age groups and the measurements. The statistical significance level (α) was taken as 5% in the calculations and IBM SPSS Statistics for Windows 25.0 (IBM Corp., Armonk, NY, USA) was used for the calculations.

Results

The study included 112 participants, 57 of whom were male (50.9%) and 55 of whom were female (49.1%). The average age was 98 ± 52.9 months. Information on the descriptive statistics is shown in Tables 1 and 2.

Table 1. General characteristics of the participants.

		N	%
Sex	Boy	57	50,9%
	Girl	55	49,1%
	Total	112	100,0%
Age (month)	0-48	28	25,0%
	49-96	30	26,8%
	97-144	34	30,4%
	145-202	20	17,9%
	Total	112	100,0%

Table 2. Descriptive information about the ages of the participants.

		N	Mean	Std. Dev.	Min.	Max.
Age (month)	Boy	57	93,00	54,546	12	201
	Girl	55	103,33	51,186	18	202
	Total	112	98,07	52,939	12	202

It was observed that there was a statistically significant and very high level of agreement at all levels in the kappa test, which determines intra-rater agreement in the measurement of repeated ADC values (κ=0.839-0.895 for measurements made from the eight specified regions; $p<0.05$).

The ADC values obtained from the levels determined in CC and the TL level were not related to gender (p=0.240-0.847). Apparently, the gender of the individual did not cause a significant change in the ADC values. The distribution of the average of the ADC values in the determined regions by gender is shown in Figure 4.

The mean ADC values determined by considering gender were as follows: from CC genu 0.75 × 10-5 mm/sn², from CC body 0.82 × 10-5 mm/sn², from CC splenium 0.77 × 10-5 mm/sn², 0.78 × 10–5 mm/sn², and from TL 0.81 × 10-5 mm/sn². The ADC values and age groups were compared (Table 3), and it was observed that the ADC value decreased with increasing age. A statistically significant correlation was found between the ADC values obtained

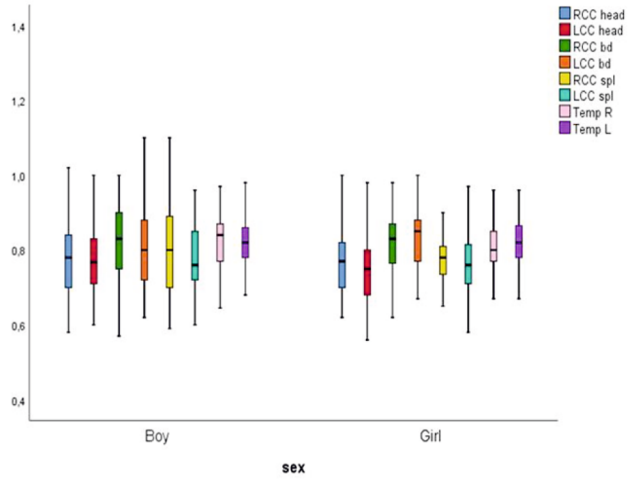

Figure 4. This graph shows the change of ADC values according to genders and their ADC mean values according to the cerebral regions examined.

from the genu and body sections from the left part of the CC and both parts of the TL and the age groups (p<0.05). This correlation was weaker at the other measurement points (p = 0.45-0.50).

The ADC values obtained from the genu part of the right part of the CC in the 0-48 and 49-96 month age groups were similar. The 0-48 month age group had higher ADC values than the 97-144 and 145-202 month age groups. Similarly, the ADC values obtained from the left side genu of the CC in the 0-48 and 145-202 month groups were similar. Higher values were found in the 0-48 month group than those of 49-96 and 97-144 month groups.

The 0-48 and 49-96 month age groups were similar with regards to the measurements conducted on the body section in the right part of the CC. The values were higher in the 0-48 month age group than in the other age groups. In the measurements obtained from the same level in the left part of the CC, values of the 0-48 month age group were higher than those of the other age groups.

In measuring the ADC values performed on the splenium level of the CC, the 0-48 and 49-96 month age groups were similar, while the values in these groups were higher than those of the 97-144 and 145-202 month age groups. The 145-202 month age group had a lower value than the other age groups in the left part.

A statistically significant difference was found on both sides in the measurements performed at the TL level according to age (p<0.05). In the right part, the 0-48 month age group had higher values than the other age groups. In the left part, the 0-48 and 97-144 month age groups were different from each other.

Table 3. The comparison results of ADC values by age groups (ignoring gender).
ADC: apperant diffusion coefficient,
RCC head: The head of Corpus Callosum right side,
LCC: The head of Corpus Callosum left side,
RCC bd: The body of Corpus Callosum right side,
LCC bd: The body of Corpus Callosum left side,
RCC spl: The splenium of Corpus Callosum right side,
LCC spl: The splenium of Corpus Callosum left side,
Temp R: Temporal lobe: Cerebral white matter in right parahypocampal sulcus region,
Temp L: Cerebral white matter in left parahypocampal sulcus region.

		N	Mean ($x10^{-5}$)	Std. Dev.	Min.	Max.	*p.
RCC genu	0-48 month	28	,8089^{a}	,10436	,60	1,02	,045
	49-96 month	30	,7767^{ab}	,09904	,62	,95	
	97-144 month	34	,7521^{b}	,08580	,62	,92	
	145-202 month	20	,7410^{b}	,07518	,58	,86	
	Total	12	,7709	,09493	,58	1,02	
LCC genu	0-48 month	28	,8150^{a}	,13407	,60	1,20	,003
	49-96 month	30	,7382^{b}	,08218	,60	,90	
	97-144 month	34	,7265^{b}	,08395	,56	,89	
	145-202 month	20	,7645^{ab}	,07338	,62	,88	
	Total	112	,7585	,10193	,56	1,20	
RCC bd	0-48 month	28	,8671^{a}	,09786	,68	1,20	,010
	49-96 month	30	,8273^{ab}	,09483	,66	,97	
	97-144 month	34	,8009^{b}	,10760	,57	1,00	
	145-202 month	20	,7760^{b}	,08494	,62	,90	
	Total	112	,8201	,10194	,57	1,20	
LCC bd	0-48 month	28	,8700^{a}	,08287	,68	1,00	,007
	49-96 month	30	,8067^{b}	,08079	,68	1,00	
	97-144 month	34	,7974^{b}	,12094	,57	1,10	
	145-202 month	20	,7810^{b}	,08849	,66	,90	
	Total	112	,8151	,10074	,57	1,10	
RCC spl	0-48 month	28	,8229^{a}	,12073	,64	1,10	,050
	49-96 month	30	,8080^{a}	,11391	,60	1,10	
	97-144 month	34	,7774^{b}	,08621	,60	,96	
	145-202 month	20	,7480^{b}	,09833	,59	,98	
	Total	112	,7917	,10735	,59	1,10	
LCC spl	0-48 month	28	,7971^{a}	,07798	,65	,97	,012
	49-96 month	30	,8033^{a}	,09245	,65	1,10	
	97-144 month	34	,7609^{ab}	,11102	,60	1,10	
	145-202 month	20	,7285^{b}	,06268	,58	,89	
	Total	112	,7755	,09107	,58	1,10	
Temp R	0-48 month	28	,8621^{a}	,06315	,76	,98	,001
	49-96 month	30	,8097^{b}	,05968	,68	,89	
	97-144 month	34	,7822^{b}	,06503	,62	,88	
	145-202 month	20	,7720^{b}	,09534	,51	,95	
	Total	112	,8113	,07545	,51	,98	
Temp L	0-48 month	28	,8675^{a}	,06484	,74	1,00	,002
	49-96 month	30	,8317^{ab}	,11151	,70	1,23	
	97-144 month	34	,7865^{b}	,06391	,68	,92	
	145-202 month	20	,7845^{b}	,07134	,67	,96	
	Total	112	,8165	,08533	,67	1,23	

**Significance levels according to ANOVA test results*
a, b: shows differences between groups (Duncan post-hoc test)

It was observed that the ADC values obtained from the right and left parts of the CC and TL did not statistically significantly vary between the age groups (p=0.14-0.859).

Correlation analysis results between age groups and the ADC values are shown in Table 4, separated by gender, where it can be seen that a statistically significant negative correlation was observed in the male patients between the age groups and the ADC values obtained from the genu section of the right part of the CC. The degree of this relation was 37.2%. On the other hand, no statistically significant correlation was observed in the female patients between the age groups and the obtained values. A negative correlation was observed in the females between the age groups and the ADC measurements performed on the splenium section of the left part of the CC. The degree of this correlation was 39.5%. On the other hand, no significant correlation was observed in the males. An inverse relationship was found between the ADC values and age, although the correlation was not high. The diffusion restriction and ADC value decreased as the age of the participants increased.

Table 4. The gender-separated correlation analysis between age and ADC values. Abbreviations are the same as in table 3.

		Boy (n=57)	Girl (n=55)
		Age (month)	Age (month)
RCC genu	r	-,372**	-,176
	p	,004	,199
LCC genu	r	-,307*	-,119
	p	,020	,388
RCC bd	r	-,320*	-,323*
	p	,015	,016
LCC bd	r	-,306*	-,283*
	p	,020	,036
RCC spl	r	-,228	-,282*
	p	,088	,037
LCC spl	r	-,237	-,395**
	p	,076	,003
Temp R	r	-,348**	-,354**
	p	,008	,008
Temp L	r	-,225	-,218
	p	,092	,110

*$p<0.05$; **$p<0.01$; r:Pearson corelation coefficient

Discussion

The aim of this study was to show the changes in the size of the diffusion of water molecules in the determined age groups and white matter areas. ADC is a measure of the magnitude of diffusion of water molecules within tissue, and it is commonly clinically calculated using DWI. The ADC values are calculated automatically by software and then displayed as a parametric map that reflects the degree of diffusion of water molecules through different tissues. Then, by use of a dedicated workstation, ADC measurements are recorded for a given region by drawing ROIs on the ADC map (19). The ADC of tissue is expressed in units of mm2/s. The ADC value of the white matter in adults, regardless of gender, is roughly 0.670 to 0.802×10-5 mm/s2. There is no unanimity regarding the boundaries of the range of normal diffusion, but ADC values less than 1 to 1.1×10-5 mm2/s are generally acknowledged in adults as indicating restriction. However, this is entirely dependent on the organ being imaged and the pathology (14).

The FA is a quantitative index that provides information on the spatial orientation of fiber tracts and reflects the axonal tract coherence forming the white matter microstructure. Thus, the FA is high if axonal integrity and directionality are maintained, while it is low in areas of axonal loss and/or axonal demyelination. The white matter microstructure organization can thus be described by both ADC and FA, which are indeed considered as complementary indexes, showing alterations of white matter when increased and decreased, respectively (20). To further support the influence of myelination, a strong correlation was found between the FA and nb0 (b=0) changes. It has been suggested that T2 shortening is caused by the water loss induced by the development of the hydrophobic inner layer of the myelin sheath. Strong correlations between the nb0 and FA in many regions have suggested that myelination, or at least axonal properties that mature concomitantly with myelination, are an important facet of the FA increase. However, myelination is not the sole determining factor for anisotropy (5).

The FA values and DTI method used in previous studies were not used as an assessment tool in this study. In the presented study, only ADC value measurements were used. The aim was to determine the interpretability of the normal myelination process with the diffusion value obtained, without the need for an additional procedure in daily radiology practice. Another aim was to obtain basic mathematical values that would provide simpler evaluation without the need for advanced technical applications in order to demonstrate diffusion changes that might occur with pubertal process and evaluate pubertal pathologies.

According to the results of this study, differences were found in ADC values showing the mathematical value of diffusion in children in different age groups and in certain parts of CC and TL white matter. The ADC values obtained from the genu, body, and splenium of the CC and from the

TL white matter from both sides were found to be higher when compared to the other areas in the study. The most significant statistical changes in these regions were obtained in the genu and left part of the body parts of the CC and bilateral TL white matter areas. When all of the measurements were interpreted, it could be understood that the ADC values decreased with age. Non-myelinated white matter has high water and low molecular contents, and so it showed non-restricted ADC values. Neil et al. imaged newborns at 36 h after birth and measured the ADC values in all of the subjects. They reported that a correlation existed between the ADC values and the gestational age of the newborns, suggesting the potential role of brain water in the elevation of ADC values in neonates (21). With the progression of myelination, there is a drop in the water content and progressive increase of the molecular contents, and consequently. more restricted ADC values, as confirmed by Forbes et al., Löbel et al., and Zhai et al. (22-24). They used diffusion to detect the progression of myelination and their results showed a significant decrease in the ADC values in the white matter with an increase in the age of their subjects. In this study, it was observed that the ADC values decreased with age in both genders in all of the regions where the measurements were taken. In both genders, in subjects who were over 145 months of age, it was seen that the values taken in some regions had increased. However, these increases were not statistically significant.

Faadel et al., in their study of the brain images of healthy infants, reported that the average of the ADC values obtained from the CC genu and splenium were 1.35×10-5 mm^2/s and 0.98×10-5 mm^2/s, respectively (25). In the same study, it was found that the same values gradually decreased in children aged 3 years ($p<0.05$). In the current study, in accordance with this result, it was seen that the ADC value decreased as the age increased. The reason why these values were different from each other may have been the different designs of the age groups. Differences due to the tissues or measurement changes of the participants caused by technical characteristics may have been the cause.

In this study, it was found that the ADC values obtained from the CC and TL did not vary according to gender. The ADC values obtained from the genu and body parts on the left side of the CC and TL on both sides varied according to age. A non-significant statistical connection was observed between the values obtained from the other parts of CC and age. This finding confirmed that myelination development varies regionally. Findings obtained in this study were in agreement with those of previous studies on the sequence of the myelination process (8,15,20). Autopsy studies have shown that the corticospinal tract, parts of the CC, and the superior cerebellar peduncles mature early, which was in concordance with MRI studies. The late maturation of the association tracts was also confirmed by histological analyses. On the other hand, autopsy studies have shown that the fornix, which has relatively high FA in newborns, does not reach full myelination until 2 years of age (4,5). This study concluded that axonal membranes play a primary role in myelination. However, fornix measurements were not taken because it was not possible to determine the fornix levels correctly in the ADC map.

Sex steroid hormone receptor density is high in the parahippocampal region of the temporal lobe. In the presented study, diffusion changes in white matter adjacent to this area were measured. In all of the age groups, the ADC values from the TL were significantly higher than those obtained from the CC ($p<0.05$). This finding suggested that there is less myelination at the TL level. The ADC values obtained in the TL decreased significantly with age. No studies on diffusion changes in the temporal lobe and parahippocampal region white matter could be found in the literature. The ADC values obtained from children without pubertal pathology can be considered normal and may help in the assessment of children with pubertal abnormalities.

There were limitations that cannot be ignored in this study. In the neurological examination notes obtained from the patient records, it was learned that some of the school-aged children used their right hands. This information was available for 5% of the subjects. Apart from this, information on this subject was not available. The choice of right-hand or left-hand usage of the other enrolled children was unknown. In the retrospective study, sex hormones lab results were not available for all of the participants. Therefore, their pubertal status was determined clinically. These were the biggest limitations. The measurements were made by a single radiologist. When performed by different observers, the repeatability of the measurements would be more reliable. To increase reliability, an inter-rater reliability assessment was conducted for repeated ADC value measurements. Another limitation was the presence of uncontrollable parameters in the diffusion measurements. The ADC map reflects not only true diffusion, but depends on spatial orientation microscopic perfusion and pulse sequence timing. Of these parameters, only sequences used for imaging could be standardized. Moreover, a limitation to keep in mind was that the extent of myelination was not the only interpretation of the changes in the ADC. However, one of the goals of the study was to find answers to questions with standard sequences in daily practice. Therefore, this risk was accepted.

Conclusion

DWI and ADC measurements can be applied in the study of normal brain development and myelination. ADC values decrease as age increases, regardless of gender. Using ADC values is helpful in the assessment of the myelination development in certain areas of white matter in the brain. Practically obtaining age-related changes in ADC values may help distinguish white matter pathologies from expected age-related changes.

Yazarlık katkısı: Fikir/Hipotez: MK Tasarım: MK Veri toplama/Veri işleme: MK Veri analizi: MK Makalenin hazırlanması: MK Makalenin kontrolü: MK

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Kaynaklar

1. Deoni SC, Mercure E, Blasi A et al. Mapping infant brain myelination with magnetic resonance imaging. J Neurosci 2011;31: 784-791.
2. Aubert-Broche B, Fonov V, Leppert I, Pike GB, Collins DL. Human brain myelination from birth to 4.5 years. Med Image Comput Comput Assist Interv 2008;11:180-187.
3. Tortori- Donati P, Biancheri R, Rossi A, Raybaud C. Pediatric neuroradiology: brain head, neck and spine. First edition. New York: Springer 2010;21-40.
4. Brody BA, Kinney HC, Kloman AS, Gilles, FH. Sequence of central nervous system myelination in human infancy. I. An autopsy study of myelination. J Neuropathol Exp Neurol 1987;46:283-301.
5. Hermoye L, Saint-Martin C, Guy C et al. Pediatric diffusion tensor imaging: Normal database and observation of the white matter maturation in early childhood. NeuroImage 2006;29: 493-504.
6. Barkovich AJ. Concepts of myelin and myelination in neuroradiology. AJNR Am J Neuroradiol 2000;21:1099-1109.
7. Counsell SJ, Maalouf EF, Fletcher AM et al. MR imaging assessment of myelination in the very preterm brain. AJNR Am J Neuroradiol 2002;23:872-881.
8. Ladoucer CD, Pepper JS, Crone EA, Dahl RE. White matter development in adolescence: The influence of puberty and implications for affective disorders. Dev Cogn Neurosci 2012;2:36-54.
9. Girard N, Raybaud C, Du Lac P. MRI study of brain myelination. J Neuroradiol 1991;18:291-307.
10. Simerly RB, Chang C, Muramatsu Swanson LW. Distribution of androgen and estrogen receptor mRNA-containing cells in the rat brain: An in situ hybridization study. J Comp Neurol 1990; 294:76-95.
11. Stanfield BB, Cowan WM. The development of the hippocampal region. In: Peters A, Jones EG, eds. Cerebral Cortex: Development and Maturation of the Cerebral Cortex. New York: Plenu 1988:7:91-131.
12. Barkovich AJ. Concepts of myelin and myelination in neuroradiology. AJNR Am J Neuroradiol 2000;21:1099-109.
13. Bonekamp D, NagaeL M, Degaonkar M et al. Diffusion Tensor Imaging in Children and Adolescents: Reproducibility, Hemispheric, and Age-Related Differences. Neuroimage 2007;15;34: 733-742.
14. Andrews TJ, Osborne MT, Does MD. Diffusion of Myelin Water. Magn Reson Med 2006;56:381-385.
15. Prayer D, Prayer L. Diffusion-weighted magnetic resonance imaging of cerebral white matter development. Eur J Radiol 2003;45:235-243.
16. Prunas C, Delvecchio G, Perlini C et al. Diffusion imagng study of the Corpus Callosum in bipolar disorder. Psychiatry Res Neuroimaging 2018;271:75-81.
17. Genç S, Seal M, Dhollander T et al. White matter alternations at pubertal onset. Neuroimage 2017;156:286-292.
18. Zhang L, Thomas KM, Davidson MC, Casey BJ, Heier LA, Ulug AM. MR quantitation of volume and diffusion changes in the developing brain. AJNR Am J Neuroradiol 2005;26:45-49.
19. Giorgio A, Watkins KE, Douaud G et al. Changes in white matter microstructure during adolescence. Neuroimage 2008;39:52-61.
20. Neil JJ, Shiran SI, McKinstry RC et al. Normal brain in human newborns: apparent diffusioncoefficient and diffusion anisotropy measured by using diffusion tensor MR imaging Radiology 1998;209:57-66.
21. Forbes J, Pipe G, Bird CR. Changes in brain water diffusion during the 1st year of life. Radiology 2002;222:405-409.
22. Lobel O, Sedlacik J, Gullmar D, WA et al. Diffusion tensor imaging: the normal evolution of ADC, RA, FA, and eigenvalues studied in multiple anatomical regions of the brain. Neuroradiology 2009;51:253-263.
23. Zhai G, Lin W, Wilber KP, Gerig G, Gilmore JH. Comparisons of regional white matter diffusion in healthy neonates and adults performed with a 3.0-T head-only MR imaging unit. Radiology 2003;229: 673- 681.
24. Fadeel SRA, Montasser MM, Etaby AN, Darweesh RMA. The role of diffusion weighted magnetic resonanceimaging in assessment of normal myelination in infantile brain. Alexandria Journal of Medicine 2015;51:271-276.