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Evaluation of changes in myelination in the brain during infancy and childhood using ADC maps

Bebek ve çocukluk döneminde beyinde miyelinizasyon ile ilgili değişikliklerin ADC haritaları kullanılarak değerlendirilmesi

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Abstract

Aim: Myelinization has a critical role in achieving rapid synchronization between the neural system and high-grade cognitive functions. Because of this critical role, it is important to quantitatively determine the degree of myelination. Today, structural changes due to myelination can be evaluated quantitatively by diffusion magnetic resonance imaging (MRI) and apparent diffusion coefficient (ADC) measurements. The aim of this study was to evaluate myelination-related changes in different regions of the brain during infancy and childhood in the normal population by measuring ADC values in routine MRI examinations.

Methods: In this cross-sectional study, 109 patients aged 0-17 years who underwent brain MRI examination with 3.0T device and whose myelination and maturation were interpreted as normal in conventional sequences were evaluated. In all examinations, ADC maps from 30 different locations were evaluated and measured in the workstation based on T2-weighted images.

Results: There is a functional relationship between ADC values and the myelination process during infancy and childhood in the normal population. ADC values decrease in all localizations with increasing age, especially during the first 2 years. During the postnatal period, ADC values, which are higher in the white matter, decrease as maturation of white matter is completed and increase in the cortical gray matter. No significant difference was found between bilateral structures except the thalamus, caudate nucleus or centrum semiovale regions. There was no gender-dependent significant difference in the patients aged between zero and 2 years.

Conclusion: ADC values for each localization can be easily obtained by diffusion weighted imaging and ADC maps, which are frequently used in routine MRI examinations. The relationship between ADC values and myelination process can be revealed in the whole brain and normative values can be obtained for multiple regions in the brain.

Keywords: Myelination, Diffusion weighted imaging, Magnetic resonance imaging, Apparent diffusion coefficient

Öz

Amaç: Nöral sistem arasında hızlı senkronizasyonun gerçekleşmesinde ve yüksek dereceli bilişsel fonksiyonların sağlanmasında myelinizasyonun kritik bir yeri vardır. Bu kritik rolü nedeniyle myelinizasyonun derecesini kantitatif olarak belirlemek çok önemlidir. Günümüzde difüzyon manyetik rezonans görüntüleme (MRG) ve görünür difüzyon katsayısı (ADC) ölçümleri ile myelinizasyona bağlı oluşan yapısal değişiklikler kantitatif olarak değerlendirilebilir. Çalışmamızın amacı normal popülasyonda bebeklik ve çocukluk çağında beynin farklı bölgelerinde miyelinizasyonla ilişkili değişikliklerin rutin MRG incelemelerinde ADC değerleri ölçülerek değerlendirilmesidir.

Yöntemler: Bu kesitsel çalışmada, 3.0T cihaz ile beyin MRG incelemesi yapılan ve miyelinizasyonu ve maturasyonu konvansiyonel sekanslarda normal olarak yorumlanan yaşları 0-17 arasındaki 109 hasta değerlendirildi. Tüm incelemelerde T2 ağırlıklı görüntüler baz alınarak 30 farklı lokalizasyondan ADC haritaları iş istasyonunda değerlendirilerek ölçüm yapıldı.

Bulgular: Normal populasyonda bebeklik ve çocukluk çağında miyelinizasyon süreci ve ADC değerleri arasında fonksiyonel bir ilişki bulunmaktadır. Yaş arttıkça ADC değerleri ilk 2 yaşta daha belirgin olmak üzere tüm lokalizasyonlarda azalmaktadır. Postnatal süreçte beyaz cevherde daha yüksek olan ADC değerleri beyaz cevher maturasyonu tamamlandıkça azalmakta ve kortikal gri cevherde daha yüksek hale gelmektedir. Talamus, kaudat nükleus ve santral sentrum semiovale dışında her iki hemisferde karşılıklı yapılarda anlamlı farklılık bulunmamıştır. Yapılan karşılaştırmada 0 ile 2 yaş arasındaki hastalarda cinsiyete bağlı anlamlı bir fark yoktu.

Sonuç: Beyin MRG incelemelerinde rutin pratikte sıklıkla kullanılan difüzyon ağırlıklı görüntüleme ve ADC haritaları ile her bir lokalizasyon için ADC değerleri kolayca elde edilebilmektedir. Böylelikle ADC değerleri ile miyelinizasyon süreci ilişkisi tüm beyinde ortaya konabilmekte ve beyinde multipl bölge için normatif değerler elde edilebilmektedir.

Anahtar kelimeler: Miyelinizasyon, Difüzyon ağırlıklı görüntüleme, Manyetik rezonans görüntüleme, Görünür difüzyon katsayısı

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Introduction

Myelination is an extremely sensitive and multi-staged process that begins in fetal life and is largely completed during the 2nd postnatal year. While some structures complete their maturation process in the initial stages of fetal development, others may remain incompletely myelinated until the 3rd and 4th decades of life [1,2].

Brain myelination maturation extends from the inferior to the superior, from the central to the peripheral, and from the posterior to the anterior regions. For example, the brainstem is myelinated before the cerebellar hemispheres, the posterior limb of the internal capsule before the anterior limb and deep periventricular white matter before subcortical U fibers [3,4].

There is no improved technique for directly visualizing myelin structure. Myelin can only be evaluated qualitatively [5]. Commonly used magnetic resonance (MR) techniques include conventional anatomic imaging, i.e., T1-weighted and T2-weighted sequences, as well as MR spectroscopy and diffusion tensor imaging (DTI). Nowadays, standard magnetic resonance imaging (MRI) techniques are not particularly capable of determining the amount of myelin. Instead, these techniques evaluate changes in axonal size and density, membrane structure including lipid and protein content, and a combination of water and macromolecule content [5,6].

Diffusion-weighted imaging is sensitive to the movement of water molecules. It is frequently used with advantages such as image acquisition in brief time and no need for contrast material. Diffusion weighted images are evaluated together with apparent diffusion coefficient (ADC) maps and quantitative measurement of diffusion coefficient can be performed [7,8].

In our study, mean ADC values during the myelination process at each localization for each age group were determined by measurement of ADC values from 30 different localizations of the brains of children with normal cranial MRI findings, and ADC changes during myelination between the two hemispheres and the two genders were comparatively analyzed. The aim of our study is to contribute to the development of reference values for intracranial pathologies that lead to ADC changes but do not show signs in conventional sequences.

Materials and methods

The cranial MRI results of 109 patients who were referred to the Radiology Department of Dicle University, Faculty of Medicine with complaints of headache, nausea, convulsion and a prediagnosis of intracranial mass between December 2014-January 2018 were evaluated retrospectively by two neuroradiologists. Patients with pathological cranial MRIs or those not fit for evaluation due to artefacts were excluded. 50 males and 59 females between the ages of 0-17 years were included in our study.

MRI protocol

All cranial MRI examinations were performed with a 3.0 Tesla MRI device (Achieva, Philips Medical systems, Best, the Netherlands) using an 8-channel cranial coil and images were evaluated at the Philips Extended MR Workspace workstation. MRI protocol routinely used for brain imaging in our hospital includes T2-weighted TSE (turbo spin-echo) sequences in the axial and sagittal plane, FLAIR sequence (fluid-attenuated-inversion-recovery) and axial T1-weighted SE (Spin echo) sequences.

Evaluation method

Diffusion weighted images of the areas to be examined on routine MRI images were analyzed at the Philips Extended MR Workspace workstation. Basing on T2-weighted images, ROI was carefully placed in oval, round, or rectangular shape in the areas to be examined by cross-linking on 'b=0' images, which are better than the other maps in revealing anatomical detail. The minimum and maximum sizes of placed ROI according to the localization were 6 mm^2 and 300 mm^2, respectively. For each patient, the mean ADC values, standard deviation, minimum and maximum ADC values ($x10^{-3}$ mm^2/sec) in these areas were manually calculated on ADC maps (Figure 1).

Patients were divided into 10 groups according to age. Mean values in all localizations, distribution of mean values according to age, differences between males and females, differences between the right and left hemisphere of the brain at the same localization were calculated for each group.

Statistical analysis

ADC values were measured separately for each localization. To determine age-dependent changes, mean ADC values were calculated for each group at each location. Individuals were divided into subgroups depending on age range (0-3 months, 3-6 months, 6-12 months, 12-24 months, 24-36 months, 3-5 years, 5-8 years, 8-11 years, 11-14 years and 14 years) and age-dependent changes were calculated with 95% reliability.

Wilcoxon signed rank test was used to compare the same regions in both hemispheres and white matter, cortical gray matter and deep gray matter. In order to compare gender-dependent differences in gray and white matter, individuals were divided into two groups: 0-2 years and 2-17 years. Mann Whitney U test was used to evaluate gender-dependent differences between the same localizations.

Results

ADC values in infants and children decrease in all 30 regions as age increases, especially during the first year. For example, the mean ADC value for the right lentiform nucleus (Region 5) in the youngest age group (0-3 months) was 0.971 x 10^{-3} mm^2/sec, which decreased to 0.850 x 10^{-3} mm^2/sec between 6-12 months and 0.707 x 10^{-3} mm^2/sec in the oldest age group (14-17 years) (Figure 2). In the left frontal white matter (Region 14), the mean ADC value was 1.275 x 10^{-3} mm^2/sec in the youngest age group (0-3 months), 1.057 x 10^{-3} mm^2/sec in the 6-12 month range, and 0.752 x 10^{-3} mm^2/sec in the 14-17 year-old group (Figure 3). For the left occipital cortex (Region 10), the mean ADC value in the 0-3 month-old group was 1.080 x 10^{-3} mm^2/sec, 0.885x 10^{-3} mm^2/sec between 6-12 months and 0.793 x 10^{-3} mm^2/sec in the oldest age group (Figure 4). The mean ADC values and standard deviations by age groups for each localization are listed in Tables 1-4.

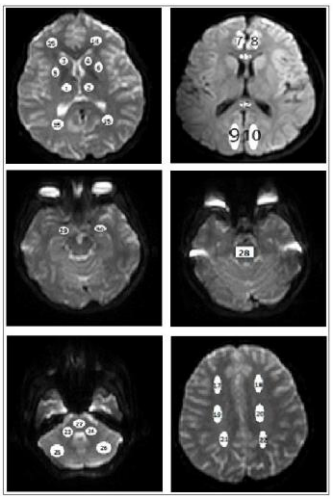

Figure 1: Localizations of ADC measurement

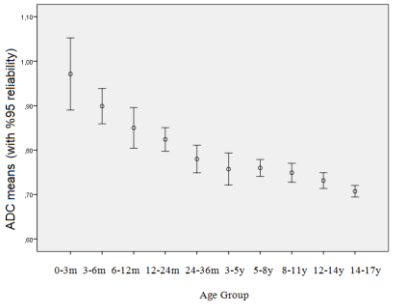

Figure 2: Mean age-dependent ADC values in right lentiform nucleus

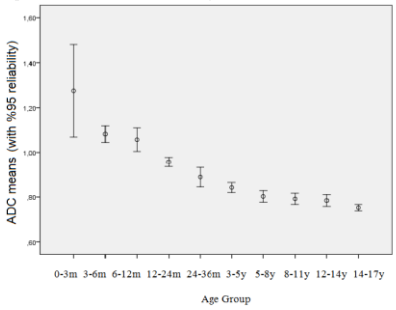

Figure 3: Age-dependent mean ADC values in left frontal white matter

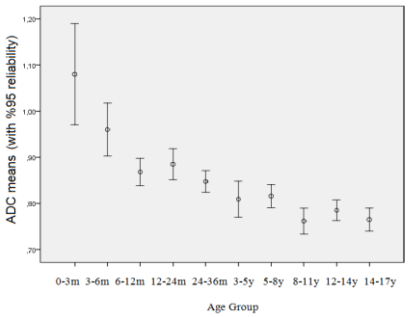

Figure 4: Age-dependent mean ADC values in left occipital cortex

Table 1: Cerebellum: ADC values with respect to age groups in middle cerebellar peduncle and hemispheres (Region 23-26)

23 (Right middle cerebellar peduncle)			24 (Left middle cerebellar peduncle)		
Age group	N	Mean (SD)	Age group	N	Mean (SD)
0-3 Months	8	0.93 (0.05)	0-3 Months	8	0.91 (0.07)
3-6 Months	9	0.80 (0.05)	3-6 Months	9	0.78 (0.06)
6-12 Months	11	0.78 (0.04)	6-12 Months	11	0.77 (0.05)
12-24 Months	10	0.77 (0.07)	12-24 Months	10	0.75 (0.04)
24-36 Months	12	0.75 (0.05)	24-36 Months	12	0.73 (0.06)
3-5 Years	11	0.70 (0.05)	3-5 Years	11	0.69 (0.03)
5-8 Years	12	0.71 (0.04)	5-8 Years	12	0.71 (0.04)
8-11 Years	12	0.68 (0.05)	8-11 Years	12	0.70 (0.04)
12-14 Years	12	0.70 (0.04)	12-14 Years	12	0.69 (0.05)
14-17 Years	12	0.68 (0.03)	14-17 Years	12	0.67 (0.03)
25 (Right cerebellar cortex)			26 (Left cerebellar cortex)		
Age group	N	Mean (SD)	Age group	N	Mean (SD)
0-3 Months	8	0.87 (0.12)	0-3 Months	8	0.88 (0.14)
3-6 Months	9	0.75 (0.07)	3-6 Months	9	0.76 (0.09)
6-12 Months	11	0.73 (0.02)	6-12 Months	11	0.75 (0.04)
12-24 Months	10	0.72 (0.05)	12-24 Months	10	0.73 (0.05)
24-36 Months	12	0.72 (0.04)	24-36 Months	12	0.70 (0.03)
3-5 Years	11	0.69 (0.02)	3-5 Years	11	0.67 (0.03)
5-8 Years	12	0.68 (0.02)	5-8 Years	12	0.68 (0.03)
8-11 Years	12	0.65 (0.02)	8-11 Years	12	0.65 (0.02)
12-14 Years	12	0.68 (0.03)	12-14 Years	12	0.65 (0.02)
14-17 Years	12	0.65 (0.02)	14-17 Years	12	0.64 (0.03)

N: number of patients, SD: standard deviation

Table 2: Deep Gray Matter and Brain Stem: ADC values with respect to age groups at levels of thalamus, caudate and lentiform nuclei and amygdala, mesencephalon and pons (region 1-6, 27-30)

1 (Right thalamus)			2 (Left thalamus)		
Age group	N	Mean (SD)	Age group	N	Mean (SD)
0-3 Months	8	0.92 (0.08)	0-3 Months	8	0.93 (0.09)
3-6 Months	9	0.87 (0.07)	3-6 Months	9	0.84 (0.05)
6-12 Months	11	0.82 (0.02)	6-12 Months	11	0.81 (0.03)
12-24 Months	10	0.83 (0.03)	12-24 Months	10	0.82 (0.02)
24-36 Months	12	0.82 (0.09)	24-36 Months	12	0.79 (0.10)
3-5 Years	11	0.77 (0.03)	3-5 Years	11	0.76 (0.03)
5-8 Years	12	0.78 (0.04)	5-8 Years	12	0.77 (0.04)
8-11 Years	12	0.72 (0.03)	8-11 Years	12	0.70 (0.04)
12-14 Years	12	0.75 (0.02)	12-14 Years	12	0.74 (0.01)
14-17 Years	12	0.71 (0.03)	14-17 Years	12	0.71 (0.03)
3 (Right caudate nucleus)			4 (Left caudate nucleus)		
Age group	N	Mean (SD)	Age group	N	Mean (SD)
0-3 Months	8	1.03 (0.12)	0-3 Months	8	1.01 (0.12)
3-6 Months	9	0.95 (0.06)	3-6 Months	9	0.93 (0.07)
6-12 Months	11	0.87 (0.06)	6-12 Months	11	0.86 (0.08)
12-24 Months	10	0.85 (0.04)	12-24 Months	10	0.85 (0.04)
24-36 Months	12	0.82 (0.08)	24-36 Months	12	0.81 (0.11)
3-5 Years	11	0.80 (0.04)	3-5 Years	11	0.79 (0.04)
5-8 Years	12	0.78 (0.03)	5-8 Years	12	0.78 (0.04)
8-11 Years	12	0.76 (0.02)	8-11 Years	12	0.75 (0.03)
12-14 Years	12	0.74 (0.02)	12-14 Years	12	0.73 (0.02)
14-17 Years	12	0.71 (0.03)	14-17 Years	12	0.70 (0.03)
5 (Right lentiform nucleus)			6 (Left lentiform nucleus)		
Age group	N	Mean (SD)	Age group	N	Mean (SD)
0-3 Months	8	0.97 (0.09)	0-3 Months	8	0.97 (0.11)
3-6 Months	9	0.89 (0.05)	3-6 Months	9	0.90 (0.05)
6-12 Months	11	0.85 (0.06)	6-12 Months	11	0.85 (0.09)
12-24 Months	10	0.82 (0.03)	12-24 Months	10	0.81 (0.04)
24-36 Months	12	0.78 (0.04)	24-36 Months	12	0.77 (0.07)
3-5 Years	11	0.75 (0.05)	3-5 Years	11	0.74 (0.04)
5-8 Years	12	0.76 (0.02)	5-8 Years	12	0.75 (0.04)
8-11 Years	12	0.74 (0.03)	8-11 Years	12	0.72 (0.04)
12-14 Years	12	0.73 (0.02)	12-14 Years	12	0.73 (0.02)
14-17 Years	12	0.70 (0.02)	14-17 Years	12	0.70 (0.03)
29 (Right amygdala)			30 (Left amygdala)		
Age group	N	Mean (SD)	Age group	N	Mean (SD)
0-3 Months	8	1.15 (0.12)	0-3 Months	8	1.08 (0.41)
3-6 Months	9	0.97 (0.02)	3-6 Months	9	0.97 (0.03)
6-12 Months	11	0.96 (0.09)	6-12 Months	11	0.95 (0.06)
12-24 Months	10	0.91 (0.03)	12-24 Months	10	0.89 (0.05)
24-36 Months	12	0.87 (0.06)	24-36 Months	12	0.83 (0.06)
3-5 Years	11	0.83 (0.04)	3-5 Years	11	0.83 (0.05)
5-8 Years	12	0.85 (0.05)	5-8 Years	12	0.85 (0.06)
8-11 Years	12	0.83 (0.04)	8-11 Years	12	0.83 (0.03)
12-14 Years	12	0.83 (0.03)	12-14 Years	12	0.80 (0.03)
14-17 Years	12	0.80 (0.03)	14-17 Years	12	0.81 (0.03)
27 (Mesencephalon)			28 (Pons)		
Age group	N	Mean (SD)	Age group	N	Mean (SD)
0-3 Months	8	0.91 (0.07)	0-3 Months	8	0.89 (0.10)
3-6 Months	9	0.90 (0.05)	3-6 Months	9	0.80 (0.03)
6-12 Months	11	0.87 (0.03)	6-12 Months	11	0.76 (0.02)
12-24 Months	10	0.82 (0.05)	12-24 Months	10	0.76 (0.06)
24-36 Months	12	0.78 (0.05)	24-36 Months	12	0.72 (0.04)
3-5 Years	11	0.79 (0.04)	3-5 Years	11	0.71 (0.07)
5-8 Years	12	0.76 (0.08)	5-8 Years	12	0.70 (0.07)
8-11 Years	12	0.74 (0.04)	8-11 Years	12	0.67 (0.05)
12-14 Years	12	0.73 (0.03)	12-14 Years	12	0.67 (0.03)
14-17 Years	12	0.69 (0.05)	14-17 Years	12	0.65 (0.03)

N: number of patients, SD: standard deviation

Table 3: Cortical Gray Matter: ADC values with respect to age groups at levels of frontal and occipital gray matter (regions 7, 8, 9, 10)

7 (Right frontal cortex)			8 (Left frontal cortex)		
Age group	N	Mean (SD)	Age group	N	Mean (SD)
0-3 Months	8	1.06 (0.08)	0-3 Months	8	1.09 (0.08)
3-6 Months	9	1.02 (0.05)	3-6 Months	9	1.0 (0.06)
6-12 Months	11	0.96 (0.03)	6-12 Months	11	0.97 (0.03)
12-24 Months	10	0.92 (0.05)	12-24 Months	10	0.92 (0.04)
24-36 Months	12	0.90 (0.09)	24-36 Months	12	0.91 (0.07)
3-5 Years	11	0.88 (0.03)	3-5 Years	11	0.88 (0.05)
5-8 Years	12	0.87 (0.03)	5-8 Years	12	0.87 (0.03)
8-11 Years	12	0.87 (0.03)	8-11 Years	12	0.87 (0.02)
12-14 Years	12	0.86 (0.02)	12-14 Years	12	0.86 (0.02)
14-17 Years	12	0.85 (0.02)	14-17 Years	12	0.86 (0.04)
9 (Right occipital cortex)			10 (Left occipital cortex)		
Age group	N	Mean (SD)	Age group	N	Mean (SD)
0-3 Months	8	1.06 (0.09)	0-3 Months	8	1.08 (0.13)
3-6 Months	9	0.92 (0.06)	3-6 Months	9	0.96 (0.07)
6-12 Months	11	0.88 (0.04)	6-12 Months	11	0.88 (0.04)
12-24 Months	10	0.87 (0.04)	12-24 Months	10	0.86 (0.04)
24-36 Months	12	0.84 (0.04)	24-36 Months	12	0.84 (0.03)
3-5 Years	11	0.83 (0.05)	3-5 Years	11	0.83 (0.05)
5-8 Years	12	0.83 (0.03)	5-8 Years	12	0.82 (0.03)
8-11 Years	12	0.82 (0.03)	8-11 Years	12	0.78 (0.4)
12-14 Years	12	0.82 (0.03)	12-14 Years	12	0.80 (0.3)
14-17 Years	12	0.80 (0.04)	14-17 Years	12	0.79 (0.03)

N: number of patients, SD: standard deviation

Table 4: Deep white matter, white matter: Frontal and peritrigonal white matter and centrum semiovale (regions 13-22).

11 (Corpus callosum genu)			12 (Corpus callosum splenium)		
Age group	N	Mean (SD)	Age group	N	Mean (SD)
0-3 Months	8	1.17 (0.12)	0-3 Months	8	1.13 (0.12)
3-6 Months	9	1.10 (0.13)	3-6 Months	9	1.05 (0.12)
6-12 Months	11	1.00 (0.11)	6-12 Months	11	0.90 (0.13)
12-24 Months	10	0.84 (0.05)	12-24 Months	10	0.82 (0.06)
24-36 Months	12	0.83 (0.04)	24-36 Months	12	0.76 (0.09)
3-5 Years	11	0.78 (0.06)	3-5 Years	11	0.78 (0.06)
5-8 Years	12	0.79 (0.05)	5-8 Years	12	0.77 (0.07)
8-11 Years	12	0.76 (0.07)	8-11 Years	12	0.74 (0.11)
12-14 Years	12	0.75 (0.04)	12-14 Years	12	0.75 (0.06)
14-17 Years	12	0.75 (0.06)	14-17 Years	12	0.74 (0.03)
13 (Right frontal white matter)			14 (Left frontal white matter)		
Age group	N	Mean (SD)	Age group	N	Mean (SD)
0-3 Months	8	1.26 (0.23)	0-3 Months	8	1.27 (0.24)
3-6 Months	9	1.10 (0.04)	3-6 Months	9	1.08 (0.04)
6-12 Months	11	1.07 (0.07)	6-12 Months	11	1.05 (0.07)
12-24 Months	10	0.95 (0.03)	12-24 Months	10	0.95 (0.02)
24-36 Months	12	0.89 (0.04)	24-36 Months	12	0.88 (0.06)
3-5 Years	11	0.84 (0.03)	3-5 Years	11	0.84 (0.03)
5-8 Years	12	0.79 (0.04)	5-8 Years	12	0.80 (0.04)
8-11 Years	12	0.78 (0.04)	8-11 Years	12	0.79 (0.03)
12-14 Years	12	0.77 (0.05)	12-14 Years	12	0.78 (0.04)
14-17 Years	12	0.75 (0.03)	14-17 Years	12	0.75 (0.02)
15 (Right occipital white matter)			16 (Left occipital white matter)		
Age group	N	Mean (SD)	Age group	N	Mean (SD)
0-3 Months	8	1.25 (0.21)	0-3 Months	8	1.26 (0.23)
3-6 Months	9	1.13 (0.04)	3-6 Months	9	1.12 (0.08)
6-12 Months	11	1.13 (0.11)	6-12 Months	11	1.13 (0.09)
12-24 Months	10	0.98 (0.07)	12-24 Months	10	0.97 (0.27)
24-36 Months	12	0.92 (0.09)	24-36 Months	12	0.90 (0.08)
3-5 Years	11	0.86 (0.04)	3-5 Years	11	0.86 (0.03)
5-8 Years	12	0.85 (0.06)	5-8 Years	12	0.86 (0.07)
8-11 Years	12	0.81 (0.04)	8-11 Years	12	0.83 (0.05)
12-14 Years	12	0.81 (0.04)	12-14 Years	12	0.81 (0.04)
14-17 Years	12	0.79 (0.03)	14-17 Years	12	0.81 (0.03)
17 (Right frontal centrum semiovale)			18 (Left frontal centrum semiovale)		
Age group	N	Mean (SD)	Age group	N	Mean (SD)
0-3 Months	8	1.17 (0.06)	0-3 Months	8	1.15 (0.20)
3-6 Months	9	1.06 (0.07)	3-6 Months	9	1.03 (0.08)
6-12 Months	11	1.01 (0.04)	6-12 Months	11	1.00 (0.05)
12-24 Months	10	0.88 (0.05)	12-24 Months	10	0.89 (0.07)
24-36 Months	12	0.82 (0.02)	24-36 Months	12	0.82 (0.02)
3-5 Years	11	0.78 (0.04)	3-5 Years	11	0.79 (0.04)
5-8 Years	12	0.77 (0.04)	5-8 Years	12	0.77 (0.05)
8-11 Years	12	0.74 (0.03)	8-11 Years	12	0.73 (0.02)
12-14 Years	12	0.74 (0.03)	12-14 Years	12	0.74 (0.02)
14-17 Years	12	0.71 (0.03)	14-17 Years	12	0.70 (0.03)
19 (Right central centrum semiovale)			20 (Left central centrum semiovale)		
Age group	N	Mean (SD)	Age group	N	Mean (SD)
0-3 Months	8	1.15 (0.20)	0-3 Months	8	1.12 (0.16)
3-6 Months	9		3-6 Months	9	1.02 (0.09)
6-12 Months	11	0.98 (0.07)	6-12 Months	11	0.97 (0.09)
12-24 Months	10	0.85 (0.05)	12-24 Months	10	0.84 (0.04)
24-36 Months	12	0.82 (0.02)	24-36 Months	12	0.81 (0.03)
3-5 Years	11	0.76 (0.05)	3-5 Years	11	0.74 (0.05)
5-8 Years	12	0.77 (0.05)	5-8 Years	12	0.77 (0.08)
8-11 Years	12	0.73 (0.06)	8-11 Years	12	0.72 (0.04)
12-14 Years	12	0.74 (0.04)	12-14 Years	12	0.73 (0.04)
14-17 Years	12	0.69 (0.04)	14-17 Years	12	0.65 (0.05)
21 (Right posterior centrum semiovale)			22 (Left posterior centrum semiovale)		
Age group	N	Mean (SD)	Age group	N	Mean (SD)
0-3 Months	8	1.17 (0.22)	0-3 Months	8	1.16 (0.20)
3-6 Months	9	1.02 (0.05)	3-6 Months	9	1.00 (0.06)
6-12 Months	11	1.00 (0.07)	6-12 Months	11	1.03 (0.10)
12-24 Months	10	0.92 (0.06)	12-24 Months	10	0.89 (0.07)
24-36 Months	12	0.86 (0.05)	24-36 Months	12	0.84 (0.05)
3-5 Years	11	0.79 (0.05)	3-5 Years	11	0.79 (0.05)
5-8 Years	12	0.80 (0.05)	5-8 Years	12	0.82 (0.08)
8-11 Years	12	0.77 (0.06)	8-11 Years	12	0.75 (0.04)
12-14 Years	12	0.76 (0.03)	12-14 Years	12	0.77 (0.03)
14-17 Years	12	0.72 (0.02)	14-17 Years	12	0.72 (0.03)

N: number of patients, SD: standard deviation

Table 5: Comparison of ADC values at different localizations in both age groups ($x10^{-3}$ mm^2/sn

	0-2 Years			2-17 Years		
	DGM	WM	CGM	DGM	WM	CGM
N	38	38	38	71	71	71
Minimum	0.77	0.87	0.84	0.67	0.71	0.7
Maximum	1.18	1.51	1.22	1.04	0.94	1.03
Mean	0.8832	1.0459	0.9514	0.7563	0.7912	0.8022
SD	0.08083	0.13897	0.09442	0.05058	0.05331	0.04903

N: Number of patients, DGM: Deep Gray Matter, WM: White matter, CGM: Cortical Gray Matter, SD: Standard Deviation

The mean ADC values of white matter and gray matter were compared after all patients were divided into two subgroups according to age (0-2 years and 2-17 years).

Significant differences were found between all matched comparisons between white matter, cortical and deep gray matter in both age groups (P<0.001). Descriptive analytic results are presented in Table 5. There was a significant difference in all matched regions (P<0.001).

We analyzed the age-dependent distribution of ADC values in both subgroups (0-2 and 2-17 years). The mean ADC values of 0 to 2-year-old males and females were similar (P=0.645). There were no gender-related differences in any localization for this group. Mann-Whitney U test revealed distorted age distribution in the older age group, and no comparisons could be made.

When comparing the paired regions in both hemispheres, significant differences were detected between caudate nucleus (P=0.042) and central centrum semiovale (P=0.02). No significant differences were found in other matched regions.

Discussion

Until myelination is completed, ADC values decrease, especially during the first 2 years [9,10]. Changes in ADC values in response to structural adjustments due to increased anisotropy during cerebral development provide an objective, investigator-independent measurement of signal intensity. This decrease in ADC values is multifactorial due to the decrease in the total amount of water and the increase in lipid and macromolecules [11,12]. In addition, the increase in perfusion after birth as defined by Kehrer et al. [13] may also help explain changes in ADC values .

In their study performed on prenatal healthy children by obtaining measurements from 10 different localizations, Han et al.'s [14] results show similarities with our postnatal measurements. Accordingly, the supratentorial region had higher ADC values than the infratentorial region and the highest ADC values were observed in the frontal white matter, followed by occipital white matter.

The comparison of mean ADC values of white, cortical, and deep gray matter performed by Bültmann et al. [15] revealed comparable results to our study. They have found a significant difference between the structures compared. We found that ADC values were highest in supratentorial white matter after birth and higher than that in the gray matter, and cortical gray matter had the highest values after myelination and maturation of the brain. The significant difference they found in peritrigonal white matter between both hemispheres was not detected in our study, which can be explained by the fact that this region, called the terminal zone, is sensitive to differences in ROI positioning. In our study, the difference in the centrum semiovale and the caudate nucleus can be explained by the small differences in the standardization of ROI and the proximity of the caudate nucleus to the CSF.

Our findings are similar to the those of the study performed by Schneider et al. [16], in which they measured ADC values at 9 different sites in normal intrauterine fetuses (mean gestational age: 31 (3) weeks). Their values were higher than our postnatal results, but this can be explained by the decrease in ADC values as myelination increases. In addition, the researchers have been able to show that the brain stem, thalamus, and cerebellum have lower ADC values, which shows signs of earlier maturation with regards to the hypothesis of myelination occurring from the caudal towards the cranial areas. In our study, the postnatal ADC values in the brainstem and infratentorial structures were lower than the structures located cranially.

Schneider et al. [16] paid attention to the centrum semiovale, seen as loose white matter fibers after combining all deep white matter due to early myelin deposition and maturation in corticospinal tracts. Consistent with this observation, our ADC

values were slightly lower in the central, peri-rolandic part of the centrum semiovale than in the frontal and parietal parts, and, higher than the brain stem, which shows that the myelination of the centrum semiovale occurs slightly later when compared with sensory pathways in the brain stem and slightly earlier than the frontal and parietal regions. These findings support that myelination extends from the central regions toward the peripheral regions. In general, our measurements showed higher ADC values in all supratentorial deep white matter structures (except corpus callosum) compared to gray matter and infratentorial white matter, which showed later myelination.

The data on ADC values in neonatal brains with normal findings in the meta-analysis of Coats et al. [17] resembles those of ours. Higher ADC values were observed in the white matter than gray matter and the highest values were found in the frontal and occipital white matter, while the lowest ADC values were detected in the hind limb of the internal capsule and thalamus within the supratentorial part of the brain. In our study, the highest values were found in frontal and occipital white matter and the lowest values were observed in the thalamus and basal ganglia.

Our postnatal results are akin to those obtained by Engelbrecht et al. [18]. Increased ADC values in accordance with to monocyte expression function decreased with age in all investigated regions. Engelbrecht et al. [18] reportedly detected the highest values in the frontal and occipital white matter and the lowest values in the brain stem, which is consistent with our data.

Limitations

There are some factors limiting our study. Firstly, we selected patients without signal abnormalities or with focal anomalies which are not reflected in imaging, who had different clinical indications for conventional MRI examinations. Although we studied patients without any symptoms, our lack of a group without any complaints may be considered a deficiency. The disadvantage of our study is that there is a need for sedation or intubation during evaluation of healthy individuals during infancy or childhood. Another weakness of our study is that we use three directions instead of full diffusion tensor imaging. Therefore, examinations can yield different results depending on the position of the head or the orientation of the white matter fibers. Also, ADC measurements are extremely sensitive even to small motion artifacts and yield different results according to the size of the ROI used. Measurements in the regions close to CSF are easily affected by CSF volume. However, since we use diffusion sequences in routine MRI examinations in our clinic and obtain easily accessible results, these potential weaknesses are acceptable. The fact that our data is objective, reproducible, realistic, and comparable to the literature indicates that despite our weaknesses, our study is applicable in the evaluation of myelination.

Conclusion

The main result of our study is the ability to define ADC values for gray and white matter structures throughout the myelination process in the brain based on applicable diffusion weighted sequences. Using diffusion-weighted images and conventional sequences, we demonstrated reproducible ADC values in infancy and childhood. The obtained data show a close similarity when compared with the literature data. Our values showed a direct correlation with different myelination and maturation processes in different brain regions. For this reason, ADC values obtained from routine clinical MRI examinations can be used to assess whether postnatal maturation is appropriate for age. Our data will be useful in detecting faint or diffuse abnormalities that cannot be evaluated in conventional sequences. Our values can be used in clinical routine and diffusion-weighted imaging and ADC maps should be used as part of the standard evaluation of pediatric maturation and myelination.

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