



# The role of diffusion weighted magnetic resonance imaging in assessment of normal myelination in infantile brain



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## KEYWORDS

Diffusion weighted magnetic resonance imaging;  
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**Abstract** *Background:* Myelination is a dynamic process starting during fetal life and proceeds predominantly after birth in a well-defined, predetermined manner. MR techniques such as diffusion-weighted images and the measurement of the apparent diffusion coefficient (ADC) have been applied to the study of normal brain development.

*Aim of the work:* To demonstrate the role of Diffusion Weighted Imaging and ADC maps in assessing normal progression of the infantile brain myelination.

*Patients and methods:* The present work included 30 infants with normal MRI study of the brain, normal psychomotor development and normal neurological examination. Conventional MRI, DWI and ADC maps were done for all the infants, the average ADC values were calculated in selected areas in white matter.

*Results:* The age of studied children ranged from 1 month to 3 years, 13 males (43.3%) and 17 females (56.7%). In each of the selected areas of the white matter of the brain, examined ADC showed the highest values at birth and there was a significant decrease with age ( $p < 0.05$ ).

*Conclusion:* ADC values decrease with progressive increase of age. Using ADC values is useful in assessment of normal myelination development in the infantile brain and matches the results of conventional MRI.

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## 1. Background

Myelination is a dynamic process that starts during fetal life and proceeds predominantly after birth, at least until the end of the third year in a well-defined predetermined manner.<sup>1</sup>

It is useful to characterize myelination evolution in normal brain development in order to allow assessment of neurodevelopment that can enhance our understanding of early brain

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growth changes during both normal and abnormal brain development.<sup>2</sup>

MR imaging is a safe, noninvasive method for evaluating the development of myelination in infants. Diffusion weighted MRI and ADC maps depend on the fact that as the formation of myelin by the oligodendrocytes proceeds, an increase in brain cholesterol and glycolipids concentration and a decrease in water content take place. This results in a change of white matter diffusion properties.<sup>3</sup>

Myelination begins at around 20 weeks gestational age (GA) and continues up to around 2 years of age. As myelination precedes, the water content of white matter (WM) decreases, causing a reduction in signal intensity (SI) on T2 weighted imaging. There is a corresponding increase in glycolipids, cholesterol and proteins, which causes an increase in SI on T1 weighted imaging. Changes in the SI of WM due to myelination are demonstrated at different ages on T1 and T2 weighted imaging. T1 weighted imaging is better at demonstrating myelination in the first 6–8 months after birth and T2 weighted imaging is better between 6 and 18 months.<sup>4</sup>

The water content of the brain tissues declines between 24 weeks and term. Myelin is seen in many gray matter nuclei and white matter tracts of the brainstem and cerebellum around 28 weeks of gestational age. However, new myelin is not seen between 28 and 36 weeks gestational age.<sup>5</sup>

During the first year of life, myelin spreads throughout the brain according to a predetermined scheme of chronological and topographic sequences. It proceeds centrifugally, from inferior to superior and from posterior to anterior. In the brain-stem, myelination proceeds from the dorsal to the ventral areas. In the cerebral hemispheres, it proceeds from the central sulcus toward the pole and from the occipital and parietal lobes toward the frontal and temporal lobes. Sensory fibers myelinate before motor fibers, and projection pathways earlier than association pathways; sensitive, visual, and auditory tracts are already myelinated at birth.<sup>3</sup>

Diffusion magnetic resonance imaging (DWI) studies the diffusivity of water, i.e. the random microscopic movement of water molecules, or Brownian motion, induced by thermal energy. The movement of water molecules is affected by various tissue components (cell walls, membranes, intracellular organs, macromolecules).<sup>6–8</sup>

MR measurement of the Brownian movement of water molecules can be applied at different, increasingly complex levels: DWI, ADC maps, DTI and Tractography.<sup>9</sup>

## 2. Aim of the work

The aim of the work is to demonstrate the role of Diffusion Weighted Imaging and ADC maps in assessing normal progression of the infantile brain myelination.

## 3. Patients and methods

The present work included 30 infants with the following inclusion criteria:

1. Normal MRI study of the brain.
2. Normal psychomotor development.
3. Normal by neurological examination.

All infants included in the study underwent the following:

1. Full history taking.
2. Thorough clinical examination.
3. All the infants were sedated and no discomfort or complications were found by care takers.
4. Conventional Magnetic Resonance Imaging including T1 WI, and T2 WI were done and they were essentially normal.
5. Diffusion Weighted Imaging and ADC maps were done for all the infants, the average ADC values were calculated in selected areas in the white matter as follows:

Supra tentorial region (7 sites)	<ul style="list-style-type: none"> <li>• Genu and splenium of the corpus callosum.</li> <li>• Anterior and posterior limb of the internal capsule.</li> <li>• Corona radiata.</li> <li>• Centrum semiovale (pre and post central gyrus).</li> </ul>
Infra tentorial region (3 sites)	<ul style="list-style-type: none"> <li>• Middle cerebellar peduncle.</li> <li>• Ventral aspects of the brain stem at the level of the pons.</li> <li>• Dorsal aspects of the brain stem at the level of the pons.</li> </ul>

6. Regions of interest of five pixels were outlined manually in these areas by using a combination of the image with a *b* value of 0 images and ADC maps to help identify relevant anatomy.
7. Data from the medical ethics were considered, the infant's parents were aware of examination, informed consent was obtained.

## 4. Imaging parameters

MR imaging performed at 1.5 T was done for all patients using both conventional and DW sequences. DW imaging was performed with a maximum diffusion-sensitizing gradient of a *b* value of 1000 s/mm<sup>2</sup> in three orthogonal planes. By using an echo-planar technique, transverse images were obtained, both with and without the diffusion gradient: 6500/101 (repetition time msec/echo time msec); section thickness, 5 mm; intersection gap, 2.5 mm; field of view, 20 cm; matrix size, 128\_128; one signal acquired. Conventional MR sequences comprised transverse (480/16) and sagittal (450/8) T1-weighted sequences and transverse T2-weighted sequences (3000/30–90).

## 5. Statistical analysis

Statistical analysis was performed. A general linear regression model was used to examine the relationship between ADC and subject age.

## 6. Results

The present work included 30 children with their ages ranging from 1 month to 3 years, they were 13 males and 17 females (Table 1). Nineteen of them had ophthalmological

**Table 1** Distribution of the studied cases according to demographic data ( $n = 30$ ).

	No.	%
Sex		
Male	13	43.3
Female	17	56.7
Age (month)		
Min.–Max.	1.0–36.0	
Mean $\pm$ SD	15.10 $\pm$ 9.63	
Median	13.0	

abnormalities (e.g. retinoblastoma) and were recommended for MRI for preoperative evaluation of their condition or for post management follow up, eleven had minor trauma and were recommended for MRI to exclude intracranial hemorrhage. All of them were neurologically free.

Table 2 shows the minimum and maximum ADC values measured at different white matter areas of the brain of the studied population.

In each of the nine areas of the brain, examined ADC showed the highest values at birth and there was a significant decrease with age, ( $p < 0.05$ ). (Table 3).

In the middle cerebellar peduncle, the ADC values ranged between ( $1.32 \times 10^{-5}$  mm<sup>2</sup>/s) at age of 1 month and reaches ( $0.62 \times 10^{-5}$  mm<sup>2</sup>/s) at 3 years with mean  $\pm$  SD value of ( $0.81 \pm 0.16$ ) and median value of ( $0.76 \times 10^{-5}$  mm<sup>2</sup>/s) (Fig. 1).

In the dorsal aspect of the brain stem, the ADC values ranged between ( $1.28 \times 10^{-5}$  mm<sup>2</sup>/s) at age of 1 month and reaches ( $0.74 \times 10^{-5}$  mm<sup>2</sup>/s) at 3 years with mean  $\pm$  SD value of ( $0.89 \pm 0.10$ ) and median value of ( $0.90 \times 10^{-5}$  mm<sup>2</sup>/s) (Fig. 2).

In the ventral aspect of the brain stem, the ADC values ranged between ( $1.27 \times 10^{-5}$  mm<sup>2</sup>/s) at age of 1 month and reaches ( $0.72 \times 10^{-5}$  mm<sup>2</sup>/s) at 3 years with mean  $\pm$  SD value of ( $0.93 \pm 0.13$ ) and median value of ( $0.92 \times 10^{-5}$  mm<sup>2</sup>/s) (Fig. 3).

In the genu of the corpus callosum, the ADC values ranged between ( $1.35 \times 10^{-5}$  mm<sup>2</sup>/s) at age of 1 month and reaches ( $0.64 \times 10^{-5}$  mm<sup>2</sup>/s) at 3 years with mean  $\pm$  SD value of ( $0.98 \pm 0.20$ ) and median value of ( $0.93$ ) (Fig. 4).

In the splenium of the corpus callosum, the ADC values ranged between ( $1.71 \times 10^{-5}$  mm<sup>2</sup>/s) at age of 1 month and reaches ( $0.65 \times 10^{-5}$  mm<sup>2</sup>/s) at 3 years with mean  $\pm$  SD value

**Table 3** Correlation between age and the measured ADC values.

	Age	
	<i>r</i>	<i>p</i>
Middle cerebellar peduncle	−0.584*	0.001
Ventral brain stem	−0.696*	<0.001
Dorsal brain stem	−0.790*	<0.001
Genu corpus callosum	−0.796*	<0.001
Splenium corpus callosum	−0.469*	0.009
Anterior limb internal capsule	−0.620*	<0.001
Posterior limb internal capsule	−0.867*	<0.001
Corona radiata	−0.771*	<0.001
Centrum semiovale	−0.681*	<0.001

*r*: Pearson coefficient.

\* Statistically significant at  $p \leq 0.05$ .

of ( $0.86 \pm 0.20$ ) and median value of ( $0.84 \times 10^{-5}$  mm<sup>2</sup>/s) (Fig. 5).

In the anterior limb internal capsule, the ADC values ranged between ( $1.23 \times 10^{-5}$  mm<sup>2</sup>/s) at age of 1 month and reaches ( $0.62 \times 10^{-5}$  mm<sup>2</sup>/s) at 3 years with mean  $\pm$  SD value of ( $0.83 \pm 0.12$ ) and median value of ( $0.82 \times 10^{-5}$  mm<sup>2</sup>/s) (Fig. 6).

In the posterior limb of the internal capsule, the ADC values ranged between ( $0.99 \times 10^{-5}$  mm<sup>2</sup>/s) at age of 1 month and reaches ( $0.65 \times 10^{-5}$  mm<sup>2</sup>/s) at 3 years with mean  $\pm$  SD value of ( $0.81 \pm 0.09$ ) and median value of ( $0.80 \times 10^{-5}$  mm<sup>2</sup>/s) (Fig. 7).

In the corona radiata, the ADC values ranged between ( $1.01 \times 10^{-5}$  mm<sup>2</sup>/s) at age of 1 month and reaches ( $0.71 \times 10^{-5}$  mm<sup>2</sup>/s) at 3 years with mean  $\pm$  SD value of ( $0.86 \pm 0.08$ ) and median value of ( $0.86 \times 10^{-5}$  mm<sup>2</sup>/s) (Fig. 8).

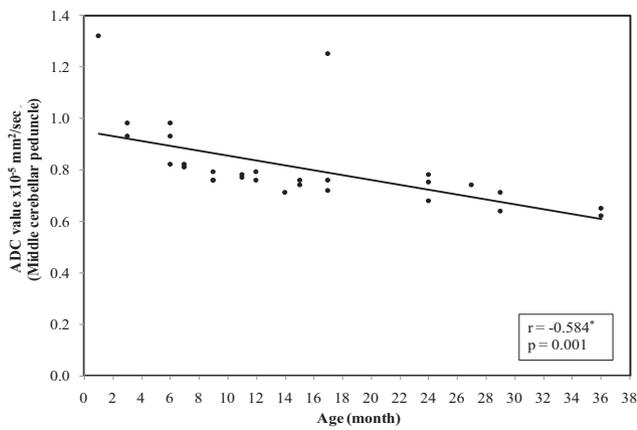
In the centrum semiovale, the ADC values ranged between ( $1.43 \times 10^{-5}$  mm<sup>2</sup>/s) at age of 1 month and reaches ( $0.72 \times 10^{-5}$  mm<sup>2</sup>/s) at 3 years with mean  $\pm$  SD value of ( $0.95 \pm 0.17$ ) and median value of ( $0.89 \times 10^{-5}$  mm<sup>2</sup>/s) (Fig. 9).

## 7. Discussion

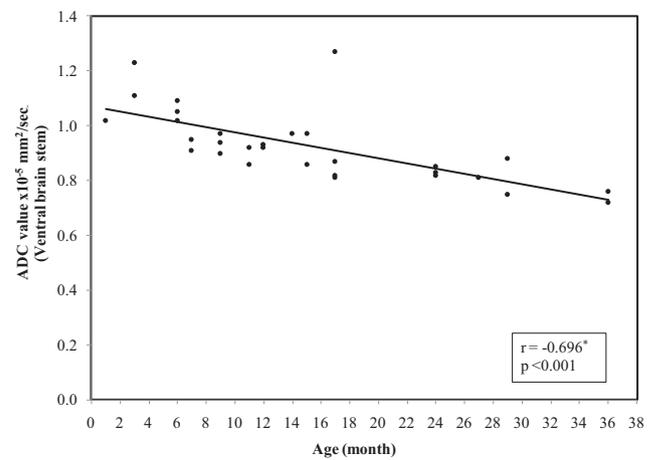
MR imaging is a noninvasive method for evaluating the development of myelination in infants. Diffusion weighted MRI and ADC maps depend on the fact that as the formation of myelin by the oligodendrocytes proceeds, an increase in brain cholesterol and glycolipids concentration and a decrease in water content occur. This leads to a change of white matter diffusion properties.<sup>3</sup>

**Table 2** Distribution of the measured ADC values in the selected white matter areas.

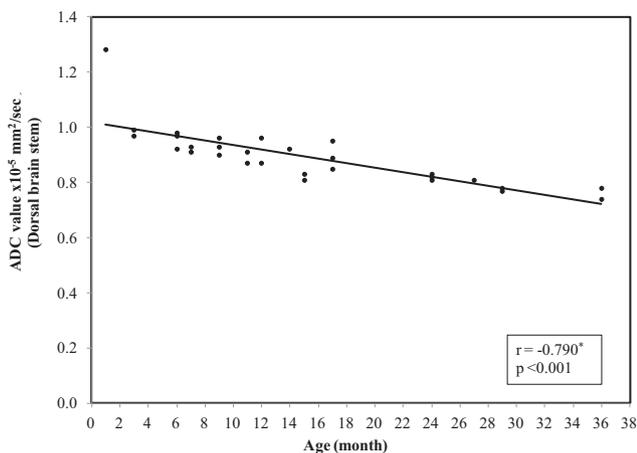
	Min.–Max.	Mean $\pm$ SD	Median
Middle cerebellar peduncle	0.62–1.32	0.81 $\pm$ 0.16	0.76
Ventral brain stem	0.72–1.27	0.93 $\pm$ 0.13	0.92
Dorsal brain stem	0.74–1.28	0.89 $\pm$ 0.10	0.90
Genu corpus callosum	0.64–1.35	0.98 $\pm$ 0.20	0.93
Splenium corpus callosum	0.65–1.71	0.86 $\pm$ 0.20	0.84
Anterior limb internal capsule	0.62–1.23	0.83 $\pm$ 0.12	0.82
Posterior limb internal capsule	0.65–0.99	0.81 $\pm$ 0.09	0.80
Corona radiata	0.71–1.01	0.86 $\pm$ 0.08	0.86
Centrum semiovale	0.72–1.43	0.95 $\pm$ 0.17	0.89



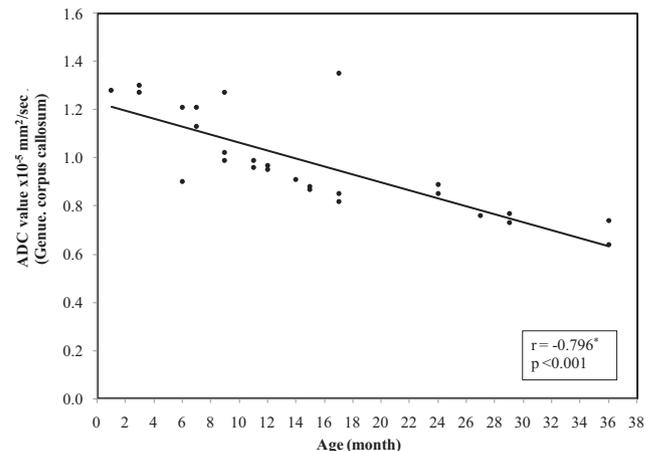
**Figure 1** Correlation between age (by months) and ADC value in middle cerebellar peduncle. The restriction appeared at age of 3 months with significant decrease in the ADC values with progression of the age ( $p = 0.001$ ).



**Figure 3** Correlation between age and ADC value in ventral brain stem. The restriction appeared at age of 6 months in some of the cases and at the age of 7 months in other cases with a significant decrease in the ADC values with progression of the age ( $p < 0.001$ ).



**Figure 2** Correlation between age (by months) and ADC value in dorsal brain stem. The restriction was present at age of 1 month with a significant decrease in the ADC values with progression of the age ( $p < 0.001$ ).



**Figure 4** Correlation between age and ADC value in genu of the corpus callosum. The restriction appeared at age of 9 months with a significant decrease in the ADC values with progression of the age ( $p < 0.001$ ).

In the present work we measured the ADC value in selected areas of the white matter in thirty infants whose ages ranged from 1 month to 36 months. The non myelinated white matter has high water and low molecular contents and so showed non restricted ADC values (more than  $1 \times 10^{-5} \text{ mm}^2/\text{s}$ ).

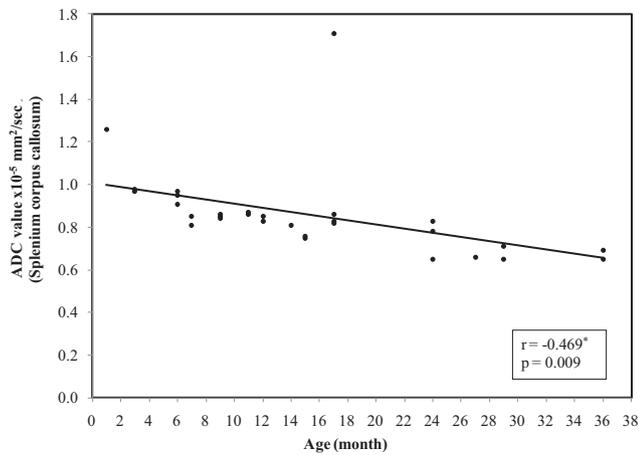
Neil et al. imaged 22 newborns 36 h after birth. ADC was measured in all subjects. Neil et al. reported that a correlation existed between ADC and gestational age, suggesting the potential role of brain water in the elevation of ADC in neonates.<sup>10</sup>

With progression of myelination there is a drop in the water content and progressive increase of the molecular contents with consequent more restricted ADC values as confirmed by Forbes et al., Löbel et al. and Zhai et al. They used diffusion to detect the progression of myelination and their results showed a significant decrease in ADC values in the white matter with increase in the age of their subjects.<sup>11–13</sup>

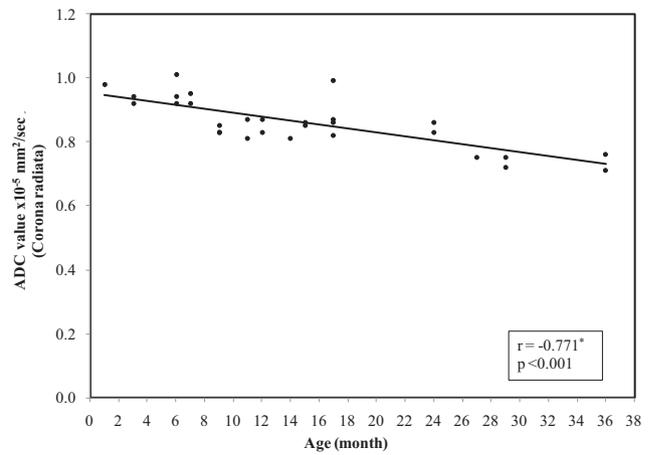
This is also confirming the results of Engelbrecht et al. who measured the ADC values in 44 children in variant white matter locations including the genu and splenium of the corpus callosum, the anterior and posterior limb of the internal capsule, the middle cerebellar peduncle, frontal and occipital white matter and the anterior and posterior pons. These sites showed non restricted ADC values before the brain maturation and restricted ADC values after brain maturation.<sup>14</sup>

Our results revealed that water diffusion of the measured white matter locations decreased during maturation, with the most significant change within the first year thereafter becoming more gradual.

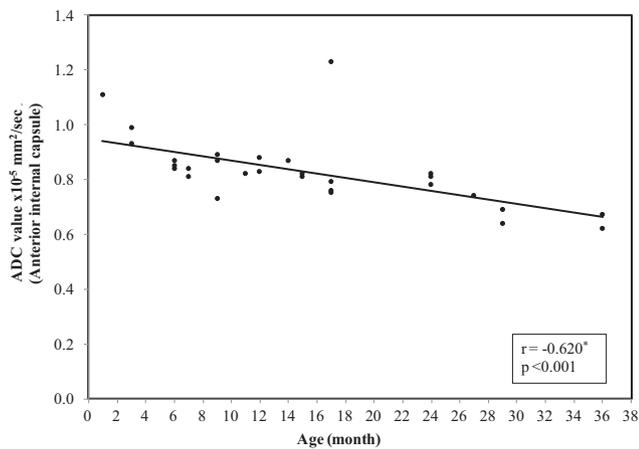
Robust negative correlations were found between age and the measured average ADC values in each of the measured locations ( $p < .005$ ), these findings were consistent with the findings reported in a study by Zhang et al.<sup>15</sup>



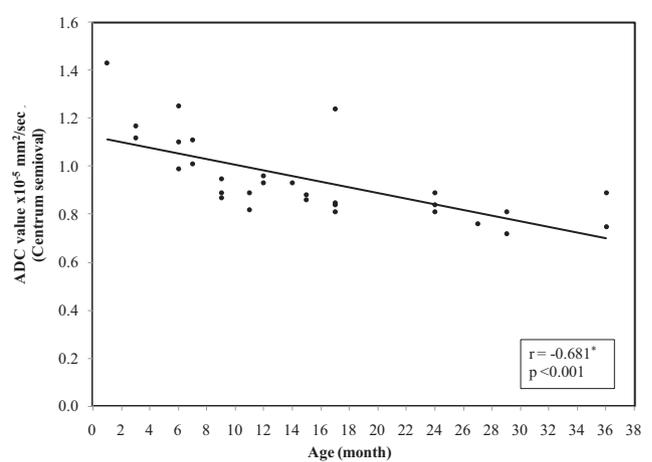
**Figure 5** Correlation between age and ADC value in splenium of the corpus callosum. The restriction appeared at age of 3 months with a significant decrease in the ADC values with increase the age ( $p = 0.009$ ).



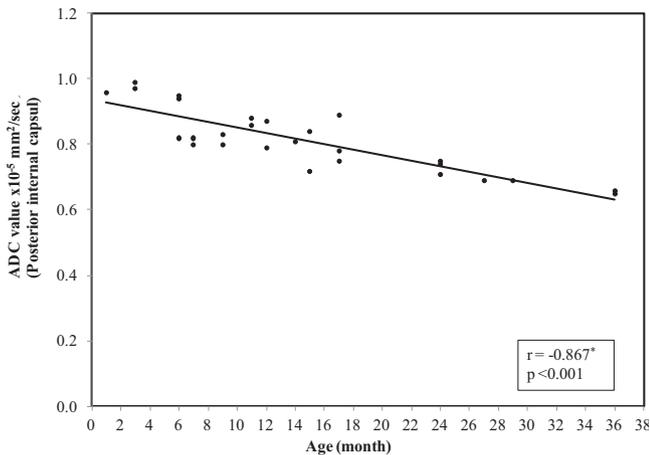
**Figure 8** Correlation between age and ADC value in corona radiata. The restriction was present at age of 1 month with a significant decrease in the ADC values with increase the age ( $p < 0.001$ ).



**Figure 6** Correlation between age and ADC value in anterior limb internal capsule. The restriction appeared at age of a significant decrease in the ADC values with increase the age ( $p < 0.001$ ).



**Figure 9** Correlation between age (by months) and ADC value in centrum semiovale. The restriction appeared at age ranging between 6 and 9 significant with a decrease in the ADC values with increase the age ( $p < 0.001$ ).



**Figure 7** Correlation between age (by months) and ADC value in posterior limb internal capsule. The restriction was present at age of 1 month with a significant decrease in the ADC value with increase the age ( $p < 0.001$ ).

The differences in ADC we detected in white matter match with those predicted noted from the sequential pattern of myelination observed in conventional MR studies.

### 8. Conclusion

It is important to characterize myelination evolution in normal brain development in order to better study demyelination diseases. Diffusion-weighted images and the measurement of the ADC can be applied to the study of normal brain development and myelination. ADC values decrease with progressive increase of age. Using ADC values is helpful in the assessment of the normal myelination development in the infantile brain and matches the results of the conventional MRI imaging.

### Conflict of interest

None declared.

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