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Age-Dependent Changes in Magnetization Transfer Contrast of White Matter in the Pediatric Brain

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BACKGROUND AND PURPOSE: **It is unknown to what extent magnetization transfer contrast (MTC) in white matter of the brain changes during myelination. The goal of this study was to measure the age-dependent changes of MTC in different regions of the pediatric brain and to evaluate their relation to T2 relaxation times.**

METHODS: **Seventy children aged 1 week to 80 months without evidence of organic brain disease underwent MR imaging of the brain. A double-echo spin-echo (SE) sequence and an SE sequence with and without an off-resonance pulse were performed in the axial orientation. Using paired images, we calculated MTC ratios in 13 predefined regions of the brain and compared them with the T2 relaxation times measured in the same areas. Regression analysis was performed for both parameters to evaluate age dependency.**

RESULTS: **MTC in white matter increased during myelination from a range of 13% to 19% to a range of 34% to 37%. At the same time, T2 relaxation times decreased from a range of 115 to 160 milliseconds to a range of 60 to 70 milliseconds after myelination. For both MTC and T2 relaxation times, age dependency could be expressed by a monoexponential function.**

CONCLUSION: **A strong positive correlation exists between MTC ratios and the degree of myelination in the pediatric brain, and an inverse correlation exists between MTC and T2 relaxation times. Fast proton relaxation within macromolecules in the myelinated white matter and subsequent MT may be the most important reason for the decreasing T2 relaxation time of white matter during brain myelination.**

Myelination in the human CNS is a predetermined process that follows a predictable topographic and chronological pattern (1). Anatomic examinations have shown that human CNS myelination begins in the spinal cord 12 to 14 weeks into pregnancy (2) and continues into the third decade in the region of intracortical fibers of the cerebral cortex (3). The most rapid and dramatic changes occur between midgestation and the end of the second postnatal year (4, 5). A more than threefold increase of brain weight during this period is mainly due to brain myelination.

Prior to myelin formation, cholesterol, phospholipids, fatty acids, and monoglycerides are abundant in white matter. With the onset of active myelin synthesis, the amount of cholesterol and phospholipids increases even further and the myelin-associated lipids (sphingomyelin, cerebrosides, and sulfatides) appear (6). With the progress of myelination, the total water content of the brain decreases from 90% at birth to 82% in childhood (7).

It has been repeatedly demonstrated that MR imaging is perfectly feasible for monitoring the normal progress of myelination as well as for recognizing disturbances by means of a combination of T1- and T2-weighted images (8–12). Myelination leads to decreased signal intensity on T2-weighted images and increased signal intensity on T1-weighted images. Contributing factors to these changes in signal intensity may be a decrease in free water and total water content and an increase in cholesterol and glycolipids (10, 11, 13). However, it is unknown to what extent the individual factors influence the age-dependent shortening of T1 and T2 relaxation times.

The specific T1 and T2 relaxation times of tissue are determined by their biochemical composition and biophysical structure through a variety of separate and distinct relaxation mechanisms. These relaxation mechanisms involve nuclear magnetic dipole-dipole interactions between the protons of water and those of macromolecules (14). Biological tissues can be looked at as a two-component system consisting of

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water and macromolecules, such as proteins, lipids, carbohydrates, and nucleic acids. Owing to their very short T2 relaxation times of less than 1 millisecond, macromolecule protons cannot be detected directly by MR imaging but rather indirectly by their effect on the T1 and T2 relaxation times of surrounding water protons. Magnetization transfer (MT) is a relatively new imaging technique to generate contrasts that may reflect a certain structural variation within tissue. MT contrast is mainly achieved by the application of off-resonance radiofrequency irradiation designed to preferentially saturate immobile protons associated with macromolecules. These saturated protons may then exchange magnetization with mobile protons in the aqueous phase (15). Hence, application of an MT pulse will lead to interaction between these two pools of protons with a resulting decrease of the observed signal intensity of brain tissue as compared with that on a reference image obtained without saturation.

MT imaging has been used in a variety of clinical applications, mainly for tissue characterization and augmentation of contrast enhancement (16–19). Since the presentation of Chew et al (20) it has been speculated that the amount of magnetization transfer in the white matter of the pediatric brain correlates with the degree of myelination. However, a detailed study with a sufficiently large number of infants was lacking. In this article, we present our findings of the age-dependent changes in magnetization transfer contrast (MTC) of white matter in the pediatric brain.

Methods

Magnetization transfer imaging was performed in 95 children during a clinically indicated MR examination of the brain. All imaging was performed on a 1.5-T unit using a double-echo sequence (2000/20,80 [TR/TE]) in the axial orientation followed by coronal and sagittal spin-echo (SE) sequences (600/14). For MT imaging in the axial orientation, an SE sequence (785/14) was run twice, first with and then without an off-resonance pulse (7.5-millisecond gaussian pulse, 1.5-kHz off resonance). Both the reference image and the image with MT saturation were obtained with a constant gain and image scale. Section thickness and position corresponded to those images obtained with a double-echo sequence. The imaging studies showed no demonstrable abnormalities.

Indications for the MR examinations included suspected brain tumor, suspected encephalitis, and exclusion of brain disease in children with lymphoma or leukemia. Twenty-five children were excluded from the study because of mental retardation, the rest had normal neurologic findings.

The age of the children ranged from 1 week to 80 months, with a mean age of 30 months (age distribution is given in the Table). In five children with a gestational age of less than 40 weeks, age was corrected by the time of prematurity. Thirty-two children were male and 38 were female. No child was studied more than once. Informed consent for performing the additional MT sequence was given by the parents prior to examination.

Quantification of the MT effect was performed for all of these 70 children. Using paired images (Figs 1 and 2), we calculated MTC ratios in 13 predefined regions within the brain (the CSF, the frontal and occipital white matter, twice in the cortical gray matter, the genu of the corpus callosum, the anterior and posterior internal capsule, the caudate nucleus, the anterior and posterior pons, the midbrain, and the middle cerebellar peduncle). Circular regions of interest (ROIs) with a minimum pixel size of 15 were hand-placed in the image without an MT pulse and automatically transferred by the system's software to the same region on the corresponding image with an MT pulse. Mean values ± 1 SD were displayed for the selected pixels. MTC was calculated by means of the equation $MTC = (M_0 - M_s)/M_0 \cdot 100\%$, where M_0 represents the measured signal intensity on the image without an off-resonance pulse and M_s the measured signal on the corresponding image with an off-resonance pulse. In the same regions, T2 relaxation times were calculated from the double-echo sequence using software supplied by the manufacturer. For each location, age dependencies of MTC and T2 relaxation times were evaluated by means of regression analysis.

Age distribution of children

Age (mo)	No. of Children
0–1	7
2–3	4
4–6	5
7–12	6
13–36	24
37–80	23

Results

With ROI analysis we measured low MTC values in unmyelinated white matter (13% to 19%), which increased during myelination to 34% to 37%. The age dependency of MTC ratios could be described by a monoexponential function, $y = a - b \cdot e^{-x/c}$, where y represents the MTC ratio at age x and a, b, and c are parameters influencing the results. Data from the patients were used in a fitting procedure to establish the normative curves for each anatomic location. R^2 represents the part of the variance that could be expressed by the above equation. The resulting values for R^2 varied from .78 to .96 in white matter and from .6 to .77 in gray matter. Figures 3, 4, and 5 show normative curves and the values of R^2 for the different locations.

The T2 relaxation times measured in identical regions decreased from 115 to 160 milliseconds in unmyelinated white matter to 60 to 70 milliseconds after myelination. The age dependency of T2 relaxation times was also expressed in relation to the above as a monoexponential function. R^2 varied from .86 to .95 in white matter and from .8 to .83 in gray matter. The normative curves and the values of R^2 for the different ROIs are given in Figures 6, 7, and 8.

The difference of $a - b$ represents the MTC ratio or the T2 relaxation time of the brain at birth within the equation $y = a - b \cdot e^{-x/c}$. The value of a equals the MTC ratio or the T2 relaxation time after completion of brain maturation and c represents the slope of the curves. At birth, the highest MTC values and the lowest T2 relaxation times were measured in the mesencephalon, the posterior pons, and the middle cerebellar peduncle. The lowest MTC values and the highest T2 relaxation times were found in frontal and occipital white matter. After completion of brain myelination, the corpus callosum had the highest MTC values and the lowest T2 relaxation times, while the

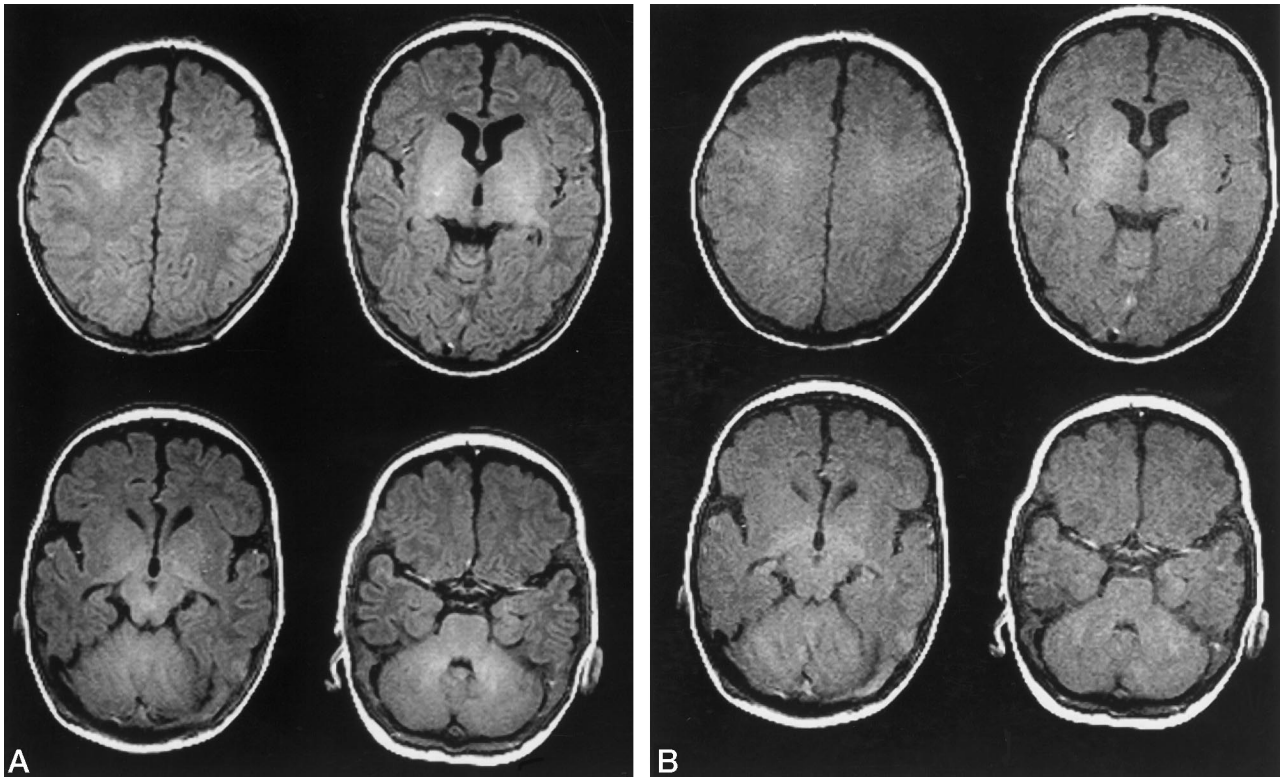

FIG 1. Axial T1-weighted images (785/14/1) of the brain in a 2.5-month-old child obtained without (*A*) and with (*B*) an off-resonance pulse. The loss of signal intensity in unmyelinated white matter is moderate on the MTC images.

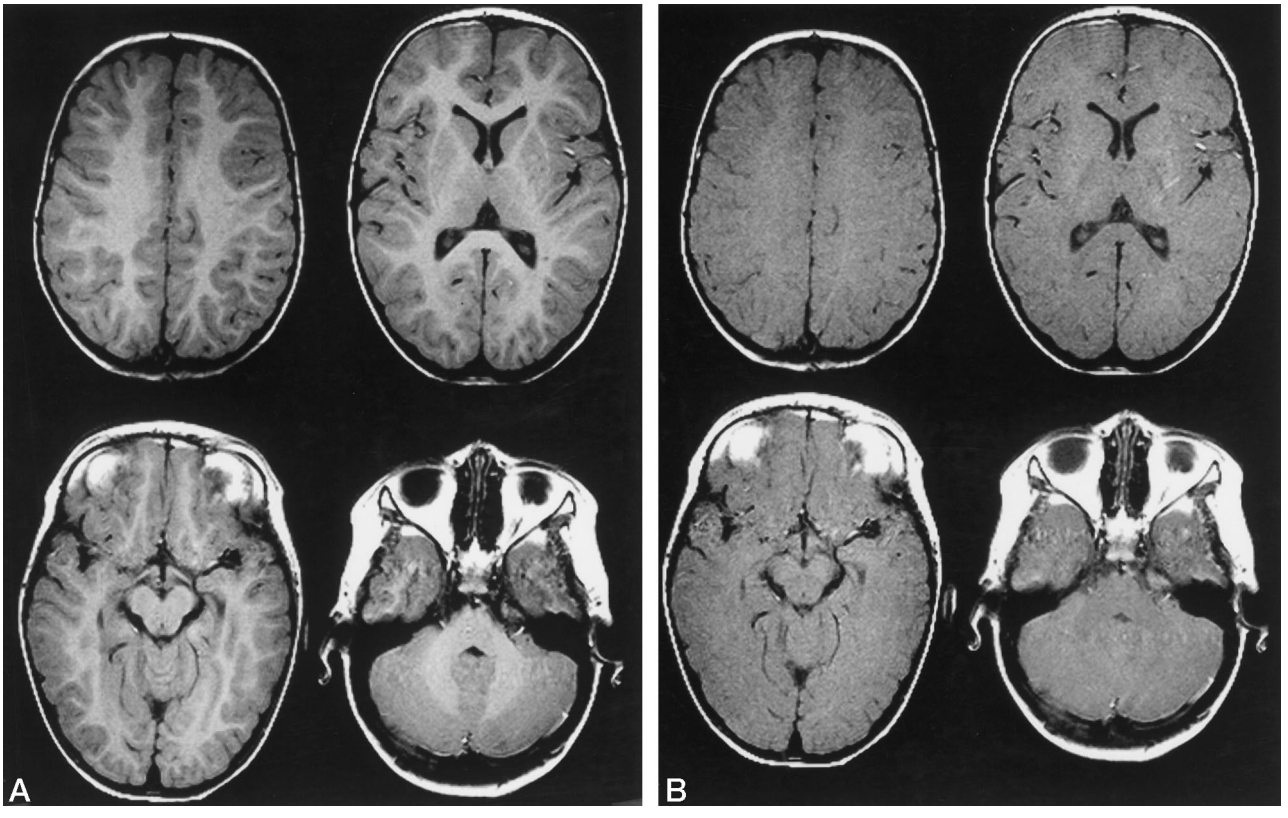

FIG 2. Axial T1-weighted images (785/14/1) of the brain in a 30-month-old child obtained without (*A*) and with (*B*) an off-resonance pulse. The severe loss of signal intensity in myelinated white matter indicates high MTC values in this region.

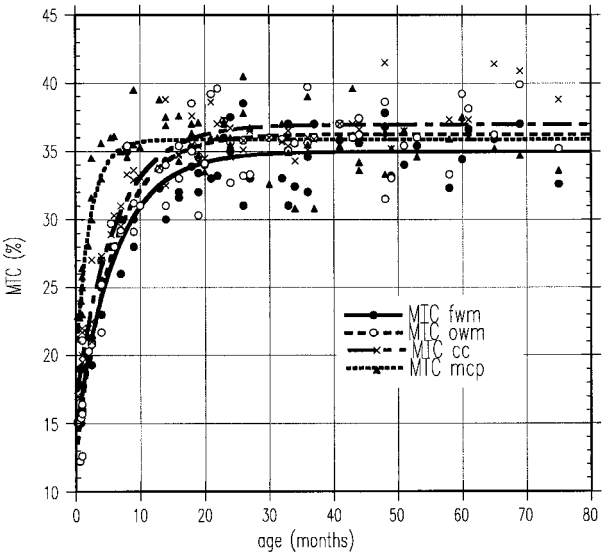

FIG 3. Age dependency of MTC values within frontal white matter (fwm, R^2 = .96), occipital white matter (owm, R^2 = .95), genu of corpus callosum (cc, R^2 = .96), and middle cerebellar peduncle (mcp, R^2 = .86).

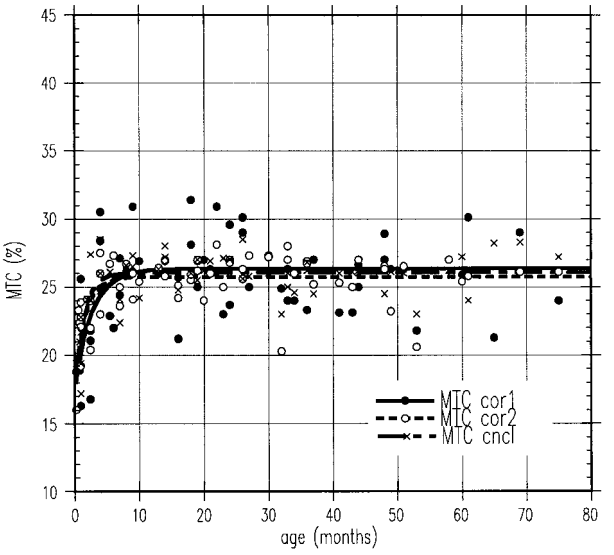

FIG 5. Age dependency of MTC values within gray matter of frontal cortex (cor 1, R^2 = .60), gray matter of occipital cortex (cor 2, R^2 = .66), and caudate nucleus (cncl, R^2 = .77).

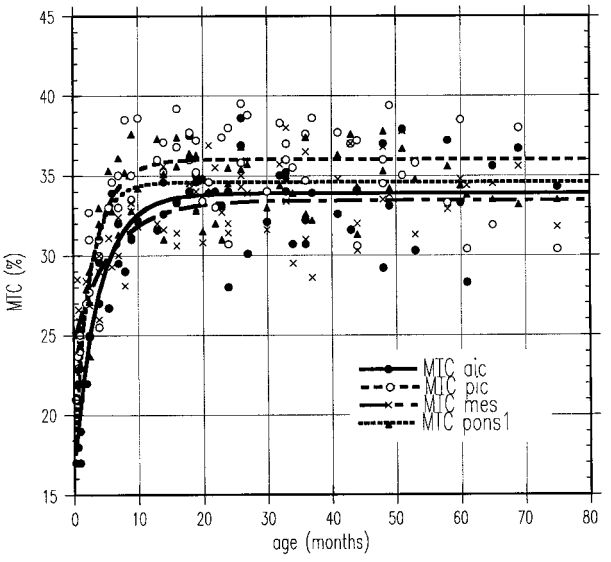

FIG 4. Age dependency of MTC values within anterior internal capsule (aic, R^2 = .89), posterior internal capsule (pic, R^2 = .87), mesencephalon (mes, R^2 = .78), and anterior pons (pons 1, R^2 = .90).

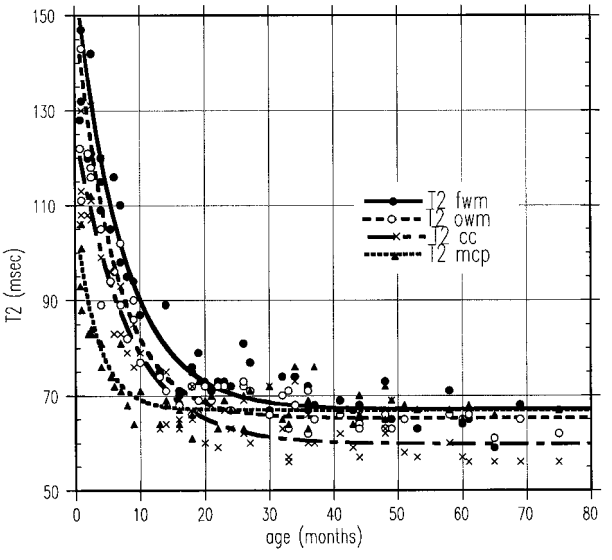

FIG 6. Age dependency of T2 relaxation times within frontal white matter (fwm, R^2 = .95), occipital white matter (owm, R^2 = .88), genu of corpus callosum (cc, R^2 = .95), and middle cerebellar peduncle (mcp, R^2 = .87).

lowest values of MTC and the highest T2 relaxation times were measured in the mesencephalon and anterior pons.

The parameter *c* within the above equation of the curves indicates the slope of the graph. A low value of *c* predicts a quick increase of MTC values and a quick decrease of T2 relaxation times, respectively. Low values of *c* were measured in the middle cerebellar peduncle, the posterior pons, and the posterior internal capsule, while *c* was high in the frontal and occipital white matter. The increase of MTC values was faster than the decrease of T2 relaxation times in all ROIs, with the exception of occipital white matter. This could be confirmed by significantly higher values of *c* ($P < .05$) for graphs representing the age dependency of T2 relaxation times compared with the curves of the age-dependent changes of MTC.

Discussion

For the past 10 years attempts have been made to quantify the progress of myelination by means of sequential MR examinations of the maturating brain. The initial results of T1 and T2 relaxation times derive from an early report on MR imaging of the pediatric brain (9). MR examinations in newborns obtained with a 0.35-T scanner revealed T1 relaxation times of 1615 milliseconds and T2 relaxation times of

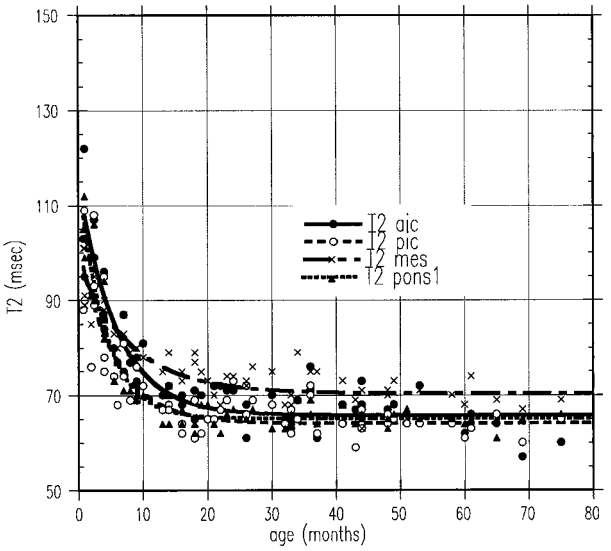

FIG 7. Age dependency of T2 relaxation times within anterior internal capsule (aic, R^2 = .93), posterior internal capsule (pic, R^2 = .86), mesencephalon (mes, R^2 = .90), and anterior pons (pons 1, R^2 = .96).

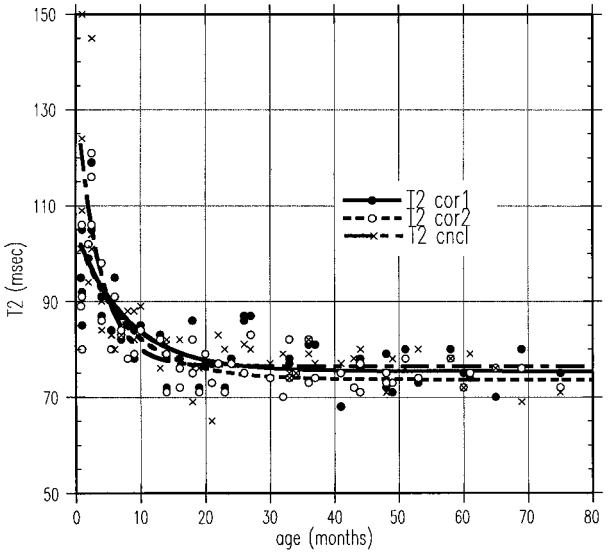

FIG 8. Age dependency of T2 relaxation times within gray matter of frontal cortex (cor 1, R^2 = .80), gray matter of occipital cortex (cor 2, R^2 = .80), and caudate nucleus (cncl, R^2 = .83).

91 milliseconds within white matter of the brain. The relaxation times decreased to 1150 milliseconds (T1) or 64 milliseconds (T2) at the age of 6 months and to 580 milliseconds (T1) or 57 milliseconds (T2) at the age of 1 year (9). However, the value of this study was diminished by the fact that no separate measurements for myelinated and unmyelinated white matter had been performed. More precise figures of T2 relaxation times during myelination of the brain have been published (13). These examinations, performed in 23 children aged 7 weeks to 16 years, were obtained on a 1.5-T MR scanner. Especially in older children, the values of T2 relaxation times in the frontal and occipital white matter and in the corpus callosum corresponded well with our results. The authors mentioned a decrease in the T2 relaxation times during the first 2 years but were not able to precisely quantify this process owing to the small number of children (seven) in this age group.

The responsible mechanisms for the decreasing T1 and T2 relaxation times during brain myelination are still a matter of ongoing discussion (10–13). The increasing signal intensity on T1-weighted images most probably is due to the increasing amount of lipids in the brain during myelination. However, these changes cannot explain the decreasing signal intensity on T2-weighted images. Because the total water content decreases only mildly, from 90% to 82%, during brain maturation (7), we speculate that the main reason for the age-dependent shortening of T2 relaxation time is a shift from free-water protons to bound protons. This shift is caused by the rising amount of macromolecules during brain myelination.

For some years it has been suspected that there is an increasing MT effect within cerebral white matter during brain myelination (20). It was demonstrated in patients with multiple sclerosis that demyelination leads to decreasing MTC values. The first results of MTC measurements in children with demyelination of white matter due to adrenoleukodystrophy revealed decreased MTC values in regions with irreversible demyelination (21, 22). As MT techniques become more widely used for general diagnostic purposes, it is increasingly important to have a normal baseline available for image and measurement interpretation. In this article we present the first systematic examinations in the field of age dependency of MTC in the maturating brain. Our examinations revealed low MTC values in unmyelinated white matter (13% to 19%) followed by a nearly threefold rise after myelination. MTC values of gray matter in the pediatric brain did not differ from those in unmyelinated white matter. During brain maturation, MTC values in gray matter rose moderately to 25% to 26%.

The values of MTC in the brain of children after completion of maturation in our study corresponded to those reported in the literature from young adults. Depending on the MR scanner and the MR sequences used, MTC values for white/gray matter turned out to be between 32%/24% (23) and 46%/39% (24). There is no clear dependency between the measurable MT effect and the field strength or the type of MR sequence used. Corresponding to the results in young adults, we found the highest MTC ratios within the corpus callosum and the lowest ratios within frontal and occipital white matter of the maturated brain (25, 26). The most probable reason is the different amount of myelinated fibers within various locations of white matter. The higher MT found in the corpus callosum may correspond histologically to the presence of a large number of heavily myelinated white matter fibers there (27). The MTC values of the brain at birth allow a quantification of the degree of myelination within the different brain regions, as indicated by the values of $a-b$ in the regression graphs. The highest ratios at birth were mea-

sured in the mesencephalon, the occipital pons, and the cerebellar peduncles. The results corresponded to neuropathologic and MR examinations of pediatric brain at birth with detectable myelin in these anatomic regions (1, 5, 11, 28, 29).

To clarify the question as to why myelination of white matter leads to increased MTC values, it is useful to compare our results with those from in vitro T1, T2, and MTC measurements of multilamellar vesicle suspensions with different lipid compositions (30). Suspensions consisting of phosphatidylcholine with cholesterol or sphingomyelin caused greater shortening of T1 and T2 and a slightly greater MT effect than did phosphatidylcholine alone. Suspensions consisting of galactocerebroside and phosphatidylcholine caused the greatest decrease in relaxation times and a threefold greater MT effect than the combination of phosphatidylcholine and cholesterol or phosphatidylcholine and sphingomyelin (30). The results from biochemical examinations of the maturating brain showed a strong correlation between the myelination of white matter and the concentration of galactocerebrosides (31). These results lead to the assumption that the increasing amount of galactocerebrosides during brain myelination is the most important contributing factor to the increase in MT effect. The lower concentration of galactocerebrosides in gray matter (7%) and the higher amount in myelinated white matter (26%) would explain the difference of MTC values between gray matter and myelinated white matter (30). In vitro examinations of aqueous solutions of gel-phase lipid bilayers showed a linear increase of MT effect depending on the number of –OH groups per unit area. For galactocerebrosides, the four –OH groups of galactose lead to a strong MT effect (32–34).

Our examinations revealed an inverse correlation between the MTC values and the T2 relaxation times during brain maturation. Many different factors affect the complex process of MR relaxation in tissue. The two major determinants of relaxation times in MR imaging are the tissue-water content and the degree and nature of interaction between water protons and tissue macromolecules. T2 relaxation time as well as MT effect depend on the concentration, mobility, and structure of the tissue macromolecules. A high concentration of macromolecules leads to high MTC values. Additionally, the motion restriction of temporarily immobilized water protons on the surface of macromolecules leads to increased spin-spin exchange and therefore to a decreased T2 relaxation time. Comparing the slope of the curves for MTC and T2 relaxation times, the increase of MTC values was slightly more pronounced than the decrease of T2 relaxation times during the progress of myelination. This may be explained by the influences of the T1 relaxation time. The application of the off-resonance signal to the pool with the restricted motion proton signal results in a decrease in the observed T1 relaxation times in nonirradiated spins (34).

Conclusion

The inverse correlation between MT effect and T2 relaxation time reflects the changes in the concentration, mobility, and structure of tissue macromolecules during brain myelination. The shift from mobile to immobile tissue protons explains the decreasing signal intensity on T2-weighted images during brain myelination. MTC might be a suitable tool for estimating the degree of myelination in the pediatric brain, owing to the strong correlation between MTC ratios and the amount of myelin in white matter. Our data provide a quantitative normative baseline, which is necessary for the correct interpretation of MT measurements in the brain of children with demyelinating diseases.

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