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The role of magnetization transfer MRI in the evaluation of brain and in the diagnosis of brain diseases in pediatrics

Pediatrik olgularda beynin değerlendirilmesinde ve pediatrik beyin hastalıklarının tanısında manyetik transfer MRG'nin yeri

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Abstract

Aim: It is aimed to evaluate the contribution of Magnetization Transfer (MT) to conventional magnetic resonance imaging in pediatric central nervous system pathologies, and to present the MT findings and the changes in Magnetization Transfer Ratio (MTR) with age in normal pediatric cases.

Materials and Methods: A total of 126 pediatric patients (48 girls and 78 boys), who presented to our hospital with various neurological complaints, were divided into two different age groups: 28 infants (1 month-2 years) and 98 children (2-18 years). They underwent conventional and MT MRI examinations. T-test, correlation analysis and variance analysis were used for statistical evaluation of data of the cases in the normal group.

Results: No statistically significant difference was found in the MTR of 66 normal cases (36 boys and 30 girls) in 18 anatomical locations between the genders. Correlation analysis performed in normal cases revealed that increased MTR was significantly correlated with increasing age, excluding the MTR of thalamus, in all age groups (28 cases were between 0 and 24 months of age, 26 were between 24 and 108 months of age, and 12 were between 109 and 192 months old). Among grey matter structures, the highest MTR was observed in globus pallidus, dentate nucleus and nucleus ruber. In the comparison of the cases with neurometabolic and neurodegenerative diseases and CNS pathologies such as infections and tumors, diagnosed based on clinical examination and conventional MRI, with age-matched normal cases, demonstrated lower MTR in the areas involved.

Conclusion: It is thought that MT imaging, which is yet not available in routine practice, is helpful in diagnosis not alone but together with other MRI sequences.

Keywords: Pediatric, magnetic resonance ımaging, magnetization transfer.

Öz

Amaç: *Pediatrik grup santral sinir sistemi (SSS) patolojilerinde MT'nin konvansiyonel MRI sekanslarına katkısı, normal olgularda MT bulguları ve yaşa göre gösterdiği değişikliklerin sunulması amaçlandı.*

Gereç ve Yöntem: *Hastanemize değişik nörolojik yakınmalarla başvuran 126 hasta (48 kız, 78 erkek), 28 olgu infant (1 ay-2 yıl), 98 çocuk (2-18 yıl) olmak üzere 2 farklı yaş grubundaydı. Konvansiyonel ve MT MRI incelemeleri yapıldı. Normal gruptaki olgularımızın verilerinin istatistiksel değerlendirilmesinde t-test, korelasyon ve varyans analizi yöntemleri kullanıldı.*

Bulgular: *Altmış altı normal olgunun (36 erkek, 30 kız çocuğu), 18 anatomik lokalizasyonda cinsiyet ile Manyetizasyon Transfer Ratio (MTR) arasında anlamlı istatistiksel fark saptanmadı. Normal gruptaki (28 olgu 0-24 ay, 26'si 24-108 ay, 12'si 109-192 ay) yaş grubunda olgularda MTR değerlerinin ilerleyen yaş ile artışı korelasyon analizine göre yapılan incelemede talamus dışında istatistiksel olarak anlamlı bulundu. Gri cevher yapılarında en yüksek değer globus pallidus, nucleus dentatus ve nucleus ruberde izlenmiştir. Klinik ve konvansiyonel MRG teknikleri ile tanısı konulan nörometabolik ve nörodejeneratif hastalıklarda, SSS enfeksiyonları, beyin tümörleri gibi SSS patolojilerinde aynı yaş grubundaki normal olgularla karşılaştırmalı olarak yapılan değerlendirmede etkilenen alanlarda daha düşük MTR değeri bulundu.*

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Sonuç: *Rutin kullanıma girmemiş olan MT görüntülemenin tek başına değil ama diğer MR sekansları ile birlikte tanıya yardımcı olduğu düşünülmektedir.*

Anahtar Sözcükler: *Pediyatrik, magnetik rezonans görüntüleme, magnetizasyon transfer.*

Introduction

Magnetization Transfer (MT) is one of the novel techniques that have not been put into practice yet. MT is a specific MR saturation technique that reveals the contrast, which originates from structural differences between the tissues. There are two main proton pools in the tissues: Free water proton pool and macromolecular bound proton pool. Many physicochemical interactions occur between these two proton pools and these interactions form the basis of MT imaging (1,8).

Myelin is the main macromolecule responsible for MT effect in the brain. Signal intensity decreases and Magnetization Transfer Ratio (MTR) increases according to the degree of myelination. MT analysis helps in the evaluation of myelination process and the diseases with myelination defect. Although it is not being used in routine practice, studies revealed that MT provides helpful information in making diagnosis and in monitoring treatment course in many diseases in the pediatric patient group. It was observed that lesions in many disease groups such as ischemia and infection could be seen before they have been reflected in conventional MRI and that more lesions than detected in conventional MRI could be identified. It provides supportive data for diagnosis in determining the nature and characteristic of the lesion (9).

The present study discussed the contribution of MT to the other conventional MR sequences in pediatric CNS pathologies as well as MT findings and changes in MTR with age in normal cases.

Materials and Methods

Cranial MRI of a total of 126 pediatric patients (48 girls and 78 boys), who presented to the MR unit of our hospital between 2007 and 2015 with various complaints, were retrospectively reviewed. Parents of all patients previously gave consent to the use of the patients' medical records for the purpose of study. The cases were divided into two different age groups: 28 infants (1 month to 2 years) and 98 children (2 to 18 years). Sedation was performed using 50 to 100 mg / kg chloral hydrate in the pediatric patients to prevent artifacts.

Conventional MRI and MT MRI examinations were performed with 1.5 T MRI scanner (Magnetom Vision, Siemens, Erlangen, Germany) using standard head bandage. For conventional MRI examinations, axial T 2 A, axial and sagittal T 1 A, and coronal FLAIR imaging were obtained by TSE and IR (TR/TE: 3800/90 - 11520/60) and FLAIR (TR / TE: 8000 / 110) sequences. In addition, diffusion-weighted images were obtained using echo planar imaging sequence. In some cases, post-contrast three-dimensional T1 A images were also included in the examination. MT images were obtained in two phases (1500 kHz off - resonance saturation pulse on and off) using the parameters: TSE sequence, TR / TE : 654 / 16 ms, FoV 230 mm, image matrix 156 x 256, and FA: 60 degrees. While the majority of the images were obtained in axial plane, sagittal plane as well was used in some cases. In all images, a section thickness of 5 mm was used in a total of 19 sections. Measurements were done in 18 anatomic locations in the normal brain and in lesion areas in the diseased brain parenchyma using the region of interest (ROI) method. The lowest pixel value was 5. MT images were created in two phases as saturation pulse was switched-off (Mo) and on (Ms). MTR was calculated using the values obtained from Mo and Ms by ROI method. (Mo – Ms) / Mo x 100 formula was used to calculate MTR.

Data of the cases in the normal group were analyzed using SPSS software version 20. T-Test, correlation analysis and variance analysis were used for statistical evaluation.

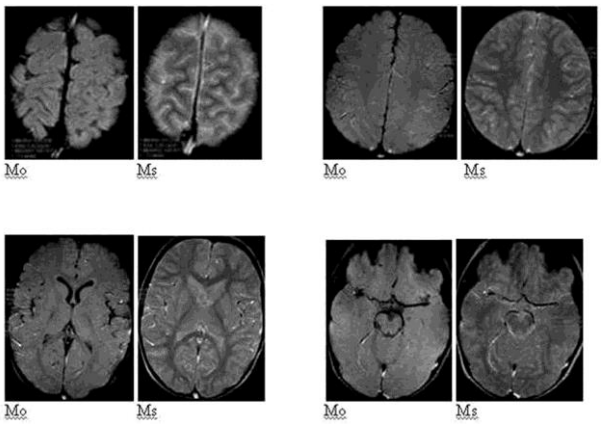

Figure-1. A 3-year-old normal case. MT images obtained from different anatomic locations while saturation pulse was switched-off (Mo) and on (Ms).

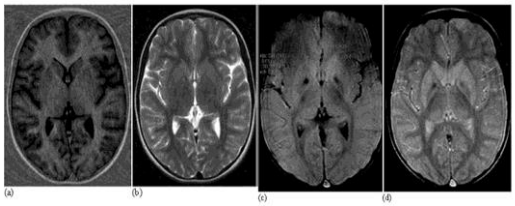

Figure-2. A 9-year-old case with chronic liver disease. While no remarkable sign is observed on T1 A (a) and T 2 A (b) images, signal changes due to paramagnetic substance accumulation are seen in globus pallidus on MT (c, d) images.

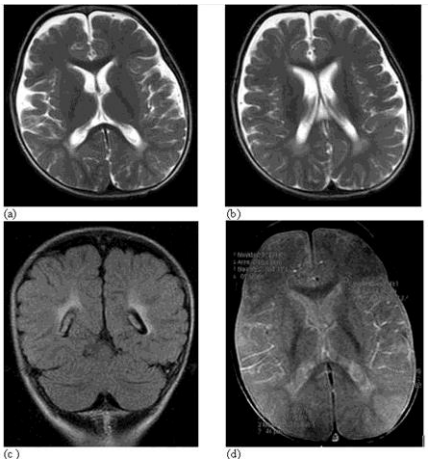

Figure-3. A 1-year-old case with neurometabolic disease. High signal intensity is observed in the posterior periventricular white matter on T 2 A images (a, b) and FLAIR image (c). High signal intensity is observed in the posterior periventricular white matter also on MT (d) image and MT measurements show difference as compared to the normal-appearing anterior periventricular white matter.

Results

Sixty six (52.3%) of the study participants were considered normal based on clinical and imaging findings, whereas distribution of the remaining 60 cases (%.47.6) among common pediatric cerebral diseases is summarized in Table-1.

Of the 66 normal cases, 36 were boys and 30 were girls; 28 of these cases were in the 0-24-month age group, 26 were in the 24-108-month age group and 12 were in the 109-192-month age group. No statistically significant difference was found in the MTR of normal cases in 18 anatomical locations between the genders.

Correlation analysis performed in normal cases revealed that increased MTR was significantly correlated with increasing age, excluding the MTR of thalamus, in all age groups.

In the present study, the normal cases were divided into three age groups and the changes in MTR at different locations were analyzed for each group using the T-test.

The 0-24-month age group was considered as Group I, 24-108-month age group was considered as Group II, and 109-192-month age group was considered as Group III. No statistically significant difference was determined in MTR changes in periventricular white matter anterior and periventricular white matter posterior, nucleus ruber, pons, and cerebellum between the age groups. There was a statistically significant difference between Group I and Group II in terms of MTR changes in posterior limb of the internal capsule and thalamus; whereas, a significant difference was found between Group II and Group III in terms of MTR changes in corpus callosum splenium. While a significant difference was observed between Group I, II and I and III in terms of MTR changes in the Cortex, centrum semiovale posterior, corpus callosum genu Caudate Nucleus, Putamen, Globus Pallidus and Dentate Nucleus, no significant difference was determined between Group II and Group III.

Table-1. Distribution of the Cases According to Common Pathologies.

Disease Group	Number	Ratio
Neurodevelopmental diseases	8	6.3%
Retardation in maturation	4	
Hypomyelination	1	
Cerebellar Hypoplasia	2	
Cerebellar Dysplasia	1	
Neurodegenerative diseases	3	2.3%
Chronic liver disease	2	
Congenital Myopathy	1	
Neurometabolic diseases	24	19%
Metachromatic leukodystrophy	2	
Maple syrup urine disease	1	
Glutaric Aciduria	3	
Aminoaciduria	1	
Kearns-Sayre	1	
No specific diagnosis	16	
Neurocutaneous syndromes	1	0.7%
Ischemia-Injury	12	9.5%
Diffuse axonal injury	1	
Hypoxic Ischemic Encephalopathy	2	
Acute Necrotizing Encephalopathy	1	
Rasmussen's Encephalitis	1	
Periventricular Leukomalacia	5	
Gliosis	2	
Infection	2	1.5%
Tuberculosis	1	
Congenital Infection	1	
Tumoral lesions	7	5.5%
Pilocytic Astrocytoma	2	
Hamartoma	1	
Germ-Cell Tumor	1	
Arachnoid Cyst	2	
Lymphohistiocytosis	1	
Others	3	2.3%
Cavernoma	1	
Organized Hematoma	1	
Bleeding	1	
Normal	66	52.3%

MTR values increase with age and myelination process in the cortex and deep grey matter structures as well as in the structures of white matter. We failed to obtain a database that would form a standard for pediatric age group in the present study. Similar to the other studies, the most important factor seems to be the heterogeneous changes in the brain due to myelination and the resultant variations. Another factor is the fact that MTR is a more subjective method that depends on the researcher as compared particularly to volumetric MT histogram analysis. Different MTR values can be obtained from the same location by different users, even by the same user

at different pixels. Volumetric MT Imaging Histogram Analysis is user-independent and forms quantitative data about whole cerebral volume. As compared to calculation of MTR by ROI method, it is advantageous owing to the facts that it provides information about whole cerebral volume and is user-independent. Another advantage of volumetric MT histogram is the fact that measurement and assessment take less time than ROI method. Unlike ROI, however, it requires different software programs.

An extensive lesion was observed in the centrum semiovale of the case with metachromatic leukodystrophy in the neurometabolic disease group. Comparison with age-matched normal cases revealed significantly lower MTR values in the lesion areas. Moreover, lower MTR values were obtained in the splenium of corpus callosum, posterior limb of the internal capsule, thalamus, caudate nucleus and globus pallidus as compared to the age-matched normal cases. This data suggests that not only the white matter, but also the grey matter structures may be affected in microstructural level.

In comparison of the three cases with glutaric aciduria with age-matched normal cases, it was observed that MTR values were lower in the dentate nucleus, white matter, cortex, corpus callosum, periventricular white matter, thalamus, putamen and hippocampus. Observation of low MTR values in many more areas than in conventional sequences suggests that the disease might be more extensive at microstructural level.

MTR values in the involved areas were lower in the cases with Kearns - Sayre Syndrome, Congenital Myopathy, Fukuyama congenital muscular dystrophy, Maple Syrup Urine Disease, cerebellar dysplasia, delayed myelin maturation, periventricular leukomalacia, gliosis, hypoxic ischemic encephalopathy, acute necrotizing encephalopathy, Rasmussen encephalitis and hepatic encephalopathy as compared to the age-matched normal cases.

In the present study, there were four patients with mass lesions, of which two were pilocytic astrocytoma, one was hamartoma and the other was germ-cell tumor. All cases had lower MTR values as compared to the normal brain tissue.

In the present study, MTR values calculated from the lesion yielded negative results in two cases with arachnoid cyst (AC), just as MTR values of the cerebrospinal fluid.

Very high MTR values were obtained from calcification areas in the case with tuberous sclerosis. However, very low MTR values were determined from atrophic areas so as to reflect serious tissue destruction.

In the case with tuberculosis, the lesion was less visible in pre-contrast images as compared to the conventional post-contrast images and MT images. MTR of brightening meninges revealed lower MTR values as compared to the white matter and grey matter.

The case with diffuse axonal injury had lower MTR values so as to reflect the presence of edema. MTR values were also found to be lower in the patients with bleeding.

Discussion

Today, along with developing technologies, MRI has shown great progression in assessing pathologies of the central nervous system (CNS). New techniques are being developed each passing day to augment the information obtained by MRI. Primarily, the macromolecular bound proton pool is responsible for MT effect. Since myelin is the main macromolecule that creates MT effect in the brain, MT imaging is sensitive in the evaluation of the diseases that involve development of myelination and myelin (10). T1 and T2 relaxation times are shortened with the development of myelination because of decreased water content and increased cholesterol and glycolipid concentration (11). Brain maturation is associated with shortened T1 and T2 relaxation times, decreased diffusion of water, increased diffusion anisotropy and increased MT. As myelination process occurs at different rates in different regions during brain maturation, variations in myelination in different localizations occur both during brain development and in adult brain. A standard for the changes in MT in different regions of the brain, particularly in childhood and infancy, could not be determined (2).

Numerous studies determined the highest MTR values in the corpus callosum due to the presence of massive myelinated axons (12). Among grey matter structures, the highest values were obtained from thalamus. Cortical MTR values were determined to be significantly lower than the MTR values of the white matter. A study found no significant difference between the two genders for MTR values. It was observed that MTR values were higher in the left hemisphere; however it was not associated with being left handed or the right handed (12). In the present study, in the two infants at the age of 5 weeks, who were the youngest participants, the highest MTR values were observed in the posterior limb of the internal capsule. The internal capsule is one of the few areas myelinated at birth. In the normal cases, however, the highest MTR value was determined in the dentate nucleus among deep grey matter structures. It was observed that MTR value significantly increased with increasing age.

It is thought that MT-MRI, with its sensitivity to the presence of myelin, would contribute to conventional MRI sequences in demonstrating disruption of myelination and in determining pathologies with myelin disorders. Neurometabolic diseases are a group of pathologies that develop due to disruption during or after the development of myelin. MT imaging may help conventional MR sequences in early diagnosis and in the treatment process of the disease.

In a study, which investigated glial reactivity before cellular injury, it was observed that MTR value showed a relative increase due to protein expression in glial reactivity areas (13,14).

A study conducted with MT and diffusion in Hypoxic-Ischemic Encephalopathy (HIE) reported that both quantitative methods are more sensitive than conventional MRI sequences in detecting lesions, particularly in the normal-appearing white matter areas (15). There are studies suggesting that there is decrease in MTR values in the presence of cytotoxic or vasogenic edema (16).

Tumors display lower MTR values as compared to normal brain tissue. It was observed that solid tumors display higher MTR values than that of soft tumors, and this was attributed to the structure and protein content of the tumor. It was determined that meningioma displays significantly higher MTR values as compared to the other tumors (17).

In arachnoid cyst, however, negative MTR values are obtained because CNS signal with MT is higher than CNS signal without MT (18).

In the studies performed with MT in tuberous sclerosis, significantly lower values were observed in the lesions and in normal-appearing white matter as compared to the control group. Lower MTR values were determined in the cortical tubers as compared to subependymal nodules (19).

In tuberculous meningitis, MT imaging reveals significantly lower MTR values in the meninges that are hyperintense, as compared to the grey matter and white matter (20).Detectability of the lesion with cranial MRI is enhanced in diffuse axonal injury. MTR provides a quantitative index of structural integrity of the tissue. Lexa et al. demonstrated that MTR changes are correlated with histological changes in wallerian degeneration and the changes can be observed before they appear in T2-weighted images. Mc Gowan et al. (21) determined that MT imaging is more sensitive than T2 A to histological axonal injury in rotational acceleration brain injury. Sinson et al. (22) determined permanent neurological deficit in a group of trauma patients with abnormal MTR values also in normal-appearing white matter; however, they fail to determine abnormal MTR values in the normal-appearing white matter of a group of patients with good clinic.

Conclusion

In the light of the literature, the results of the present study indicate that MT imaging provides helpful information in making diagnosis. Myelin is the most important macromolecule responsible for MT effect in the brain. Therefore, MT imaging is sensitive to the presence of myelin. It provides quantitative data about myelin. Thus, it is helpful in evaluating brain maturation and during diagnosis and monitoring of diseases associated with myelin destruction. However, heterogeneous environment over the course of brain maturation leads to interobserver and intraobserver differences in MT measurements. Specific software programs are required for objective quantitative measurements. In the present study, contrast resolution was not adequate enough to distinguish the anatomic configurations, particularly in the cases under the age of 2 years. It is thought that MT imaging, which is yet not available in routine practice, would help in diagnosis not alone but together with the other MRI sequences**.**

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