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Role of Magnetic Resonance Spectroscopy in Diagnosis of Developmental Delay in Children

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: MR spectroscopy examines molecules like hydrogen ions and protons. The technique of proton spectroscopy is more commonly used. Metabolites, or metabolic products, come in a variety of forms. The aim of this work is to evaluate the role of MR spectroscopy in diagnosis of infants and children presented with developmental delay.
Methods: This study was carried out on 30 children presented with developmental delay aged between 3 months to 12 years referred for brain MR spectroscopy for diagnosis of delay in milestones. All patients were subjected to: Full history, clinical examination, some patients need I.Q testing and MRS assessment.
Results: There was no significant difference in N-acetyl-aspartate/creatine and Cho/Cr ratios in cases ≤ 2 years between the study group and the control group. N-acetyl aspartate/creatine ratio in cases >2 years was significantly lower in the study group patients than that of control group P<0.05. Cho/Cr was significant increase in study group compared to control group (p< 0.05).
Conclusions: the proton MR spectroscopy can be used to diagnose and follow developmental delay especially in children more than two years as we found typical changes in NAA/Cr and Cho/Cr.

Keywords: Magnetic resonance spectroscopy; developmental delay; children.

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1. INTRODUCTION

Human development is a continuous process that begins at conception and can be hampered by a variety of factors such as genetics, environment, diet, and chronic diseases. Delays in milestones can be measured using four domains: gross motor, fine motor, social, and language skills [1]. The brain goes through important developmental changes after birth, including neuronal structure, glial cell proliferation and differentiation, and myelination. The concentration of total N-acetyl aspartate increased throughout childhood, with the exception of the right caudate head, where it remained constant. Total creatine levels fell in the caudate nucleus and splenium, but only marginally in the frontal white matter and genu. It remained relatively constant in the frontal white matter. Except in the parietal white matter, where it remained constant, the concentration of choline-containing compounds decreased across the board [2].

Proton MR spectroscopy revealed anomalies in the NAA/Cr and Cho/Cr ratios in children over the age of two who had developmental delays. As part of the neuroimaging examination of developmental delay, proton MR spectroscopy should be conducted. Proton MR spectroscopy can be utilized as a diagnostic tool as well as a neuroimaging marker to determine long-term functional outcomes. MR spectroscopy is a non-invasive diagnostic procedure that measures biochemical changes in the brain.

MR spectroscopy is performed on the same machine that is used for conventional MRI. An MRI scan generates detailed images by utilising a powerful magnet, radio waves, and a computer. Spectroscopy is a group of tests that are added to an MRI scan of the brain or spine to detect chemical metabolism. Molecules like hydrogen ions and protons are studied using MR spectroscopy. The use of proton spectroscopy is more prevalent. Metabolites, or metabolic products, come in a variety of forms [3].

Developmental delay is still clinically diagnosed and is age-dependent. Prior to the discovery of clinical proton MR spectroscopy, researchers anticipated that serial MR imaging exams would be required to distinguish halted myelination from slow but progressive growth. Similarly, serial proton MR spectroscopy may be required to make a similar assessment, especially in children under the age of two [4].

The present study seeks evaluating the role of MR Spectroscopy in diagnosing infants and children presented with developmental delay.

2. PATIENTS AND METHODS

This study was carried out on 30 children presented with developmental delay aged between 3 months to 12 years referred for brain MR spectroscopy for diagnosis of delay in milestones. Exclusion criteria were children with congenital heart diseases causing cardiac failure, children with renal failure, ccontraindications to MRI examination like metallic protheses, metallic gums, metallic aneurysmal clips and gadolinium-based contrast media and patients with known genetic disorders.

All patients were subjected to: Full history, clinical examination, some patients need I.Q testing and MRS assessment.

All participants were studied with a 1.5-T whole-body MR imager equipped with high-performance gradients, using a manufacturer supplied quadrature head coil. Routine sequences performed in all children were sagittal T1-weighted (300/14/1 [TR/TE/excitations]), axial fast spin-echo T2-weighted (3000/91/1), axial fast fluid-attenuated inversion recovery (FLAIR) (10,002/172/1, TI 2.2 seconds), and axial T1-weighted (500/14/1).

Coronal fast FLAIR (10,002/172/1, TI 2.2 seconds) and coronal spoiled gradient recalled acquisition in the steady state (SPGR) T1weighted volumetric (17/5/1, flip angle 45°) sequences were obtained in 12 of the 26 children. No contrast material was administered for any sequence. Thirteen children were sedated with chloral hydrate 50 mg/kg.

The developmental quotient (DQ) was calculated in all children.

Age-appropriate developmental tests (Denver, Griffiths, Bayley, and Kaufman) were used to evaluate the DQ or IQ of the patients and to subdivide them into three groups: severe (DQ or IQ <50), moderate (DQ or IQ 50–75), or mild (DQ or IQ >75).

Proton MR Spectroscopy was performed in all patients by using a point-resolved spectroscopy (PRESS) sequence (2000/144 [TR/TE]) with 128 averages; voxel sizes of 8.0 cm3 were used.

Voxels were placed in the frontal and parieto-occipital subcortical white matter bilaterally.

The NAA/Cr and Cho/Cr ratios at MR spectroscopy were analyzed without clinical knowledge regarding the participants.

3. STATISTICAL ANALYSIS

Data were fed to the computer and analysed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) (119) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean and standard deviation. Significance of the obtained results was judged at the 5% level. The used tests were: Chi-square test for categorical variables, to compare between different groups, student t-test for normally quantitative variables, to compare between two studied groups, Mann Whitney test for abnormally quantitative variables, to compare between two studied groups.

4. RESULTS

Table 1 shows the gender and age of the studied group. Both factors weren't statistically significant between groups.

Table 2 showed clinical presentation of the children of our study group.

Table 3 showed distribution of the study group according to developmental delay type.

We found insignificant difference in N-acetyl-aspartate/creatine ratio in cases ≤ 2 years among both groups. N-acetyl aspartate/creatine ratio in cases >2 years was significantly less in the study group rather than that of the control group P<0.05.

Cho/Cr was no statistically significant difference among both groups in cases ≤2 years. Cho/Cr was significantly raised in the study group compared to the control group (p< 0.05).

5. DISCUSSION

MRS (proton magnetic resonance spectroscopy) is an advanced MRI method that provides information beyond what can be observed on standard anatomical scans. It's a non-invasive method of measuring brain metabolite concentrations, allowing researchers to examine brain metabolism. MRS has been used on clinical populations in the hopes of delivering valuable information concerning brain damage, but much of this promise for preterm-born children has yet to be realized [5].

Our current study discovered that N-acetyl-aspartate/creatine in Frontal subcortical white matter or Parieto-occipital subcortical white matter were lower than in control and difference were non-significant in children ≤ 2 years. And differences were significant in children > 2 years.

Table 1. Gender and age of the studied group, and distribution of the study and control groups according to age and gender

Age (years)	Sex		Total
	Male (n= 18)	Female (n= 12)	No
3 months – 1 year	4	2	6
> 1 year – 2 years	3	2	5
> 2 years – 3 years	3	1	4
> 3 years – 4 years	3	2	5
> 4 years – 5 years	2	2	4
> 5 years –6 years	1	2	3
> 6 years – 11 years	2	1	3
Total	18	12	30

		Study Group (n=30)	Control Group (n=10)	P Value
Age		4.26±3.291	3.83±3.127	0.988
Gender	Male	18(60.0%)	7(70.0%)	0.715
	Female	12(40.0%)	3(30.0%)	
	Total	30(100%)	10(100%)	

p: p value for comparing between the two studied groups, Data are represented by mean± SD or frequency (%)

Table 2. Clinical presentation of the children of our study group

Clinical presentation	Age	Sex
Cannot support his head	8 months	Male
Doesn't recognize mother	7 months	Male
Doesn't respond to sounds	9 months	Female
Can't roll on	10 months	Male
Cannot sit without support	11 months	Female
Can't crowl	12 months	Male
Cannot say papa, mama	14 months	Female
Cannot stand alone	15 months	Male
Delayed response to others speech	17 months	Female
Don't take a step	18 months	Male
Don't take a step	19 months	Male
Cannot say two words	22 months	Male
Cannot walk unassisted	24 months	Male
Delayed response to other's stimulation	2 years & 6 months	Female
Cannot go downstairs in a child manner	2 years & 10 months	Male
Say only one or two words	3 years & 1 months	Male
Cannot walk in a steady manner	3 years & 3 months	Female
Speak few words	3 years & 5 months	Male
Delayed response and interaction	3 years & 7 months	Male
Cannot speak a complete sentence	4 years	Female
Cannot speak a complete sentence	4 years & 2 months	Male
Delayed emotional response, interaction, delayed understanding.	4 years & 5 months	Male
Cannot catch a pen and draw	5 years	Female
Cannot paint by color pencil, weak catching pencil.	5 years	Female
Delayed interaction, speak	5 years & 2 months	Female
Cannot speak a complete sentence	5 years & 6 months	Female
Cannot draw letters	6 years	Male
Learning difficulties	6 years & 5 months	Female
Learning difficulties	7 years	Male
Learning difficulties	9 years	Male

Table 3. Distribution of the study group according to developmental delay type, (n= 30)

Developmental delay	
Fine and Gross motor delay in milestones.	13(43.33%)
Behavioral, cognitive, Communicational and Language delay in milestones	17(56.67%)
Total	30(100%)

Data are represented by mean± SD or frequency (%)

Table 4. Comparison between the two studied groups according to N-acetyl-aspartate/creatine in cases ≤ 2 years and >2 years

N-acetyl aspartate/creatine	Study group(n=13)	Control group(n=5)	t	P
≤ 2 years				
Frontal subcortical white matter	2.08±0.141	2.02±0.396	0.528	0.605
Parieto-occipital subcortical white matter	2.06±0.185	1.88±0.164	1.916	0.073
>2 years				
Frontal subcortical white matter	2.15±0.118	2.48±0.084	5.849	<0.001*
Parieto-occipital subcortical white matter	2.13±0.282	2.44±0.114	2.370	0.028*

*t: T-student test p: p value for comparing between the two studied groups, Data are represented by mean± SD or frequency (%), *: Statistically significant at P <0.05*

Table 5. Comparison between the two studied groups according to Cho/Cr in cases ≤2 years and > 2 years

Cho/Cr	Study group (n=13)	Control group (n=5)	t	P
≤2 years				
Frontal subcortical white matter	1.75±0.161	1.90±0.173	1.779	0.094
Parieto-occipital subcortical white matter	1.69±0.144	1.74±0.182	0.587	0.565
> 2 years				
Frontal subcortical white matter	1.61±0.209	1.28±0.249	2.999	0.007*
Parieto-occipital subcortical white matter	1.79±0.256	1.36±0.114	3.636	0.002*

*t: T-student test p: p value for comparing between the two studied groups, Data are represented by mean± SD or frequency (%), *: Statistically significant at P <0.05, Cho: choline, Cr: creatine*

Konus et al. [6] showed that in compare between Idiopathic Infantile Nystagmus and control assessed by MRS there was statistically insignificant difference in the NAA/ Cr ratio between both groups.

In Fayed et al. [7] discovered that the metabolite ratios were significantly lower in children with IDD: In compared to control, NAA/Cr (P.016) The most persuasive explanation for a favorable association between NAA and cognition performance is that NAA may play a key role in transporting water through the hydrophobic myelin sheath during axonal firing, allowing neurons to fire more quickly and with more focused synchronization.

Mangia et al. [8] discovered that the long-term type 1 diabetes does not appear to have a significant impact on the brain neurochemical profile in either white or grey matter as evaluated by MRS, according to the study. They discovered reduced NAA and glutamate concentrations in the occipital grey matter of individuals with type 1 diabetes, which they believe could indicate partial neuronal death or dysfunction as a result of long-term type 1 diabetes.

Furthermore, Filippi et al.[9] found that all children over the age of two who had mild developmental delays had significantly aberrant proton MR spectra as compared to control children. The aberrant proton MR spectra were similar to those of healthy youngsters under the age of two. The NAA/Cr ratios of all of these children decreased statistically significantly. They believe that children with developmental delays and normal brain MR images may have hypomyelination or lower synaptic density as an underlying reason, which might have been discovered with proton MR spectroscopy but missed with regular MR imaging. Damaged myelin, loss of normal myelin, or a decrease in the number of normal neurons can all cause a fall in the NAA/Cr ratio, which may be undetectable with regular MR imaging but identifiable with proton MR spectroscopy.

In a study conducted by Martin et al. [10] NAA (correlation coefficient, cc = 0.38, p = 0.001) and NAA/Cr (cc = 0.31, p = 0.005) they studied the deep grey matter spectra and there was the expected positive connection with age. In deep grey matter, no additional metabolites were found to be significant. The central white matter spectra yielded significant positive correlations, and mIns (sugars [myo-inositol) (cc = 0.30, p = 0.003).

In the study of Kadota et al., [11] revealed that the decreased NAA/Cr ratios of children with psychomotor delay may be linked to myelin degradation, loss of normal myelin, synaptic intensity, or a reduction in the number of neurons, according to the researchers. The elevated Cho/Cr ratios in the group with growth retardation may have been linked to the loss of mature myelin or the inability of choline to penetrate the macromolecules involved in myelin synthesis, according to the same article.

In the current study we found that choline/creatine in Frontal subcortical white matter or Parieto-occipital subcortical white matter were increased in the study group and differences were insignificant in children ≤ 2 years P value = 0.094, 0.565 respectively. And difference was significant in children > 2 years P value = 0.007, 0.002 respectively.

While Konus et al [6] examined the Cho/Cr ratios to reveal a statistically significant difference between two groups. In the brain, the Cho resonance peak occurs at 3.2 ppm and reflects

the total Cho-containing molecules, including phosphocholine, glycerophosphocholine, and phosphatidylcholine.

Coullon et al. [12] studied the individuals with bilateral anophthalmia, researchers discovered a higher Cho level in the pericalcarine cortex, which they explained by altered cholinergic pathway activity and an increase in the number of cells (or an increase in the grey matter proportion) in an ophthalmic subject.

Only a few studies with children with psychomotor delays who underwent MRS have been published in the literature. In a study by Filippi et al. [9] The Cho/Cr ratio ($P < 0.024$ in frontal white matter and $P < 0.002$ in parieto-occipital white matter) was statistically significant higher in all children with developmental delay who were older than 2 years. The Cho/Cr ratio should rapidly decrease throughout the first two years of life, and the proton MR spectra of children older than two years should begin to resemble that of healthy adults.

Hashimoto et al, [13] MRS was utilized to compare the metabolite ratios collected from the right frontoparietal lobe white matter of children aged 2 to 13 years old with psychomotor delay to age-matched healthy children. The psychomotor delay group had lower NAA/ Cr ratios, but there was no significant difference in Cho/Cr ratios between the two groups, according to the researchers. The NAA/Cho ratios of both groups were observed to increase with age in the same study. The psychomotor delay group, on the other hand, saw a slower increase. These findings were interpreted as indicating that brain development was delayed in patients with psychomotor delay, as seen by the low NAA concentration compared to age-matched healthy youngsters. Neuronal activity did not decline but proceeded slowly in children with autism, according to Hashimoto et al, [13].

On the other hand, our Cho/Cr ratio observation did not match that of Lucato et al. [14] who discovered a rise in the Cho/Cr ratio in the basal ganglia of the patient group.

Martin et al, [10] compared the NAA/Cr, myoinositol/Cr, and Cho/Cr ratios in the frontoparietal white matter and deep grey matter of 48 children with psychomotor delay with the values in the frontoparietal white matter and deep grey matter of 23 healthy children, and no significant differences in metabolite levels and ratios were found between the two groups.

Proton MR spectroscopic abnormalities in children with developmental delays who have normal-appearing white matter on brain MR images may be a very general result at this time. As a result, these aberrations should be regarded with caution, especially because the NAA/Cr and Cho/Cr ratios change rapidly throughout early brain development. Despite the fact that ratios are less sensitive and specific than direct metabolite quantification, they are becoming more widely used in clinical practise. Even though the specific nature of reported alterations in the NAA/Cr or Cho/Cr ratio is unknown, information about the amount and severity of these changes could be useful in determining long-term functional outcome. If studied longitudinally, abnormal proton MR spectra may provide additional diagnostic or objective quantitative assessment of neurodevelopment, particularly in children [9].

6. CONCLUSIONS

The proton MR spectroscopy can be used to diagnose and follow developmental delay especially in children more than two years as we found typical changes in NAA/Cr and Cho/Cr.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

Informed consent was obtained from parents of infants and children or controls after full explanation of the benefits and risks of the procedure.

ETHICAL APPROVAL

This study was approved by the Research Ethical Committee of Faculty of Medicine, Tanta University.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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