Original Research Article

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

Abstract

Background: MR spectroscopy analyses molecules such as hydrogen ions or protons. Proton spectroscopy is more commonly used. There are several different metabolites, or products of metabolism. 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.

Introduction:

Development in human is a continuous process which begins from conception, during this process several factors like genetic, environmental, nutritional and chronic diseases can have adverse effects of delay in milestone which can be evaluated using four domains of gross motor, fine motor, social and language skills [1].

After birth, the brain undergoes major developmental changes including neuronal organization, proliferation and differentiation of glial cells, and myelination The concentration of total N-acetyl aspartate increased in all regions during infancy and childhood except in the right caudate head where it remained constant. The concentration of total creatine decreased in the caudate nucleus and splenium and minimally in the frontal white matter and genu. It remained largely constant in the parietal white matter. The concentration of choline-containing compounds had the tendency to decrease in all regions except in the parietal white matter where it remained constant [2].

In children with developmental delay who are older than 2 years, proton MR spectroscopy depicted abnormalities in the NAA/Cr and Cho/Cr ratios. Proton MR spectroscopy should be performed as part of the neuroimaging evaluation of developmental delay. Proton MR spectroscopy can be used as a diagnostic tool and neuroimaging marker to assess long-term functional outcome Magnetic Resonance (MR) spectroscopy is a non-invasive diagnostic test for measuring biochemical changes in the brain.

MR spectroscopy is conducted on the same machine as conventional MRI. The MRI scan uses a powerful magnet, radio waves, and a computer to create detailed images. Spectroscopy is a series of tests that are added to the MRI scan of the brain or spine to measure the chemical metabolism.

MR spectroscopy analyses molecules such as hydrogen ions or protons. Proton spectroscopy is more commonly used. There are several different metabolites, or products of metabolism [3].

The diagnosis of developmental delay remains a clinical one that is age-dependent. Before the development of clinical proton MR spectroscopy, investigators thought that serial MR imaging examinations would be needed to differentiate arrested myelination from slow but progressive development. Likewise, serial proton MR spectroscopy may be needed to make a similar assessment, particularly in children aged 2years or younger [4] (1 1,12).

The aim of this work is to evaluate the role of MR Spectroscopy in diagnosis of infants and children presented with developmental delay.

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. This study was approved by the Research Ethical Committee of Faculty of Medicine, Tanta University. Informed consent was obtained from parents of infants and children or controls after full explanation of the benefits and risks of the procedure. Exclusion criteria were children with congenital heart diseases causing cardiac failure, children with renal failure, contraindications to MRI examination like metallic protheses, metallic gums, metallic aneurysmal clipses 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.

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.

Results:

Table 1 showed age and gender distribution of the study group. Age and gender were no statistically significant differences between groups.

Table 1: Age and gender distribution of the study 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 showed clinical presentation of the children of our study group.

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

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 (%)

There was no significant difference in N-acetyl-aspartate/creatine ratio 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. (**Error! Reference source not found.**)

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	2.06±0.185	1.88±0.164	1.916	0.073

white matter				
>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

Cho/Cr was no statistically significant difference between the control and the study groups in cases ≤2 years. Cho/Cr was significant increase in study group compared to control group (p< 0.05). (**Error! Reference source not found.**)

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

Discussion:

Proton magnetic resonance spectroscopy (MRS) is an advanced MRI technique that offers additional data beyond what can be seen on conventional anatomical scans. It is a non-invasive way to measure the concentrations of brain metabolites, allowing for the study of brain metabolism. MRS has been applied to clinical populations in hopes of providing important information about brain injuries, but to date, much of this promise for preterm-born populations has not been realized [5].

In the current study we found 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.

Konus et al. [6] showed that in compare between Idiopathic Infantile Nystagmus and control assessed by MRS there was no statistically significant difference in the NAA/ Cr ratio between 2 groups.

In Fayed et al. [7] showed that in the children with IDD, found a significant decrease in the following metabolite ratios: NAA/Cr (P.016) in comparison to control, The most compelling argument for the positive relationship between NAA and cognition performance is that NAA may play a critical role in moving water across the hydrophobic myelin sheath during axonal firing, thus potentially allowing neurons to fire more rapidly and perhaps with more focused synchrony.

Mangia et al. [8] reported that long-standing type 1 diabetes mellitus likely does not substantially affect the brain neurochemical profile in either white matter or grey matter as measured by MRS. They found lower NAA and glutamate concentrations in the occipital grey matter of patients with type 1 diabetes mellitus, and they thought that this may represent partial neuronal loss or dysfunction as a consequence of long-term type 1 diabetes mellitus.

Furthermore, Filippi et al.[9] revealed that all children older than 2 years with mild developmental delay had markedly abnormal proton MR spectra compared with those of the control children. The abnormal proton MR spectra resembled those of healthy children much younger than 2 years. All these children had statistically significant decreases in the NAA/Cr ratio.They hypothesize that children with developmental delay and normal brain MR images may have hypomyelination or decreased synaptic density as an underlying cause, which was detected with proton MR spectroscopy but missed with routine MR imaging. If there is a decreased NAA/Cr ratio owing to damaged myelin, loss of normal myelin, or decreased

numbers of normal neurons, this could be occult to routine MR imaging and still detectable 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) showed the expected positive correlation with age in the deep gray matter spectra. All other metabolites did not reach significance in deep gray matter. 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] the investigators speculated that among the older children, the lower NAA/Cr ratios of children with psychomotor delay might have been associated with myelin damage, loss of normal myelin, synaptic intensity, or a reduction in the number of neurons. In the same report, the authors suggested that the increased Cho/Cr ratios in the group with growth retardation might have been associated with destruction of mature myelin or the inability of choline to enter into the macromolecules involved in myelin formation.

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 were significant in children > 2 years P value = 0.007 , 0.002 respectively.

While Konus et al [6] showed that there was a statistically significant difference between 2 groups when the Cho/Cr ratios were compared, In the brain, the resonance peak for Cho occurs at 3.2 ppm and represents the total Cho-containing compounds, including phosphocholine, glycerophosphocholine and phosphatidylcholine.

Coullon et al. [12] found an elevated Cho level in the pericalcarine cortex in patients with bilateral anophthalmia and explained this increase by altered cholinergic pathway activity and an increase in the number of cells (or an increase in the grey matter proportion) in an ophthalmic subjects.

Few studies reported in the literature have been conducted with children with psychomotor delay who underwent MRS. In a study by Filippi et al. [9] all children with developmental delay who were older than 2 years had statistically significant elevations in the Cho/Cr ratio ($P < 0.024$ in frontal white matter and $P < 0.002$ in parieto-occipital white matter). During the first 2 years of life, there should be a rapid decline in the Cho/Cr ratio, and the proton MR spectra of children older than 2 years should begin to resemble that of healthy adults.

Hashimoto et al, [13] used MRS to evaluate children aged from 2- to 13-year-old children with psychomotor delay and age-matched healthy children, comparing the metabolite ratios obtained from the right frontoparietal lobe white matter. Those investigators found lower NAA/ Cr ratios in the psychomotor delay group but no significant difference in the Cho/Cr ratios of the two groups. In the same study, the NAA/Cho ratios of both groups were found to increase with age. This increase, however, was slower in the psychomotor delay group. The interpretation of these results was that brain development was delayed in patients with psychomotor delay; therefore, the NAA concentration was low compared with that of age-matched healthy children. Hashimoto et al. concluded that neuronal activity did not deteriorate but progressed slowly in children with psychomotor delay.

On the other hand, our observation of Cho/Cr ratio was not similar to that of Lucato et al. [14] who found an increase 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 gray matter of 48 children with psychomotor delay with the values in 23 healthy children and found no significant difference between the two groups in terms of metabolite levels and ratios.

Abnormalities detected with proton MR spectroscopy in children with developmental delay who have normal-appearing white matter on brain MR images may be a relatively nonspecific finding at present. Thus, these abnormalities should be interpreted in a prudent

manner, especially since NAA/Cr and Cho/Cr ratios vary rapidly in early brain development. Although the use of ratios is less sensitive and specific than direct quantification of metabolites, their use is becoming widespread in clinical practice. Information regarding the magnitude and severity of observed changes in the NAA/Cr or Cho/Cr ratio could be valuable in assessing long-term functional outcome even though the exact nature of these changes is not clear. Abnormal proton MR spectra, if followed longitudinally, may offer another diagnostic or objective quantifiable assessment of neurodevelopment, especially as more children with developmental delay are studied with proton MR spectroscopy [9].

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.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. 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.

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