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# Magnetic Resonance Spectroscopy Findings in The Variable Pediatric White Matter Disorders in Suez Canal Area

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## ABSTRACT

**Background:** When MRI and magnetic resonance spectroscopy (MRS) are used together, they allow for the correlation of anatomical and pathological features in a selected region of the brain. **Aim:** This study aimed at describing the variable changes in the brain metabolites' levels and ratios in the pediatric white matter diseases.

**Patients and methods:** MR spectroscopy of the affected white matter and basal ganglia was held on 22 eligible infants and children with clinically and radiologically proven white matter diseases. According to the established diagnosis, the cases were classified into five groups including: hypomyelination, inborn errors of metabolism, congenital muscular dystrophies (CMD), and secondary demyelinating disorder.

**Results:** All the cases of CMD (5 cases) showed decreased Cr level, while only one third of the cases of hypomyelination showed decreased Cr level. Increased mIn level in the affected white matter was seen in 8 cases, half of these cases were finally diagnosed with CMD, however these findings were statistically insignificant. Cho/NAA ratio was increased in the affected white matter in half of the cases diagnosed with CMD and half of the cases diagnosed with hypomyelination. Lactate levels in the basal ganglia showed statistically significant difference among the different groups of disorders, as lactate level was high in the basal ganglia of about two thirds of the cases of inborn errors of metabolism.

**Conclusion:** MRI is the modality of choice in evaluating pediatric white matter disorders, however MR spectroscopy have an adding value in narrowing the differential diagnosis list, define single appropriate diagnosis, or even direct specific investigation.

**Key words:** spectroscopy, white matter disorder and pediatric**.**

## INTRODUCTION

Magnetic resonance spectroscopy (MRS) delivers information about cell content and metabolism in a noninvasive manner. The technical foundation of MRS depends on identifying metabolites by their varying resonance frequencies [(1)]. This information is represented in a graph where different peaks correspond to specific compounds. So, MRS is complementary to conventional MRI sequences in some cases, as it allows further characterization of the changes occurring on the biochemical level [(7)].

MRS can be conducted by using signals emitted by either: hydrogen protons ($^{1}H$), phosphorus ($^{31}P$), or carbon ($^{13}C$), atoms. However, unlike $^{31}P$ or $^{13}C$ MRS, $^{1}H$-MRS has become widely accessible in routine clinical practice, and that is likely because hydrogen is the most prevalent atom in the human body, and its nucleus produces a strong radiofrequency signal, resulting in a favorable signal-to-noise ratio at 1.5 T, which allows for adequate detection and resolution [(1)].

Pediatric white matter diseases are representing wide spectrum of disorders [(9)]. The role of MR spectroscopy in the diagnostic work-up of patients with white matter disorders is not yet well defined, however it provides additional information helpful in assessment of these patients [(2)]. Therefore, when MRI and MRS are used together, they allow for the correlation of anatomical and pathological features in a selected region of the brain [(8)].

Our study aims at describing the changes in the metabolites' levels and ratios detected by MRS in the variable pediatric white matter diseases.

## PATIENTS AND METHODS

**Ethical statement:**

**This study followed the STARD reporting guidelines [(3)]. Our Institutional Review Board of Suez Canal University, approved the study (Approval number: 4158), and informed written consent was given by each patient's guardian. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.**

**Study design and population:**

This unicentric prospective study was held on 22 eligible infants and children with clinically and radiologically proven white matter disease. The study was done in Radiology Department at Suez Canal University Hospital.

**Inclusion criteria were:** Pediatric age (from age of 1 day to 18 years), conventional MRI shows evidence of white matter affection/disease, and the diagnosis of white matter disorder was established.



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**Exclusion criteria were:** Neoplastic lesions and hypoxic ischemic insults.

**MRI protocol:**

MRS of the brain was done on a 1.5 Tesla MR scanner (Philips Medical Systems, Achieva 1.5T A-series). One single voxel in the basal ganglia (routinely only done on one side, covering putamen/pallidum) and one single voxel in the affected white matter (routinely also done only on one side, in the centrum semiovale) both at short and long echo time were our standard protocol. The volume at both levels should be at least 2×2×2 cm with 64 repetitions (in neonates 1.2×1.2×1.2 cm is acceptable to reduce partial volume effects, in which case higher acquisition repetitions – 96 or 128 – is recommended).

**MRS images analysis:**

MR spectroscopy was done in twenty-two cases, each case was evaluated by examining the affected white matter and the basal ganglia for the levels of the different metabolites (including N-acetyl aspartate (NAA), Choline (Cho), creatine (Cr), myoinositol (mIn), lipid and lactate) and the ratios (including NAA/Cr, Cho/Cr, Cho/NAA and mIn/Cr).

According to the established diagnosis of each case, the cases were classified into five groups including: hypomyelination, inborn errors of metabolism, congenital muscular dystrophies (CMD), and secondary demyelinating disorder. The MRS findings were interpreted in the five groups.

***Statistical analysis***

We used IBM Statistical Package for Social Sciences software (SPSS), 21st edition, IBM, United States for data analysis. Comparison between groups was done by the Chi-Square test. Statistical significance was $P < 0.05$.

**RESULTS**

MR spectroscopy of the affected white matter and basal ganglia, was done in 22 cases, 10 (45.5%) male patients and 12 (54.5%) females, with the mean age of the cases was 40.36 months and median age was 14.5 months. Five cases were diagnosed with congenital muscular dystrophy (CMD, mainly merosin-deficient congenital muscular dystrophy (MDC 1A)), 10 cases diagnosed with hypomyelinating disorder (Pelizeus-Merzbacher disease (PMD)), 6 cases with inborn errors of metabolism (4 cases of Leigh syndrome, 1 case of propionic acidemia, and one case of isovaleric acidemia), and one case with secondary demyelinating disorder (congenital infection CMV).

In each case the level of the following metabolites NAA, choline (Cho), creatine (Cr), lipid, lactate and myoinositol (mIn) was assessed, and the ratios including NAA/Cr, Cho/Cr, Cho/NAA and mIn/Cr were also assessed and interpreted as decreased, normal, or increased by comparing these findings with MRS findings of normal studied children having same ages.

**MRS findings in white matter of examined cases (table 1)**

In the five cases diagnosed with CMD (mainly merosin-deficient congenital muscular dystrophy (MDC 1A)), NAA, Cr, and Choline levels were low in the affected white matter of all cases, with elevation of the myoinositol level in four cases, and one case showed normal myoinositol level.

Decreased choline levels in the white matter were evident in about 70% of the cases of hypomyelination, with decreased NAA levels seen in half of the cases. In cases with inborn errors of metabolism (6 cases), NAA level showed normal levels in white matter of about half of the cases and showed decreased levels in the other half, choline level in white matter also was normal in half of the cases and decreased in two cases, while mIn level in white matter was increased in one third of cases.

Among all the metabolites measured in white matter, only creatine (Cr) showed statistically significant difference between the groups of disorders, all the cases of CMD (5 cases) showed decreased Cr level, while only one third of the cases of hypomyelination showed decreased Cr level and the other two thirds showed normal Cr level.

Increased mIn level in the affected white matter was seen in 8 cases, half of these cases was finally diagnosed with CMD, however these findings were statistically insignificant.

Cho/NAA ratio was increased in the affected white matter in half of the cases finally diagnosed with CMD and half of the cases diagnosed with hypomyelinating disorder, while it was normal levels in the white matter in half of cases diagnosed CMD and decreased in half of the cases diagnosed with hypomyelination. These findings were statistically significant.

**Table (1):** Interpretation of MR spectroscopy of the white matter of examined cases in different groups of pediatric white matter disorders.

| Variables | Total number (n=22) | CMD (n = 5) | Hypomyelination (n=10) | Inborn errors of metabolism (n = 6) | Demyelination (n = 1) | P-value |
|---|---|---|---|---|---|---|
| **MRS NAA** | | | | | | |
| Decreased | 14 (63.6) | 5 (100) | 5 (50) | 3 (50) | 1 (100) | 0.32 [a] |
| Normal | 6 (27.3) | 0 | 3 (50) | 3 (50) | 0 | |
| Increased | 2 (9.1) | 0 | 2 (20) | 0 | 0 | |
| **MRS Cho** | | | | | | |
| Decreased | 14 (63.6) | 5 (100) | 7 (70) | 2 (33.3) | 0 | 0.06 [a] |
| Normal | 5 (22.7) | 0 | 2 (20) | 3 (50) | 0 | |
| Increased | 3 (13.6) | 0 | 1 (10) | 1 (16.7) | 1 (100) | |
| **MRS Cr** | | | | | | |
| Decreased | 8 (36.4) | 5 (100) | 3 (30) | 0 | 0 | 0.026 [a] |
| Normal | 13 (59.1) | 0 | 6 (60) | 6 (10) | 1 (100) | |
| Increased | 1 (4.5) | 0 | 1 (10) | 0 | 0 | |
| **MRS mln** | | | | | | |
| Normal | 14 (63.6) | 1 (20) | 8 (80) | 4 (66.7) | 1 (100) | 0.12 [a] |
| Increased | 8 (36.4) | 4 (82) | 2 (20) | 2 (33.3) | 0 | |
| **MRS Lipid** | | | | | | |
| Normal | 21 (95.5) | 5 (100) | 10 (100) | 6 (100) | 0 | 0.04 [a] |
| Increased | 1 (4.5) | 0 | 0 | 0 | 1 (100) | |
| **MRS Lactace** | | | | | | |
| Normal | 21 (95.5) | 5 (100) | 10 (100) | 6 (100) | 0 | 0.04 [a] |
| Increased | 1 (4.5) | 0 | 0 | 0 | 1 (100) | |
| **MRS NAA/Cr** | | | | | | |
| Decreased | 8 (36.4) | 0 | 4 (40) | 3 (50) | 1 (100) | 0.35 [a] |
| Normal | 13 (59.1) | 5 (100) | 5 (50) | 3 (50) | 0 | |
| Increased | 1 (4.5) | 0 | 1 (10) | 0 | 0 | |
| **MRS Cho/Cr** | | | | | | |
| Decreased | 6 (27.3) | 0 | 4 (40) | 2 (33.3) | 0 | 0.2 [a] |
| Normal | 8 (36.4) | 1 (20) | 4 (40) | 3 (50) | 0 | |
| Increased | 8 (36.4) | 4 (80) | 2 (20) | 1 (16.7) | 1 (100) | |
| **MRS Cho/NAA** | | | | | | |
| Decreased | 5 (22.7) | 0 | 5 (50) | 0 | 0 | 0.03 [a] |
| Normal | 7 (31.8) | 3 (60) | 0 | 4 (66.7) | 0 | |
| Increased | 10 (45.5) | 2 (40) | 5 (50) | 2 (33.3) | 1 (100) | |
| **MRS mIn/Cr** | | | | | | |
| Normal | 14 (63.6) | 1 (20) | 8 (8) | 4 (66.7) | 1 (100) | 0.12 [a] |
| Increased | 8 (36.4) | 4 (40) | 2 (20) | 2 (33.3) | 0 | |

[a] P-values are based on Fisher Exact test. Statistical significance at P<0.05

NAA= N-acetylaspartate; Cho= Choline; Cr= creatine; mIn= myoinositol.

**Table (2):** Interpretation of MR spectroscopy of the basal ganglia of examined cases in different groups of pediatric white matter disorders.

| Variables | Total number (n=22) | CMD (n = 5) | Hypomyelination (n=10) | Inborn errors of metabolism (n = 6) | Demyelination (n = 1) | P-value |
|---|---|---|---|---|---|---|
| **MRS NAA** | | | | | | |
| Decreased | 9 (40.9) | 1 (20) | 5 (50) | 3 (50) | 0 | 0.7 [a] |
| Normal | 13 (59.1) | 4 (80) | 5 (50) | 3 (50) | 1 (100) | |
| **MRS Cho** | | | | | | |
| Decreased | 7 (31.8) | 1 (20) | 4 (40) | 2 (33.3) | 0 | 0.41 [a] |
| Normal | 13 (59.1) | 4 (80) | 6 (60) | 2 (33.3) | 1 (100) | |
| Increased | 2 (9.1) | 0 | 0 | 2 (33.3) | 0 | |
| **MRS Cr** | | | | | | |
| Decreased | 4 (18.2) | 1 (20) | 3 (30) | 0 | 0 | 0.5 [a] |
| Normal | 18 (81.8) | 4 (80) | 7 (70) | 6 (100) | 1 (100) | |
| **MRS mln** | | | | | | |
| Normal | 21 (95.5) | 5 (100) | 1 (100) | 5 (83.3) | 1 (100) | 0.5 [a] |
| Increased | 1 (4.5) | 0 | 0 | 1 (16.7) | 0 | |
| **MRS Lipid** | | | | | | |
| Normal | 22 (100) | 5 (100) | 10 (100) | 6 (100) | 1 (100) | - |
| **MRS Lactate** | | | | | | |
| Normal | 18 (81.8) | 5 (100) | 10 (100) | 2 (33.3) | 1 (100) | 0.004 [a] |
| Increased | 4 (18.2) | 0 | | 4 (66.7) | 0 | |
| **MRS NAA/Cr** | | | | | | |
| Decreased | 9 (40.9) | 1 (20) | 5 (50) | 3 (50) | 0 | 0.62 [a] |
| Normal | 13 (59.1) | 4 (80) | 5 (50) | 3 (500 | 1 (100) | |
| **MRS Cho/Cr** | | | | | | |
| Decreased | 6 (27.3) | 1 (20) | 3 (30) | 2 (33.3) | 0 | 0.7 [a] |
| Normal | 13 (59.1) | 4 (80) | 6 (60) | 2 (33.3) | 1 (100) | |
| Increased | 3 (13.6) | 0 | 1 (10) | 2 (33.3) | 0 | |
| **MRS Cho/NAA** | | | | | | |
| Decreased | 2 (9.1) | 0 | 1 (10) | 1 (16.7) | 0 | 0.6 [a] |
| Normal | 15 (68.2) | 5 (100) | 6 (60) | 3 (50) | 1 (100) | |
| Increased | 5 (22.7) | 0 | 3 (30) | 2 (33.3) | 0 | |
| **MRS mIn/Cr** | | | | | | |
| Normal | 21 (95.5) | 5 (100) | 10 (100) | 5 (83.3) | 1 (100) | 0.5 [a] |
| Increased | 1 (4.5) | 0 | 0 | 1 (16.7) | 0 | |

[a] P-values are based on Fisher Exact test. Statistical significance at $P<0.05$

NAA= N-acetylaspartate; Cho= Choline; Cr= creatine; mIn= myoinositol.

**MRS findings in basal ganglia of examined cases (table 2)**

Lactate levels in the basal ganglia showed statistically significant difference among the different groups of disorders, as lactate level was high in the basal ganglia of about two thirds of the cases with final diagnosis of inborn errors of metabolism (4 cases), 3 cases diagnosed with primary mitochondrial disease and one case diagnosed with isovaleric acidemia. Lactate level in the basal ganglia was normal in other groups.

In 80% of cases diagnosed with CMD, the main metabolites including: NAA, Cho and Cr levels were normal in the basal ganglia, while mIn, lipids and lactate levels were normal in the basal ganglia of all cases of CMD.

In cases diagnosed with hypomyelination, NAA level in basal ganglia was normal in half of the cases and decreased in the other half, while Cho level was normal in about 60% of the cases and decreased in 40% of the cases and Cr was normal in 70% of the cases and decreased in 30% of the cases.

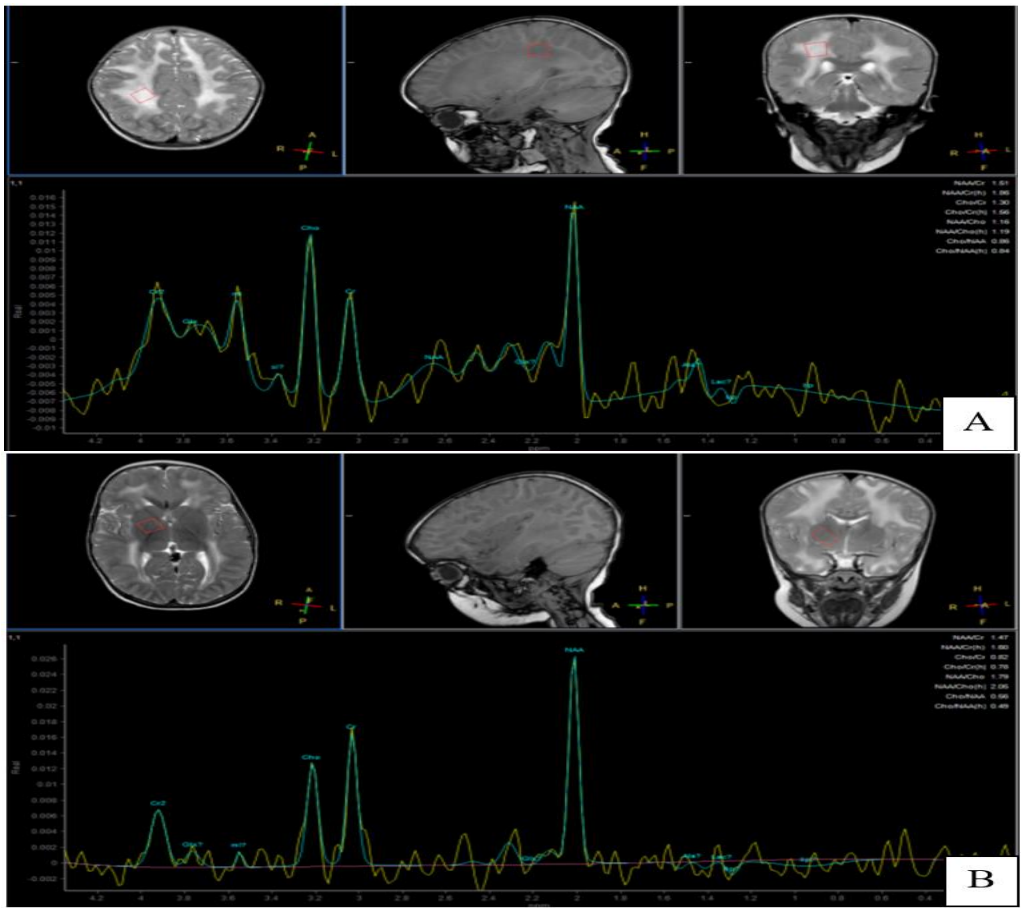


**Figure (1):** A 32 months old female child, complaining of developmental delayed diagnosed with Congenital muscular dystrophy, merosin-deficient type. (A) shows MR spectroscopy at right high parietal white matter, TE= 31, showing decreased NAA, Cr levels with mild reduction of Cho level and mildly elevated mIn level. (B) shows MR spectroscopy at right basal ganglia, TE= 31, showing normal NAA, Cho, Cr and mIn level.

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## DISCUSSION

In the present study MR spectroscopy of the affected white matter and basal ganglia was done in 22 cases. In cases of hypomyelinating disorders (10 cases), choline was decreased in 70% of the cases, with NAA was decreased in 50 % of the cases and normal in 30% of the cases, and increased Cho/NAA ratio in 50% of the cases. These results consistent with other studies suggesting that decreased Cho representing hypomyelination process, with NAA ranging from mildly decreased to normal levels in hypomyelination [(1)]. In the present study MRS of the basal ganglia in cases of hypomyelination revealed either normal level of the main metabolites NAA, Cho, and Cr or decreased levels, to the best of our knowledge there are limited information about MRS findings in basal ganglia of hypomyelinating disorders.

MRS of the white matter in cases diagnosed with CMD (5 cases, mainly diagnosed with merosin-deficient congenital muscular dystrophy) revealed decreased levels of the main metabolites: NAA, Cho & Cr, this result was in agreement with the results of a previous study by [(4)], described the quantitative MRS of cerebral metabolites in laminin a2 chain deficiency (merosin-deficient congenital muscular dystrophy) and reported reduced concentrations of N-acetylaspartate, creatine, and to a milder degree of choline in the affected white matter. **Brockmann *et al.*** [(4)] also reported normal myoinositol level in the affected white matter of patients with laminin a2 chain deficiency, unlike our results of elevated myoinositol level in about 82% (4 out of 5 cases) of our cases. On the other hand, elevated myoinositol in white matter of children with CMD was reported in a study by **Lai *et al.*** [(5)].

The main metabolites showed normal levels at the basal ganglia of about four out of five cases diagnosed with CMD in our study, that was expected since the basal ganglia showed normal MRI features in these cases.

In the present study, elevated lactate level at the basal ganglia was statistically significant in cases with inborn errors of metabolism, as 4 cases (66.7%) showed elevated lactate peaks at the basal ganglia, three of which with final diagnosis of primary mitochondrial disease (leigh syndrome), these results were consistent with a previous study by **Chi *et al.*** [(6)], that reported detected lactate peaks in 85.7% of the children with mitochondrial

diseases and observed higher detection rate of lactate peak at acute phase of the disease than at stationary phase of the disease.

Multiparametric MRI assessment is the modality of choice in evaluating white matter disorders in pediatric patients, however MR spectroscopy have an adding value in narrowing the differential diagnosis list, define single appropriate diagnosis or even direct specific investigation to establish the appropriate diagnosis.

**Conflict of interest:** All authors have no conflicts of interest to disclose.

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