

# Initial Experiences with Proton MR Spectroscopy in Treatment Monitoring of Mitochondrial Encephalopathy

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**Purpose:** Mitochondrial encephalopathy (ME) is a rare disorder of energy metabolism. The disease course can roughly be evaluated by clinical findings. The purpose of this study was to evaluate metabolic spectral changes using proton MR spectroscopy (MRS), and to establish a way to monitor ME by neuroimaging.

**Materials and Methods:** Proton MRS data were retrospectively reviewed in 12 patients with muscle biopsy-confirmed ME (M : F = 7 : 5, Mean age = 4.8 years). All received <sup>1</sup>H-MRS initially and also after a ketogenic diet and mitochondrial disease treatment cocktail (follow up average was 10.2 months). Changes of N-acetylaspartate/creatine (NAA/Cr) ratio, choline/creatine (Cho/Cr) ratio, and lactate peak in basal ganglia at 1.2 ppm were evaluated before and after treatment. Findings on conventional T2 weighted MR images were also evaluated. **Results:** On conventional MRI, increased basal ganglia T2 signal intensity was the most common finding with ME (n = 9, 75%), followed by diffuse cerebral atrophy (n = 8, 67%), T2 hyperintense lesions at pons and midbrain (n = 4, 33%), and brain atrophy (n = 2, 17%). Lactate peak was found in 4 patients; 2 had disappearance of the peak on follow up MRS. Quantitative analysis showed relative decrease of Cho/Cr ratio on follow up MRS ( $p = 0.0058$ , paired t-test, two-tailed). There was no significant change in NAA/Cr ratio. **Conclusion:** MRS is a useful tool for monitoring disease progression or improvement in ME, and decrease or disappearance of lactate peak and reduction of Cho/Cr fraction were correlated well with improvement of clinical symptoms.

**Key Words:** Magnetic resonance spectroscopy, mitochondrial diseases

## INTRODUCTION

Mitochondrial encephalopathy (ME) is a heterogeneous group of clinical syndromes associated with mitochondrial energy metabolism abnormalities. Presentation is nonspecific with encephalomyopathy, failure to thrive, seizures, ophthalmoplegia, and sensorineural hearing loss.<sup>1,2</sup> Impaired energy production results from overall dysfunction of the mitochondrial respiratory chain, which is composed of five enzymatic complexes embedded in the inner mitochondrial membrane.

There is no specific treatment for ME, and only conservative care is available. One treatment is ketogenic diet therapy with a mitochondrial disease treatment cocktail of coenzyme Q10, riboflavin, L-carnitine, and high-dose multivitamins;

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some favorable results have been reported.<sup>3,4</sup>

Diagnosis and monitoring can be achieved by clinical findings and imaging techniques such as CT, conventional MR imaging, and diffusion weighted MRI.<sup>5-7</sup> MR spectroscopy (MRS) is a useful tool in evaluation of brain tissue metabolites; applications in mitochondrial encephalopathy are well documented.<sup>8-13</sup> However, previous studies have been limited to a single MRS study; there are no reports on serial metabolite distribution changes during treatment. The purpose of this study is to evaluate changes in the metabolic spectrum by MRS spectroscopy, and to establish a way to monitor disease course by neuroimaging.

## MATERIALS AND METHODS

The institutional review board approved retrospective analysis of MRS data from patients with mitochondrial encephalopathy. From July 2005 to October 2007, there were 46 patients with muscle biopsy-confirmed mitochondrial disease. Twelve received <sup>1</sup>H-MRS (M : F = 7 : 5, Mean age = 4.8 years, range from 1 to 17 years) initially and also after ketogenic diet and mitochondrial disease treatment cocktail administration. The average interval between MRS scans was 10.2 months (range 5 to 17 months). Data were retrospectively reviewed.

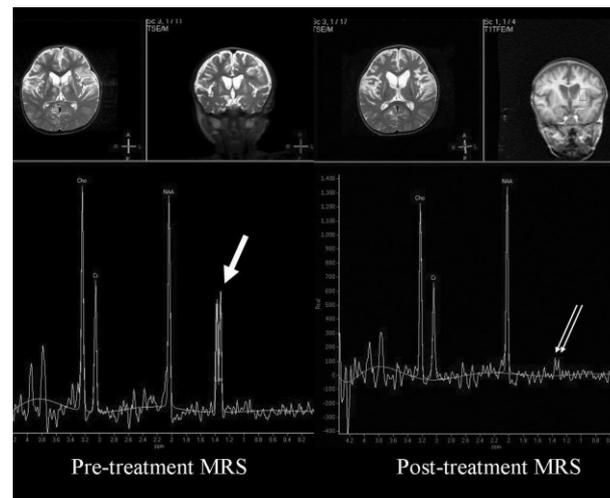
Localized <sup>1</sup>H-MRS was performed on a 3.0T MRI system (Achieva, Philips Medical Systems, Best, Netherlands) using an 8-channel SENSE head coil. Two water-suppressed <sup>1</sup>H-MR spectra were obtained from a voxel located in the basal ganglia (voxel, 2 × 2 × 2 mL). The following spectral acquisition parameters were used with the point resolved spectroscopy sequence (PRESS) method: Spectra BW = 2,000 Hz, TR = 2.0 s, TE = 288/144 ms, acquisition number = 128. All raw data were processed using the SpectroView software package (Philips Medical System, Best, Netherlands), with Gaussian line broadening of 3Hz, zero, and linear phase correction. Peaks were identified with known chemical shifts: lactate at 1.2 ppm, N-acetylaspartate at 2.02 ppm, phosphocreatinine and creatinine at 3.05 ppm, and choline-containing compounds at 3.22 ppm. Pre- and post-treatment MR spectra were evaluated for change in choline/creatinine (Cho/Cr) and N-acetylaspartate/creatinine (NAA/Cr) ratios. Presence of a lactate doublet peak was also monitored at 1.2 ppm, and confirmed by showing inversion on half TE sequence (TE = 144 ms) [(-): absence of lactate doublet, (+): faint presence of lactate doublet, (++): definite presence of lactate doublet]. Morphological findings on conventional T2 weighted images were also assessed, with emphasis on abnormal signals in the basal ganglia, brain stem, and any atrophic changes in brain parenchyma.

## RESULTS

Six, five, and one patient were diagnosed with mitochondrial respiratory chain (MRC) I, MRC IV, and MRC II deficiency, respectively (Table 1). Clinically, 2 (patients No. 2 and 11) had Leigh disease and 1 (patient No. 8) had Kearns-Sayre Syndrome. The other 9 had uncategorized MRC encephalopathies. All had mild to moderate clinical improvement between pre- and post-treatment MRS studies, such as decreased seizure frequency, improved general condition, and improved developmental status.

On conventional T2 weighted images (T2WI), all had abnormal findings. Increased basal ganglia T2 signal intensity was the most common finding with ME (n = 9, 75%), followed by diffuse cerebral atrophy (n = 8, 67%). Four (33%) patients had increased midbrain and pons signal lesions. Cerebellar atrophy (17%) was found in 2 patients, along with diffuse cerebral atrophy (Table 1). Lactate peak was found in 4 patients; 2 had disappearance of the peak on follow up scan. One patient showed marked reduction of lactate peak after ketogenic diet and mitochondrial cocktail therapy (Case #2, Fig. 1), but the other patient showed no remarkable change of lactate peak before and after treatment.

Quantitative analysis showed relative decrease of Cho/Cr ratio on follow up MRS ( $p = 0.0058$ , paired t-test, two-tailed). There was no significant change in NAA/Cr ratio. However, all three patients with normal basal ganglia signal on T2WI showed elevated NAA/Cr ratio after ketogenic diet. On anatomical imaging, there were no remarkable changes of brain atrophy or newly developed T2 hyperintense lesions.



**Fig. 1.** Two-year-old male with Leigh disease (case 2). Pre-treatment MRS shows high lactate peak (arrow) at basal ganglia. One year follow up MRS shows decrease of lactate (double arrows) and restoration of NAA. NAA, N-acetylaspartate.

**Table 1. Patient Characteristics According to Mitochondrial Enzyme Defect, MR Findings and MRS Findings**

Patient no.	Sex	Age	Defect enzyme	Scan interval	BG signal change	Cerebral atrophy	Brain stem lesion	Cerebellar atrophy	Lactate doublet (1st / 2nd scan)	Pre-treatment NAA / Cr	Post-treatment NAA / Cr	Pre-treatment Cho / Cr*	Post-treatment Cho / Cr*
1	F	4	II	8	+	-	-	-	- / -	1.558	1.350	1.016	1.056
2	M	2	IV	12	+	+	+	-	++ / +	1.505	1.557	1.719	1.624
3	F	2	I	8	+	-	-	-	++ / ++	2.054	2.062	1.656	1.349
4	M	9	I	6	-	+	-	-	- / -	1.677	1.811	0.952	0.823
5	F	2	I	12	+	-	-	-	+ / -	1.810	1.250	1.391	0.927
6	M	1	I	6	+	+	-	-	- / -	1.798	1.105	1.042	0.944
7	M	5	I	5	+	+	+	+	- / -	1.293	2.080	1.496	1.28
8	F	17	IV	17	+	+	-	-	- / -	1.970	1.732	1.25	0.898
9	F	1	IV	12	+	+	+	+	- / -	1.622	1.420	1.742	1.673
10	M	6	I	12	-	+	-	-	- / -	1.359	1.740	1.591	1.09
11	M	4	IV	12	+	-	-	-	++ / -	1.737	1.660	1.333	0.98
12	M	5	IV	12	-	+	+	-	- / -	2.198	2.270	1.511	1.67

BG, basal ganglia; NAA, N-acetylaspartate; Cho, choline; Cr, creatinine.

Lactate doublet: doublet peak at 1.2 - 1.4 ppm, (++) marked increase, (+) positive, (-) negative.

\*Significant reduction between pre-treatment Cho/Cr and post-treatment Cho/Cr ( $p=0.0058$ , paired t-test, two-tailed).

## DISCUSSION

Mitochondrial respiratory chain disease or encephalopathy is a rare disorder of energy metabolism. Clinical characteristics and prognosis are still under investigation. With the development of electron microscopic diagnosis and enzyme assay technique, many children with previous uncertain etiologies have been diagnosed with ME. Typical imaging findings are non-specific cortical T2 hyperintensities, progressive atrophy, and encephalitis, similar to findings without evidence of infectious etiologies.

Using brain MR examinations, we investigated 12 patients with established ME, and found a wide range of structural and metabolic abnormalities. Our results are in agreement with previous studies which support the role of MRS as a confirmatory test.<sup>1,11,12,14,15</sup> Our study also supports the use of MRS for monitoring ME treatment by measuring the Cho/Cr ratio and lactate peak. As clinical symptoms and neurologic function improve, the Cho/Cr ratio and lactate amplitude decrease.

As MRS can detect biochemical metabolites concentration in vivo, it is more sensitive than MR imaging in assessment of brain tissue metabolite alterations, such as increased lactate fraction. In our study, all patients had various T2WI MR findings which did not change during treatment, while differences in metabolite fraction were seen on serial MRS.

Although there are doubts about ketogenic diet efficiency,<sup>16</sup> recent studies present remarkable successes. Prasad, et al.<sup>17</sup> showed that in intractable epilepsy treated with ketogenic diet, nearly one third became seizure-free, another third had significantly reduced seizure frequency, and the remainder did not benefit significantly. Our patients had no remarkable complications with conservative treatment. Instead, seizure frequency was decreased and neurologic function improved. These clinical findings were correlated well with MRS changes.

This study has some limitations. First, there are no age matched controls for pediatric MRS data. We could only compare two consecutive studies with longitudinal analysis. Previous MRS studies of healthy children have revealed that basal ganglia NAA increases until adolescence.<sup>18</sup> Therefore, NAA increase during ME disease course cannot be explained by treatment effects. Also, Gupta, et al.<sup>19</sup> showed that adequate treatment for hypoparathyroidism induced gradual Cho/Cr reduction, similar to our study. As choline decreases according to myelination and maturation, Cho/Cr reduction is not affected solely by a ketogenic diet. However, lactate peak is definitely abnormal in disease conditions, such as ME, therefore, reduction or resolution is a good indicator for disease monitoring or

treatment assessment.

Second, this study is a retrospective review of MRS data in a large patient pool, therefore, follow up periods are quite variable. Ideal and future study design should include pre- and post-treatment serum and CSF lactate level check, uniform follow up periods and more homogenous patient group selection. Definition of mitochondrial encephalopathy is still under investigation, therefore, we included wide variety of diseases, however, future application should be focused on more specific disease group. Third, as there is no specific treatment for ME, multiple therapies, such as antiepileptics, ketogenic diets, and mitochondrial disease cocktails, were used. It is, therefore, difficult to identify treatments responsible for clinical improvement and MRS changes.

In short, this is a primitive and pilot study of MR spectroscopy uses in mitochondrial disease. Diverse patient characteristics and follow up periods are basic limitations of this study. Furthermore, obtaining normal controls for MR spectroscopy is necessary. Data from normal children and sham control are basically impossible due to disease nature and ethical problems. However, this study has clarified some of the diverse findings of ME on routine MRI & MR spectroscopy; these results can provide benefits to future research.

In conclusion, we found that MRS is a useful tool for monitoring disease progression or improvement in ME. Despite lack of change on T2 weighted images, MRS depicted metabolite changes during ketogenic diet and mitochondrial cocktail therapy. Decreased lactate peak and Cho/Cr fraction were correlated well with improvement of clinical symptoms.

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