

Transient Improvement of Pyruvate Metabolism after Coenzyme Q Therapy in Kearns-Sayre Syndrome: MRS Study

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Abstract

Coenzyme Q therapy has been used to support metabolic derangements in patients with mitochondrial encephalomyopathies. Biochemical analysis of the living human brain can be performed by magnetic resonance spectroscopy (MRS). We report upon a KSS patient who was serially imaged with localized proton MRS to monitor the efficacy of CoQ treatment. A 17-year-old girl with KSS was serially imaged with localized proton MRS performed on a GE 1.5 T SIGNA MRI/MRS system. The elevated lactate contents of lesions decreased after one month of CoQ therapy but were re-elevated 10 months after treatment. We conclude that MRS presents us with a powerful tool for monitoring the effects of therapeutic trials in mitochondrial encephalomyopathies.

Key Words: Kearns-Sayre syndrome, MRS, CoQ, lactate

INTRODUCTION

Kearns-Sayre syndrome (KSS) is one of the mitochondrial encephalomyopathies characterized by chronic progressive external ophthalmoplegia, defects in cardiac conduction, pigmentary retinal degeneration, endocrinopathies, "ragged red fiber" on microscopic examination of muscle and mitochondrial DNA (mtDNA) deletion on molecular analysis.¹ The mtDNA mutation leads to generalized defects in the synthesis of mitochondrial polypeptides and finally impairs oxidative phosphorylation and energy metabolism. In highly oxidative tissues such as the brain and skeletal muscles, bioenergetic demands exceed the pathologically-limited oxidative phosphorylative capacity, and consequently this energy failure results in the dysfunction of such vulnerable organs.²

Biochemical analysis of the living human brain can be performed by magnetic resonance spectroscopy (MRS).³ The brain lactate contents may be used as

an indirect index of impairment of oxidative metabolism.⁴ Kuwabara et al. demonstrated, using proton MRS, that brain lactate in the resting state was higher in KSS patients than in controls.⁵

We have previously reported upon this patient in terms of clinical, pathologic and radiologic findings, including MRS results.⁶ Here we describe that serial imaging with localized proton MRS revealed a transient decrease of the lactate content in the brain, after CoQ treatment, which was coincident with clinical improvement.

CASE REPORT

A 17-year-old girl complained of aggravated progressive external ophthalmoplegia for 3 months. There was neither consanguinity nor a positive family history. Pregnancy, birth and development were normal until age 11, when bilateral ptosis was first observed. Two years later, she was operated upon for bilateral blepharoplasty.

Examination revealed bilateral retinal pigmentary degeneration, mild cognitive dysfunction, bilateral ptosis, external ophthalmoplegia and cerebellar ataxia. ECG showed no conduction abnormalities. The CSF contained no cells, 88 mg/dl of proteins and normal glucose. Fasting serum lactate (36.4 mg/dl; normal, 10 to 25 mg/dl) and CSF lactate were abnormally

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high (23.7 mg/dl; normal, 3 to 12 mg/dl). Serum LH, GH, FSH and ACTH levels were within normal limits. Electromyography (EMG) showed myogenic changes in the biceps brachii muscle and pathologic examination of biopsied muscle showed typical ragged red fibers on modified Gomori trichrome staining. A T2-weighted MRI of the brain revealed high signal intensities in bilateral cerebral white matter, cerebellar white matter, thalami and brainstem. Coenzyme Q (Q₁₀) therapy was started from 50 mg of CoQ daily and then daily doses were increased to 100 mg. After one month of CoQ therapy, we found mild improvements in cognitive function, external ophthalmoplegia and cerebellar ataxia. However, 10 months after CoQ therapy, she complained of progressive cerebellar ataxia and external ophthalmoplegia. Follow-up MRI showed no interval changes.

Magnetic resonance spectroscopy studies: Localized proton MR spectroscopy was performed on a GE 1.5 T SIGNA MRI/MRS system (Milwaukee, WI, USA). STEAM (stimulated echo acquisition method) was used as the localization method in this study, and 9 ml. was adopted as the voxel size. Image guided STEAM-spectra were obtained with a TE of 30 msec, TR of 3.0 sec, 48 AVG and 2 NEX. Proton MRS showed elevated lactate content in the involved regions of the brain (Fig. 1). After one month of CoQ therapy, proton MRS showed normalization of the lactate level to baseline in the previously involved region of the brain (Fig. 1). Follow-up proton MRS performed 10 months (Fig. 1) and 16 months after CoQ therapy showed that lactate content had subsequently increased. The choline/creatinine, lactate/creatinine and NAA/creatinine metabolite ratios were as shown in Table 1.

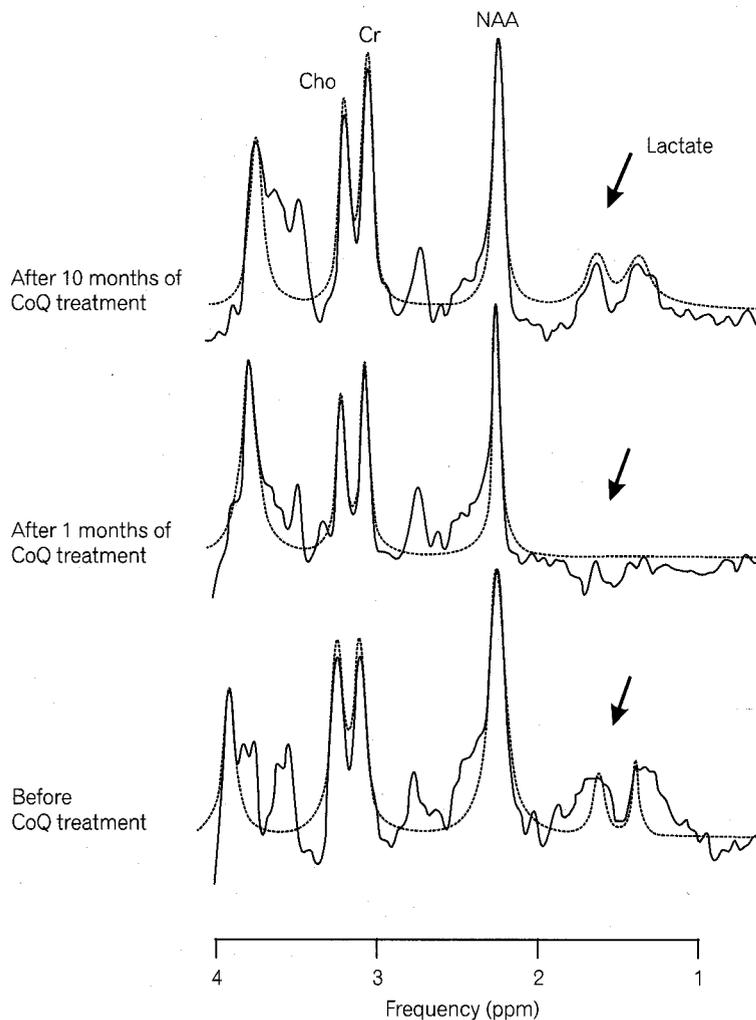


Fig. 1. Serial Proton MRS Showing a Transient Improvement in Lactate Metabolism during CoQ Treatment. The lower line indicates MRS results performed before CoQ treatment, and the middle line shows the decreased amount of lactate (black arrow) after 1 month of CoQ treatment. After 10 months of treatment, the neurologic deficits returned, and the MRS (upper line) again shows the increased lactate content (Cho, choline; Cr, creatine; NAA, N-acetylaspartate).

Table 1. Metabolite Ratio of Deep Cerebral White Matter with High Signal Intensity on T2WI

	Chol/Cr	NAA/Cr	Lac/Cr
Before CoQ treatment	0.994	2.140	0.423
After 1 month of treatment	1.641	2.255	0*
After 10 months of treatment	0.702	1.259	0.242
After 16 months of treatment	0.840	1.844	0.475

Chol, Choline; Cr, Creatine; Lac, lactate; NAA, N-acetylaspartate.

*not detectable.

DISCUSSION

In this patient, CoQ therapy improved lactate metabolism for only a limited period both clinically and radiologically. Derangement of energy-dependent ionic balance may cause cellular dysfunction and the subsequent increases in intracellular calcium and reactive oxygen radicals may induce cell death to submaximal noxious stimuli. Moreover, an overload of metabolites (lactate) and a chronic deficiency of end products (CoQ) may underlie mitochondrial dysfunction. Antioxidants, electron-transfer mediators, enzyme cofactors and calcium blocking agents have been tried in patients with mitochondrial encephalomyopathies.⁷ CoQ replacement treatment was reported to be effective in some patients with KSS.^{8,9} Although we don't know the exact mechanism of CoQ, its effect is probably due to its antioxidant properties and its action as an electron transfer mediator, which circumvents the reduced activity of Complex III in the disabled mitochondria.

As it did in this patient, proton MRS may provide a short-term and objective means of visualizing brain lactate metabolism. The initial lactate/creatine ratio was elevated in a brain lesion that was associated with high signal intensity on T2WI. After 1 month of CoQ treatment, the elevated lactate/creatine ratio decreased to an undetectable range and the choline/creatine ratio sympathetically increased, which may have been a nonspecific finding, but also indicated improved neuronal activity. 10 months after treatment, the normalized lactate/creatine ratio increased to a level that was similar to the baseline level before treatment, and this deteriorated further 16 months after treatment. The choline/creatine ratio also decreased as the lactate increased, and the N-acetyla-

spartate/creatine ratio, indicative of neuronal viability, decreased as the clinical symptoms worsened. These findings collectively suggest that one-month of therapy with CoQ improved pyruvate metabolism and neuronal activities, but that these effects were only transient, as in 10 months pyruvate metabolism had returned to the baseline level.

The rarity of mitochondrial diseases, their heterogeneous nature and the lack of reliable clinical outcome measures have been the main obstacles in evaluating the efficacy of therapeutic drug trials. Measuring the lactate contents in the serum and CSF may not always provide precise information on brain pyruvate metabolism. However, a dynamic and short-term improvement of pyruvate metabolism can be measured by proton MRS in the living brain during therapeutic intervention. A decreased lactate/creatinine ratio on MRS studies was recently reported in a MELAS patient who clinically improved after treatment with sodium dichloroacetate.¹⁰ Treatment may involve the normalization of the lactate/creatinine ratio, however, this could also be the natural course of the MELAS stroke-like episode. Proton MRS can actually image the brain metabolism, but the analysis of data requires a more careful consideration of the disease process. In contrast, KSS is static or slowly progressive in nature.¹ Therefore, the changes in lactate contents, proved by the proton MRS, represent the effects of CoQ treatment, although its effects did not last. After the 16-month follow-up, we concluded that CoQ therapy did not improve the pyruvate metabolism in this patient and discarded the treatment. We suggest that MRS may provide us with a powerful tool to monitor the effects of drugs with unknown efficacies and to evaluate the ongoing disease process in mitochondrial encephalomyopathies.

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