Quantitative MR Spectroscopy for Monitoring Treatment of Cerebrotendinous Xanthomatosis

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Introduction

Cerebrotendinous xanthomatosis (CTX) is a rare inborn error of metabolism, 27-sterol hydroxylase (CYP27) deficiency [1]. This autosomal recessive disorder classically causes symptoms of juvenile cataracts, tendon xanthomas, chronic diarrhea, and complex neurodegenerative symptoms, including cognitive impairment. Dysfunction of the CYP27 enzyme results in abnormal metabolism of cholesterol; instead of normal production of the bile acids chenodeoxycholate and cholate, an alternative pathway is activated, producing cholestanol and bile alcohol. The lack of normal bile acids leads to malabsorption of fats. Cholestanol accumulates in most body tissues, including in the brain, while the bile alcohol is excreted in feces. The diagnostic hallmark of this disease is elevated serum cholestanol in the setting of normal serum cholesterol. Unless treated, CTX results in progressive neurological symptoms, including dementia, ataxia, seizures, psychiatric disorders, and peripheral neuropathy. Arthritis, gallstones, kidney stones, osteoporosis, and endocrine dysfunction can also result. The treatment for this disease is oral supplementation with chenodeoxycholate; this supplies the missing bile acid, which addresses the symptoms related to malabsorption, and also provides feedback inhibition of activation of the alternative metabolic pathways of cholesterol to stop further deposition of cholestanol in the tissues. Administration of an oral statin drug, such as simvastatin (Zocor) or atorvastatin (Lipitor), inhibits accumulation of cholesterol.

We report here a study of two siblings with CTX undergoing treatment with chenodeoxycholate and simvastatin. Metabolite levels in the brain were measured with quantitative MRS just prior to starting treatment and following one year of treatment. Serum metabolite levels were also monitored, as were changes in symptoms, physical exam, and EMG.

Methods

Subjects: Two siblings with CTX ("A" male age 22 with severe symptoms, "B" female age 26 with mild symptoms), and their unaffected sister ("C" age 24, as normal control) were studied. The affected siblings were studied prior to and following one year of treatment with chenodeoxycholate and simvastatin.
MRI/MRS: Clinical MRI included T_1-weighted, T_2-weighted, FLAIR, and gradient echo images. Post-contrast images were acquired only for the baseline study, and these were acquired following spectroscopy. MRS consisted of TE=35ms, TR=2000ms, and PRESS technique. 20x20x20mm voxels were located in the left centrum semiovale and in the left cerebellar white matter. Scanner: GE Signa 1.5T.
Quantification: Metabolite levels were calculated relative to the unsuppressed water peak using LCModel [2].
Lab/physical exam: Serum tests included lipid panel, liver function panel, CBC, hsCRP, homocysteine, and cholestanol. EMG and carotid US were also performed. History and physical included special attention to neurological symptoms.

Results

The MRI examinations were completely normal. Key laboratory and physical findings are given in Table 1, along with changes after 1 year of treatment. Patient A's cholestanol normalized, and he had significant improvement in his gastrointestinal and neurological symptoms. Patient B's cholestanol decreased but did not normalize, and her symptoms improved somewhat. Brain metabolite levels are given in Tables 2 and 3 and in the plots below. NAA became more normal at both locations. Creatine became more normal in the cerebellum. Choline remained high in the cerebellum.

Table 1. Symptoms and laboratory tests.

patient A	pre-treatment	post-treatment	patient B	pre-treatment	post-treatment
serum cholestanol	20.5 µg/ml	3.0 µg/ml	serum cholestanol	18.0 µg/ml	7.1 µg/ml
serum total cholesterol	118 mg/dl	100 mg/dl	serum total cholesterol	179 mg/dl	162 mg/dl
appetite	poor	improved	appetite	poor	improved
dietary fat intolerance	severe	much improved	dietary fat intolerance	mild	improved
xanthomas	yes	unchanged	xanthomas	yes	slightly smaller
cognitive function	impaired	improved	cognitive function	normal	normal
tremor	often	improved	tremor	rare	none
EMG	abnormal	improved	EMG	not done	not done

Table 2. Left centrum semiovale white matter. Metabolites in mM ± uncertainty (+/- %relative to subject C).

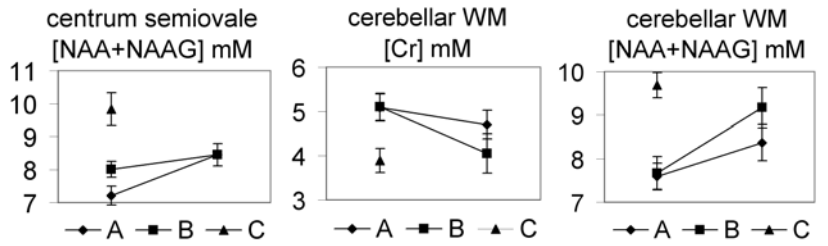
subject	disease	Cr pre-Tx	Cr post-Tx	NAA+NAAG pre-Tx	NAA+NAAG post-Tx	Cho pre-Tx	Cho post-Tx
A	severe	3.92 ± .23 (+11%)	3.71 ± .26 (-9%)	7.21 ± .29 (-27%)	8.45 ± .34 (-14%)	1.58 ± .09 (+11%)	1.29 ± .09 (-9%)
B	mild	4.13 ± .17 (+7%)	4.53 ± .23 (+17%)	8.01 ± .24 (-19%)	8.45 ± .34 (-14%)	1.47 ± .06 (+4%)	1.53 ± .08 (+7%)
C	normal	3.86 ± .27		9.84 ± .49		1.42 ± .11	

Table 3. Left cerebellar white matter. Metabolites in mM ± uncertainty (+/- %relative to subject C).

subject	disease	Cr pre-Tx	Cr post-Tx	NAA+NAAG pre-Tx	NAA+NAAG post-Tx	Cho pre-Tx	Cho post-Tx
A	severe	5.09 ± .31 (+31%)	4.70 ± .33 (+21%)	7.60 ± .30 (-22%)	8.37 ± .42 (-14%)	1.68 ± .10 (+48%)	1.63 ± .13 (+44%)
B	mild	5.11 ± .31 (+31%)	4.05 ± .45 (+4%)	7.67 ± .38 (-21%)	9.17 ± .46 (-5%)	1.60 ± .11 (+41%)	1.85 ± .18 (+63)
C	normal	3.89 ± .27		9.84 ± .29		1.13 ± .10	

Conclusions

Symptoms and metabolite levels improved in both patients. The more severely affected patient had both better symptomatic improvement and better normalization of laboratory values and brain metabolite levels. Although MRS does not measure the abnormal metabolite (cholestanol) directly, it measures damage to the key end-organ (the brain) via assessment of choline, creatine, and NAA. Our findings suggest that the treatment not only halts progression of the disease, but it probably also reverses some of the damage to the brain. Reversibility implies that low NAA does not simply indicate neuronal loss, but that at least some component of the abnormality results from reversible neuronal dysfunction. We propose that this study serves as a model of how quantitative spectroscopy can be used to measure response to treatment or to monitor progression of disease for other inborn errors of metabolism that cause damage to the brain.



References

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