

Spectral Characteristics of Late Infantile Neuronal Ceroid Lipofuscinosis ("Batten Disease") Investigated In Vivo by ¹H Magnetic Resonance Spectroscopic Imaging at 3.0 T

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Background

Late infantile neuronal ceroid lipofuscinosis (LINCL) is a member of a family of debilitating autosomal recessive, progressive childhood neurodegenerative lysosomal storage disorders collectively known as Batten Disease. Batten Disease affects 1 in 12,500 to 100,000 births each year, making it the most common neurodegenerative disease of childhood.¹ The disease manifests itself at age 2 to 4 years with initial symptoms of seizures, ataxia, myoclonus, impaired speech and developmental regression. A gradual decline follows and afflicted children generally become wheelchair bound and blind between 4 and 6 years, with death occurring by age 8 to 12 years. Though there are currently no known effective therapies for LINCL other than symptom management, an understanding of the CNS manifestations of the disease might prove critically important in assessing the degree of disease severity, progress or arrest in eventual clinical trials of promising therapies. In recent years, *in vivo* magnetic resonance spectroscopy (MRS) has emerged as a powerful noninvasive technology for assessing the neurochemistry and metabolic status of a variety of neurological disorders and thus could provide useful biochemical information with respect to CNS involvement in LINCL. Although a number of MRS studies of various forms of Batten disease have been reported²⁻⁵, all of these were conducted with the single-voxel MRS technique, which offers limited spatial resolution and anatomic coverage. In this study, we have taken advantage of the higher spatial resolution and anatomic coverage offered by multislice ¹H magnetic resonance spectroscopic imaging (MRSI) at 3.0 T to assess the extent of the spatial heterogeneity of the CNS manifestation of the disease, and to begin to correlate its spectral characteristics with disease severity and/or duration.

Material and Methods

Study subjects: The population of study subjects consisted of 8 patients meeting the diagnosis of LINCL, based on clinical phenotype and genotype with the CLN2 gene mutations known to be associated with the disease. At the time of MRSI evaluations, 4 (3 males, 1 female) of the patients were 6 years old, 1 (male) was 7 years old, 2 (males) were 9 years old, and 1 (female) was 13 years old. The mean age at diagnosis was 4.4 years +/- 0.8 and the mean duration of the illness for all patients was 3.8 years +/- 2.5. On the LINCL disease severity rating scale (where 0-3 = severe; 4-6 = moderate; 7-8 = mild; 9 = normal), 6 of the patients (4 males, 2 females) had a severity rating of 3 (severe), and 2 had ratings of 4 and 5 (both considered moderate). Informed consent was obtained from each patient's parents or legal guardians.

Neuroimaging Studies: All MR neuroimaging scans were conducted on a 3.0 T GE Signa "LX" scanner. Following a 3-plane T₁-weighted localizer imaging series, a complete high resolution structural brain MRI protocol was implemented. A multislice ¹H MRSI scan was then performed using the method of Duyn *et al.*⁶ to record data from 4 interleaved 15-mm brain sections (with 3.5 mm gaps) with TE/TR 280/2300 ms, FOV 240 mm, 32x32 circularly sampled k-space phase-encoding steps, and 512 time-domain points. The strong pericranial lipid resonances were suppressed using octagonally-tailored outer volume suppression pulses, and water was suppressed with a single CHESS pulse followed by spoiler gradients. The raw data were separated into individual slices and then processed by the standard fast Fourier transform algorithm.

Results

Spatial Heterogeneity: Spectra in voxels throughout the four investigated brain sections were examined for signs of abnormal metabolite changes. Representative spectra from a number of voxels within one of the slices are shown in Fig. 1. Except for the 13-year old female patient, who had the longest disease duration, the following significant spectral abnormalities were noted: there was a robust decrease of N-acetyl-L-aspartate (NAA) and a mild-to-moderate increase of choline (Cho) diffusely throughout all brain sections. In addition, there was a significant elevation of lactate (Lac) in the bodies of the lateral ventricle, as well as a milder elevation of this metabolite in most voxels diffusely within the brain parenchyma.

Changes with Disease Severity and Duration: Amongst the 6 subjects who had a LINCL disease severity of 3 (high severity), there was a tendency for the abnormalities noted above to worsen with disease duration. This is illustrated in Fig. 2 for a voxel from the periventricular white matter of three subjects with the same disease severity but different durations. Levels of NAA tended to decrease, and those of Cho and Lac tended to increase with disease duration. The extreme case was that of the 13-year old female patient, who had harbored the disease the longest (9 years) and has died since her scan was performed. Not only does the spectrum from this subject show complete absence of NAA, there is also a decrease in total spectral intensity, including an apparent proportionately larger decrease in Cho. Interestingly, spectral changes between patients with different disease severity indexes (e.g., 3 vs. 5; data to be shown) but similar disease durations were less dramatic than changes due to differences in disease duration, indicating likely variability in clinical markers at the late stage of the disease.

Discussion

The MRSI spectral features of LINCL reported here are in good agreement with previous long echo time (TE) single-voxel MRS studies of the disease, which noted a dramatic loss of NAA, elevation of Cho, and presence of Lac. Considering the diffuse nature of the disease, this agreement between our spectroscopic imaging study and previous single-voxel studies is not surprising, since an MRS scan targeting a region of any size is likely to find approximately the same level of CNS disease involvement regardless of the location. This suggests that both single-voxel and spectroscopic imaging are adequate techniques for investigating the neurological manifestation of LINCL. The observation of a dramatic decrease of NAA – a putative neuronal marker -- throughout the brain of these patients is consistent with the neurodegenerative nature of the disease, and the observed elevation of Lac provides further evidence in support of a postulated mitochondrial dysfunction⁷ in the family of Batten disease. A potentially novel finding of this study is the observation that MR spectral characteristics might be more profoundly affected by the duration of the disease than by the LINCL severity rating scale. The complete loss of the NAA signal intensity in the patient who had harbored the disease the longest (9 years; Fig. 2), shortly before her death raises the question of whether the rate of loss of NAA, which might coincide with the rate of neurodegeneration, might not be a reliable measure of the degree of disease progression, severity or arrest – a parameter that might be useful in assessing the efficacy of promising treatments. A larger study of LINCL could clarify the potential utility of this "NAA disease severity index."

References

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