Diffusion Tensor MRI in Mucolipidosis Type IV

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**Introduction:** Mucolipidosis type IV (MLIV) is a rare disorder caused by a mutation of a gene located on chromosome 19 encoding for the putative cation channel Mucolipin. Clinical manifestations include severe psychomotor delay, corneal clouding, retinal dystrophy, and optic atrophy. Diagnosis relies on a skin or conjunctival biopsy and on measurements of gastrin plasma levels. Unfortunately MLIV is often misdiagnosed (1) because these specialized tests are only performed when the correct diagnostic hypothesis is formulated. Finding specific MRI markers of the disease would be helpful in facilitating the diagnostic process. A previous MRI study of MLIV (2) found rather non-specific changes such as, diffuse signal abnormalities in white matter, signal changes consistent with ferritin deposition in the basal ganglia and thalamus, atrophy of the cerebellum in older patients and hypoplastic corpus callosum in all severely affected patients. Because of the known morphological changes in white matter, we hypothesized that diffusion tensor MRI (DT-MRI) could potentially detect microstructural and architectural features of the diseased tissue that not apparent in conventional MRI. We studied MLIV patients with DT-MRI in order to assess if specific abnormalities could be detected that would help in formulating a correct diagnostic hypothesis.

**Methods:** Eleven MLIV patients (9 females, 2 males, mean age 13.3 years, age range 5 – 22), four young and four elderly healthy subjects were included. All subjects were scanned with an interleaved EPI sequence on a 1.5 T magnet Signa Horizon EchoSpeed System with gradient pulses up to 22 mT/m. Twelve different gradient directions were sampled with b-values ranging between 0.6 s/mm\textsuperscript{2} and 960 s/mm\textsuperscript{2}. Imaging acquisition parameters were: 24 axial slices, 3.5 mm slice thickness, 0.5 mm gap, 128x128 in-plane resolution (8 interleaves, 16 echoes per interleave), 220-mm FOV, TR ≥ 5 seconds, TE = 80 msec, cardiac gating. Following image reconstruction, the diffusion tensor was estimated in each voxel, and the principal diffusivities, $<D> = 1/3 \text{Trace}(D)$, as well as the fractional anisotropy index (FA) were calculated. In one patient we collected data suitable for analysis with a recently proposed dual compartment tensor fitting method (3), which allows one to evaluate the diffusivity of parenchymal water in cortical gray matter by removing CSF contamination in the estimated diffusion parameters.

**Results and Discussion:** DT-MRI revealed severe abnormalities in both $<D>$ and FA in MLIV patients. Figure 1 and 2 show whole brain histograms of the distributions of $<D>$ and FA values from pooled data of four ML IV patients (crosses), four young healthy subjects (squares), and four elderly subjects (circles). The distribution of $<D>$ values in MLIV patients is shifted to the right with respect to the controls. The distribution of FA shows severe under representation of high anisotropy values (0.4 – 0.8). Given that moderate brain atrophy has been reported in MLIV, the group of elderly subjects was included to show that changes $<D>$ and FA observed in ML IV patients are much larger than those observed in brain atrophy due to aging.

Dual compartment analysis of the data set acquired with multiple b values confirmed that the increase in $<D>$ values is related to parenchymal abnormalities, not CSF contamination. Moreover, $<D>$ was elevated in the parenchymal compartment of cortical gray matter, although less than in white matter. Previous structural MRI studies of MLIV did not reveal cortical abnormalities in MLIV.

Fig 3 shows a color coded map (4) of the Pons in a MLIV patient (top) and a healthy control (bottom). Although anisotropy was severely reduced in white matter throughout the brain, pathways running in the tegmentum of the pons and mesencephalon (arrows) showed almost normal values. This result is in agreement with autopsy findings that reported brain stem tegmental pathways (including the medial longitudinal fasciculi, superior cerebellar peduncles, and medial and lateral lemnisci) as histologically unremarkable in MLIV (5).

**Conclusions:** DT-MTI reveals severe abnormalities not detected by conventional MRI in the brain of MLIV subjects. The finding of normal values of $<D>$ and FA in the tegmental pathways of the brain stem could represent a specific “signature” of the disorder that would facilitate the diagnostic process.
