Leucoencephalopathy with brainstem and spinal cord involvement and high lactate: quantitative magnetic resonance imaging

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Leucoencephalopathy with brainstem and spinal cord involvement and elevated lactate is a white matter disorder caused by DARS2 mutations. The pathology is unknown. We observed striking discrepancies between improvement on longitudinal conventional magnetic resonance images and clinical deterioration and between large areas of high signal on diffusion-weighted imaging and small areas with low apparent diffusion coefficient values. These observations prompted a longitudinal and quantitative magnetic resonance imaging study. We investigated eight patients (two males, mean age 27 years). Maps of T2 relaxation times, fractional anisotropy, apparent diffusion coefficients, signal on diffusion-weighted imaging, and axial and radial diffusivities were generated. Brain metabolites, obtained by chemical shift imaging, were quantified. Data analysis focused on: (i) white matter with low apparent diffusion coefficient; (ii) white matter with high T2 values; (iii) white matter with intermediate T2 values; and (iv) normal-appearing white matter. The areas were compared with similarly located areas in eight matched controls. In five patients, T2-weighted images, spectroscopy, apparent diffusion coefficient maps and diffusion-weighted imaging maps were compared with those obtained 5–7 years ago. In white matter with low apparent diffusion coefficient, axial and radial diffusivities were decreased and fractional anisotropy was high. T2 values were intermediate. These areas with truly restricted diffusion were small and often observed at the periphery of areas with high T2 values. In the white matter with high and intermediate T2 values, apparent diffusion coefficients and axial and radial diffusivities were increased and fractional anisotropy decreased. The signal on diffusion-weighted imaging was highest in white matter with high T2 values, an effect of T2 shinethrough. Chemical shift imaging in both white matter types showed increased lactate, increased myo-inositol and decreased N-acetylaspartate, most pronounced in white matter with high T2 values. Normal-appearing white matter was comparable with white matter of control subjects. Over time, mild decreases in T2 signal intensities, signal on diffusion-weighted imaging and in extent of the low apparent diffusion coefficient areas were seen. In conclusion, the disease process in leucoencephalopathy with brainstem and spinal cord involvement and elevated lactate is extremely slow.
We hypothesize that diffusion restriction is the first stage of the disease caused by intramyelinic water accumulation, followed by slow shift and then loss of the surplus of water. On conventional T2 images this leads to improvement. We hypothesize that it is loss of water rather than structural restoration that causes the change in T2 signal intensity, which would be in better agreement with the slow clinical deterioration.

Keywords: white matter disorder; MRI; diffusion tensor imaging; T2 relaxometry; chemical shift imaging
Abbreviations: LBSL = leucoencephalopathy with brainstem and spinal cord involvement and elevated lactate

Introduction
Leucoencephalopathy with brainstem and spinal cord involvement and elevated lactate (LBSL) is an autosomal recessive white matter disorder, first described in 2003 by its unique pattern of MRI abnormalities (van der Knaap et al., 2003). LBSL typically involves the cerebral and cerebellar white matter and specific tracts in the brainstem and spinal cord (van der Knaap et al., 2003; Scheper et al., 2007). The signal changes are often inhomogeneous and spotty. Proton magnetic resonance spectroscopy shows elevated lactate in the affected white matter in most patients. Slow neurological deterioration with signs of pyramidal, cerebellar and dorsal column dysfunction generally starts in childhood (van der Knaap et al., 2003), but adult onset has also been reported (Petzold et al., 2007; Labauge et al., 2007). In 2007, the related gene, DARS2, was found, which codes for mitochondrial aspartyl transfer RNA synthetase (Scheper et al., 2007). The pathological basis of the disease is unknown.

LBSL is an intriguing disorder with several apparent inconsistencies. On long-term follow-up MRI we noticed slow improvement of the white matter signal on T2-weighted images in multiple patients, contrasting with slow but inexorable clinical deterioration ending in wheelchair dependency. We also noticed that diffusion-weighted images display large areas of high signal in the affected white matter, suggesting restricted diffusion, whereas the corresponding maps of the apparent diffusion coefficient only showed small areas with low values. A similar discrepancy between diffusion-weighted imaging and apparent diffusion coefficient maps is not seen in other leucodystrophies (van der Knaap and Valk, 2005). These observations and the lack of insight into the pathology of the disease prompted a longitudinal and quantitative MRI study, including diffusion tensor imaging, T2 relaxometry and chemical shift imaging, in order to obtain a better understanding of the white matter microstructure in LBSL and its changes over time.

Materials and methods
Subjects
Eight patients with genetically confirmed LBSL (two males, aged 17–49 years, mean age 27 years) were included in the study (see Supplementary Table 1 for DARS2 mutations). The quantitative magnetic resonance data were obtained as an extension of the routine clinical MRI with informed consent of the patients and approval of the Institutional Review Board. Similar quantitative magnetic resonance data were obtained in eight matched healthy volunteers (two males, aged 13–44 years, mean age 27 years). Five patients had previous MRI examinations performed in the same institute 5–7 years ago, which were used to study longitudinal changes in LBSL.

Magnetic resonance imaging
All studies were performed in 2009 and 2010 on a Siemens Sonata 1.5 Tesla scanner (Siemens) with an eight-channel phased-array head coil. The imaging protocol included axial T2-weighted fast spin-echo images (repetition time = 2450 ms, echo time = 24 and 85 ms, pixel size 1 × 1 × 4 mm3), axial fluid-attenuated inversion recovery images (repetition time = 9000 ms, echo time = 108 ms, inversion time = 2500 ms, pixel size 1 × 1 × 5 mm3) and sagittal T1-weighted images using a three-dimensional magnetization-prepared rapid acquisition gradient-echo sequence (repetition time = 2700 ms, echo time = 5 ms, inversion time = 950 ms, pixel size 1 × 1 × 1 mm3).

Regarding the quantitative MRI techniques, acquisition parameters were selected to yield the highest information content for each method within clinically acceptable acquisition times.

Chemical shift imaging was performed using a point resolved spectroscopy sequence (repetition time = 3000 ms, echo time = 30 ms, six measurements with weighted phase-encoding) on a single 15-mm slice (field of view 160 × 160 mm2 or 140 × 160 mm2 depending on the head size, volume of interest 80 × 100 mm3 or 70 × 100 mm3 respectively, 16 × 16 phase encodings, interpolated to 32 × 32, resulting in interpolated nominal voxel size of 4.4–5.5 × 15 mm3) centred on the corpus callosum with an axial orientation. Unsuppressed water reference scans were obtained with both head and body coil as receiving coils (8 × 8 phase encodings, interpolated to 32 × 32, repetition time = 1500 ms, echo time = 30 ms; Pouwels et al., 2010).

Diffusion tensor imaging was acquired with a multi-slice echo planar imaging sequence with a fixed b-value of 900 s/mm2 along 99 gradient encoding directions and 10 non-diffusion weighted (b0) volumes. The imaging parameters were repetition time = 5400 ms, echo time = 103 ms, 29 slices and pixel size 1.45 × 1.45 × 2.0 mm3. To achieve this high resolution at sufficiently high signal-to-noise ratio and keep the duration of the acquisition within 10 min, only part of the brain was scanned (58-mm slab positioned on the top of the mid-brain with one slice corresponding to the middle of the chemical shift imaging slice).

For T2 relaxometry a Carr–Purcell–Meiboom–Gill sequence was used to acquire images at 32 different echo times (echo times = 10.4–332.8 ms, with echo spacing of 10.4 ms). Other parameters included repetition time = 2500 ms, one measurement, slice thickness 5 mm and pixel size 1.45 × 1.45 × 5 mm3. Five slices (gap 5 mm) were acquired with one slice corresponding to the middle of the chemical shift imaging slice.

The previous MRIs of 5–7 years ago were performed on a Siemens Vision 1.5 Tesla scanner. The MRI protocol included axial T2-weighted
spin-echo images (repetition time = 3000 ms, echo times = 22, 60 and 120 ms, pixel size 1 x 1 x 5 mm³), diffusion tensor imaging-derived diffusion-weighted imaging and apparent diffusion coefficient maps (echo planar imaging sequence, b-value = 1044 s/mm², eight gradient encoding directions, one non-diffusion weighted (b0) volume, pixel size 2 x 2 x 5 mm³, repetition time = 3600 ms, echo time = 123 ms; Horsfield and Jones, 2002; van der Knaap et al., 2003), and short echo time magnetic resonance spectroscopy (stirred echo acquisition mode sequence, repetition time = 6000 ms, echo time = 20 ms, mixing time 10 ms, 64 accumulations, single volume of interest in the centre of the white matter with high T2 signal).

Data processing
For quantification of metabolite concentrations in chemical shift imaging, the voxel-wise ratio of the unsuppressed water signal (signal intensity body coil/signal intensity head coil) and the transmitter amplitude of the body coil was used (Natt et al., 2005; Pouvels et al., 2010). For each subject all spectra within the volume of interest were analysed using LCModel (Provencher, 1993). Metabolite concentrations were expressed as mmol/l volume of interest. Concentrations were determined for the metabolites N-acetylaspartate, including a small contribution of N-acetylaspartylglutamate (marker for neuronal integrity), choline-containing compounds (marker for membrane lipid density and turnover), myo-inositol (glial marker), creatine and phosphocreatine (with its presence in all cells a marker for cell density) and lactate. Spectral quality was expressed as signal-to-noise ratio and full width at half maximum values as determined by LCModel.

The diffusion tensor was calculated with FMRIB’s Diffusion Toolbox [Oxford Centre for Functional MRI of the Brain (FMRIB) software library; http://www.fmrib.ox.ac.uk/fsl], resulting in apparent diffusion coefficient, fractional anisotropy, axial diffusivity (largest eigenvalue, λ1) and radial diffusivity (mean of the two lowest eigenvalues, λ2 and λ3). Based on the equation diffusion-weighted imaging signal = S(0) x exp (−900 x apparent diffusion coefficient), the signal on the diffusion-weighted imaging map was established as a semi-quantitative measure for brightness.

Pixel-wise T2 maps were generated using available software supplied by Siemens that fitted the relaxation time curves to a mono-exponential decay, i.e. $S(t) = S(0) \times \exp(-t/T2)$. The Carr–Purcell–Meiboom–Gill sequence used was hindered too much by odd-even signal variation in the first two echoes to use a multi-exponential approach.

Region of interest definition
We were struck by the apparent mismatch between high signal of almost all abnormal cerebral white matter on diffusion-weighted imaging, but only small areas with low signal on the corresponding apparent diffusion coefficient maps, dissimilar from what is seen in other leucodystrophies (van der Knaap and Valk, 2005). Data analysis was, therefore, first concentrated on the small areas with low signal on apparent diffusion coefficient maps. In addition, three types of cerebral white matter were analysed as defined by their signal on T2-weighted images (T2 signal): areas with high, intermediate and low signal intensity, the latter corresponding to normal-appearing white matter. These three areas defined by their T2 signal were chosen as not to overlap the areas with low apparent diffusion coefficient. Examples of the different white matter areas are shown in Fig. 1A and D. Normal-appearing white matter suitable for location of the region of interest was mainly found in the anterior frontal white matter, whereas other white matter areas were generally found in the semi-serial centre. The brainstem abnormalities typical of LBSL were not included in this study because the small size of those abnormalities hampered region of interest placement.

Regarding chemical shift imaging, voxels that best corresponded to the described white matter areas were analysed, with the exception of white matter with low apparent diffusion coefficient, because these areas were too small to fully fill chemical shift imaging voxels.

Diffusion tensor imaging parameters and T2 values were extracted using a region of interest analysis. The identical in-plane resolution of diffusion tensor imaging and T2 relaxometry allowed the definition of homologous regions of interest, but with a difference in slice thickness being 2 mm for diffusion tensor imaging and 5 mm for T2 relaxometry. To make optimal use of the high spatial resolution of diffusion tensor imaging and T2 relaxometry, regions of interest were small, consisting of 4–9 pixels (8.4–18.9 mm²). These regions of interest did not correspond to the relatively large chemical shift imaging voxels.

Depending on the presence of the different white matter areas in each patient, 0–5 regions of interest or voxels per type of white matter area per subject were analysed. In the overall analysis, one subject never contributed >25% of the regions of interest or voxels for one white matter type. For each area included in a patient, a matching area in the corresponding control subject was included.

Statistical analysis
The ANOVA F-test was used to assess differences in magnetic resonance parameters between patients and controls. Because multiple magnetic resonance parameters were tested, the Family-Wise Error Rate was controlled per white matter area by means of Holm’s procedure.

A conservative significance level of 0.01 was applied to Holm’s multiplicity-adjusted P-values.

Within patients and per magnetic resonance parameter, Tukey’s Honest Significant Difference method was used to assess whether there were magnetic resonance parameter differences between the (pairs of) white matter areas. The same conservative significance level of 0.01 was applied to Tukey’s multiplicity-adjusted P-values.

Evaluation of abnormalities on conventional magnetic resonance imaging
The MRIs were evaluated by consensus of two investigators as described previously (van der Knaap et al., 1999). Lesions were defined as T2 hyperintense areas. Atrophy was defined as volume loss leading to enlargement of ventricles and subarachnoid spaces. White matter rarefaction was defined as T2 hyperintense white matter areas with low signal on fluid-attenuated inversion recovery images, but not as low as the signal of CSF. In order to minimize the effects of subjective rating, all items were only scored as present or absent.

Results
Magnetic resonance imaging abnormalities
Examples of the MRI abnormalities in LBSL are shown in Fig. 1. All patients displayed inhomogeneous cerebral white matter abnormalities (Fig. 1A), mainly in the periventricular and deep white matter with sparing of the U-fibres. U-fibre involvement
was only seen in the rolandic area ($n=4$). The splenium of the corpus callosum and the pyramidal tracts in the posterior limb of the internal capsule were affected. Infratentorially, abnormalities were seen in the pyramidal tracts ($n=8$; Fig. 1B), the intraparenchymal parts of the trigeminal nerve ($n=8$), the mesencephalic trigeminal tracts ($n=8$; Fig. 1B), the cerebellar white matter ($n=7$; Fig. 1B), the superior cerebellar peduncles ($n=7$; Fig. 1B), the inferior cerebellar peduncles ($n=7$), the anterior spinocerebellar tracts ($n=6$) and the medial lemniscus ($n=6$; Fig. 1B). Less frequent were abnormalities of the transverse pontine fibres ($n=2$). Rarefaction of the cerebral white matter occurred in three patients. Grey matter structures were preserved. There was mild enlargement of the subarachnoidal spaces and lateral ventricles in all patients. Atrophy of the cerebellum was seen in five patients.

**Diffusion tensor imaging**

High-resolution diffusion-weighted imaging maps (Fig. 1C) showed hyperintensity of the white matter in most of the white matter with high $T_2$ signal. Corresponding apparent diffusion coefficient maps displayed a low signal often only in the border of the areas with high signal on diffusion-weighted imaging and $T_2$-weighted images (Fig. 1D).

Table 1 shows values of fractional anisotropy, apparent diffusion coefficient, axial and radial diffusivities and diffusion-weighted imaging signal for patients and controls in the different white matter areas. The diffusion parameters in regions of interest selected for low apparent diffusion coefficient were significantly different from diffusion parameters in all other white matter areas in patients as well as from diffusion parameters in controls. Low apparent diffusion coefficient was accompanied by low axial and radial diffusivities, while fractional anisotropy was greatly increased. In contrast, in white matter with intermediate and high $T_2$ signal, apparent diffusion coefficient and axial and radial diffusivities were higher and fractional anisotropy was lower than in the other areas and than in controls. The only significant difference between the intermediate and high $T_2$ regions was in the intensity of the diffusion-weighted imaging signal, which was highest in white matter with high $T_2$ signal. When comparing changes in axial diffusivity with those in radial diffusivity, absolute decreases or increases were similar, but the changes in radial diffusivity were relatively larger. The diffusion parameters in normal-appearing white matter were comparable with those of control values.

Three regions of interest, which were initially defined as high $T_2$ regions, were considered outliers, because of very high apparent diffusion coefficient, low fractional anisotropy and low
diffusion-weighted imaging signal intensity. These regions of interest were located in periventricular parietal white matter in only three patients, and were not included in the current analysis.

Analysis of three consecutive diffusion tensor imaging slices (6 mm) in order to better match the slice thickness of the T2 relaxometry measurement showed similar results (data not shown).

**T2 relaxometry**

An example of a T2 map is shown in Fig. 1F. The T2 values of the different white matter areas are summarized in Table 1. Highest T2 values were found in white matter with a hyperintense signal on T2-weighted images. Normal-appearing white matter had lowest T2 values, which were comparable with those of control subjects. White matter with low apparent diffusion coefficient had moderately increased T2 values, similar to the T2 values of white matter with intermediate T2 signal.

**Chemical shift imaging**

The results are summarized in Table 2. The spectral quality (Fig. 2A–D) was similar for patients and controls with mean (±SD) full width at half maximum of 3.0 (±0.8) and 3.4 (±1.0) Hz and mean signal-to-noise ratio of 11.8 (±2.4) and 15.2 (±3.1), respectively.

In patients, lactate elevation was most pronounced in white matter with high T2 signal; a moderate elevation was seen in white matter with intermediate T2 signal. Myo-inositol was elevated in white matter with intermediate T2 signal. These N-acetylaspartate differences between regions within patients did not reach statistical significance. Choline-containing compounds and creatine and phosphocreatine were similar to control subjects in all areas. All metabolites in normal-appearing white matter were in the control range. Chemical shift imaging data of the small white matter areas with low apparent diffusion coefficient were not available.

**Relationship between diffusion tensor imaging, T2 relaxometry and chemical shift imaging**

White matter with low apparent diffusion coefficient displayed a decrease in diffusivity in all directions and an increase in fractional anisotropy as compared with control subjects. The T2 values were similar to those of white matter with intermediate T2 signal.

In white matter with high T2 signal, increased T2 values were associated with increased diffusivity in all directions and decreased fractional anisotropy, a decrease in N-acetylaspartate and an increase in lactate and myo-inositol as compared with control subjects. Highest T2 values were associated with highest signal on diffusion-weighted imaging and were often observed in areas adjacent to areas with low apparent diffusion coefficient.

White matter with intermediate T2 signal and mildly elevated T2 values had a similar concentration of myo-inositol and similar diffusion parameters as white matter with high T2 signal, but a lower
signal intensity on diffusion-weighted imaging. The increase of lactate and the decrease of N-acetylaspartate were less pronounced than in white matter with high T2 signal.

Normal-appearing white matter was comparable with white matter of control subjects for all parameters.

**Longitudinal changes**

In comparison with the MRI abnormalities seen 5–7 years ago, a mild decrease in the extent of the cerebral abnormalities on T2-weighted images was observed in all patients (Fig. 3A and C). The youngest patients displayed the most pronounced decreases. A decline in T2 hyperintensity of white matter lesions resulted in a less symmetric and more inhomogeneous appearance of the white matter abnormalities. Some areas with high T2 signal on previous MRIs now displayed intermediate T2 signal. No new lesions were seen. Infratentorially, there was also a small reduction in white matter abnormalities in most patients, except for the two youngest patients who showed increased involvement of the cerebellar white matter and peduncles.

The decline in T2 hyperintensity over time was associated with a decrease in hyperintensity on diffusion-weighted imaging maps. Despite differences in diffusion tensor imaging acquisition methodology, especially with regard to spatial resolution, a decrease was evident in the extent of the areas with low signal on apparent diffusion coefficient maps in combination with small shifts in localization (Fig. 3B and D). Some former hypointense regions now had an increased apparent diffusion coefficient.

Taking slight differences in spectroscopic methodology and localization into account, magnetic resonance spectroscopy showed a more or less stable picture in four of the five patients. One patient displayed a decrease in lactate on follow-up, in combination with decreases of choline-containing compounds and myo-inositol to almost normal values.

**Table 2 Brain metabolite concentrations (mean ± SD) in the defined white matter areas**

<table>
<thead>
<tr>
<th>MR parameters</th>
<th>Patients</th>
<th>Control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T2 hyperintense white matter</td>
<td>T2 intermediate white matter</td>
</tr>
<tr>
<td>Number of regions of interest</td>
<td>19</td>
<td>33</td>
</tr>
<tr>
<td>N-acetylaspartate (mM)</td>
<td>5.2 ± 1.5a</td>
<td>6.1 ± 1.2a</td>
</tr>
<tr>
<td>Creatine and phosphocreatine (mM)</td>
<td>4.1 ± 0.6</td>
<td>4.6 ± 0.9</td>
</tr>
<tr>
<td>Choline-containing compounds (mM)</td>
<td>1.4 ± 0.2</td>
<td>1.6 ± 0.4</td>
</tr>
<tr>
<td>Myo-inositol (mM)</td>
<td>4.4 ± 0.6bc</td>
<td>4.7 ± 0.7bc</td>
</tr>
<tr>
<td>Lactate (mM)a</td>
<td>1.4 ± 0.4bcde</td>
<td>0.8 ± 0.4bcde</td>
</tr>
</tbody>
</table>

- a Significantly different from corresponding white matter of control subjects.
- b Lactate is not visually detectable in the spectra of control subjects, but is included in the LCModel analysis to allow comparison with patients.
- c Significantly different from white matter with intermediate T2.
- d Significantly different from white matter with low T2.
- e Significantly different from white matter with high T2.
Discussion

We applied longitudinal and quantitative MRI techniques to gain insight into the white matter abnormalities in LBSL and better understand the discrepancies between diffusion-weighted imaging and apparent diffusion coefficient and between longitudinal improvement on MRI and clinical deterioration of LBSL patients, also seen in our patients during the 5–7 years of follow-up (four of the five patients lost either supported or unsupported walking during this time). On the basis of our findings, we could formulate a hypothesis on the histopathological sequence of events in LBSL white matter. A limitation of our study is, of course, that no histopathology is available to confirm our hypothesis. However, in a previous study we could correlate the same quantitative magnetic resonance parameters directly with histopathology and found them to be a reliable predictor of histopathological parameters (van der Voom et al., 2006).

The first type of abnormal white matter we defined is characterized by striking diffusion restriction. It is mainly observed in small areas at the periphery of white matter with high T$_2$ signal. The increased fractional anisotropy in this area is associated with relatively larger decrease in radial diffusivity than in axial diffusivity. LBSL is one of the first white matter disorders of which axial and radial diffusivities are described and the interpretation of changes in these diffusivities in white matter disease is not quite clear. In general, restricted diffusion is seen in conditions that lead
to compression of the interstitial spaces, such as cytotoxic oedema (Schaefer et al., 2000), high cell density (Sugahara et al., 1999), storage of substances (Oguz et al., 2004) and myelin vacuolation (Vermathen et al., 2007). LBSL is not a storage disorder. In LBSL, the restricted diffusion is chronic and it is associated with only mildly elevated $T_2$ values. These observations exclude cytotoxic oedema. Micro-vacuolation of myelin is a type of pathology seen in mitochondrial disorders (Hart et al., 1977; Brockington et al., 1995). Micro-vacuolation of myelin would be consistent with the stronger relative decrease of radial diffusivity than axial diffusivity seen in LBSL, suggesting this as the most likely pathology, although we cannot exclude that increased cell density contributes to the diffusion restriction. Regarding longitudinal changes, we found that some areas with low apparent diffusion coefficient had a high apparent diffusion coefficient on follow-up. We never observed a change from high apparent diffusion coefficient to low. This and the localization at the border of the abnormal white matter suggest that low diffusivity precedes high diffusivity and high $T_2$ values.

The largest part of the abnormal white matter in LBSL has a high $T_2$ resulting in a high signal on $T_2$-weighted images. The diffusivity is increased in all directions and fractional anisotropy is decreased, indicating less anisotropic diffusion. Lactate is highest in these areas and N-acetylaspartate is lowest. The combination of high $T_2$ and increased diffusivity in all directions indicates increased tissue water content and increased size of the interstitial water compartment. It is important to notice that the relative increase in diffusivities and the relative decrease in fractional anisotropy are moderate in comparison with other leucodystrophies (van der Voorn et al., 2006). Apparently the structure of the abnormal white matter in LBSL is relatively preserved, which is in agreement with the comparatively mild clinical disease course.

The apparent discrepancy between diffusion-weighted imaging (reflecting changes in both apparent diffusion coefficient and $T_2$) and apparent diffusion coefficient maps in LBSL is caused by these large white matter areas with high $T_2$. The high $T_2$ combines with a moderately increased apparent diffusion coefficient, leading to high signal on diffusion-weighted imaging due to $T_2$ shinethrough and not diffusion restriction. In other leucodystrophies a similarly long $T_2$ is generally associated with higher apparent diffusion coefficient values (van der Voorn et al., 2006), resulting in a lower signal on diffusion-weighted images. Only in the small areas in LBSL with a very low apparent diffusion coefficient, the high signal on diffusion-weighted images is caused by true diffusion restriction, emphasizing that apparent diffusion coefficient maps are indispensable in the evaluation of diffusion abnormalities.

White matter with an intermediate $T_2$ signal, without low apparent diffusion coefficient, is the third type of white matter in LBSL. The intermediate $T_2$ signal is associated with moderate increases of diffusivity similar to those seen in high $T_2$ areas, an intermediate increase of lactate, and intermediate decreases of fractional anisotropy and N-acetylaspartate. These findings suggest that the tissue water content and the size of the interstitial water compartment are lower than in white matter with high $T_2$ signal, but higher than normal. Over time transitions of white matter with high $T_2$ signal into white matter with intermediate $T_2$ signal are observed, but not in the reverse direction, suggesting that white matter with intermediate $T_2$ signal is the final stage of the disease and that permanent tissue damage is mild.

The quantitative magnetic resonance parameters of normal-appearing white matter were similar to those of control white matter, so white matter that looks normal on conventional images appears to have a normal microstructure in LBSL.

The longitudinal analysis is limited by differences in MRI protocols used, but allows qualitative comparisons. It is clear that the disease process in LBSL is extremely slow. The cerebral white matter in LBSL is apparently going through different stages and the magnetic resonance parameters differ in the different stages. The parameters indicate that in all stages the white matter architecture is relatively mildly affected. We hypothesize that the diffusion restriction is the first stage and is caused by chronic myelin splitting and intramyelinic vacuole formation. This intramyelinic oedema is followed by a shift of water from the intramyelinic to the interstitial compartment resulting in a high $T_2$ and increased diffusivity. Subsequent loss of the interstitial water leads to intermediate $T_2$, which defines the final stage of the white matter pathology. On conventional $T_2$-weighted images the change from high to intermediate $T_2$ signal suggests improvement. However, if our hypothesis is correct, it is loss of interstitial water rather than structural restoration that causes the shift in $T_2$ signal intensity, which would be in better agreement with ongoing slow clinical deterioration.

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Supplementary material

Supplementary material is available at Brain online.

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