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## Megalencephalic leukoencephalopathy with subcortical cysts in an adult: quantitative proton MR spectroscopy and diffusion tensor MRI

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**Abstract** A 37-year-old macrocephalic woman was investigated for increasing gait disturbance due to longstanding spasticity and ataxia. MRI showed widespread bilateral increase in signal from cerebral white matter on T2-weighted images. Numerous subcortical cysts were visible in anterior-temporal and parietal regions. These clinical and neuroradiological features are those of megalencephalic leukoencephalopathy with subcortical cysts (MLC), a recently delineated white-matter disease with onset in childhood. Quantitative localised proton MR spectroscopy of white matter revealed marked reduction of N-acetylaspartate, creatine, and choline with normal values for myo-inositol, consistent with axonal loss

and astrocytic proliferation. Diffusion tensor imaging showed an increased apparent diffusion coefficient and reduced anisotropy in affected white matter pointing to reduced cell density with an increased extracellular space. These findings are in line with histological changes alterations known to occur in MLC.

**Keywords** Leukoencephalopathy · Subcortical cysts · Magnetic resonance spectroscopy · Diffusion tensor imaging

### Introduction

Among the hitherto unclassified megalencephalic leukoencephalopathies in childhood, a novel disorder originally called "leukoencephalopathy with swelling and a discrepantly mild clinical course" [1] and now termed megalencephalic leukoencephalopathy with subcortical cysts [2] has been delineated during the last decade. Affected children present with macrocephaly within the first year of life, slow deterioration of motor skills due to increasing ataxia and spasticity, and discrepantly mild cognitive impairment [1, 3, 4, 5, 6]. MRI shows extensive signal changes in cerebral white matter early in the course and subcortical cysts in the temporal

and parietal regions [7]. Histological examination reveals cavitating spongiform leukoencephalopathy with vacuoles in the outermost lamellae of myelin sheaths [8]. Subcortical white matter shows intense fibrillary astrogliosis, but myelinated axons are well preserved. Cortical neuronal structure is normal.

Parental consanguinity and disease in siblings suggest autosomal recessive inheritance. The gene locus has been assigned to chromosome 22q<sub>tel</sub> [9] and mutations in a gene renamed *MLC1* have been identified as the cause [2].

Since 1995, more than 70 patients with this disorder have been reported [1, 3, 4, 5, 6, 10, 11], predominantly infants and children. Several adult cases have been identified: a 20-year-old woman in the original report by

van der Knaap et al. [1], three women and four men whose ages ranged from 19 to 49 years in a large series reported by Singhal et al. [4], two patients aged 19 and 20 years described by Ben-Zeev et al. [6] and a 28-year-old man reported by De Stefano et al. [11]. Descriptions of neuroradiological features in these adult cases are confined to few patients, and assessment of metabolic abnormalities in disordered cerebral white matter using proton MR spectroscopy (MRS) has been performed in only two adults [1, 11]. To our knowledge, diffusion tensor imaging has not been used to investigate this condition. We report conventional and diffusion tensor MRI and localised proton MRS of a woman diagnosed as having MLC at the age of 37 years.

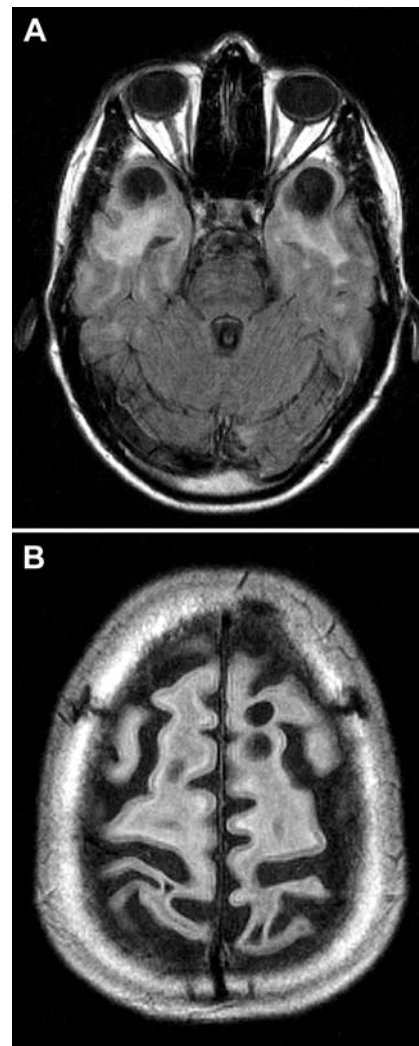
### Case report

A 37-year-old woman was investigated for increasing gait disturbance. She was the second child of consanguineous healthy parents, whose mothers were half sisters. An elder brother was healthy. After uneventful pregnancy she was born at term with normal weight and length. Her head circumference is not documented, but was allegedly normal. Her motor and mental development was initially normal: sitting at 6 months, first words at 12 months. However, abnormal enlargement of her head within the first year of life caused early concern. Electroencephalography and fundoscopy were reportedly normal. Pneumoencephalography was considered, but not performed, as her motor and cognitive skills were adequate for age. In her second year a mild delay in motor development became obvious. She walked freely at 2 years, but was never able to ride a bicycle due to poor balance. From her 7th year onwards her gait slowly deteriorated. Her speech and memory were better than her brother's. She performed well at normal school and completed a training for office administrator. Increasing ataxia and spasticity resulted in crutch dependency around her 30th year. She lives independently and works full-time with a telecommunications company.

Neurological examination showed macrocephalus with a head circumference of 62.5 cm (5 cm above the 98th centile). Cranial nerves and fundi were normal. The patient showed marked dysarthria, ataxia, pyramidal signs and a spastic tetraparesis affecting predominantly the legs. She walked slowly with uncertain, broad-based steps, using two crutches. There was a mild thoracic scoliosis. Mental abilities appeared normal but detailed psychometric testing was not performed. Routine blood analyses were normal. Sonography of the ovaries showed no cysts or other abnormality.

MRI (Fig. 1) was obtained at 1.5 tesla, with T2-weighted spin-echo and fluid-attenuated inversion recovery (FLAIR) images (TR 9000 TE 110 ms, flip angle 180°, 0.98×0.90×5.9 mm<sup>3</sup> resolution). MRI was subsequently performed at 2.0 tesla (Fig. 2) using the standard head coil; the protocol included T1-weighted 3D-FLASH [12] in axial, sagittal and coronal planes (TR 15 TE 4 ms, flip angle 20°, 0.8×0.8×4 mm<sup>3</sup> resolution) and a dual-echo fast spin-echo sequence with spin density and T2-weighting (TR 3500 ms, five echoes per shot, mean TE 16 and 98 ms, respectively, flip angle 120°, 0.8×0.8×4 mm<sup>3</sup> resolution).

Fully relaxed short-echo time proton MR spectra (TR 6000 TE 20 ms, 64 acquisitions) were acquired with use of a single-voxel stimulated-echo acquisition mode (STEAM) localisation sequence [13]. Volumes of interest were placed in paramedian parietal grey matter (Fig. 2a), parieto-occipital white matter (Fig. 2b), and basal ganglia. Spectral analysis and quantification of absolute metabolite concentrations were accomplished as described elsewhere [14]. Previous studies of regional age-dependence of



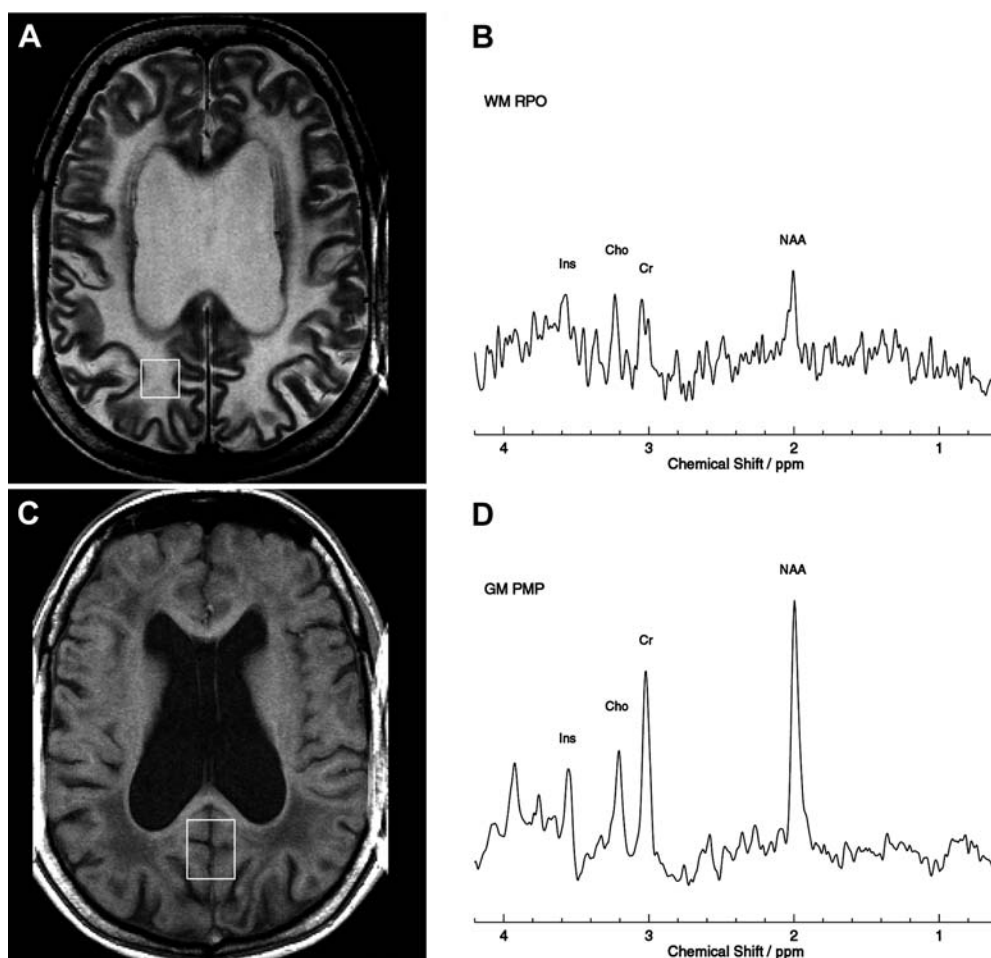
**Fig. 1A, B** Axial fluid-attenuated inversion-recovery images. There are subcortical cysts in both anterior temporal and parietal regions

cerebral metabolites [15] provided age-matched controls. Major metabolites detectable by MRS comprise N-acetylaspartate and N-acetylaspartylglutamate (tNAA), creatine and phosphocreatine (tCr), choline-containing compounds (Cho), and myo-inositol (Ins).

Axial diffusion-tensor imaging (DTI, Fig. 3) was performed with a single-shot STEAM sequence [16] comprising a non-diffusion-weighted image and six images with diffusion-weighting in noncollinear directions at a b value of 1000 s/mm<sup>2</sup> (TR 6000 TE 70 ms, flip angle 11°, 2×2×6 mm<sup>3</sup> resolution, 16 averages). Maps of the apparent (isotropic) diffusion coefficient (ADC) and relative anisotropy [17] were calculated with the imager's modified image calculation algorithm. For comparison, a healthy female volunteer aged 39 years was imaged with the same DTI protocol.

(Fig. 1) shows marked enlargement of cerebrospinal fluid (CSF) spaces without signs of increased intracranial pressure. There was diffuse increase in signal from cerebral white matter bilaterally, including the area commonly referred to as the U fibres, on T2-weighted images. The corpus callosum and internal capsule were spared. Numerous subcortical cysts were visible in the anterior temporal and parietal lobes, with diameters ranging from 1 to 2 cm. The basal ganglia were normal, as was the cerebellar white matter.

**Fig. 2A–D** MRI and spectroscopy. **A, C** Axial T2-weighted and T1-weighted images show diffuse signal change in the white matter. Localised proton spectra of white and grey matter reveal **B** marked reduction of tN-acetylaspartate (tNAA), t creatine and choline in white matter and **D** only mild decrease of tNAA in parietal grey matter



MRS of parieto-occipital white matter revealed markedly decreased concentrations of tNAA, tCr, and Cho, whereas Ins was normal (Fig. 2). Parietal grey matter showed only mild reduction of tNAA, and the spectrum of the basal ganglia was normal. Quantitative analyses of absolute metabolite concentrations are given in Table. 1.

Diffusion tensor measurements are shown in Fig. 3. Compared to the normal volunteer the ADC was considerably increased in high-signal white matter. Thus, in the white matter volume selected for MRS (Fig. 2a), the ADC was  $2.2 \times 10^{-3} \text{ mm}^2/\text{s}$ , three-times the value ( $0.7 \times 10^{-3} \text{ mm}^2/\text{s}$ ) in a comparable region in the control. Anisotropy of white matter was reduced throughout most of the brain (Fig. 3), including the “U fibres”, the optic and pyramidal tracts and cerebellum. This also holds for the corpus callosum, although to some extent the difference may reflect partial-volume effects with grey matter and CSF. In the white-matter volume indicated in Fig. 2a anisotropy was 0.09 whereas in a comparable control region it was 0.24.

## Discussion

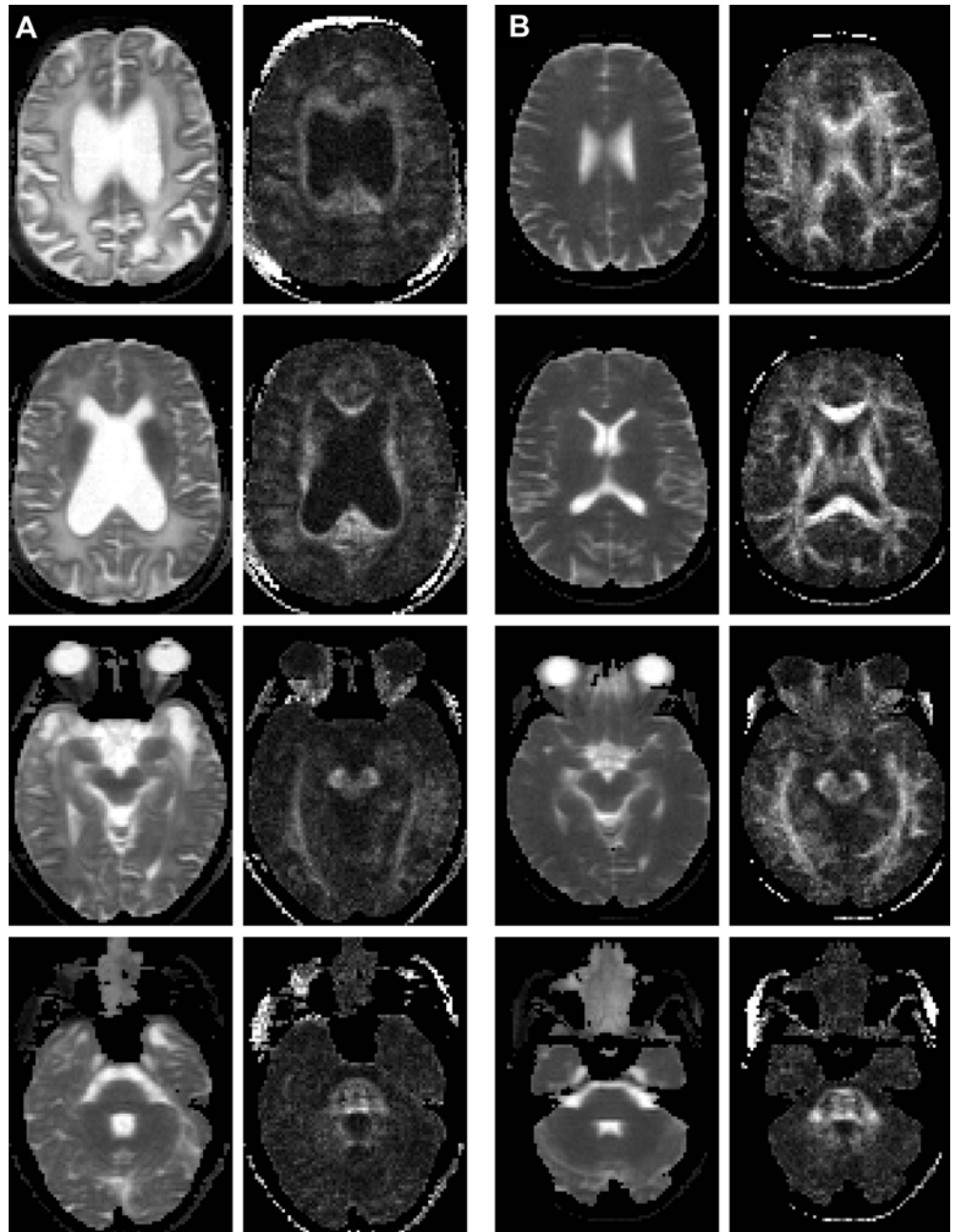
The history, neurology and MRI of this woman are diagnostic of MLC. Macrocephalus developing within the first year of life, gradually increasing ataxia and spasticity, and remarkably well preserved cognitive

functions are the characteristic clinical pattern. More specific features are displayed by MRI, showing the features detailed above. Initial swelling of white matter is later replaced by enlargement of CSF spaces.

Quantitative proton MRS underlines the MRI evidence of a white-matter disorder without cortical involvement. Most striking MRS features are marked decrease in tNAA, tCr, and Cho, with normal Ins in abnormal-appearing hemispheric white matter. tNAA is present in neuron cell bodies, axons, dendrites, and synaptic terminals [18] and is considered a marker of neuronal viability. Recent studies have validated MRS measurements of tNAA as an axon-specific monitor of CNS white matter in vivo [19]. tCr is involved in energy metabolism and is a constituent of both neurones and glia. Cho is highly concentrated in oligodendrocytes and mainly represents contributions from precursor molecules for membrane synthesis and corresponding membrane degradation products [20]. Ins has been identified as a glia-specific marker [21].

Reduction of tNAA and tCr is consistent with damage to or loss of vital neuroaxonal tissue. In contrast, histological examination in a case of MLC revealed preserva-

**Fig. 3A, B** Axial maps of the ADC (left) and relative anisotropy (right) of **A** the patient and **B** a normal control



tion of myelinated axons in subcortical white matter [8]. However, this was a brain biopsy from a 13-year-old boy whose MRI still showed swelling of white matter. Our patient with a threefold duration of disease and enlargement of CSF spaces, indicating brain atrophy, had presumably reached the stage of axonal damage. Evidence of neuroaxonal loss was largely confined to white matter, as concentrations of tNAA were only mildly reduced in cortical grey matter and normal in basal ganglia.

Reduction in Cho in white matter points to loss of oligodendrocytes, although corroborative histological

findings are lacking. Elevation of Ins (in combination with decreased Cho) probably reflects proliferation of astrocytes, which is in excellent agreement with histopathology [8].

In contrast to the severe metabolic alterations detected in white matter, a mild reduction of tNAA was the only abnormality in the parietal grey matter. Again, this is in line with the histology study mentioned above [8], which failed to detect any major abnormality in the cortex. Our basal ganglia spectrum was completely normal; again, corroborative pathological studies are not available.

**Table 1** Cerebral metabolite concentrations (mM, mean  $\pm$  SD)

	N-acetylaspartate and acetylaspartylglutamate	Creatine and phospho-creatine	Choline-containing compounds	Myo-inositol
White matter				
Right parieto-occipital	2.3 <sup>a</sup>	2.2 <sup>a</sup>	0.7 <sup>a</sup>	4.0
Controls (60)	8.2 $\pm$ 0.7	4.9 $\pm$ 0.6	1.6 $\pm$ 0.2	4.2 $\pm$ 0.7
Gray matter				
Paramedian parietal	6.9 <sup>b</sup>	5.5	1.1	4.3
Controls (45)	9.1 $\pm$ 0.7	6.5 $\pm$ 0.5	1.2 $\pm$ 0.1	4.4 $\pm$ 0.6
Basal ganglia				
Right	7.2	6.6	2.2	5.2
Controls (28)	9.2 $\pm$ 1.0	6.1 $\pm$ 0.8	1.8 $\pm$ 0.2	3.7 $\pm$ 0.8

<sup>a</sup> > 4 SD different from control

<sup>b</sup> > 2 SD different from controls

Mejaski-Bosnjak et al. [10] reported MLC in an 8-year-old girl investigated using similar MRI and MRS methods. The child had a severe clinical course leading to wheelchair-dependency at 5 years of age. MRI revealed multiple large cysts in frontal, temporal and parietal subcortical white matter. Localised MRS of affected white matter free of cysts showed loss of all metabolites, pointing to complete disintegration of neuroaxonal and glial tissue. In our adult patient reported here, the milder clinical course is paralleled by less severe metabolic changes.

Two reports on proton MRS in adults with MLC have been published. Van der Knaap et al. [1], in the report delineating this disorder, detected a reduced NAA/Cr ratio, an elevated Cho/Cr and normal Ins/Cr using qualitative PRESS and STEAM techniques in a 20-year-old woman; they examined only white matter. De Stefano et al. [11] used proton MRS imaging and found decreased NAA/Cr and normal Cho/Cr in the white matter of a 28-year-old man. Neither investigation gave absolute quantification of metabolite concentrations. Our study confirms these qualitative findings and renders a refined assessment of metabolic abnormalities in this disorder *in vivo*.

The markedly increased ADC in the patient's high-signal white matter indicates severe damage to its integrity, with respect to myelination and axonal structure. This suggests reduced cell density with increased

extracellular space. Because parallel axon bundles are the source of anisotropy in white matter, its reduction implies a loss of myelinated axons as one of the sources of the reduced cell density expected from the increased ADC. The diffusion tensor measurements are thus consistent with the MRS observations.

Infantile megalencephalic leukoencephalopathies are Alexander's and Canavan's diseases, type I glutaric aciduria and L-2-OH-glutaric aciduria. These are commonly associated with rapid deterioration and severe impairment of neurological function resulting in marked disability and a shortened life span. Variants of Alexander's and Canavan's disease with early onset and benign, slowly progressive clinical course protracting into young adulthood are rare. MLC behaves discrepantly. Though signal changes in cerebral white matter are distinct and widespread very early in the course, suggesting severe neurological dysfunction, motor and especially mental performance in these patients is surprisingly well preserved for many years. There are thus presumably a considerable number of adult patients with as-yet unrecognised MLC who will seek medical advice. Neuroscientists should therefore consider MLC in an adult patient with an unclassified white matter disease.

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