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LBSL (leukoencephalopathy with brain stem and spinal cord involvement and high lactate) without sparing of the u-fibers and globi pallidi: A case report

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ABSTRACT

Leukoencephalopathy with brain stem and spinal cord involvement and high lactate (LBSL) is a recently identified leukoencephalopathy, first described by Van der Knaap in 2003. To date 24 cases have been described. Distinctive features were as follows. First, brain MRI showed white matter abnormalities and involvement of brain stem structures. Second, sparing of the u-fibers was an invariant, distinctive feature of the syndrome. Third, whenever evaluated, spinal cord was always involved. Fourth, brain [1H]-MR spectroscopy failed to show a lactate peak in all cases. In our little child, the diagnosis was confirmed by genetic analysis but unlike previous report both the u-fibers and globus pallidus were involved; spectroscopic data were more consistent with hypomyelination than demyelination. Our findings add to the phenotype variability of this novel disease.

1. Introduction

More than 50% of diagnosis of leukoencephalopathies remain unclassified [1] despite a lot of new laboratory, instrumental and molecular investigation.

A new, slowly progressive leukoencephalopathy characterized by onset between infancy and adolescence, brain stem and spinal cord involvement, and high lactate peak at brain spectroscopy (LBSL), has recently been described by Van der Knaap et al. [2]. Only a few cases have been reported, showing a constellation of MRI and [1H]-MRS abnormalities [2–9]. Clinical features consist of slowly progressive spino-cerebellar ataxia, spasticity, additional symptoms referable to degeneration of the dorsal columns, and occasionally mild cognitive decline [3–9].

This autosomal recessive [2] disorder is caused by mutations in the *DARS2* gene, which is located on the chromosome 1, and encodes the mitochondrial aspartyl-tRNA syntetase [7].

We describe the case of a child affected carrying *DARS2* mutations associated with very early onset, rapid degeneration of motor and cognitive functions. This early-onset, genetically confirmed LBSL patient showed previously undescribed involvement of the U-fibers and globi pallidi.

2. Case report

A two-year-old girl, born after uneventful, at-term pregnancy from non-consanguineous parents, presented with progressive neurological regression with loss of previously acquired psychomotor milestones.

Her psychomotor development was normal until 7 months of life: since then, no other neurological milestones were acquired. The language was limited to 4–5 words.

Physical examination showed severe hypotonia, more evident at the lower limbs, with absence of deep tendon reflexes, with no pyramidal signs. In the sitting position, the child showed trunk and heads tremors. Subsequently, we detected a progression of the clinical picture consisting in spasticity in the distal legs and bilateral pes equinus. At the age of three years the motor pattern was unchanged. Seizures have been never reported.

Neurophysiologic studies showed progressive, mild peripheral neuropathy: sensory and motor nerve conduction studies (NCS) were both abnormal and EMG study showed bilateral chronic denervation potentials in different muscular districts. Visual and brain stem auditory evoked potentials were normal.

The following laboratory parameters were normal: blood count, homocysteine and methylmalonic acid, lysosomal enzymes (arylsulfatase-A, galactocerebrosidase, β-galactosidase, and hexosaminidase-A), folic acid, ammonia, creatine kinase, blood and urinary amino acids, organic acids, very long-chain fatty acids, phytanic acid, lactate, piruvate, hydroxybutyrate, and acetoac-

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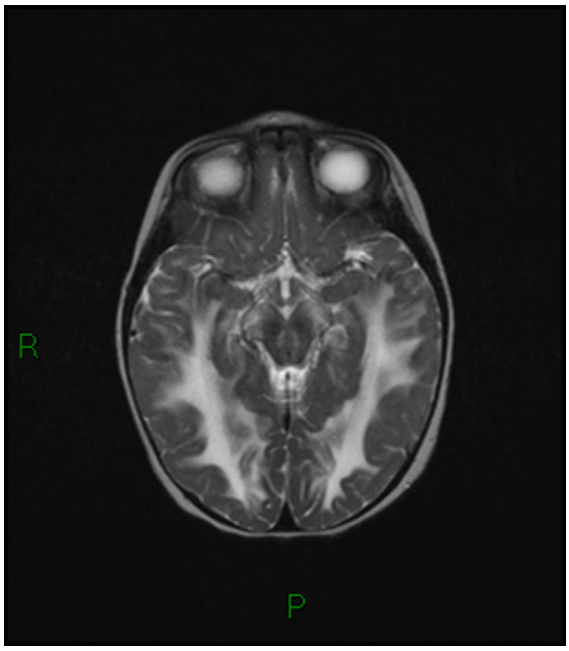

Fig. 1. T2-weighted image of the brain showing extensive white matter alteration, without sparing of the u-fibers. Signal alterations at the level of brain stem resembles what we dubbed "inversed giant panda face".

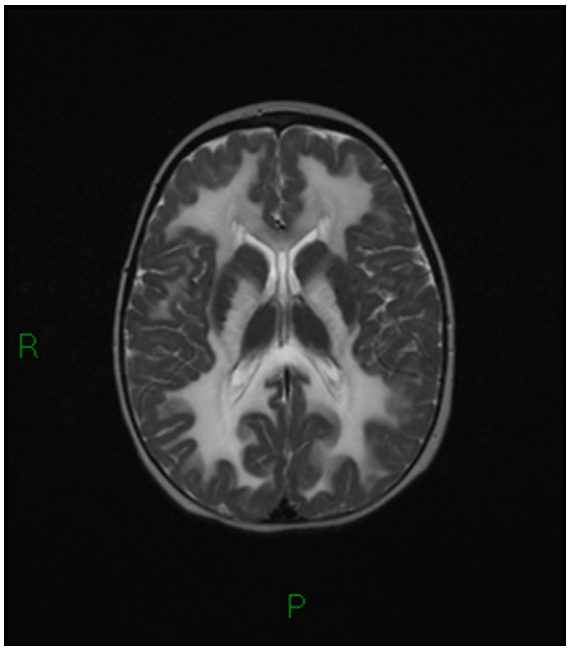

Fig. 2. T2-weighted image showing extensive white matter signal alteration and involvement of both nuclei pallidi.

etate. Moderately high levels of lactate (2.8 mM) were found in the cerebrospinal fluid.

MRI of the brain and spinal cord, and brain spectroscopy were performed on a 1.5 T unit (Siemens Avanto). Brain imaging protocol included pre and post-contrast sagittal and axial T1-weighted images (TR 535, TE 13), axial and coronal DP and T2 weighted images (TR 3500, TE 14/182), axial FLAIR images (TR 9000, TI 2500, TE 104), and axial diffusion weighted images (b0-1000); spine imaging protocol included sagittal T1-weighted (TR 397, TE 12), and T2-weighted (TR 3700, TE 103) images of the whole rachis; axial T2-weighted images (TR 4220, TE 101) were also performed at cervical and dorsal levels. Infratentorial alterations were seen in the following areas: inferior-posterior part of the medulla oblongata, longitudinal medial fasciculus, VIth nerve nuclei, medial lemniscus, lateral lemniscus, cerebellar white matter, dentate nuclei, pyramidal tracts, red nuclei, cerebellar peduncles, and intraparenchymal trajectories of the trigeminal nerves; selective involvement of midbrain structures showed a pattern that we dubbed as "giant panda face" (Fig. 1).

Supratentorial alterations were observed in the internal and external capsules, globi pallidi, and corpus callosum; periventricular, lobar, and subcortical white matter, including the u-fibers, showed marked signal alteration (Fig. 2). White matter was abnormalities were observed also in T1-weighted images. Diffusion weighted images showed diffusion restriction in cerebral peduncles, globi pallidi, posterior limbs of the internal capsules, genu of the corpus callosum, and subcortical white matter, particularly in the u-fibers; increased diffusivity was detected in periventricular and lobar white matter (Fig. 3a, b).

Spinal cord examination showed signal alteration in the posterior and lateral white matter tracts (Fig. 4).

Multivoxel (^{1}H-MRS) spectroscopy sequences (SE) with Echotime (TE) of 30 and 135 ms were acquired in centrum semiovale of both hemispheres. Acetylaspartate (NAA)/Creatine (Cr), myoInositol (mI)/Cr, and Choline (Cho)/Cr ratios were measured and compared to those obtained in 9 normal patients aged 14 months to 5 years. Data processing was performed by software provided by the manufacturer.

NAA/Cr ratio was 1.55, a significantly lower value in comparison with age matched healthy controls (mean 2.21, s.d. ± 0.35).

mI/Cr (0.50) and Cho/Cr (1.16) ratios did not show statistically significant differences in comparison with the mean values of the age-matched group (mI/Cr 0.56, s.d. ± 0.11; Cho/Cr 1.00, s.d. ± 0.26).

A doublet peak of lactate (Lac) was demonstrated at 1.33 ppm at TE of 30 and 135 ms. Actually, ^{1}H-MRS showed elevated lactate in all analyzed voxels (Fig. 5).

2.1. Molecular genetic studies

Based on the MRI and [^{1}H]-MRS findings that suggested LBSL, we sequenced the exons and flanking intron regions of the *DARS2* gene. We found a novel heterozygous mutation in the 3′-end region of intron 2, a 228-12C>G transversion, which alters the consensus sequence of the acceptor site of exon 3, therefore predicting abnormal intron2/exon 3 splicing. We then found a second, already described [7], heterozygous allelic mutation in the donor splice site of intron 5 (492+2T>C), which also predicts abnormal exon 5/intron 5 splicing. Therefore, both allelic *DARS2* mutations predict the synthesis of a variable amount of aberrant and truncated aspartyl-tRNA synthetase species. However, these changes are likely to behave as "leaky" mutations, which allow a variable percentage of the gene to be transcribed normally. This consideration may explain why these *DARS2* mutations are compatible with extra-uterine life.

3. Discussion

A novel leukoencephalopathy with brain stem and spinal cord involvement and high brain lactate (LBSL) has recently been described by Van der Knaap et al. [2].

In this disorder, clinical signs and symptoms generally start in the early childhood and adolescent years and progress gradually [2–7]. Familial and adult onset form of LBSL has also been reported but; usually, in the adult onset disease, the level of lactate is normal [5,6].

The clinical picture is characterized by onset in childhood and slowly progressive course, the main clinical features including slowly progressive cerebellar ataxia, tremor, muscle weakness,