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Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL): Assessment of the involved white matter tracts by MRI☆

Hassan Kassem[a], Ahmed Wafaie[b,*], Sherif Abdelfattah[b], Tarek Farid[c]

[a] Department of Radiology, Benha University, Egypt
[b] Department of Radiology, Cairo University, Egypt
[c] Pediatric Department, Egyptian National Research Center, Egypt

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ABSTRACT

Background and purpose: Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation (LBSL) is a recently identified autosomal recessive disorder with early onset of symptoms and slowly progressive pyramidal, cerebellar and dorsal column dysfunction. LBSL is characterized by distinct white matter abnormalities and selective involvement of brainstem and spinal cord tracts. The purpose of this study is to assess the imaging features of the involved white matter tracts in cases of LBSL by MRI.
Patients and methods: We retrospectively reviewed the imaging features of the selectively involved white matter tracts in sixteen genetically proven cases of leukoencephalopathy with brainstem and spinal cord involvement and elevated brain lactate (LBSL). All patients presented with slowly progressive cerebellar sensory ataxia with spasticity and dorsal column dysfunction. MRI of the brain and spine using 1.5 T machine and proton magnetic resonance spectroscopy (^{1}H MRS) on the abnormal white matter were done to all patients. The MRI and MRS data sets were analyzed according to lesion location, extent, distribution and signal pattern as well as metabolite values and ratios in MRS. Laboratory examinations ruled out classic leukodystrophies.
Results: In all cases, MRI showed high signal intensity in T2-weighted and FLAIR images within the cerebral subcortical, periventricular and deep white matter, posterior limbs of internal capsules, centrum semiovale, medulla oblongata, intraparenchymal trajectory of trigeminal nerves and deep cerebellar white matter. In the spine, the signal intensity of the dorsal column and lateral cortico-spinal tracts were altered in all patients. The subcortical U fibers, globi pallidi, thalami, midbrain and transverse pontine fibers were spared in all cases. In 11 cases (68.8%), the signal changes were inhomogeneous and confluent whereas in 5 patients (31.2%), the signal abnormalities were spotty. MRI also showed variable signal abnormalities in the sensory and pyramidal tracts in addition to the brainstem and cerebellar connections. Proton MRS showed consistent elevation of the lactate within the abnormal white matter.
Conclusion: Distinct MRI findings in the form of selective affection of subcortical and deep white matter tracts of the brain (involving the posterior limb of internal capsules and sparing the subcortical U fibers), dorsal column and lateral cortico-spinal tracts of the spinal cord should lead to the diagnosis of LBSL supported by the presence of lactate peak in ^{1}H MRS. The disease can be confirmed by the analysis of the disease gene DARS2.

1. Introduction

Approximately half of childhood leukoencephalopathies remain unclassified despite extensive laboratory, instrumental and molecular investigation [1]. Some of leukoencephalopathies have been identified and categorized based on their distinct abnormalities detected on MRI [2]. Leukoencephalopathy with brain stem and spinal cord involvement and high lactate (LBSL) is a recently identified leukoencephalopathy, first described by Van der Knaap et al. [3].

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* Corresponding author. Tel.: +20 1223938137.
E-mail address: a_wafaie@yahoo.com (A. Wafaie).

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This autosomal recessive disorder [2] is caused by mutations in the DARS2 gene, which is located on the chromosome 1, and encodes the mitochondrial aspartyl-tRNA synthetase [4].

It has previously been reported from Netherlands [3], Turkey [5], Finland [6], Russia [7], Brazil [8], Poland [9], India [10] and USA [11]. To the best of our knowledge, this is the first report from the Arab countries and Africa.

The objective of this study is to assess the MR neuro-imaging features of the involved white matter tracts in the first reported Arabian and African cases of LBSL and to compare them with the earlier published reports.

2. Patients and methods

We retrospectively reviewed the imaging features and enhancement pattern of the selectively involved white matter tracts in sixteen genetically proven cases of leukoencephalopathy with brainstem and spinal cord involvement and elevated brain lactate (LBSL). The patients were 9 males and 7 females with an age range (at the time of symptoms onset) of 18 months to 12 years (mean age: 6.2 years). The time interval between onset of symptoms and MRI examination ranged from 3 to 14 months (mean time interval: 8.2 months). The patients came from 14 unrelated families. Two pairs of patients were siblings. All cases were an autosomal recessive disorder, caused by mutations in the DARS2 gene, encoding the mitochondrial aspartyl-tRNA synthetase.

Detailed clinical evaluation was taken by an experienced consultant pediatric neurologist. All patients presented with slowly progressive cerebellar sensory ataxia, spasticity and dorsal column dysfunction and none of them had acute neurological deficit at time of MRI examination.

Several serum, cerebrospinal fluid and urine laboratory tests were performed to exclude classic leukodystrophies, infectious, demyelinating, metabolic, paraneoplastic and inflammatory etiologies. The serum studies included lysosomal enzymes, transaminases, plasma amino acids, creatine kinase, lactate, ceruloplasmin, vitamin E, vitamin B12, folic acid and very long-chain fatty acids. The C.S.F studies included CSF cell count, protein, lactate and immunoglobulin G index. C.S.F screening for infection including detection of Herpes simplex virus (HSV), cytomegalovirus (CMV), Epstein–Barr virus (EBV), toxoplasmosis and *Mycobacterium tuberculosis* were also done for all patients. The urine studies included oligosaccharides and estimation of sialic, amino and organic acids.

MRI of the brain and spine and proton magnetic resonance spectroscopy (^{1}H MRS) on the abnormal white matter were performed to all patients using G.E signa LX 1.5 T machine. Our brain MRI protocol included sagittal spin echo (SE) T1-weighted images (TR 535, TE 13), axial and coronal fast spin echo (FSE) T2-weighted images (TR 3500, TE 182), axial fluid-attenuated inversion recovery (FLAIR) (TR 9000, TI 2500, TE 104), axial spin echo (SE) T1-weighted images (TR 535, TE 13) and axial diffusion weighted images (b0-1000). Post gadolinium sagittal and axial T1-weighted images were performed in all cases.

Single-voxel point-resolved proton spectroscopy sequences (PRESS) with echo time (TE) of 35 and 144 ms were obtained in all cases. The voxels were located in the centrum semiovale and in the deep periventricular white matter. Voxels were $2 \times 2 \times 2$ cm in size. N-acetylaspartate (NAA) was assigned at 2.02 parts per million (ppm), choline (Cho) at 3.2 ppm, creatine (Cr) at 3.03 ppm and lactate (Lac) at 1.3 ppm. Metabolite ratios (NAA/Cr and Cho/Cr) were also measured. All data processing was performed by software provided by the manufacturer.

Spinal cord MRI protocol included sagittal T1-weighted (TR 397, TE 12), and T2-weighted (TR 3700, TE 103) images of the whole spine. Axial T2-weighted images (TR 4220, TE 101) were performed at cervical and dorsal levels. The T1-weighted sequences were acquired before and after intravenous administration of gadolinium.

2.1. Image analysis

MR examinations of the brain and spine and MRS data sets were reviewed by two experienced radiologists in consensus with an emphasis on the exact lesion location, extent and distribution in respect to the white matter tracts in brain and spine, metabolite values and ratios in ^{1}H MRS. The pattern of white matter affection was classified into two groups according to MR signal characteristics: (a) Inhomogeneous and confluent "confluent patchy lesions not necessarily homogeneous or symmetrical" and (b) Spotty "dot-like lesions with normal white matter in between".

The study was approved by the ethical committees of our institutions.

3. Results

Sixteen cases were enrolled in this study. In all cases, MRI revealed high signal intensity in T2-weighted and FLAIR images within the cerebral subcortical, periventricular and deep white matter. In 11 cases (68.8%), the signal changes were inhomogeneous and confluent involving all lobes, predominating within frontal and parietal regions and partially sparing the temporal lobes. In 5 patients (31.2%), the signal abnormalities were spotty, affecting only the frontal and parietal lobes. These spots showed low signal intensity in FLAIR. There was no statistically significant difference in the mean age of patients (p-value: 0.767) nor the mean onset of symptoms-investigation time interval (p-value: 0.658) between the two MRI patterns of white matter affection (inhomogeneous/confluent and spotty) (Student's t-test).

The corpus callosum showed diffuse signal abnormality in 12 patients (75%), in 4 of them (25%), the abnormal signal changes were restricted to the splenium of the corpus callosum.

In all cases, MRI of the brain showed signal abnormalities in the posterior limbs of the internal capsules, centrum semiovale, medulla oblongata, intraparenchymal trajectory of trigeminal nerves and the deep cerebellar white matter either partially or diffusely. In the spine, the signal intensity of the dorsal column and the lateral cortico-spinal tracts of the spinal cord were also altered in all patients (Fig. 1). Conversely, the subcortical U fibers, globi pallidi, thalami, midbrain and the transverse pontine fibers were spared in all cases.

On the posterior fossa, some structures were affected in some patients and spared in others like the subcortical cerebellar white matter which showed signal abnormalities in 87.5%, the medial lemniscus in 50% and the mesencephalic trigeminal tract in 62.5% of cases. Signal alteration was also observed along the whole length of the pyramidal white matter tract in 56% of patients.

Regarding the cerebellar connections, both the superior and middle cerebellar peduncles were involved in 68.8% of cases, whereas the inferior cerebellar peduncle was affected in only half of the cases. The anterior spinocerebellar tract was the least white matter tract involved in our study showing signal alteration in only 2 of our patients (12.5%).

On diffusion weighted images, diffusion restriction was found in most of the length of the corticospinal and sensory tracts in 56% of cases in addition to involvement of the superior and inferior cerebellar peduncles and the mesencephalic trigeminal tracts in 68.8%, 50% and 62.5% of cases, respectively (Fig. 2). These parts of the white matter tracts also showed heterogeneous enhancement in the same cases after gadolinium administration.