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

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Background and purpose: Leukoencephalopathy with brainstem 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 (1H 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 1H MRS. The disease can be confirmed by the analysis of the disease gene DARS2.

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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].
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 Netherland [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 LBLSL 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 (LBLSL). 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, folate 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 (1H MRS) on the abnormal white matter were performed to all patients using GE 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 × 2 × 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 1H 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.
Single-voxel MR spectroscopy \(^{1}\text{H} \) MRS with echo-time (TE) of 35 and 144 ms were acquired in the deep white matter and centrum semiovale of both cerebral hemispheres. The MRS showed consistent elevation of the lactate within the abnormal white matter in all analyzed voxels. A doublet peak of lactate (Lac) was demonstrated at 1.33 ppm at both TE of 35 and 144 ms. The lactate peak showed inverted doublet at 1.3 ppm on using 144 ms TE (Figs. 1 and 2). A significant decrease in N-acetylaspartate (NAA) and increase in myoinositol (mIos) were also found in the white matter of all patients. In 68.8% of cases, mild elevation of the white matter choline peak (Cho) was also observed. The white matter creatine (Cr) was normal in all patients.

Spinal MRI studies were obtained in all cases. They showed signal abnormalities in the lateral corticospinal tracts and dorsal columns uniformly over the entire length of the spinal cord without evidence of associated cord atrophy in all patients (Figs. 1 and 2 and see Tables 1 and 2).
The signal of elevated T2 signal in the periphery of the deep cerebellar white matter. The medulla oblongata, inferior cerebellar peduncles, and pyramidal tracts are spared; (B) axial DWI of the brainstem shows selective involvement of the intraparenchymal trajectories of the trigeminal nerves (white arrow) and superior cerebellar peduncle (black arrow); (C) axial DWI shows extensive patchy involvement of the posterior limb of the internal capsules (black arrow), periventricular white matter, genu and splenium of the corpus callosum; (D–F) ADC map images corresponding to A–C showing dark signal intensity of the involved white matter tracts denoting restricted diffusion. Restricted diffusion is indicated by high signal on DWI (A–C) and low signal on ADC (D–F); (G) axial T2 shows extensive patchy and confluent deep white matter hyperintensity. The U fibers are spared; and (H) axial T2 of the spinal cord at the level of C1–2 shows increased signal involving the dorsal column (black arrow) and lateral corticospinal tracts (white arrow). Single voxel MR spectroscopy at short TE (35 ms) shows markedly elevated lactate peak (arrow).

4. Discussion

A novel leukoencephalopathy with brain stem and spinal cord involvement and high brain lactate (LBSL) has recently been described in 2003 by Van der Knaap et al. [2]. This disorder is characterized by childhood onset of slowly progressive neurological symptoms including cerebellar ataxia, tremors, muscle weakness, spasticity, and mild cognitive deficit or decline [12].

In our study, all patients were symptomatic, presented in the childhood period and showed consistent elevation of lactate on MRS. However, Labauge et al. reported adult onset form of LBSL in which, the level of lactate is normal [13]. Labauge et al. also reported the first asymptomatic adult patient with a typical MRI aspect of LBSL [14].

LBSL is an autosomal recessive disease, caused by mutations in the DARS2 gene, encoding the mitochondrial aspartyl-tRNA synthetase, which explains the persistent lactate peak found in LBSL patients at brain MRS analysis [4].

Patients with LBSL have distinct clinical characteristics and MRI pattern, which are different from those seen in all other known leukoencephalopathies [11].

Table 2
Table 2 Structures variably affected by MRI in LBSL patients (n = 16).

<table>
<thead>
<tr>
<th>Structure</th>
<th>Involvement rate % (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Supratentorial</td>
<td></td>
</tr>
<tr>
<td>Corpus callosum</td>
<td>75 (n = 12)</td>
</tr>
<tr>
<td>Anterior limb of internal capsule</td>
<td>6 (n = 1)</td>
</tr>
<tr>
<td>External capsules</td>
<td>56 (n = 9)</td>
</tr>
<tr>
<td>Putamen</td>
<td>18.8 (n = 3)</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>12.5 (n = 2)</td>
</tr>
<tr>
<td>II. Infratentorial</td>
<td></td>
</tr>
<tr>
<td>Subcortical cerebellar white matter</td>
<td>87.5 (n = 14)</td>
</tr>
<tr>
<td>Pyramidal tract</td>
<td>56 (n = 9)</td>
</tr>
<tr>
<td>Medial lemniscus</td>
<td>50 (n = 8)</td>
</tr>
<tr>
<td>Middle cerebellar peduncles</td>
<td>68.8 (n = 11)</td>
</tr>
<tr>
<td>Superior cerebellar peduncles</td>
<td>68.8 (n = 11)</td>
</tr>
<tr>
<td>Pyramids</td>
<td>75 (n = 12)</td>
</tr>
<tr>
<td>Inferior cerebellar peduncle</td>
<td>50 (n = 8)</td>
</tr>
<tr>
<td>Mesencephalic trigeminal tract</td>
<td>62.5 (n = 10)</td>
</tr>
<tr>
<td>Anterior spinocerebellar tract</td>
<td>12.5 (n = 2)</td>
</tr>
</tbody>
</table>

N.B: The involvement was judged by signal alteration of the affected structures.
Petzold et al. [11], described the MRI features in LBSL patients as “spotty” cerebral white matter changes, abnormality of the pyramidial and sensory tracts over their entire length, and a remarkably selective involvement of cerebellar and trigeminal tracts. This coincides with the MRI features found in our patients, however in only 31.2% of our cases, the signal abnormalities were spotty showing low signal intensity in FLAIR, affecting only the frontal and parietal lobes, whereas, the signal changes of the remaining 68.8%, were inhomogeneous and confluent involving all lobes, predominating within frontal and parietal regions and partially sparing the temporal lobes. There was no statistically significant difference in the mean age between the two MRI patterns of white matter affection (inhomogeneous/confluent and spotty). Furthermore, no significant difference was found in the mean onset of symptoms-investigation time interval between these two white matter patterns of affection in MRI in our study population.

The subcortical U fibers and globi pallidi were spared in all our patients. This is consistent with all previously described cases, except the case reported by Galluzzi et al. who showed involvement of the subcortical U-fibers and globi pallidi [12].

In all patients of the present study, 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 deep cerebellar white matter. MRI of the spinal cord revealed altered signal in posterior columns and lateral corticospinal tracts over the entire length in all cases. These abnormalities are in absolute agreement with earlier reports (Figs. 1 and 2).

However, there were other structures that were variably affected in our study as they showed abnormal signal alteration in some patients and normal spared signal in others, like the corpus callosum, medial lemniscus and mesencephalic trigeminal tract, and the cerebellar connections as well as the pyramidial and anterior spinocerebellar tracts.

The midbrain showed no abnormal signal intensity and this, although an atypical finding in our patients, has been also described in few previous reports [7,8]. Similarly the transverse pontine fibers, which were not affected in our study, were also not invariably involved in the previous reports [8].

Some previous reports have emphasized the involvement of the sensory and pyramidial tracts over their entire length in all LBSL patients [6]. However, in our cases, involvement of the medial lemniscus and pyramidial tract was not constant in all cases and found only in 50% and 56% of patients respectively. Actually, this is concordant with some other previous studies that found normal signal intensity in the pyramidial tracts and medial lemniscus in some of their cases [7,8].

To standardize the MRI-based diagnosis of LBSL, Sen et al. [10], described major and supportive criteria for diagnosis of LBSL. The major criteria include signal abnormalities in the following regions: (1) cerebral white matter, which is either nonhomogeneous and spotty or homogeneous and confluent, with relative sparing of the ‘U’ fibers; (2) dorsal columns and lateral corticospinal tracts of the spinal cord; (3) pyramids in the medulla oblongata. The supportive criteria include: signal abnormalities in splenium of the corpus callosum, posterior limb of the internal capsule, medial lemniscus in the brainstem, superior cerebellar peduncles, inferior cerebellar peduncles, intraparenchymal part of the trigeminal nerve, mesencephalic trigeminal tracts, anterior spinocerebellar tracts in the medulla and cerebellar white matter with subcortical preponderance. They described that all the major criteria and one of the supportive criteria should be fulfilled for diagnosis of LBSL.

Galluzzi et al. have described distinctive features of LBSL as follows; first, white matter abnormalities and involvement of brain stem structures by brain MRI; 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 [12].

Diffusion restriction was found in most of the length of the corticospinal tracts in 56% of cases of our series in addition to involvement of the superior and inferior cerebellar peduncles and mesencephalic trigeminal tracts in 68.8%, 50%, and 62.5% of our cases, respectively. The diffusion hyperintensity of the white matter in DWI showed low ADC at the border of white matter abnormalities and elevated ADC values in rest of the white matter (Fig. 2A–G). This pattern has been also reported previously in LBSL [10].

Several diagnostic possibilities can be excluded when analyzing the MRI features. The most frequent differential diagnosis of LBSL is mitochondrial disorder. Although brainstem and spinal cord are frequently involved in mitochondrial disorders, the selective involvement of specific brainstem and spinal cord tracts is unique for LBSL [11]. Elevated serum and CSF lactate values, though not essential, support the diagnosis of LBSL [10]. The other differential diagnosis is vitamin B12 deficiency, however in this disorder no brain stem abnormalities were reported and only cervical spinal cord involvement could be detected as opposed to entire spinal cord involvement in LBSL [10].

Single-voxel brain MR spectroscopy [1H MRS] showed consistent elevation of the lactate within the abnormal white matter in all analyzed voxels (Figs. 11, 21 and 20). A significant decrease in N-acetylaspartate (NAA) and increase in myoinositol (mls) were also found in the white matter of all patients indicating considerable axonal damage/loss and gliosis. In 68.8% of cases, mild elevation of the white matter choline peak (Cho) was also observed suggesting low-grade demyelination. Gliosis also can contribute to Cho elevations. The white matter creatine (Cr) was normal in all patients. The overall MRS findings in our study suggest considerable axonal damage/loss in the white matter which is concordant with most of the previous reports [3,5–7,10]. Despite that elevated Lactate is considered a criterion for the definition of this entity, it is not absolutely present in all cases reported earlier [8,11,15].

5. Conclusion

Selective affection of subcortical and deep white matter tracts in the brain (involving the posterior limb of internal capsules and sparing the subcortical U fibers), dorsal column and lateral corticospinal tracts over the entire length of the spinal cord and lactate elevation in [1H MRS] are consistent distinctive MRI findings in our study population that should lead to the diagnosis of LBSL. The disease can be confirmed by the analysis of the disease gene DARS2.

References


