

## Case Report



# Leigh Syndrome: Cranial MRI and MR Spectroscopy Findings

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### ABSTRACT

A 10 years old girl, was admitted to the intensive care unit with seizure, myotonic-clonic jerks in her hands, vomiting, respiratory failure and mild metabolic acidosis. Brain Magnetic resonance imaging (MRI) and proton MR spectroscopy (MRS) were performed. The MRI findings presented symmetric basal ganglia, brain stem, left thalamus and subthalamic nuclei involvement. MRS obtained from the basal ganglia and thalamus lesions, showed increased lactate and choline peak, decreased NAA/Crea and NAA/Cho ratios. In the CSF, there was also increased lactate. These imaging findings, clinical course and the laboratory data were used for the diagnosis of Juvenile form of Leigh syndrome. Muscle biopsy wasn't needed for the diagnosis.

**Key Words:** Leigh syndrome, brain MRI, MR Spectroscopy, basal ganglia, thalamus.

### ÖZET

#### Leigh Sendromu: Beyin MRG ve MR Spektroskopisi Bulguları

On yaşında kız çocuğu acil ünitesine; nöbet, ellerinde myotonik-klonik kasılmalar, kusma, solunum kaybı ve hafif metabolik asidoz bulguları ile başvurdu. Beyin Manyetik Rezonans Görüntüleme (MRG) ve proton-MR Spektroskopisi yapıldı. MRG bulguları; Simetrik bazal ganglion, beyin sapı, sol talamus ve subtalamik çekirdek tutulumu içermektedir. Bazal ganglion ve talamus lezyonlarından alınan MR Spektroskopisi de; artmış laktat ve kolin pikleri, azalmış NAA/Krea and NAA/Kol oranlarını gösterdi. Beyin omurilik sıvısında da artmış laktat mevcuttu. Görüntüleme bulguları ile birlikte klinik süreç ve laboratuvar verileride Leigh sendromu genç erişkin tip tanısını desteklediğinden, teşhis için kas biyopsisine gerek duyulmadı.

**Anahtar Sözcükler:** Leigh sendromu, beyin MR, MR Spektroskopisi, bazal ganglion, talamus.

Leigh syndrome (LS) or subacute necrotizing encephalomyelopathy, is an inherited, progressive neurodegenerative and metabolic disease of infancy, early childhood (1,2). LS comprises a heterogeneous group of mitochondrial diseases and clinical manifestations are extremely variable, LS is the most common mitochondrial syndrome (3). Clinically it has three different forms: 1) Neonatal form that presents with disorders of sucking, swallowing and respiration. 2) Classic infantile form that presents with psychomotor slowing, encephalopathy and seizure. 3) Juvenile form presents with insidious onset of predominant extrapyramidal manifestations (3,4). Elevation of lactate-pyruvate in the blood and CSF are the main biochemical findings of LS (5).

The typical MRI findings are symmetric hyperintense lesions of basal ganglia especially putamen and globus pallidus, brain stem and thalamus on T2W images (2). Less frequently cerebral cortex and cerebellum is involved, at the same time very few cases of white matter involvement have been reported (2,4). Pathologic examination of LS reveals

demyelination, vascular proliferation, gliosis and astrocytosis (2,5). Proton MR spectroscopy also aids in the diagnosis of LS, it shows increased and inverted lactate peak-increased choline/creatine and decreased NAA/creatine ratios (6,7). Characteristic clinical features, typical radiologic and spectroscopic findings, elevated blood or CSF lactate-pyruvate allows LS diagnosis in most patients (8). In this paper, routine brain MRI and MRS results of a LS patient is presented.

### CASE REPORT

A 10 years old girl, presented with seizure, myotonic-clonic jerks in her hands, vomiting and respiratory failure. She had no seizure and didn't suffer from these complaints before, her mental status was normal. In her daily life, her school success was not satisfactory, she wasn't so good in friendships and didn't get on well with her parents. After psychiatric consultations; Fluoxetine was prescribed, she used it for 15 days and left it just a fortnight ago. She had neither fever-headache and traumatic history nor any spasticity, her posture and gaiting was normal. At admission to intensive care unit,

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she was unconscious, uncooperative and disoriented. Her pupils were fixed-dilated and she had hypothermia. Her ECG was normal and due to her respiratory failure, she was intubated and admitted to the ventilator. In her clinical course and follow up, she had a 2 minutes long jeneralized convulsion once more and vomiting for twice. She also had bradycardia and mildly decreased blood saturation. Laboratory data included normal complete blood count-normal liver and kidney functions- normal urine analysis-normal triglyceride, cholesterol and uric acid levels. She had mild metabolic acidosis. Blood and urine aminoacid chromatographies were normal. In her first lumbar puncture; CSF analysis including lactate and pyruvate levels, was normal. Blood ammonia, lactate and pyruvate levels were normal. EEG showed no epileptic activity.

She was first admitted to CT scan in intensive care unit and a brain CT scan was performed, interpreted as normal. Afterwards we had performed her a cranial MRI and MRS. Brain MRI showed bilateral symmetric conglomerated nodular hyperintensities in the globus pallidus at T2W images (Fig 1). She also had corpus striatal necrosis and focal multipl hyperintensities in the left putamen (Fig 2). There was also bilateral involvement of the cerebral peduncles at the brain stem and left caudate nucleus (Fig 3,4). In the left thalamus, mainly posterior and lateral side of the thalamus and at the same time in the left subthalamic nuclei, there was also a focal 1.5 cm and less sized nodular well-circumscribed hyperintense lesions and signals on T2W images (Fig 1-2). Cerebellum and deep cerebral cortex-subcortical areas were preserved. After brain MRI, proton MR spectroscopy was performed by using single voxel point-resolved spectroscopy sequence. 1 cm<sup>3</sup> voxel was placed on the lesions in the left globus pallidus and the left thalamus. Two acquisitions were obtained with TE:35 and 144 ms parameters at the T2W images. The spectroscopic data were processed on a private GE 1.5 Tesla workstation. The short TE spectrum (Fig 5) showed increased myoinositol, glycine and glutamate peaks. The long TE spectrum (Fig 6) showed decreased NAA peak, increased choline (Cho) peak, decreased creatine peak (crea) and inverted lactate doubled peak at 1.3 ppm confirming the presence of the lactic acid. There were also major lipid peaks through the lesions. Cho\crea ratio was elevated, NAA\crea ratio was decreased. Subsequent to MRI and MR spectroscopy, another lumbar puncture was performed and results revealed; increased lactate in the CSF. Muscle biopsy for fiber detection was not needed and the diagnosis of juvenile form of LS was based on clinical presentations, with raised lactate level on CSF and pathognomonic symmetric bilateral basal ganglia and brain stem involvement (2,8,9).

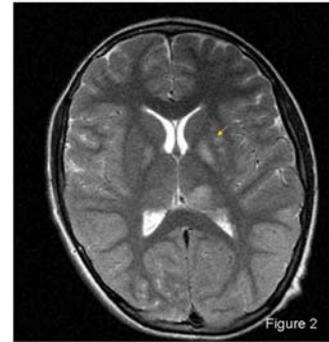


Figure 2. Left putamen and globus pallidus involvement

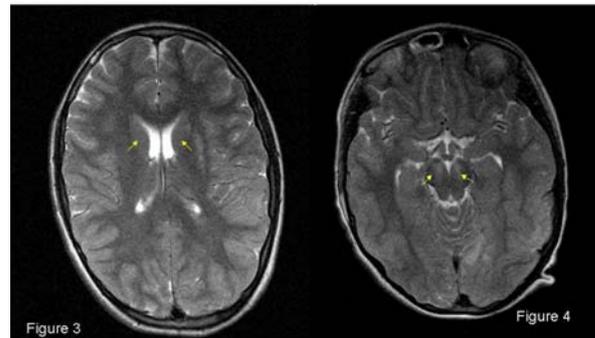


Figure 3, 4. Bilateral caudate nucleus and cerebral peduncle involvement

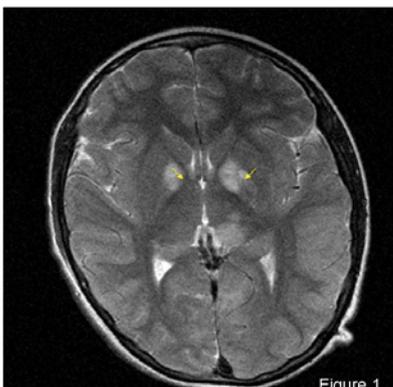


Figure 1. Simetrik basal ganglia and left thalamus lesions

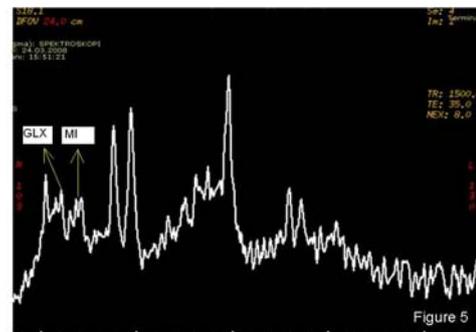


Figure 5. Increased MI, glycine and glx peaks

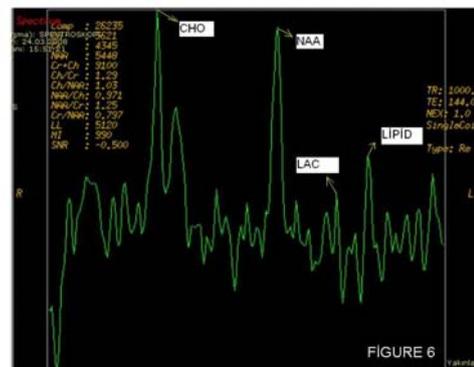


Figure 6. Increased cho, decreased NAA, increased lac and lipid peaks

## DISCUSSION

Imaging findings of LS have been reported in a number of publications and typical CT-MRI findings have been considered to be diagnostic hallmark (2,10). Involvement of the basal ganglia, principally the putamen and the globus pallidus, is the main diagnostic imaging entity with CT and MRI (5-11). With MRI; involvement of brain stem, cerebellum and subthalamic nuclei are also shown, less commonly involved sides are: Cerebral cortex-white matter and the substantia nigra (2,5,12). In our case; we had basal ganglia-brain stem thalamus and subthalamic nuclei involvement in the brain MRI sections (Fig 1, 2, 3) but cerebellum-cerebral white and gray matter-substantia nigra involvement is not seen. Dystonia is the predominant clinical symptom in the juvenile form of LS (4).

Myo-clonic, tonic-clonic and generalized seizures, spasm and respiratory disturbances such as apnea-tachypnea due to brain stem involvement are the other common symptoms (8,9). In our case, she had myo-clonic contractions in her hands, seizure, vomiting and respiratory disturbances. There was no spasm and dystonia in the extremities. Proton MR spectroscopy also play an important role in the diagnosis of LS (12,13). MR spectroscopy performed for the diagnosis of LS, shows mainly decreased ratio of NAA\Cho and NAA\Crea, inverted lactate peak at long TE (6,7,12). This finding is consistent with an increased phosphocholine turnover in the membrane lysis and biosynthesis by the swollen cells (7,14). Decreased NAA is likely due to a reduction of neurons per unit volume secondary to cell lysis, attributed to axonal loss, degradation of NAA in injured neurons and gliosis (6,7,15). Increased lactate in LS and mitochondrial encephalopathies, may be the result of prevailing glycolysis, possibly in conjunction with cell hypoxia\ischemia from a possible inadequate blood supply (7,14), but increased lactate peak is not specific for LS, it may be found in acute strokes, seizures, tumors and etc. An increase in lactate is found in the peripheral blood, CSF and brain of many patients with mitochondrial encephalopathies (12, 13). It must be mentioned that normal blood lactate does not rule out the diagnosis (16,17).

Barkovich et al (12) reported an increase in lactate at MR spectroscopy in affected areas of patients, generally basal ganglia with mitochondrial diseases. In his cases there were also involvement of cerebral white matter and they didn't see any increased lactate peak. In our case, we had also seen inverted lactate doublet from the basal ganglia and thalamus but our patient didn't have cerebral white matter lesions. Ducreux et al (7) reported a case of acute severe unusual mitochondrial encephalopathy, lactic acidosis and stroke like events. For the imaging, he performed MRS, MR Diffusion tensor imaging and fiber tracking, then confirmed the diagnosis by muscle biopsy. In his case, the lesions were shown in the mesencephalon, medulla oblongata, cerebellum and cervical spinal cord on brain MRI, from the medulla oblongata with single-voxel spectroscopy via long TE, there was normal creatine, decreased NAA, inverted lactate peak

at 1.3 ppm, increased choline peak. In our case, we had also similar findings in the MRS but in the brain MRI, medulla oblongata and cerebellum was not involved. Bowen et al (6) reported a mitochondrial encephalopathy case with a maternally inherited diabetes and deafness (MIDD). There was extensive subcortical, periventricular white matter and basal ganglia high signal intensities on T2 weighted MR studies and mildly increased lactate, increased cho\crea and mildly decreased NAA\crea ratios in the proton MR spectroscopy sampled from the periventricular white matter. He regarded the mild decrease of NAA\Crea ratio as the mild neuronal damage and mild lactate increase due to the mild mitochondrial metabolic disruption. In our case, we didn't see any involvement in the subcortical and periventricular white matter on MR studies and spectroscopically, we had inverted lactate doublet and obvious decrease in the NAA\Crea ratio. In our case the proton MR spectroscopy also showed increased choline peak and increased Cho\Crea ratio.

Ashrafi et al (17) presented 15 cases of LS aged between 6-156 average 40.5 months. 90% blood lactate is increased, on MRI studies; 100% symmetric striatal necrosis, 73 caudate nucleus involvement were the most frequent findings. Cerebral white matter and brain stem involvement were rare, about 10 percent. Only 1 patient; 13 years old girl underwent to MRS due to normal blood lactate level, MR spectroscopy showed abnormal lactate elevation in the basal ganglia and he concluded that normal blood should not rule out the diagnosis of LS. Our patient was 10 years old girl and on T2W images, there was high signaled nodular intensities in the basal ganglia-thalamus and subthalamic nuclei. We also saw the abnormal lactate elevation in the MR spectroscopy of the patient. Grodd et al (18) studied metabolic and destructive brain disorders in children, he had three cases of LS, they all had metabolic acidosis, increased lactate and pyruvate concentrations in blood and CSF.

MR studies of them showed bilateral lesions in the putamen and caudate nuclei. MR spectroscopy revealed decreased peak intensity for NAA and elevated levels of lactate in the head of caudate nucleus. In our patient; MRI and MRS findings were similar but blood lactate level was normal. As seen in the literature, MRI-MR Spectroscopy findings conjunction to clinical symptoms and laboratory findings are noteworthy in the establishment of Mitochondrial Encephalopathies. In our opinion, the demonstration of symmetric basal ganglia, brain stem and subthalamic nuclei involvement in MRI indicates a mitochondrial disorder in children, the combination of MR spectroscopy and brain MRI increases the specificity for the detection of LS especially for the juvenile form. We suggest that inverted lactate doublet peak -increased choline peak and decreased NAA\Cho and NAA\Crea ratios with conjunction to the pathognomonic brain MRI findings and elevation of lactate in CSF, is enough to diagnose the disease; have a direct impact on the clinical assessment, care and treatment of the juvenile form of LS.

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