Two Clinical Cases of LBSL: Diagnostic Problems and Possible Therapeutic Approaches

Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) is a rare autosomal-recessive disease which is first described by Marjo van der Knaap in 2003.[1] Currently, there are less than 200 clinical cases of LBSL presented in the literature. LBSL is caused by mutations in the DARS2 gene that encodes the mitochondrial aspartyl-tRNA synthetase. Decrease in the activity of mitochondrial aspartyl-tRNA synthetase leads to the non-inclusion of aspartic acid residue in the structure of all mitochondrial proteins and to the disruption of redox processes in the cell, as well as to the activation of the histotoxic hypoxia mechanism.[2]

Magnetic resonance imaging (MRI) features of LBSL are very characteristic and allow to establish a preliminary diagnosis before genetic examination.[3] The disease is characterized by slowly progressive pyramidal disorders, ataxia and decreased proprioception.[4] No specific LBSL therapy has been developed.[5] Based on the pathogenesis, therapy may include the use of antioxidants and antihypoxants.

We observed 2 patients with the late onset of LBSL who, despite the MRI findings, were initially misdiagnosed as having multiple sclerosis (MS). After the correct diagnosis, the patients were treated with the derivatives of succinic acid with good clinical effect.

Case 1

A 31-year-old woman was hospitalized in our clinic with complaints about shaky gait, intermittent numbness and burning in her legs. Neurological status: Pathological upper limb and plantar signs, muscle fatigue, hypoesthesia in the right shin, lack of vibration sense in the legs, intention tremor, ataxia in the Romberg’s test were noted.

At the age of 30, she noticed pain in her right thigh, then, progressive weakness and numbness in her legs, unsteady gait, and non-systemic dizziness. MRI revealed symmetrical multifocal lesions in the brain and spinal cord without contrast enhancement [Figure 1]. The patient was diagnosed with MS. Pulse therapy with methylprednisolone (MP) and IVIg were ineffective. The diagnosis of LBSL was suggested, and the results of the examination revealed a heterozygous mutant gene DARS2.

Considering the fact that one of the main components of LBSL pathogenesis is a decrease in the activity of mitochondrial aspartyl-tRNA synthetase and an insufficiency of mitochondrial protein functioning, which, in turn, leads to a disruption of redox processes in the cells, the patient was treated with a succinic acid derivative - Ethylmethylhydroxypyridine Succinate (EMHS) 15 days, 1000 mg intravenously (IV) daily.

After the EMHC therapy, numbness and burning sensation regressed in the legs. Intention tremor and the instability in the Romberg’s test decreased. The patient continued with an ongoing maintenance therapy with EMHS per os at a daily dose of 750 mg after discharge from the hospital. She received the same EMHS infusion courses every 6 months. Neurological status and MRI pattern upon the follow-up examination after a year were stable.

Case 2

A 27-year-old woman was referred to our clinic concerning unsteady walk, weakness in the right leg, which appeared and developed over the course of two years. MRI of the brain was performed at the place of residence, which resulted in the diagnosis MS. MP was administered without effect.

MRI study revealed a longitudinally extensive dorso-lateral spinal cord lesion involving almost the entire cord. A heterozygous DARS2 mutant gene was detected during the genetic study (a mutation affecting the
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Revised: hypoxia.

processes in cells of the brain and spinal cord in a histotoxic and activation of energy metabolism, inhibition of free-radical inclusion of succinate as a substrate in the respiratory chain which may be due to increased functional activity of enzymes, activation of aerobic glycolysis, a decrease in the oppression of oxidative processes in the Krebs cycle, and thus an increase in the content of ATP, creatine phosphate, activation of energy-synthetic functions of mitochondria.

In both cases, there was a positive effect in the reduction of cerebellar abnormalities, sensory and pyramidal disorders, which may be due to increased functional activity of enzymes, inclusion of succinate as a substrate in the respiratory chain and activation of energy metabolism, inhibition of free-radical processes in cells of the brain and spinal cord in a histotoxic hypoxia.

Our observations may indicate that the use of drugs with the mechanism of action described above may be promising in this group of patients, but it is necessary to conduct further controlled studies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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