

Article

Mitochondrial Disorders and MRI of the Brain in Patients with Leukoencephalopathy with Brainstem and Spinal Cord Involvement and Lactate Elevation in Moscow Region

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Abstract: leukoencephalopathy with lesions of the brainstem and spinal cord and increased lactate levels (LBSL) is a hereditary autosomal recessive disease caused by a mutation in the DARS2 gene, with a heterogeneous lesion of the white matter of the brain involving the brainstem and spinal pathways, an increase in lactate in abnormal white matter. **Objective.** The purpose of the study is to evaluate the features of brain MRI and mitochondrial disorders in adult patients with PE-FMF. **Material and methods.** An observation of three adult patients from the Moscow region with a hereditary mitochondrial disease of leukoencephalopathy with damage to the brainstem and spinal cord and an increase in lactate level (LBSL) is presented. The diagnosis was confirmed by molecular diagnostics. An MRI examination of the brain was performed on an MRI tomograph with a magnetic field induction of 3.0 T For the cytochemical study of the activity of mitochondrial enzymes in peripheral blood lymphocytes, the method proposed by A.G.E. Pearse modified by R.P. Narcissov. **Results.** The clinical picture of the disease is similar to multiple sclerosis. MRI of the brain showed more pronounced diffuse changes in the white matter. In all patients, dysfunction of the respiratory chain of mitochondria was noted. **Conclusion.** Taking into account the data obtained, patients are shown energotropic therapy (idebenone and carnitine preparations). Thus, when doubtful cases in the diagnosis of multiple sclerosis, LBSL should be excluded.

Keywords: mitochondria; leukoencephalopathy with damage to the brainstem and spinal cord and increased lactate levels; LBS; multiple sclerosis; energotropic medicines.

1. Introduction

Leukoencephalopathy with lesions of the brainstem and spinal cord and increased lactate levels (LBSL) is a disease with a characteristic lesion of the white matter of the brain on MRI and MRI spectroscopy (MRS) (Scheper et al., 2007) [1]. Patients gradually develop progressive cerebellar ataxia, spasticity, and dysfunction of the spinal cord, sometimes with moderate cognitive impairment. The disease is caused by mutations in the DARS2 gene located in nuclear DNA on chromosome 1. The mode of inheritance is autosomal recessive.

LBSL – this new leukoencephalopathy, which was described by van der Knaap M. S. et al. in 2003 [2] in 8 patients. The authors revealed in these patients during MRS an inhomogeneous lesion of the white matter of the brain with the involvement of the brainstem and spinal pathways. Proton MRI showed elevated lactate levels in the abnormal white matter. Clinically, patients exhibited slowly progressive pyramidal, cerebellar, and spinal dysfunction. Autosomal recessive inheritance was considered likely. Three of the 8 patients were men. Among the 8 patients were 2 sisters, as well as a brother and a sister. Linnankivi T. et al. (2004) [3] described 5 more patients with this disease. MRS revealed a decrease in the content of N-acetylaspartate and an increase in the content of lactate in the white matter of the brain in all patients. Slowly progressive sensory ataxia and tremors were noted that appeared between the ages of 3 and 16 years, and a spastic distal increase in muscle tone in adolescence. One 13-year-old patient was asymptomatic. Two of



the 5 patients were brothers. Serkov S. et al. (2004)[4] also described 5 new unrelated patients. The clinical picture was homogeneous with the onset of the disease in childhood, a slowly progressive course, cognitive impairment, pyramidal and cerebellar symptoms. In some cases, dysfunction of the spinal cord has been identified. This new leukoencephalopathy, which was described by van der Knaap M. S. et al. in 2003 [2] in 8 patients. The authors revealed in these patients during MRS an inhomogeneous lesion of the white matter of the brain with the involvement of the brainstem and spinal pathways. Proton MRI showed elevated lactate levels in the abnormal white matter. Clinically, patients exhibited slowly progressive pyramidal, cerebellar, and spinal dysfunction. Autosomal recessive inheritance was considered likely. Three of the 8 patients were men. Among the 8 patients were 2 sisters, as well as a brother and a sister. Linnankivi T. et al. 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(2006) [5] described a sister and brother whose illness began at the age of 20 and 23 with unsteady gait and stiffness in the legs. The parents were not blood relatives. Isohanni R. et al. (2010) [6] studied the clinical features of 5 patients with LBSL reported by Linnankivi et al. (2004) [3] and described 3 new patients. Six patients were of Finnish origin. Overall, the phenotype was somewhat heterogeneous, with most patients having onset between the ages of 2 and 15 years. Most had a delay in motor development in childhood. In two cases it was normal. Tremor, ataxia, dysarthria and spasticity were most often noted in patients. For the first time, the authors described in patients with LBSL axonal polyneuropathy with weakness in the distal extremities and a decrease in vibration sensitivity. Four patients had no cognitive impairment, 4 had mild speech defects, learning problems. Two patients were described in detail. One of them at the age of 8 had seizures at night. MRI of the brain revealed changes in the white matter in the infra- and supratentorial regions. At the age of 15, he developed ataxia, extensor plantar reflexes, spasticity, and axonal neuropathy. Another patient, at 19 months of age, developed motor retardation with ataxia and muscular hypotonia. Spasticity and hyperreflexia appeared by the age of 2 years 3 months. He also had a slight speech delay. An MRI of the brain revealed pathology of the white matter of the brain in the supratentorial region. Miyake, N., et al. (2011) [7] reported 3 Japanese siblings with severe PE-FMF born to consanguineous parents. A homozygous mutation in the DARS2 gene (610956.0012) was identified. At the age of 3, a 21-year-old proband developed ataxia, then nystagmus, speech impairment, limb tremor, and decreased intelligence. He could only speak 1-2 words. Other features of the proband included atrophy and weakness of the limb muscles, joint contractures, hyporeflexia, and impaired deep sensation. His 2 brothers, who developed the disease before the age of 1, died in childhood from respiratory diseases. MRI of the brain in the proband revealed leukoencephalopathy of the cerebral hemispheres, cerebellum, brain stem and spinal cord. Synofzik M. et al. (2011) [8] reported on a 25-year-old female patient who had paroxysmal ataxia with gait disturbance during exercise for 3 years. Episodes of ataxia were observed up to 5 times a day and lasted from a few seconds to 5 minutes. In recent years, their frequency has increased to 23 times a day. The patient also experienced distal limb weakness, reduced vibration sensitivity, increased muscle tone in the legs, and hyperreflexia. But she never had permanent cerebellar ataxia or a spastic gait. An increase in the level of lactate in the blood serum was noted periodically. MRI of the brain revealed damage to the white matter of the cerebellum, deep sections of the white matter of the brain and the periventricular region with the involvement of the pyramidal tracts and pathways of the spinal cord. Treatment with acetazolamide resulted in a significant reduction in the frequency of seizures. Molecular genetic analysis revealed a homozygous mutation in the DARS2 gene (R609W; 610956.0013). A mutation in the known genes for episodic ataxia was ruled out. This observation showed that LBSL can occur with mild disturbances in the form of episodic ataxia. Nikolaeva E.A. et al. (2013)[9] described a 15-year-old girl with LBSL. In her blood, a decrease in the level of coenzyme Q10 was detected, in connection with which energotropic drugs were prescribed.

Most patients with LBSL have complex heterozygous mutations in DARS2 in association with a common splicing mutation in the acceptor splicing site of intron 2 [10]. Despite the same mutation, polymorphism is described in families with a difference in the onset of 36 years (Li) [11]. Tytki-Szymanska A, et al. (2014) [12] *описали* high outcome variation between two siblings. Yahia A. et al. (2028) [13] showed the presence of intrafamily polymorphism with an earlier and more severe manifestation of the disease and a lighter course despite the change in the white matter of the brain according to MRI data. Yazici Gencdal I. et al. [14] described a patient with a mild



course of the disease, which began with her at the age of 4, when a tremor appeared in her legs. At the age of 29, she had a slight spastic gait, impaired sensitivity in her legs, ataxia, but did not need help walking. Only isolated spastic paraparesis is possible [15].

Moroz A.A. et al. (2018) [16] described a wide range of pathological mutations in 9 adult patients with LSBL in the Russian population. Karpova M.I. et al. (2019) [17] described three patients with LSBL with onset in adolescence. Rudenskaya G.E. and Zakharova E.Yu. (2020) [18] described 6 Russian patients with LSBL with onset in the 2nd and 3rd decades of life. In 2 patients, the disease course was undulating, resembling multiple sclerosis.

Lin T.K. et al. [19] studied mitochondrial function in patients with LSBL by examining proteins of the respiratory chain complex in fibroblasts. In a patient with LSBL, oxygen consumption by cells and respiratory control coefficient were reduced; in addition, mitochondrial fragmentation was increased, while their tubular elongation and interconnection were reduced. Taken together, these data suggest that DARS2 mutations disrupt the translation of complex respiratory chain proteins encoded by mitochondrial DNA, hence causing cellular respiration dysfunction and hindering mitochondrial dynamics, which underscores the role of mtARs in maintaining normal bioenergetics and mitochondrial dynamics. Stellingwerff M.D. et al. [20] found 2 MRI phenotypes: 1) early severe cerebral hypoplasia/atrophy (9 patients, 2) white matter abnormalities. Group 1 patients with antenatal onset, microcephaly and developmental delay were the most seriously affected. The DARS2 variants were heavier than the classic LSBL and heavier for Group 1 than for Group 2. Research is underway to develop LSBL gene therapy [21-23].

In view of the fact that the disease is rare, it is of interest to describe the features of MRI of the brain in patients. An increase in lactate in the affected white matter of the brain may indicate mitochondrial dysfunction in patients. The study of these disorders will contribute to the expansion of knowledge about the pathogenesis of the disease.

2. Patients and Methods

2.1. patients.

3 adult patients with LSBL from the Moscow region were examined. The diagnosis was confirmed by DNA diagnostics in the Laboratory of Hereditary Metabolic Diseases (headed by Doctor of Medical Sciences E.Yu. Zakharova) at the Medical Genetic Research Center.

2.2. MRI.

MRI of the brain was performed on a device with a magnetic field induction of 3 T. In the modes T1- and T2-WI, DWI in IP SE, TSE and FLAIR, images were obtained in the axial, coronal and sagittal planes.

2.3. Cytochemical study of the activity of mitochondrial enzymes in peripheral blood lymphocytes.

For the cytochemical study of the activity of mitochondrial enzymes in peripheral blood lymphocytes, the method proposed by A.G.E. Pearse modified by R.P. Narcissov [13]. The activity of 4 mitochondrial enzymes involved in carbohydrate metabolism (lactate dehydrogenase, LDH), amino acid metabolism (glutamate dehydrogenase, GDH), fatty acid metabolism (α -glycerophosphate dehydrogenase, α -GPDH), and complex II of the mitochondrial respiratory chain (succinate dehydrogenase, SDH) was assessed (Fig. 1). 3 adult patients with PE-FMF from the Moscow region were examined. The diagnosis was confirmed by DNA diagnostics in the Laboratory of Hereditary Metabolic Diseases (headed by Doctor of Medical Sciences E.Yu. Zakharova) at the Medical Genetic Research Center. For the cytochemical study of the activity of mitochondrial enzymes in peripheral blood lymphocytes, the method proposed by A.G.E. Pearse modified by R.P. Narcissov [24]. The activity of 4 mitochondrial enzymes involved in carbohydrate metabolism (lactate dehydrogenase, LDH), amino acid metabolism (glutamate dehydrogenase, GDH), fatty acid metabolism (α -glycerophosphate dehydrogenase, α -GPDH), and complex II of the mitochondrial respiratory chain (succinate dehydrogenase, SDH) was assessed (Fig. 1). 3 adult patients with PE-FMF from the Moscow region were examined. The diagnosis was confirmed by DNA diagnostics in the Laboratory of Hereditary Metabolic Diseases (headed by Doctor of Medical Sciences E.Yu. Zakharova) at the Medical Genetic Research Center. The activity of 4 mitochondrial enzymes involved in carbohydrate metabolism (lactate dehydrogenase, LDH), amino acid metabolism (glutamate dehydrogenase, GDH), fatty acid metabolism (α -glycerophosphate dehydrogenase, α -GPDH), and complex II of the mitochondrial respiratory chain (succinate dehydrogenase, SDH) was assessed (Fig. 1).



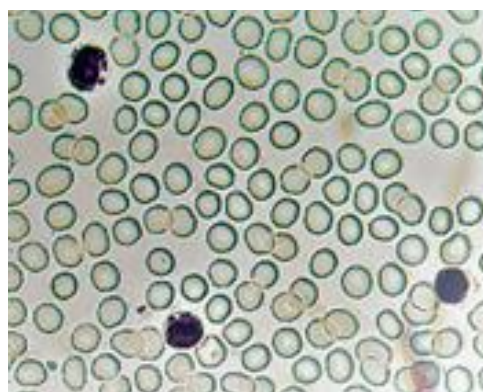


Figure 1. Detection of succinate dehydrogenase activity in lymphocytes by a quantitative cytochemical method (view under a microscope, magnification 600, dark granules along the cell periphery are the reaction product).

2.4. Lactate.

Using the ABL800 FLEX blood gas analyzer, the lactate level in heparinized whole blood was studied by the amperometric, ensemble method using a substrate-specific electrode. Lactate is determined in the blood on an empty stomach and after a load of carbohydrates at a dose of 1 g of dry glucose per kg of body weight.

3. Results

The diagnosis of LSBL in patients was confirmed by molecular diagnostics; mutations in paired DARS2 genes were identified. All examined patients with LSBL were females aged 37 and 39 years. The first symptoms of the disease appeared at 26, 28 and 37 years. The onset of the disease was acute in two cases and subacute in one. There was a violation of speech, writing, dizziness, absence of the left visual field, numbness of the extremities, gait disturbance. What was the reason to suggest the diagnosis of multiple sclerosis, given the defeat of the white matter on MRI of the brain. One patient was diagnosed with an unspecified demyelinating disease. In all cases, MRI of the brain revealed a symmetrical lesion of the white matter - diffuse focal lesions. Patient S. had bilateral diffuse-focal lesions of predominantly deep white matter at the level of the lateral ventricles with foci in the middle peduncles and hemispheres of the cerebellum, the medulla oblongata, throughout the spinal cord. Patient L. (previously described without MRI of the brain [25] showed extensive symmetrical pathological lesions without clear contours and borders, which spread along the cortico-spinal tract, at the level of the cerebellar peduncles and caudally to the posterior columns of the spinal cord. There was a similar signal characteristic of damage to the intratrunk portion and the mesencephalic pathway of the trigeminal nerve on both sides. The same changes were in the bridge. In the deep parts of the white matter of the hemispheres, paraventricular localization, different-sized foci were determined, prone to fusion (Fig. 2). Patient B. had periventricular and subcortical focal-confluent zones of increased MR signal.

The course of the disease was undulating in two cases and slowly progressing in one. On examination, one patient had a high arch of the feet. In the neurological status in two cases there was a lesion of the optic nerve. In one case, there was also involvement of the abducens nerve in the pathological process. Tendon reflexes in two cases were increased and in one patient with a pronounced violation of deep sensitivity, there were no knee and Achilles reflexes. Muscle tone in two patients was increased according to the spastic type. Vibration sensitivity in the toes was reduced in all patients. All examined patients showed instability in the Romberg position when closing their eyes. Missing during the finger-nose test was only in one case. All patients performed the heel-knee test accurately. Urinary incontinence was reported in one case. Sensitivity disturbance of the polyneuritic type was in one patient. The course of the disease was undulating in two cases and slowly progressing in one. On examination, one patient had a high arch of the feet. In the neurological status in two cases there was a lesion of the optic nerve. In one case, there was also involvement of the abducens nerve in the pathological process. Tendon reflexes in two cases were increased and in one patient with a pronounced violation of deep sensitivity, there were no knee and Achilles reflexes. Muscle tone in two patients was increased according to the spastic type. Vibration sensitivity in the toes was reduced in all patients. All examined patients showed instability in the Romberg position when closing their eyes. Missing during the finger-nose test was only in one case. All patients performed the heel-knee test accurately. Urinary incontinence was reported in one case. Sensitivity disturbance of the polyneuritic type was in one patient.



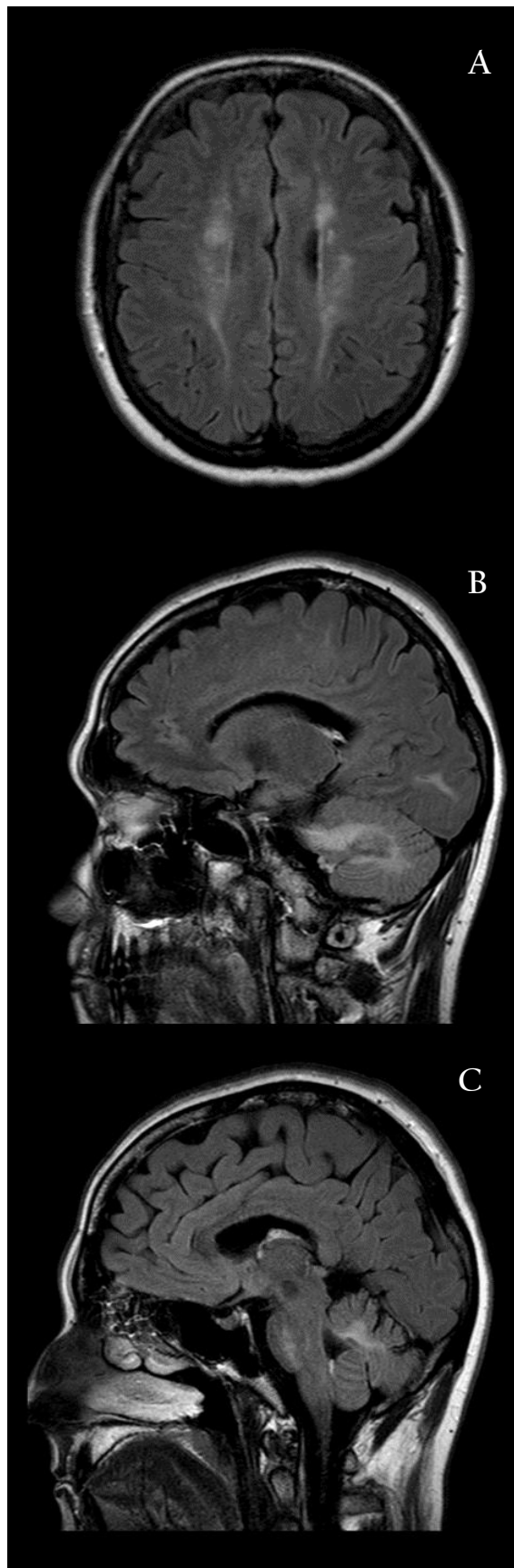


Figure 2. Brain MRI of patient L. with leukoencephalopathy with damage to the brainstem and spinal cord and increased lactate levels (a), b), c)).



The activity of mitochondrial enzymes of peripheral blood lymphocytes was changed in all the studied patients (Table 1). Dysfunction of the respiratory chain was found in 2 out of three patients. In one patient, SDH activity was reduced, in the other, it was compensatory increased. Violation of fat metabolism in mitochondria, determined by the activity of α -GPDG, was noted in two cases. In the third patient with normal values of SDH and α -GPDH, a decrease in GDH activity (impaired amino acid metabolism) was observed.

Table 1. Cytochemical activity of mitochondrial enzymes of peripheral blood lymphocytes (granules/lymphocyte (g/L)) with leukoencephalopathy, predominantly affecting the brainstem and spinal cord and elevated lactate levels in the Moscow Region

N	SDG	α -GPDH	GDH	LDH
1	15,2	5,7	7,3	19,1
2	24,7	5,6	-	-
3	18,8	9	8	16,9
Normal value (reference data)	18,5 – 19,0	9,0-12,0	9,0 – 12,0	10,0-17,0

The level of lactate in the blood was elevated only in one patient with a disease duration of 11 years. In the rest of the patients, blood lactate levels were not elevated over the course of up to 1 year and 12 years. After loading with carbohydrates, the value of the lactate index increased in all patients (Table 2).

Table 2. Blood lactate level (mmol/L) in patients with leukoencephalopathy with a predominant lesion of the brainstem and spinal cord and elevated lactate levels in the Moscow Region

N	Lactate	
	Before meals	After loading with carbohydrate
1	2,6	2,9
2	0,7	1,6
3	1,66	1,73
Normal value (reference data)	Up to 2,2	

4. Discussion

A new hereditary leukoencephalopathy described for about 20 years - LSBL was detected in three adult patients from the Moscow region with an initial diagnosis of multiple sclerosis and an unspecified demyelinating disease. The onset of the disease was acute and subacute. The course of the disease was undulating and slowly progressive. The pathological process involved the cranial nerves - the optic and trigeminal nerves. Cerebellar and pyramidal symptoms were noted. All patients had a violation of deep sensitivity in the lower extremities. In one case, there was a violation of pain sensitivity according to the polyneuritic type. In one case, urinary incontinence. On MRI of the brain, all patients had diffuse focal areas of lesions of the white matter prone to fusion. In one case, an intra-stem lesion of the trigeminal nerve was also noted, in contrast to the study by Kassem H. et al. [26], which revealed this lesion in all patients.

In the examined patients with LSBL, the level of lactate in the blood serum was increased only in 2 out of 3 examined patients. After carbohydrate loading, lactate levels increased in all patients. A dysfunction of the mitochondrial respiratory chain was noted. In one case - a decrease in the activity of complex II and in one case - its compensatory increase. The activity of α -GPDH was significantly reduced in 2 out of 3 examined patients. Therefore, taking into account the data obtained, patients are shown energy-tropic therapy (idebenone and carnitine medicines). In a patient with normal SDH and α -GPDH values, the dose of these medicines may not be high.

Thus, the clinical picture in patients with LSBL is practically indistinguishable from multiple sclerosis. In differential diagnosis at the initial stage, probably only MRI of the brain can help, when more pronounced diffuse lesions of the white matter are detected. In addition, when diagnosing multiple sclerosis, it is probably necessary to perform a lumbar puncture in order not only to exclude the infectious nature of the disease (neuroborreliosis), but also to detect oligoclonal



antibodies in the blood and cerebrospinal fluid. There is not one type, but several types of borreliosis that cause neuroborreliosis. In the absence of antibodies to various types of *Borrelia*, the patient should be referred to a geneticist for DNA diagnosis of LSBL. It is possible to perform both the sequencing of a single DARS2 gene responsible for the development of LSBL, and the use of a panel for frequent mutations for the diagnosis of mitochondrial diseases. If a frequent mutation in the DARS2 gene is not detected using the Mitochondrial Diseases panel, sequencing of the DARS2 gene should be performed, since the panel detects mutations only in exons, and mutations in introns and the promoter region are not detected.

5. Conclusions

Presents patients with LSBL from the Moscow region. The disease is a genocopy of multiple sclerosis. Its diagnosis requires both MRI of the brain with the detection of diffuse foci in the white matter, and DNA diagnostics - detection of a mutation in the DARS2 gene or sequencing using the Mitochondrial Diseases panel to identify frequent mutations. Diagnosis of the disease is important for the management of such patients. They are not shown medicines that change the course of multiple sclerosis, but it is necessary to prescribe energy-tropic drugs. Identification of a mutation in the DARS2 gene in patients with LSBL will allow subsequent use of gene therapy if it is developed, given the intensive research in this area....

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