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CLINICAL CASE OF LEUKOENCEPHALOPATHY WITH BRAIN STEM AND SPINAL CORD INVOLVEMENT AND LACTATE ELEVATION

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Abstract

Objective. To demonstrate a case history of leukoencephalopathy with predominant brain stem and spinal cord involvement and lactate elevation with onset in adult female patient.

Methods. The authors described a clinical case of adult female patient with leukoencephalopathy with predominant brain stem and spinal cord involvement and lactate elevation. An analysis of clinical information in Russian and foreign references on prevalence of this disease in population, its clinical signs, diagnostic peculiarities and management was performed.

Results. Differential diagnosis of demyelinating central nervous system lesions in the female patient aged 31 years was successively fulfilled with the identification of leukoencephalopathy with predominant brain stem and spinal cord involvement and lactate elevation with late onset at the neurological department of Smolensk Railway Station Clinical Hospital.

Conclusion. In general practice it should be remembered of possibility to encounter the clinic signs of the relatively rare hereditary disease, such as leukoencephalopathy with predominant brain stem and spinal cord involvement and lactate elevation with late onset.

Keywords: leukoencephalopathy, brain stem, spinal cord, magnetic resonance imaging, case history

КЛИНИЧЕСКИЙ СЛУЧАЙ ЛЕЙКОЭНЦЕФАЛОПАТИИ С ПОРАЖЕНИЕМ СТВОЛА МОЗГА, СПИННОГО МОЗГА И ПОВЫШЕННЫМ СОДЕРЖАНИЕМ ЛАКТАТА

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Резюме

Цель. Представить клинический случай лейкоэнцефалопатии с преимущественным поражением ствола мозга, спинного мозга и повышенным содержанием лактата у взрослой пациентки.

Методика. Представлен наблюдаемый авторами клинический случай лейкоэнцефалопатии с преимущественным поражением ствола мозга, спинного мозга и повышенным содержанием лактата с поздним дебютом у взрослой пациентки. Проведен анализ клинической информации отечественных и зарубежных источников о частоте возникновения этой патологии в общей популяции, клинической картине, особенностях диагностики и ведении.

Результаты. В клинических условиях неврологического отделения ЧУЗ «Клиническая больница ОАО «РЖД» г. Смоленск» был успешно проведен дифференциальный диагноз демиелинизирующих поражений центральной нервной системы с распознаванием лейкоэнцефалопатии с преимущественным поражением ствола мозга, спинного мозга и повышенным содержанием лактата с поздним дебютом.

Заключение. В условиях терапевтической практики следует помнить о возможности встретиться с относительно редкой наследственной патологией центральной нервной системы в виде лейкоэнцефалопатии с преимущественным поражением ствола мозга, спинного мозга и повышенным содержанием лактата с поздним дебютом.

Ключевые слова: рассеянный склероз, аутоиммунное заболевание, эмпиема плевры, клинический случай

Introduction

Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation (LBSL) is a rare inherited autosomal recessive disease of the nervous system (leukodystrophy) characterized by slowly progressive pyramidal, cerebellar and dorsal column dysfunction. Although its epidemiology is considered rare, the exact prevalence is not known. This pathology is based on mitochondrial dysfunction described by Van der Knaap et al. [1, 19]. LBSL progression is associated with DARS2 gene mutations, mapped on chromosome I (1q25.1 locus) and encoding mitochondrial aspartyl-tRNA synthetase which is necessary for the synthesis of all mitochondrial proteins [11]. Mutations do not lead to complete shutdown of this enzyme but only reduce its activity. This fact explains the clinical difference as well as relatively positive disease's outcome. It was also found that the molecules of mutant enzyme forms are much larger, breakable and stress sensitive as compared to the normal type [10]. Mutation rate in the general population is low, except of Finland, where this rate is 1:95 [7, 10].

The disease is characterized by slowly progressive spasticity and cerebellar ataxia as well as signs of damage of the posterior funicles of the spinal cord. Patients with LBSL typically first become symptomatic in early childhood, most commonly between two and six years of age, but there are early-onset and juvenile-onset forms as well. Typical symptoms include: ataxia, particularly gait ataxia, spasticity, predominantly affecting legs more than arms and proprioceptive loss. Tendon reflexes remain intact as a rule. Deep sensation is damaged significantly resulting to the sensory ataxia. Disease also involves peripheral nervous system with distal muscle weakness, hypo- and areflexia and decrease of surface sensation as well. Cognitive impairment is observed usually much later. Some patients have convulsive syndrome ceased with medication [3, 6, 14, 17-19].

Clinical features of LBSL vary from severe neonatal cases leading to death in early childhood to late forms manifested by moderate motor deficiency [15, 19]. There are only rare references described the adult LBSL cases up to date [1, 5, 9, 10, 16]. According to the authors, the age of patients with late onset of LBSL varies from 20 to 35 years. All the patients described mild symptoms of moderate spastic tetraparesis more affecting the legs, cerebellar ataxia and decrease of deep sensation. It was proved that the disease progresses slowly and without exacerbations, however, cases of exacerbation were described after infectious diseases accompanied by fever, as well as after traumatic brain injuries [1, 5, 13, 16].

LBSL with late onset is characterized by the highest percentage of erroneous diagnosis. We present here a clinical case of LBSL with the onset of the disease in adulthood.

Methods

The authors present a clinical case of leukoencephalopathy with predominant lesions of the brain stem, spinal cord and increased lactate (LBSL) with the onset in adulthood. The analysis of clinical information of Russian and foreign references on the prevalence of this pathology in the population, its clinical manifestations, diagnostic features and management of these patients was performed.

Clinical case history

32-years old female patient K.E.A. was admitted to the neurological department of Smolensk Railway Station Clinical Hospital in June of 2019 due to diagnosis: demyelinating central nervous system (CNS) disease, remitting multiple sclerosis, acute stage (case report form N4770/352). On admission she complained of weakness in her legs, difficulty in walking, impaired sensation in the upper and lower extremities. It was found that she manifested the first neurological complaints in 2013 after surgery (caesarean section), when the female patient noted some awkwardness in walking during recovery. She came to see a neurologist, and she was examined with brain magnetic resonance imaging (MRI) resulted in multiple sclerosis suspicion. The patient was observed at the local hospital. In spring of 2016 she noted the weakness increase in her legs and unsteadiness in walking. The patient was consulted at the department of neurology and neurosurgery of Smolensk State Medical University (SSMU). Foci of demyelination were identified on the brain MRI, prone to fusion involved the radiant crown, the brain stem without the contrast accumulation. Neurotrophic treatment was recommended and the administration of multiple sclerosis modifying drug, but the patient refused the latter. Another exacerbation occurred in May of 2019 after acute respiratory infection. The patient complained of weakness and sensation disorders in her legs as well as difficulty in walking. She came to see the doctors again at the department of neurology and neurosurgery of SSMU. Another brain MRI was performed. Multiple supra- and infratentorial foci of an altered signal from the brain were detected, as well as the foci of periventricular leukodystrophy were described in the spinal cord (see Fig. 1). The patient was admitted to the neurological department for thorough examination and treatment.

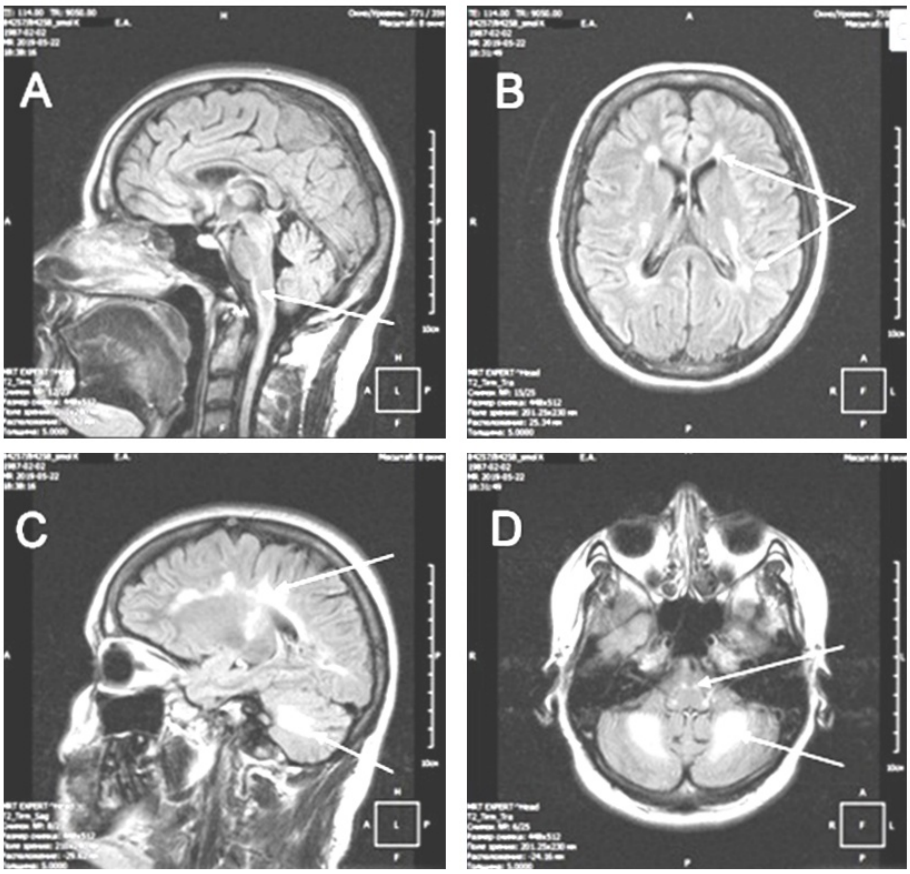

Fig. 1. Brain MRI of the female patient K.E.A., performed on 22.05.2019 with magnetic flux density of 1.5 T in T2 FLAIR mode (so called diminished signal from the cerebrospinal fluid). A – sagittal section, the white arrow indicates the lesions of the rostral parts of the brain stem. B – axial section, the arrows indicate symmetrical paraventricular foci with no damage of U-shaped fibers. C – sagittal section, the arrows indicate foci in the cerebellar radiant crown. D – axial section, the arrows indicate symmetrical foci in the cerebellum, and typical signal change from the pyramids as well

Neurological status on admission

The patient's consciousness was clear. She was smart at communicating, oriented correctly in the place, time and herself. Craniocerebral nerves: I-st cranial nerve — reaction to smells was normal. II-nd cranial nerve – she focused her eyes on different objects and she distinguished the colors properly, there were no visual fields defects. III, IV, VI cranial nerves – there was no ptosis, the eye-slits were asymmetrical, the pupils were D=S, pupillary response to light was retained directly and friendly, there was no exophthalmos, horizontal nystagmus was observed with the extreme abduction of the eyeballs. Pathologic restriction of the volume of the eyeballs movements was not revealed, there was no diplopia, convergence and accommodation were not broken. V cranial nerve – mandible movement was not limited, the skin sensitivity was normal, tenderness palpation was not revealed in the trigeminal points, conjunctival and corneal reflexes were normal. VII cranial nerve – the patient's face was symmetrical, brow reflex was normal, D=S, taste sensation on the front 2/3 of the tongue was normal. VIII cranial nerve – responds to sound stimuli were the same on both sides. IX and X cranial nerves – uvula was located in the center, palatal curtains were movable, swallowing and phonation were normal, palatal and pharyngeal reflexes were preserved, taste sensation on the back third of the tongue was normal as well. XI cranial nerve – shoulders and shoulder blades were symmetrical, the patient's head was along the median line. XII cranial nerve – tongue was in the middle, there were no fibrillations and fasciculations. Reflexes of oral automatism were negative. There were no meningeal signs. Tendon and periosteal reflexes were brisk, D=S, more hyperactive from the lower extremities. Pathological signs from the arms were not detected. There was positive Babinsky reflex from both legs. Abdominal reflexes were decreased, there were feet clonuses. Muscle strength of the upper extremities was sufficient, and it was of 3 points in the right lower extremity and of 4 points from the left side. Deep conductive sensation was abnormal (vibration sensation

on her right foot lasted 4 sec, and on the left one - 6-7 sec, on the right hand it was 7-8 sec, and on the left one – prolonged up to 9-10 sec). Exteroceptive sensation was normal. The female patient produced wobble with negative Romberg's sign. Coordination tests were performed with ataxia, diminished from the lower extremities. There were gait changes of the paretic type.Pelvic organs functions were normal. No cognitive disorders were identified while neuropsychological testing.

The patient was examined according to medical and economic standards, including blood and urine tests, blood biochemistry, HIV antibodies, HBs and HCV antigens, microprecipitation reaction with cardiolipin antigen. All the tests were within the reference values. Lumbar puncture was performed with microscopic, biochemical, microbiological examination of cerebrospinal fluid, paired blood serum and cerebrospinal fluid to reveal oligoclonal IgG, resulted in synthesis I type, which is not characteristic for autoimmune inflammatory process in the CNS. Infectious CNS lesion was also excluded. The patient underwent MRI of the cervical spine which revealed symmetrical increase of MR signal from the dorsolateral and posterior parts of the spinal cord and local expansion of the central channel of the spinal cord. Based on the above mentioned data, case history and neurological status as well, the diagnosis was changed to leukoencephalopathy with predominant lesions of the brain stem, spinal cord and increase of serum lactate in accordance with diagnostic criteria.

In October 2019 the patient gave the result of DARS2 gene analysis by means of direct automatic sequencing at the "Medical Genetics Research Center named after Academician N.P. Bochkov". The analysis of exons 3 and 5 as well as the adjacent intron sites revealed the sequences described in the databases that confirmed the diagnosis. The female patient was recommended to repeat neurometabolic treatment courses, to do physical exercises to maintain her physical activity and intellectual and mental functions and an examination of sibs as well.

Discussion

Key diagnostic features of LBSL are the focal or confluent MR signal changes (of low intensity on T1 and of high intense on T2-weighted images) in the brain white matter, including subcortical spaces, in the posterior funicles of the spinal cord, either in the lateral corticospinal tracts or in the medullar pyramids and at the chiasm of the medullar median loop. It is sufficient to detect these changes at the cervical level of the spinal cord [12, 15, 19]. T1 MRI, or T1-weighted MRI, provides images with the contrast that is derived from the longitudinal time of relaxation of the explored brain tissue. The shorter the relaxation time is, the brighter the resulting images. This image weighting is useful for assessing the cerebral cortex. T2 MRI, or T2-weighted MRI, provides images with the contrast based on the T2, or transverse relaxation time of the soft tissue being explored. Resulting images would appear brighter in case of longer transverse relaxation. T2-weighted image is useful for detecting edema and inflammation, revealing white matter lesions.

Additional criteria are the following: MR signal changes (of low intensity on T1 and of high intense on T2-weighted images) in the corpus callosum, in the posterior femur of the internal capsule, in the superior and inferior cerebellar pedunculi, in the nucleus of the midbrain pathway of trigeminal nerve, in the anterior spinocerebellar medullar tract and in the white cerebellar matter. The diagnosis is considered probable if there are all the main criteria and one additional sign of another disease, which had our female patient [5, 10, 17-19]. In most of patients MR spectroscopy reveals an increase of lactate in their altered white matter however this criteria is non-specific. Therefore this examination was not carried out in our patient. LBSL is diagnosed reliable after detection of typical MRI pattern and in case of DARS2 gene biallelic mutation. Our female patient was recommended to make DARS2 gene mutation test then to come to see a consulting neurologist at out-patients department for treatment of demyelinating and neurodegenerative diseases.

Diagnosis and differential diagnosis of LBSL is a hard task. Standard laboratory tests including cerebrospinal fluid reveal as a rule no deviations out of normal ranges. In contrast to other mitochondrial diseases, muscle tissue biopsy and morphologic assessment of myocytes, fibroblasts and lymphoblasts do not show any signs of mitochondrial dysfunction [1, 18, 19]. Hence the brain MRI may be considered as the key diagnostic method that precedes more complex molecular genetic testing.

This clinical case demonstrates the importance of correct interpretation of patient’s complaints, anamnesis, general examination results and MRI data in order to avoid diagnostic errors and to administer proper treatment and rehabilitation. Differential diagnosis of LBSL is carried out from various pathologies of the nervous system occurring white matter lesions, for example leukodystrophy and inflammatory nervous system diseases as well. The onset of LBSL may appear after infection and it may have undulating course. Therefore differential diagnosis should be carried out with acute disseminated encephalomyelitis, the foci of demyelination in the latter one are located asymmetrically on MRI, with

predominant lesion of subcortical areas and relatively intact periventricular white matter. These foci have indistinctly delimited edges of the lesion and accumulate contrast substance.

In pseudotumorous case of multiple sclerosis contrast-positive foci of demyelination are visualized with pronounced perifocal edema. The combination of ataxia and above mentioned lesions in brain white matter, in the posterior funicles, in the area of the lateral corticospinal pathways may occur in case of B_{12}-deficiency but the main changes in the latter case occur in the spinal cord. Hypomyelination involving the spinal cord and brain stem, spasticity in the patient's legs may mimic multiple sclerosis. Multiple sclerosis is the first common diagnosis in these patients and it leads to corticosteroid treatment and administration of disease-modifying medication. In case of LBSL lesion areas do not accumulate contrast substance, there is no intrathecal synthesis of oligoclonal antibodies, and there is no optic nerve lesion. These findings corresponded to the examination data of our female patient [1, 6, 19].

Unfortunately there is no etiotropic treatment for LBSL up to date. The patients are given usually nonspecific treatment: metabolic and nootropic medications, physical exercises and physiotherapy (to prevent contractures), anticonvulsant drugs in case of seizures, and psychological assistance as well.

Conclusion

1. It is necessary to analyze carefully the clinical picture and additional examinations data in order to build a proper diagnostic algorithm and to avoid any diagnostic errors, since the patients with hereditary leukodystrophy with late onset particularly LBSL may simulate the signs of common neurological diseases.
2. Comprehensive analysis of the clinical picture and genetic mapping together with MRI signs allow promptly diagnosis of the relatively rare form of leukodystrophy LBSL with onset in adulthood.

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