Adult-Onset Leukoencephalopathy with Brain Stem and Spinal Cord Involvement and Normal Lactate: Case Report

Erişkin Başlangıçlı Beyin Sapı ve Medulla Spinalis Tutulumu ve Normal Laktat ile Seyreden Lökoensefalopati: Olgu Sunumu

Özdem Ertürk[1], Cengiz Yalçınkaya[1], Aksel Siva[1], Marjo S van der Knaap[2]

[1]İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi, Nöroloji Anabilim Dalı, İstanbul, Türkiye
[2]VU Üniversitesi Tıp Merkezi, Çocuk Nörolojisi Bölümü, Amsterdam, Hollanda

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ÖZET

Beyin sapı ve medulla spinalis tutulumu ve laktat yüksekliği ile seyreden lökoensefalopati (LBSL); altta yatan genetik defektin belirlenmiş olduğu yeni tanımlanmış bir lökoensefalopati tablosudur. Klinik özelliği yavaş progresif piramidal, serebellar ve arka kordon disfonksiyonu bulgularıdır. Hastalık sıklıkla çocukluk döneminde başlamakla beraber nadir olarak erişkin başlangıçlı olgular da bildirilmiştir. Hastalık ile ilişkili olarak mitokondriyal tRNA sentetazı kodlayan *DARS2* geninde mutasyon yeni tanımlanmıştır. Hastalığın manyetik rezonans görütüleme bulguları spesifiktir, nonhomojen serebral ak madde tutulumu ile birlikte, selektif beyin sapı ve medulla spinalis traktuslarının tutulumu tanı koydurucudur. Manyetik rezonans spektroskopi (MRS)'de laktat piki sık görülmekle beraber laktat yüksekliği saptanmayan olgular da bildirilmiştir. Burada MRS'de laktat piki göstermeyen, genetik tanısı teyit edilmiş erişkin bir LBSL hastasının klinik ve radyolojik özellikleri tartışılmıştır.

Anahtar Kelimeler: Lökoensefalopati, laktik asit.

ABSTRACT

Adult-Onset Leukoencephalopathy with Brain Stem and Spinal Cord Involvement and Normal Lactate: Case Report

Özdem Ertürk[1], Cengiz Yalçınkaya[1], Aksel Siva[1], Marjo S van der Knaap[2]

[1]Department of Neurology, Faculty of Cerrahpasa Medicine, University of Istanbul, Istanbul, Turkey
[2]Department of Child Neurology, VU University Medical Center, Amsterdam, The Netherlands

Leukoencephalopathy with brain stem and spinal cord involvement and high lactate (LBSL) is a recently described leukoencephalopathy with a genetically proven underlying defect. Clinical features are slowly progressive pyramidal, cerebellar and dorsal column dysfunction with childhood or rarely adult onset. The genetic basis of the disease was recently identified, which concerned mutations in the DARS2 gene encoding mitochondrial aspartly-tRNA synthetase. The disease has distinct magnetic resonance imaging findings including inhomogeneous cerebral white matter abnormalities and selective brain stem and spinal cord tract involvement. Additionally, there are usually increased lactate levels on magnetic resonance spectroscopy (MRS) of the abnormal white matter. In this case report, we describe the clinical and radiological features of a patient with genetically proven adult-onset LBSL and normal lactate levels on MRS.

Key Words: Leukoencephalopathy, lactic acid.

INTRODUCTION

Leukoencephalopathy with brain stem and spinal cord involvement and high lactate (LBSL) is a recently described leukoencephalopathy with distinct magnetic resonance imaging (MRI) findings; the underlying defect has been proven genetically (1,2). MRI shows inhomogeneous cerebral white matter abnormalities with selective brain stem and spinal cord tract involvement. Additionally, there are usually increased lactate levels on magnetic resonance spectroscopy (MRS) (1). Clinical features consist of pyramidal, cerebellar and dorsal column dysfunction with childhood or, rarely, adult onset, and a slowly progressive course.

We describe the clinical and radiological features of a patient with adult-onset LBSL and normal lactate levels on MRS.

CASE

A 32-year-old female patient had a two-year history of weakness in both legs with gait difficulty and postural instability. The symptoms had started two years ago, settled in a month and were slowly progressive thereafter. Her family history was unremarkable for any disease and there were no consanguinity in the family. Her medical history revealed that she had a single seizure precipitated by fever at the age of two years, after which a temporary mild paresis developed in her right leg. Neurological examination at age 32 revealed a congenital convergent strabismus, prominent weakness of the legs and increased tendon reflexes. Vibration sense was diminished in the legs. She had a sensorial-paretic ataxic gait.

Laboratory studies including complete blood count, liver and kidney function tests, glucose, vitamin B_{12}, folic acid, electrolytes, cholesterol levels, and thyroid function tests were all normal. Nerve conduction studies were normal.

Cranial MRI showed multifocal abnormalities in the cerebral white matter, mainly with a periventricular location, which were hyperintense on T2-weighted images and hypointense on T1-weighted images. In the brain stem, there were also signal abnormalities in the superior cerebellar peduncles, the interparenchymal part of the trigeminal nerve, the medial lemniscus, the pyramidal tracts, and the inferior cerebellar peduncles. There were subcortical cerebellar white matter abnormalities. The sections through the upper part of the spinal cord showed signal abnormalities in the dorsal columns and the lateral corticospinal tracts, continuing over the entire part of the spinal cord visualized. There was no gadolinium enhancement in any of the lesions. The multivoxel MRS (TE 144 msec) of the cerebellar white matter lesions revealed increased choline and creatine and decreased N-acetylaspartate levels. There was no evidence of lactate elevation (Figure 1).

Sequencing of the *DARS2* gene revealed that the patient was compound-heterozygous for the following mutations: c.228-20_-21delTTinsC/p.Arg76SerfsX5 and c.397-2A>G/p.Met134-Lys165del.

DISCUSSION

Leukoencephalopathy with brain stem and spinal cord involvement and high lactate (LBSL) was first described in 2003 with the distinct MRI findings (1). These included inhomogeneous and variable cerebral white matter abnormalities and involvement of the splenium of the corpus callosum. The pyramidal tracts were affected over their entire length, including the posterior limb of the internal capsule, pyramidal tracts in the brain stem and the lateral corticospinal tracts in the spinal cord. The sensory tracts were also affected over their entire extent, from dorsal columns in the spinal cord, the medial lemniscus in the brain stem up to the thalamus, and to the corona radiata above the level of the thalamus. Other affected structures were the superior and inferior cerebellar peduncles, intraparenchymal trajectories of the trigeminal nerve and mesencephalic trigeminal tracts (1,3). The patient described in this paper had the diagnostic MRI pattern of the disease. Even though the supratentorial lesion may be confused with multiple sclerosis, the characteristic involvement of the brain stem and spinal cord excludes such confusion. This MRI pattern is different from patterns in both classic and recently defined leukoencephalopathies. It does not resemble the pattern of pontocerebellar atrophy observed in the familial spinocerebellar ataxias or the white matter changes observed in some hereditary spastic paraparesis syndromes (1). MRS findings, including decreased N-acetylaspartate and increased choline, favor axonal degeneration and secondary myelin loss, respectively (1). Increased lactate levels were found in nearly all cases in the first description of the disease (1).

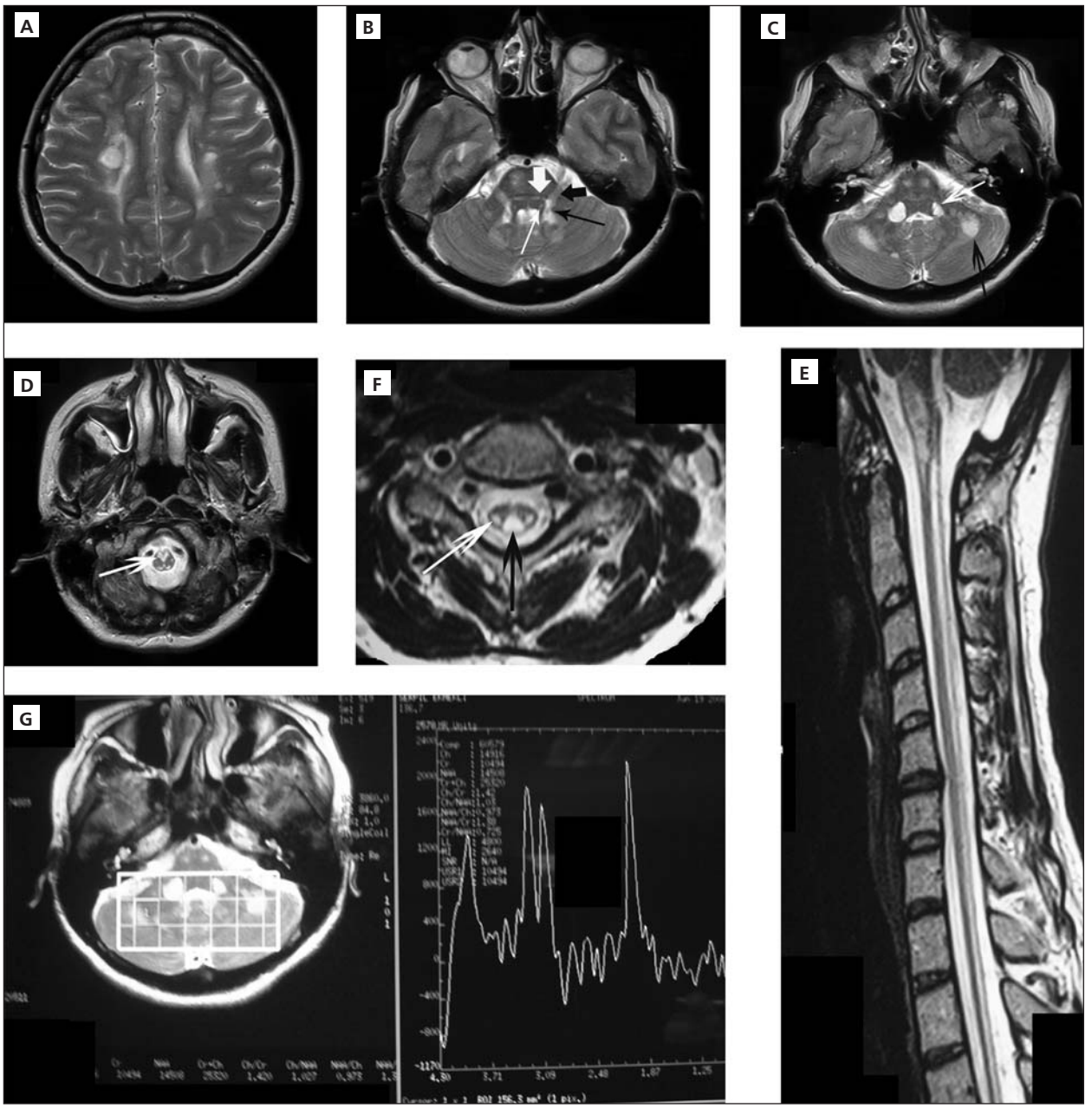

Figure 1. Axial T2-weighted **(TR 3440, TE 98)** cranial MRI showing multifocal hyperintense signals in the periventricular cerebral white matter **(A)**. In the brain stem, hyperintense signal abnormalities are seen in the intraparenchymal part of the trigeminal nerve (thick black arrow), superior cerebellar peduncles (thin black arrow), medial lemniscus (thick white arrow), mesencephalic trigeminal tracts (thin white arrow) **(B)**, and inferior cerebellar peduncles (white arrow) and cerebellar white matter (black arrow) **(C)**. There are T2-hyperintense signal abnormalities in the decussatio of the medial lemniscus and the pyramids **(D)**. The spinal cord T2-weighted **(TR 3130, TE 104)** sagittal image shows hyperintense signal in the dorsal part of the cervical spinal cord **(E)** and T2-weighted axial image **(TR 2540, TE 92)** through the high part of the cervical spinal cord shows hyperintense signal abnormalities in the dorsal columns (black arrow) and the lateral corticospinal tracts (white arrow) **(F)**. MRS of the cerebellar white matter shows increased choline and creatine and decreased N-acetylaspartate levels. There was no evidence of lactate elevation **(G)**.

The underlying pathology was better understood after the genetic basis of the disease was identified, which concerned an enzyme defect playing a role in mitochondrial protein synthesis (2). LBSL was found to be related to mutations in the *DARS2* gene, encoding mitochondrial aspartyl-tRNA synthetase (2). This enzyme is responsible for

the incorporation of aspartic acid into mitochondrial DNA-encoded proteins. Surprisingly, despite this finding, the measured complex activities were found to be normal in all available cell types of LBSL patients. It was speculated that the selective vulnerability of the brain could be explained by the high expression of mitochondrial tRNA in the brain (2).

The findings of the neurological examination in our patient indicated pyramidal, cerebellar and dorsal column dysfunction. This constellation of clinical findings is consistent with the previously described clinical features of LBSL. In the initial description of the disease, the motor deterioration of the patients was reported to have an onset in childhood or adolescence (1). Subsequent case reports supported this observation (4-6). However, more recently, a few cases were reported with later onset of clinical signs (7,8). Our case report also supports the observation that the disease may have an adult onset.

The MRI findings in our patient were diagnostic, but MRS did not show lactate elevation in the affected cerebral white matter. A few clinico-radiological LBSL cases with genetic confirmation have been reported before with normal or inconstant lactate levels (7,8). The reason why lactate is not always present is not yet known.

With this new case report of LBSL, we wish to emphasize that the disease has a distinct clinical presentation, may have an adult onset and that MRS lactate levels may be normal.

REFERENCES

1. *Van der Knaap MS, van der Voorn P, Barkhof F, Van Coster R, Krägeloh-Mann I, Feigenbaum A, et al. A new leukoencephalopathy with brainstem and spinal cord involvement and high lactate. Ann Neurol 2003;53:252-8.*
2. *Scheper GC, van der Klok T, van Andel RJ, van Berkel CG, Sissler M, Smet J, et al. Mitochondrial aspartyl-tRNA synthetase deficiency causes leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation. Nat Genet 2007;39:534-9.*
3. *Schiffmann R, van der Knaap MS. The latest on leukodystrophies. Curr Opin Neurol 2004;17:187-92.*
4. *Linnankivi T, Lundbom N, Autti T, Häkkinen AM, Koillinen H, Kuusi T, et al. Five new cases of a recently described leukoencephalopathy with high brain lactate. Neurology 2004;63:688-92.*
5. *Serkov SV, Pronin IN, Bykova OV, Maslova OI, Arutyunov NV, Muravina TI, et al. Five patients with a recently described novel leukoencephalopathy with brainstem and spinal cord involvement and elevated lactate. Neuropediatrics 2004;35:1-5.*
6. *Uluc K, Baskan O, Yildirim KA, Ozsahin S, Koseoglu M, Isak B, et al. Leukoencephalopathy with brain stem and spinal cord involvement and high lactate: a genetically proven case with distinct MRI findings. J Neurol Sci 2008;273:118-22.*
7. *Labauge P, Roullet E, Boespflug-Tanguy O, Nicoli F, Le Fur Y, Cozzone PJ, et al. Familial, adult onset form of leukoencephalopathy with brain stem and spinal cord involvement: inconstant high brain lactate and very slow disease progression. Eur Neurol 2007;58:59-61.*
8. *Petzold GC, Bohner G, Klingebiel R, Amberger N, van der Knaap MS, Zschenderlein R. Adult onset leucoencephalopathy with brain stem and spinal cord involvement and normal lactate. J Neurol Neurosurg Psychiatry 2006;77:889-91.*

Yazışma Adresi/Address for Correspondence

Asistan Dr. Özdem Ertürk

İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi
Nöroloji Anabilim Dalı 34098
Fatih, İstanbul/Türkiye

E-posta: ozdemerturk@yahoo.com

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