CASE REPORT

Leucoencephalopathy with brain stem and spinal cord involvement and lactate elevation: a novel mutation in the DARS2 gene

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SUMMARY

Leucoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) is a very rare autosomal recessive, slowly progressive neurological disorder characterised by distinctive clinical findings including cerebellar, pyramidal and dorsal column dysfunction. This is caused by a mutation in the DARS2 gene, which encodes mitochondrial aspartyl-tRNA synthetase. MRI shows distinctive abnormalities in the cerebral white matter and specific brain stem and spinal cord tracts. Here, we present a case of LBSL, with a novel c.1192-2A>G mutation.

BACKGROUND

Leucoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) is a very rare recently identified progressive neurological disorder that follows an autosomal recessive pattern. The clinical spectrum of this disease entity is variable, and the diagnosis is based on atypical history and examination findings in a patient with progressive or inherited neuropathy, walking difficulties and characteristic MRI findings. Only a very few cases have been reported on the review of literature, and here we would like to report a novel mutation in DARS2 gene that has never been described before to the best of our knowledge.

CASE PRESENTATION

A 49-year-old man presented to the neurology clinic. He carried diagnoses of Charcot Marie Tooth (CMT) disease, syringomyelia and leucodystrophy of unknown cause. He had a normal birth and developmental history until the age of 3 when he started to trip and fall frequently and later developed bilateral foot drop. His symptoms slowly progressed to the point where he became a wheelchair user at 18 years of age. He had a history of car accident at age 31 with a neck injury. Family history was negative for leucodystrophy except for his sister who also had similar problems, which started with foot drop at age 8 and left her as wheelchair user.

On examination, he was alert and oriented to time, place and person. Language was fluent. On cranial nerve examination, visual fields were full to confrontation, extraocular movement testing showed reduced adduction of the right eye. He also had right eye exotropia. Other cranial nerve examination was unremarkable. On motor examination, upper extremity strength was 4/5 in deltoids, 5/5 in biceps and triceps, 4/5 on wrist extension, 0/5 in first dorsal interosseous and abductor pollicis brevis with preserved flexor pollicis longus strength. Lower extremity strength was 0/5 on hip abduction and adduction, 1/5 in hamstrings and quadriceps, 0/5 in tibialis anterior and on toe extension. Muscle tone was normal with absent deep tendon reflexes throughout. Bilateral finger contractures and claw hands with severe thenar, hypothenar and intrinsic hand muscles atrophy were seen. Distal lower extremity muscles were also atrophied. Sensory examination revealed decreased pinprick sensation in a grading fashion bilaterally in legs and the arms. He also had absent vibration sensation in both legs below the knees. Proprioception was normal. Gait was not tested because he was a wheelchair user. Neuropsychological testing did not reveal any cognitive decline.

Blood chemistry, serum ammonia, creatine kinase, vitamin B_{12}, folate, thyroid function tests, lactate, pyruvate, copper, ceruloplasmin, leucocyte arylsulfatase A, peroxisomal panel with phytanic acid, peripheral blood smear for acanthocytes, lipid profile to rule out abetalipoproteinaemia and antinuclear antibodies were all unremarkable. A multigene panel including SMN1 gene, PMP 22 gene, SCA 1,2,3,6,7, frataxin gene, mitofusin gene and CMT1B DNA tests was all negative.

Prior brain MRI, nerve conduction studies (NCS), electromyography (EMG) and muscle biopsy results were obtained. Brain MRI showed bilateral periventricular patchy T2 white matter hyperintensities. NCS showed normal upper and lower limb sensory responses, absent peroneal and tibial compound muscle action potentials (CMAPs), small ulnar and normal median CMAPs. EMG showed poor activation of small polyphasic motor units. No definitive diagnosis was made based on these results. Muscle biopsy for suspected inherited neuropathies showed chronic and ongoing denervation along with differential fascicular loss of several large axons within myelin sheaths on nerve biopsy. Syringomyelia was diagnosed based on cervical and thoracic MRI, which showed hyperintensity lesions extending from C2 to T7 spine.

Because his clinical presentation was atypical for CMT given abnormal eye movements, prominent motor changes and previous abnormal imaging, further workup was ordered. NCS showed severe

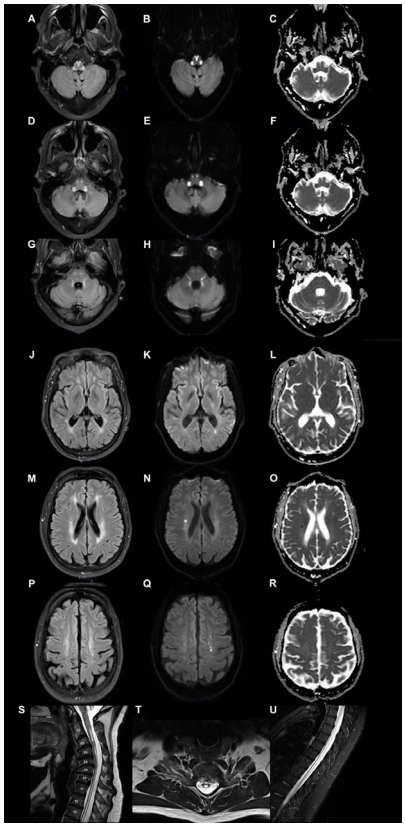

Figure 1 Axial section of the brain at the level of lower medulla shows signal abnormalities in the decussation of medial lemniscus and bilateral spinocerebellar tract on T2 fluid-attenuated inversion recovery (FLAIR) sequence (A). Diffusion restriction in image (B) with corresponding apparent diffusion coefficient in image (C). Axial section of the brain at the level of upper medulla shows signal abnormalities in the decussation of medial lemniscus, bilateral spinocerebellar tract and inferior cerebellar peduncle on T2 FLAIR sequence (D). Diffusion restriction in image (E) with corresponding apparent diffusion coefficient in image (F). Axial section of the brain at the level of lower pons shows signal abnormalities in the superior cerebellar peduncles, intraparenchymal trajectories of the trigeminal nerves and medial lemniscus on T2 FLAIR sequence (G). Hyperintensity in superior cerebellar peduncles and medial lemniscus in image (H) with no corresponding apparent diffusion coefficient in image (F). Axial section of the brain at the level of thalamus shows signal abnormalities in the juxtraventricular area around the body of lateral ventricle more significantly on left when compared with right (J). A punctate focus of diffusion restriction was noted near the body of the left lateral ventricle (K) with corresponding apparent diffusion coefficient in image (L). Axial section of the brain at the level of centrum semiovale shows signal abnormalities in the juxtraventricular, deep white matter area around the lateral ventricle (M). A punctate focus of diffusion restriction was noted near the lateral ventricle on the right side (N) with corresponding apparent diffusion coefficient in image (O). Axial section of the brain at the level of U fibres shows signal abnormalities bilaterally around the frontal horns of lateral ventricle, more significant on left when compared with right (Q). A punctate focus of diffusion restriction was noted near the frontal horns of lateral ventricle on the left side (R) with corresponding apparent diffusion coefficient in image (O). Sagittal section of cervical spine MRI shows T2 hyperintense signal over its entire length but more significant at levels C2 to C4 (S). Axial section of cervical spine shows signal abnormalities in the dorsal column and lateral corticospinal tract (T). Image (U), a sagittal section of MRI of thoracic spine, shows T2 hyperintense signal over its entire length.

axonal motor more than sensory peripheral neuropathy with no evidence of conduction blocks. MRI of the brain showed bilateral symmetrical T2 hyperintensities involving the supratentorial white matter predominantly in the periventricular region, superior and inferior cerebellar peduncles and the anterior brain stem. In addition, there was confluent diffuse abnormalities of T2 signal of the cervical and thoracic spinal cord involving the dorsal part of the spinal cord, dorsal columns and the lateral corticospinal tracts. Posterior cord hyperintensity which was presumed to be syringomyelia on previous spinal MRI corresponded to the dorsal column involvement as seen in LBSL (figure 1). These imaging findings met the MRI criteria for the diagnosis of LBSL.

Genetic analysis identified two heterozygous variants in DARS2: c.228–15C>A (previously reported in patients with LBSL) and a novel variant c.1192-2A>G that is predicted to be pathogenic.

OUTCOME AND FOLLOW-UP

Patient is a wheelchair user and is following up with a neuromuscular specialist for the conservative management.

DISCUSSION

LBSL was diagnosed based on the clinical symptoms, neuroimaging findings which met the criteria for the disease[1–3] and the presence of a DARS2 mutation.[3]

LBSL is a rare autosomal recessive hereditary disease, characterised by slowly progressive pyramidal and cerebellar dysfunction, often with concomitant dorsal column dysfunction.[2] Most affected patients retain tendon reflexes with spasticity and decreased position and vibration sense predominantly in the lower extremities.[3] However, some patients may have axonal neuropathy leading to a decreased or absent tendon reflexes and distal weakness along with sensory loss as seen in our patient.[2 4–6] It is also possible that the novel mutation in our patient is probably associated with a phenotype with less prominent pyramidal signs. LBSL predominantly involves lower more than upper extremities. The age of onset is usually in the childhood or adolescence. Neonatal or early infantile onset patients have a severe disease course[1] compared with late infantile and early childhood onset. Many of the patients with LBSL become wheelchair users in the second and third decades.

DARS2 gene encodes a member of class-II aminoacyl-tRNA synthetase family on chromosome 1q25.1. It is a mitochondrial enzyme that specifically aminoacylates aspartyl-tRNA. LBSL is caused by decreased mitochondrial aspartyl-tRNA synthetase enzyme activity, which impedes the addition of aspartic acid to mitochondrial proteins.[7] More than 50 variants in DARS2 are reported as disease causing in Human Gene Mutation Database. These include missense, splicing, nonsense, frameshift and larger deletion variants. In an overview of 60 known DARS2 mutations, it was noted that almost all patients are compound heterozygous, and most (94%) of them had one intron 2 mutation upstream of exon 3.[8] The c.228–21_−20delTTinsC variant is the most common mutation in intron 2 upstream of exon 3.[7]

LBSL diagnosis is suspected by neuroimaging which shows distinct MRI patterns.[1] The definitive diagnosis of LBSL is established by demonstration of mutations in the DARS2 gene.[7] In our patient, we identified two compound heterozygous variants in DARS2: c.228–15C>A and c.1192-2A>G. The DARS2 c.228-15A variant is located 15 base pairs upstream of splice acceptor site of intron 2. This variant has been previously reported in association with LBSL. Scheper *et al* detected this

variant in a heterozygous state in one patient with this disease.[7] The patient carried a heterozygous p.(Ser45Gly) in the other allele. Analysis of cDNA showed that c.228-15A variant affects splicing of exon 3, leading to frame shift p.(Arg76SerfsX5) and truncation of protein or nonsense-mediated mRNA decay.[7] Steenweg *et al* observed the same variant in a patient with LBSL.[1] It was observed in trans with p.(Leu250Pro) in a boy with disease onset at 11 months of age, with developmental regression, hypotonia, nystagmus and subsequent ataxia, spasticity and language delay. He never achieved walking without support. c.1192-2A>G variant affects a consensus splice site of intron 12, and it most likely leads to abnormal splicing. To our knowledge, this novel variant has never been reported in patients with LBSL.

One study confirmed that LBSL is a slowly progressive disease and has lower mortality.[8] The prognosis of this disease is better than other hereditary leucoencephalopathies, except for cases with infantile onset. Life expectancy may be normal for most of the patients but the great majority become wheelchair dependent. Currently, there is no treatment for this disease. Synofzik *et al* reported a patient with LBSL presenting with exercise-induced paroxysmal gait ataxia and areflexia as an atypical phenotype associated with a novel homozygous DARS2 mutation which showed significant dose-dependent improvement with acetazolamide, a carbonic anhydrase inhibitor.[9] The reason why acetazolamide improved the patient's symptoms is unknown.

Almost all patients with LBSL have a mutation in intron 2 upstream of exon 3, which affects the inclusion of exon 3 in the final product. By increasing exon 3, wild type mtAspRS can be increased[10] which could be an effective treatment strategy. Van berge *et al* identified cantharidin, a compound that is capable of crossing the blood–brain barrier and influence the intron 2/exon 3 splicing event. In this study, cantharidin was able to increase the inclusion of exon 3 in the lymphoblasts from patients with LBSL by inhibiting protein phosphatase 1 or 2A, indicating that protein phosphatase 1 plays an important role in splice site selection.[8 10 11] This splicing process is a promising therapeutic target for patients with LBSL, but cantharidin is toxic for patient use.[12] Research should focus on lesser toxic variants of cantharidin[13] or other protein phosphatase inhibitors.

Learning points

- It is important to consider an MRI of the brain and spinal cord to diagnose leucoencephalopathy with brain stem and spinal cord involvement and lactate elevation (LBSL) especially in patients with atypical Charcot Marie Tooth presentation.
- LBSL is a very rare autosomal recessive hereditary disorder characterised by a very slowly progressive pyramidal, cerebellar and concomitant dorsal column dysfunction.
- It shows a very distinctive neuroimaging findings with involvement of subcortical and deep white matter tracts of the brain, dorsal column and corticospinal tracts of the spinal cord.
- The diagnosis is confirmed by demonstration of mutation in the DARS2 gene and there is currently no available treatment for this disease entity.

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