LETTER TO THE EDITOR

DARS2 gene clinical spectrum: new ideas regarding an underdiagnosed leukoencephalopathy

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Sir,

We have read with great interest the article entitled ‘Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation: clinical and genetic characterization and target for therapy’ in the April issue of Brain (Van Berge et al., 2014). The authors present new data regarding clinical, neuroimaging and genetic findings linked to leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL; MIM #611105), an autosomal recessive inherited leukoencephalopathy caused by compound heterozygous mutations in the DARS2 gene (1q25.1), which codes the mitochondrial aspartyl-tRNA synthetase. LBSL represents one of the typical early-onset leukodystrophies mainly affecting children and juvenile patients with a slow progressive cerebellar ataxia with spastic paraparesis (or sometimes only retained reflexes) and findings suggestive of a posterior cord syndrome (Van der Knaap et al., 2003). Epilepsy, learning disabilities, axonal peripheral neuropathy (Yamashita et al., 2013) and mild cognitive compromise have also been described, although asymptomatic late-onset cases and radiologically diagnosed patients have also been related. Typical neuroimaging pattern is represented by diffuse symmetric non-enhancing inhomogeneous lesions, hyperintense in T2-weighted images and hypointense in T1-weighted images, with preponderant supratentorial periventricular and subcortical cerebellar lesions, sparing U fibres. The lateral corticospinal tracts, the medullary pyramids, the posterior limb of internal capsule, the spinal cord dorsal columns, the medial lemniscos, the intraparenchymal trigeminal pathways, the cerebellar peduncles, the splenium of corpus callosum are also typically involved. The leukodystrophic lesions generally present in magnetic resonance spectroscopy with high lactate peaks (Steenweg et al., 2011), although this finding is not pathognomonic or required to diagnose LBSL (Sharma et al., 2011). High lactate in CSF is rarely found.

The authors made a comprehensive and expanded analysis of clinical features in 66 patients with LBSL (Van Berge et al., 2014). They revealed that only 12% of patients start their disease after the age of 18 years, mainly in females. This group showed a slow progression and most patients presented mild to moderate motor compromise. They also showed cases of early-onset, generally with a severe motor phenotype similar to a previous Japanese study (Miyake et al., 2011), but also a nearly asymptomatic nursing with neuroradiological and molecular diagnosis of LBSL.

Most patients had compound heterozygous mutations. Although classically thought as lethal in humans, homozygosity for a DARS2 mutation was described in this study in severe early-onset cases, and also in a previous study of a 25-year-old German female with a paroxysmal recurrent exercise-induced gait ataxia (Synofzik et al., 2011). Evaluation also disclosed mild distal position and vibration sense deficits, hyper-reflexia and mild spasticity. Neuroimaging changes resembled those typical of LBSL and laboratory evaluation showing intermittent increases in serum lactate. This patient also presented with an acetazolamide-responsive episodic ataxia phenotype, resembling the clinical phenotype of classical autosomal dominant episodic ataxias.

Taking into account all the previous literature data and findings of this new study, we propose the use of a new descriptive
nomenclature more related to the mutated gene, so-called the ‘DARS2-related conditions’ or ‘DARS2-related spectrum disorders’. We believe that the use of this broader nomenclature may represent properly the clinical and neuroimaging findings of patients with different mutations from a single gene. This approach may also contribute to enrich our knowledge regarding LBSL pathogenesis.

The authors also started a new therapeutic approach using direct antisense oligonucleotide cantharidin, an important splicing modulator, affecting the intron 2/exon 3 event splicing, the most commonly affected in LBSL. Despite promising results, we propose new therapeutic approaches regarding the use of acetazolamide and other carbonic anhydrase partial inhibitors for patients who present with typical LBSL phenotype or with DARS2 mutations similarly to the episodic ataxia phenotype previously described (Synofzik et al., 2011).

References


