Acetazolamide-responsive exercise-induced episodic ataxia associated with a novel homozygous DARS2 mutation

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ABSTRACT

Background Leukoencephalopathy with brain stem and spinal cord involvement and brain lactate elevation (LBSL) was recently shown to be caused by mutations in the DARS2 gene, encoding a mitochondrial aspartyl-tRNA synthetase. So far, affected individuals were invariably compound heterozygous for two mutations in DARS2, and drug treatments have remained elusive.

Methods Prospective 2-year follow-up of the natural history of the main presenting symptoms in a homozygous DARS2 mutation carrier, followed by a 60 day treatment with acetazolamide in two different doses and with two random treatment interruptions.

Results The patient presented with exercise-induced paroxysmal gait ataxia and areflexia as an atypical phenotype associated with a novel homozygous DARS2 mutation. These features showed an excellent dose-dependent, sustained treatment response to a carbonic anhydrase inhibitor. Pathogenic mutations in episodic ataxia genes were excluded, thus making it highly unlikely that this phenotype was because of episodic ataxia as a second disorder besides LBSL.

Conclusions This case demonstrates that DARS2 mutation homozygosity is not lethal, as suggested earlier, but compatible with a rather benign disease course. More importantly, it extends the phenotypic spectrum of LBSL and reveals that at least some DARS2-associated phenotypic features might be readily treatable. However, future observations of paroxysmal ataxia and, possibly, areflexia in other DARS2-mutated patients are warranted to further corroborate our finding that DARS2 mutations can lead to a paroxysmal ataxia phenotype.
homozygous mutation c.1825 C>T p.R609W in exon 17. This mutation leads to an amino acid exchange (arginine by tryptophane) at position 609, which is highly conserved in mammals (for conservation data, see supplementary figure 1) and which is predicted by several software tools (PolyPhen, SIFT and AGVGD) to induce a pathogenic dysfunction of the DARS2 protein. The mutation was not found in 338 ethnically matched control chromosomes, as assessed by restriction fragment length polymorphism analysis using the restriction enzyme *MspI*. Testing of parents demonstrated that both mutations are located in *trans*. No mutations were found in genes typically presenting with episodic ataxia, namely KCNA1 (episodic ataxia type 1),

**Figure 1** MRI images and treatment response to acetazolamide (AZ) (A–E). In line with core findings in previous LBSL patients,2  4  5 T2-weighted axial images of the brain (A,B,E) and axial (C, cervical level) and sagittal (D) images of the spinal cord show characteristic signal abnormalities. T2 hyperintense signals are detected bilaterally in the cerebellar white matter (A) and in the periventricular and deep cerebral white matter (E, fluid-attenuated inversion-recovery). At the level of the pons (B), the intraparenchymal part of the trigeminal nerve (arrow), the white matter around the dentate nuclei (arrowhead) and the pyramidal tracts (asterisk) are involved. Within the spinal cord, the dorsal columns (C, arrowhead; D, arrows) are selectively affected along their entire length. Proton MR spectroscopy (F) of the affected cerebellar white matter demonstrated increased lactate levels (arrow) and decreased *N*-acetylaspartate (NAA) levels. (G) AZ treatment was started after a 4-week baseline phase, along with a prospective assessment of the frequency and duration of episodic ataxia and drug adverse effects by means of a standardised daily protocol. Compared with baseline and 2 accidental intermittent periods without AZ, the daily frequency of exercise-induced episodic ataxia was largely reduced during AZ treatment, with larger reductions on 250 mg twice daily compared to 125 mg twice daily.
CACNA1A (episodic ataxia type 2) and SLC1A3 (episodic ataxia type 6).

Because of the episodic character of symptoms, a probatory treatment with acetazolamide (AZ) was started. Compared with a 4-week baseline phase, a dosage of 250 mg twice daily reduced the daily frequency of episodic ataxia from a mean value of 13 to 0.5 per day (figure 1). A reduced dosage of 125 mg twice daily, which was started after typical AZ adverse effects such as parageusia, increased urination and paraesthesias, yielded a smaller but still remarkable decrease in the frequency of episodic ataxia (mean 3.4 per day). The patient twice accidentally ran out of pills for 3 days, each time leading to a strong increase in ataxia frequency (mean 10.3 per day both times; figure 1). Twelve months later, the patient was still benefiting from a daily dosage of 125 mg twice daily, with a mean of two to three episodes of ataxia per day (data not shown).

DISCUSSION
Previous reports hypothesised that homozygous DARS2 mutations might not be compatible with life or manifest as a different phenotype. In this study, we show that a homozygous state can, in fact, present with a rather mild disease course, starting not before adulthood and without permanent gait insufficiency. Thus, the main symptom in our patient is episodic, exercise-induced paroxysmal ataxia and areflexia might be presenting features, thus extending the phenotypic spectrum of LBSL. Although we cannot ultimately exclude the possibility that the patient was actually experiencing two separate disorders, namely episodic ataxia and LBSL, this possibility seems highly unlikely. First, the likelihood of harbouring pathogenic mutations for two distinct genetic disorders is very small, given the rarity of both disorders. Second, we found no mutation by screening the known ataxia genes. Third, ataxia and spasticity are key features of LBSL, this possibility seems highly unlikely. First, the episodic character of symptoms, a probatory treatment with acetazolamide (AZ) was started. Compared with a 4-week baseline phase, a dosage of 250 mg twice daily reduced the daily frequency of episodic ataxia from a mean value of 13 to 0.5 per day (figure 1). A reduced dosage of 125 mg twice daily, which was started after typical AZ adverse effects such as parageusia, increased urination and paraesthesias, yielded a smaller but still remarkable decrease in the frequency of episodic ataxia (mean 3.4 per day). The patient twice accidentally ran out of pills for 3 days, each time leading to a strong increase in ataxia frequency (mean 10.3 per day both times; figure 1). Twelve months later, the patient was still benefiting from a daily dosage of 125 mg twice daily, with a mean of two to three episodes of ataxia per day (data not shown).

REFERENCES