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

Matthis Synofzik,[1,2] Julia Schicks,[1,2] Tobias Lindig,[1,2] Saskia Biskup,[1,2,3] Thorsten Schmidt,[4] Jochen Hansel,[5] Frank Lehmann-Horn,[6] Ludger Schöls[1,2]

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[1]Department of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany
[2]German Research Center for Neurodegenerative Diseases (DZNE), University of Tübingen, Tübingen, Germany
[3]CeGaT GmbH, Center for Genomics and Transcriptomics, Tübingen, Germany
[4]Department of Medical Genetics, University of Tübingen, Tübingen, Germany
[5]Department of Sports Medicine, Medical Clinic and Policlinic, University of Tübingen, Tübingen, Germany
[6]Division of Neurophysiology, Ulm University, Ulm, Germany

Correspondence to
Professor Ludger Schöls, Department of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research, Hoppe-Seyler-Strasse 3, University of Tübingen, 72076 Tübingen, Germany; ludger.schoels@uni-tuebingen.de

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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.

Leukoencephalopathy with brain stem and spinal cord involvement and brain lactate elevation (LBSL) is a juvenile to adult-onset disorder presenting with slowly progressive pyramidal, cerebellar and dorsal column dysfunction, often leading to wheelchair dependency before age 30 years.[1] It was recently shown to be caused by mutations in the *DARS2* gene, encoding a mitochondrial aspartyl-tRNA synthetase.[2] So far, affected individuals were invariably compound heterozygous for two mutations in *DARS2*, and drug treatments have remained elusive.[1] We here report on a patient presenting with exercise-induced paroxysmal gait ataxia and areflexia associated with a novel homozygous *DARS2* mutation, demonstrating an excellent treatment response to a carbonic anhydrase inhibitor (CAI).

CASE REPORT

After normal motor and cognitive development, a 25-year-old woman of non-consanguineous German parents presented with a 3-year history of paroxysmal exercise-induced gait ataxia. Depending on her daily activities, this feature occurred up to 5 times a day, usually lasting a few seconds up to 5 min. The duration and intensity of exercise that was required to trigger such episodes varied from walking some stairways to running a few hundred meters. Repeated clinical examination during these episodes revealed remarkable ataxic staggering (without upper limb ataxia or cerebellar oculomotor disturbances) and areflexia of the upper and lower extremities (video 1). At rest, without previous exercise, there is mild distal symmetric decrease in position and vibration sense, mild leg spasticity and hyperreflexia, but no cerebellar ataxia, decreased reflexes or gait spasticity were present (video 1). At interictal intervals, the Scale for the Assessment and Rating of Ataxia[3] scored 2 of 40 points. Two years later, permanent cerebellar ataxia, areflexia and/or any other permanent gait disturbance were still absent (Scale for the Assessment and Rating of Ataxia score still 2/40 points), and the patient was still not experiencing any impairments in daily life beyond the intermittent episodes of gait ataxia (video 2). The frequency of ataxia episodes, however, had increased up to 23 times per day (mean 13 per day).

Serum lactate value was inconsistently mildly elevated at repeated testings performed at different time points in the disease course, varying from 1.2 to 3.7 mmol/l (reference value <2.2 mmol/l), whereas other serum and CSF investigation results (including CSF lactate) were normal. A graduated exercise test indicated a lactate threshold slightly below normal, ranging in the domain of untrained persons. Repeated sensory nerve conduction studies on the sural and radial nerves, motor nerve conduction studies on the tibial and ulnar nerves, tibial somatosensory-evoked potential studies and motor-evoked potential studies yielded normal results. As MRI was compatible with several major and supportive MRI criteria of LBSL, albeit not (yet) fulfilling all of them[2] (figure 1), sequencing of *DARS2* was performed, demonstrating a novel 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 *Msp*I. 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), 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

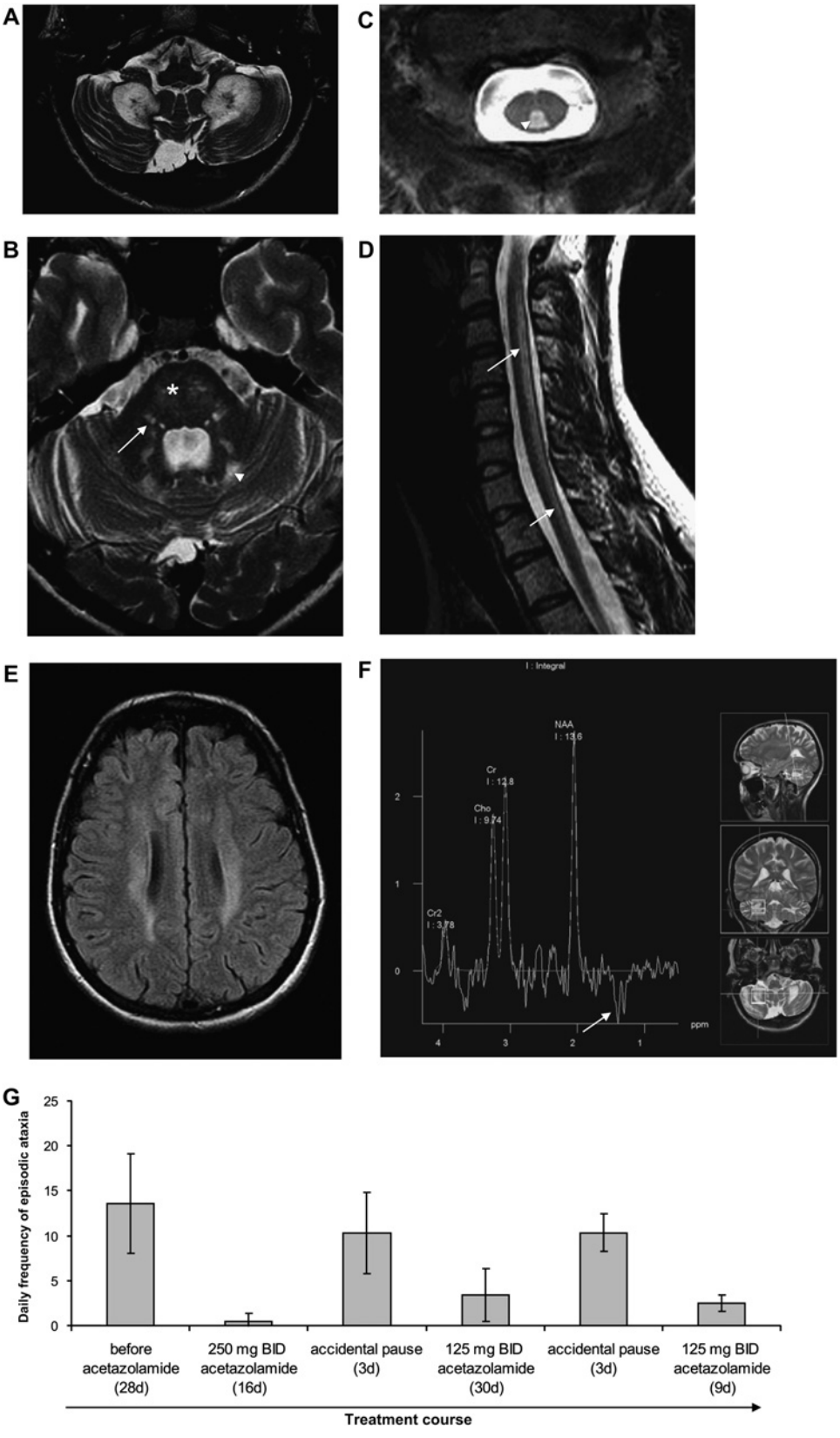

Figure 1 MRI images and treatment response to acetazolamide (AZ) (A–E). In line with core findings in previous LBSL patients,[2 4 5] T2-weighted axial images of the brain (A,B,E) and axial (C, cervical level) and sagittal (D) images of the spinal cord show characteristic signal abnormalities. T2 hyperintense 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.

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 benefitting 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.[2 6] 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 cerebellar ataxia or gait spasticity at age 27 years.

Moreover, our findings demonstrate that 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 episodic ataxia genes. Third, ataxia and spasticity are key features of LBSL.[1 2] Thus, the main symptom in our patient—spastic-ataxic staggering—is not qualitatively different from the well-established LBSL phenotype but differs only with respect to its episodic, exercise-induced nature. Nevertheless, future observations of paroxysmal ataxia and, possibly, areflexia in other *DARS2*-mutated patients are certainly warranted to further corroborate our finding that *DARS2* mutations can lead to a paroxysmal ataxia phenotype.

Although we can only speculate about the mechanism underlying these phenotypic features, the combination of a rapid onset of ataxia and areflexia together with the known disturbances of lactate homeostasis and the excellent treatment response to a CAI might point to a sudden, exercise-induced transient shift of the local pH value in cerebellar and peripheral neurons as a potential cause of their dysfunction. This shift might have been partly stabilised by the CAI: CAIs are suggested to regulate pH homeostasis in episodic ataxias and to regulate transmembrane lactic acid transport via modifying Lac−/H+ cotransport activity.[7 8] Metabolic investigations in future LBSL cohorts are warranted to further explore the exact underlying mechanism of action.

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Competing interests None.

Patient consent Obtained.

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