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

Matthias Synofzik, Julia Schicks, Tobias Lindig, Saskia Biskup, Thorsten Schmidt, Jochen Hansel, Frank Lehmann-Horn, Ludger Schöls

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.

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 oculo-motor 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 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 25 times per day (mean 15 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 (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 substitution Tp.R609W in figure 1) and...
(PolyPhen, SIFT and AGVGD) to induce a pathogenic dysfunction of the DARS2 protein. The mutation was not found in 538 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), 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, 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.
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 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. 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. Metabolic investigations in future LBSL cohorts are warranted to further explore the exact underlying mechanism of action.

Funding

The study was supported by a grant of the German Ministry of Education and Research (BMBF grant DB160838) to the Leukonet (http://www.leukonet.de). FLH is the endowed Senior Research Professor of Neuropsychology sponsored by the Charitable Hertie Foundation.

Competing interests

None.

Provenance and peer review

Not commissioned; externally peer reviewed.

REFERENCES

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

Matthias Synofzik, Julia Schicks, Tobias Lindig, et al.

J Med Genet published online July 11, 2011
doi: 10.1136/jmg.2011.090282

Updated information and services can be found at:
http://jmg.bmj.com/content/early/2011/07/11/jmg.2011.090282.full.html

These include:

References
This article cites 7 articles, 4 of which can be accessed free at:
http://jmg.bmj.com/content/early/2011/07/11/jmg.2011.090282.full.html#ref-list-1

P<P
Published online July 11, 2011 in advance of the print journal.

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections
Genetic screening / counselling (2178 articles)

Notes
Advance online articles have been peer reviewed and accepted for publication but have not yet appeared in the paper journal (edited, typeset versions may be posted when available prior to final publication). Advance online articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Advance online articles must include the digital object identifier (DOIs) and date of initial publication.

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/