The Cerebellum (2019) 18:649–653
https://doi.org/10.1007/s12311-018-0997-3

SHORT REPORT

Acetazolamide-Responsive Episodic Ataxia Linked to Novel Splice Site Variant in *FGF14* Gene

M. Schesny[1] · F. Joncourt[2] · Alexander A. Tarnutzer[1,3]

Published online: 3 January 2019
© Springer Science+Business Media, LLC, part of Springer Nature 2019

Abstract

Here we describe the case of a patient with episodic dizziness and gait imbalance for 7 years and a negative family history. On clinical examination, interictally, the patient presented with gaze-evoked nystagmus and rebound nystagmus and slight dysarthria. MRI of the brain was normal and peripheral-vestibular function was bilaterally intact. Based on genetic testing (episodic ataxia panel), a heterozygote splice site variant in intron 1 of the *FGF14* gene was identified. This report adds important new evidence to previous observations that pathogenic variants in the *FGF14* gene may result in variable phenotypes, either in progressive spinocerebellar ataxia (type 27) or in episodic ataxia as in our case. Our patient responded well to acetazolamide (reduction in the frequency of attacks by about two thirds), supporting the hypothesis of a sodium channelopathy.

Keywords Hereditary ataxia · Channelopathy · Cerebellum · Drug treatment · Haploinsufficiency

Introduction

Whereas hereditary neurodegenerative cerebellar disease is typically associated with persistent and usually slowly progressive cerebellar loss-of-function, a subgroup of patients present with episodic cerebellar complaints, being interictally (almost) symptom-free, referred to as episodic ataxia (EA). Episodic ataxias have been linked to channelopathies and are considered rare with an incidence of less than 1/100,000 [1–3]. While traditionally a clear distinction can be made between EA and progressive heredoataxia (as e.g., spinocerebellar ataxias (SCAs)), the case presented here emphasizes the overlap between these two entities. Specifically, we present a patient with episodic vertigo and dizziness accompanied by persistent mild cerebellar symptoms that was suspected for EA type 2, but eventually received a diagnosis of SCA 27, which is usually associated with progressive cerebellar loss-of-function [4, 5]. Thus, this case resembles the distinct clinical phenotypes associated with mutations in the CACNA1A gene, being either episodic (as in EA 2) or slowly progressive as in SCA 6.

Case Description

Written informed consent was obtained from the patient described in this case report. This right-handed patient aged between 20 and 30 years (exact age and gender not reported upon request of the patient) had initially presented to our clinic 4 years ago with recurring episodes of intense vertigo and dizziness for 3 years. These episodes were triggered by high emotional stress levels, physical activity, certain body positions (e.g., bending forward), and caffeine intake, lasting between few minutes to several hours, usually accompanied by nausea and sometimes resulting in vomiting. The patient denied experiencing dysphagia, diplopia, or clumsiness during these attacks. In-between the attacks, an imbalance of stance and gait being worse on downgaze and lateral gaze and slightly slurred speech was noted by the patient. The patient history was negative for seizure-like episodes or dystonic movements during the vertigo attacks. There was no worsening of symptoms during episodes of fever. The family history was negative for heredoataxias as well as other neurodegenerative disorders. The patient reported delayed motor development, being able to walk freely only around age 24–36 months. The

✉ Alexander A. Tarnutzer
alexander.tarnutzer@access.uzh.ch

[1] Department of Neurology, University Hospital Zurich, Frauenklinikstr. 26, 8091 Zurich, Switzerland

[2] Division of Human Genetics, Department of Pediatrics, University Hospital Berne, Berne, Switzerland

[3] University of Zurich, Zurich, Switzerland

patient had attended regular school and was never suspected to have abnormal intellectual development; thus, we did not order formal neurocognitive testing. Four years ago (before treatment initiation), attacks of episodic vertigo reportedly occurred up to four times per month.

Clinical examination revealed an inability to hold eccentric gaze stable, consistent with horizontal gaze-evoked nystagmus (GEN), followed by rebound nystagmus (RN) when shifting gaze back to primary position after about 10 s of eccentric gaze at approximately 30°. Both GEN and RN had a larger amplitude when looking to the left than when looking to the right. Horizontal and vertical smooth pursuit eye movements were mildly saccadic, while saccades seemed metric, although their evaluation was limited by the GEN. While tandem gait with eyes closed was slightly ataxic, the patient showed no signs of ataxia of limb movements as assessed by finger-to-nose testing, finger-to-finger testing, and heel-shin-knee testing. The horizontal head impulse test and hearing were normal and detailed cranial nerve examination demonstrated no abnormalities except for the ocular motor findings described above and slight dysarthria. A low amplitude, low intensity regular and symmetric positional tremor of the hands was noted. Tendon reflexes were symmetric and within normal range; no increased muscle tone was found.

A contrast-enhanced MRI of the brain demonstrated no signs of cerebellar atrophy and quantitative vestibular testing (including ocular/cervical vestibular-evoked myogenic-potentials (VEMPs), cold-/warm-water caloric irrigation and video head impulse testing of all six semicircular canals) were normal except for bilaterally absent oVEMP responses (most likely related to technical limitations) as shown in Fig. 1.

Based on the clinical presentation with attacks triggered by emotional and physical stress and lasting up to hours, the presence of an interictal nystagmus, and the absence of myokymia, a diagnosis of suspected EA type 2 (EA2) was made, although genetic testing for pathogenic variants in the *CACNA1A* gene was negative. Nonetheless, a treatment trial with acetazolamide (500 mg per day) was started [1], resulting in a marked reduction in the frequency (from approximately four to once per month) and intensity of the vertiginous attacks. Later on, acetazolamide had to be reduced and eventually stopped due to emerging headaches. Medication was switched to chlorzoxazone (1000 mg per day), a small-conductance calcium-activated potassium channel activator, based on reportedly beneficial effects on gait and ocular motor control in a small group of patients with downbeat nystagmus and cerebellar loss-of-function [6], with vertigo attacks continuing to occur at the lower frequency of about once per month. However, chlorzoxazone had to be stopped again due to lack of insurance coverage and episodic vertigo became more frequent and intense again. When chlorzoxazone was prescribed anew about 1 year later, the patient did not notice any improvement any more. Therefore, chlorzoxazone was stopped again after 6 months of intake. In the following, an

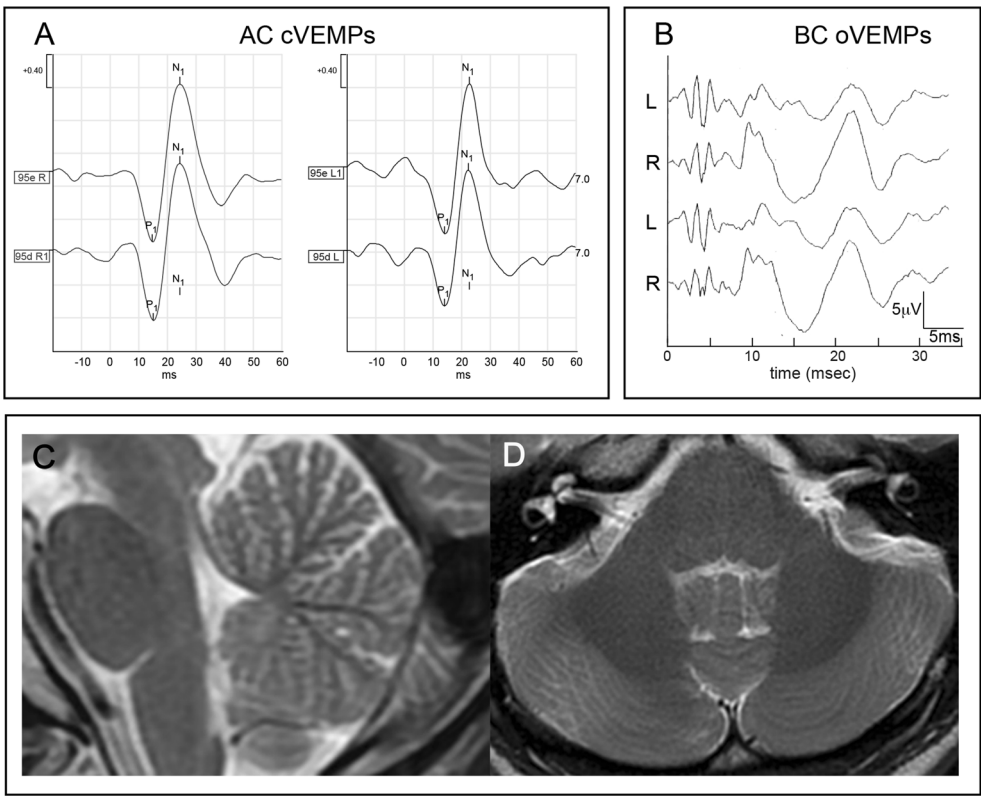

Fig. 1 Otolith functional mapping including air-conducted (AC) cVEMPs (**a** bilaterally normal with an asymmetry ratio of 5% (cut-off ≤ 30%) at 95 dB HL) and bone-conducted (BC) oVEMPs (**b** bilaterally absent). On MR-imaging (T2-weighted sequences) both on sagittal (**c**) and axial (**d**) planes, no signs for cerebellar atrophy could be depicted

episodic ataxia panel was obtained that eventually revealed the diagnosis.

Genetic Testing

A panel of genes known to be associated with episodic ataxias (*CACNA1A*, *CACNA1C*, *CACNB4*, *FGF14*, *KCNA1*, *SLC1A3*, *SLC2A1*) were obtained at the division of human genetics of the University Hospital Berne, Switzerland. Thereby, a heterozygote variant in the *FGF14* gene located at the highly conserved position + 1 of the donor splice site in intron 1 was identified (NM_175929.2 (*FGF14*):c.208 + 1G > A), as illustrated in the sequencing report (Fig. 2). According to ACMG criteria, the variant is considered to be pathogenic [7]. The variant to our knowledge has never been described before in the literature and was not found in population and variant databases (dbSNP150, 1000 Genomes (Phase 3), NHLBI Exome Sequencing Project (ESP, ESP6500SI-V2), Genome Aggregation Database (gnomAD, v.2.0.2), ClinVar, HGMD professional 2018.1). The variant is predicted to interfere with splicing: several in silico analyses all predict a complete inactivation of the donor splice site (SSF 85.71>-, MaxEnt 8.69>-, NNSplice 1.00>-, GeneSplicer 2.28>-).

Discussion

Here we report a novel splice site variant in intron 1 of the *FGF14* gene in a patient presenting with episodic ataxia with mild persistent cerebellar deficits, likely related to haploinsufficiency of the *FGF14* gene rather than protein aggregation [4]. This case further adds support to the previously described varying phenotypes caused by pathogenic variants in the *FGF14* gene [8]. While originally associated with slowly progressive cerebellar ataxia, mental retardation, and tremor and referred to as SCA 27 [4, 9], our case presents a clearly distinct phenotype resembling that of episodic ataxia, while genetic testing for *KCNA1* and *CACNA1A* was negative. Previously, five families with mutations in the *FGF14* gene and an episodic phenotype were reported. In a French Canadian family, a frameshift mutation in exon 2 resulting in a premature stop codon was described, presenting with attacks of unsteady gait, dysarthria, and diplopia lasting about 20 min and mild interictal signs (nystagmus) [10]. In a Dutch family with mild gait and ocular motor impairment and severe deterioration during episodes with high fever, a deletion of the last four exons of the *ITGBL1* (Integrin beta-like protein 1 precursor) gene and of the first four exons of the *FGF14* gene was reported [11]. Similarly, in two twin sisters with ataxia, tremor, dysarthria and learning disorders, and episodic

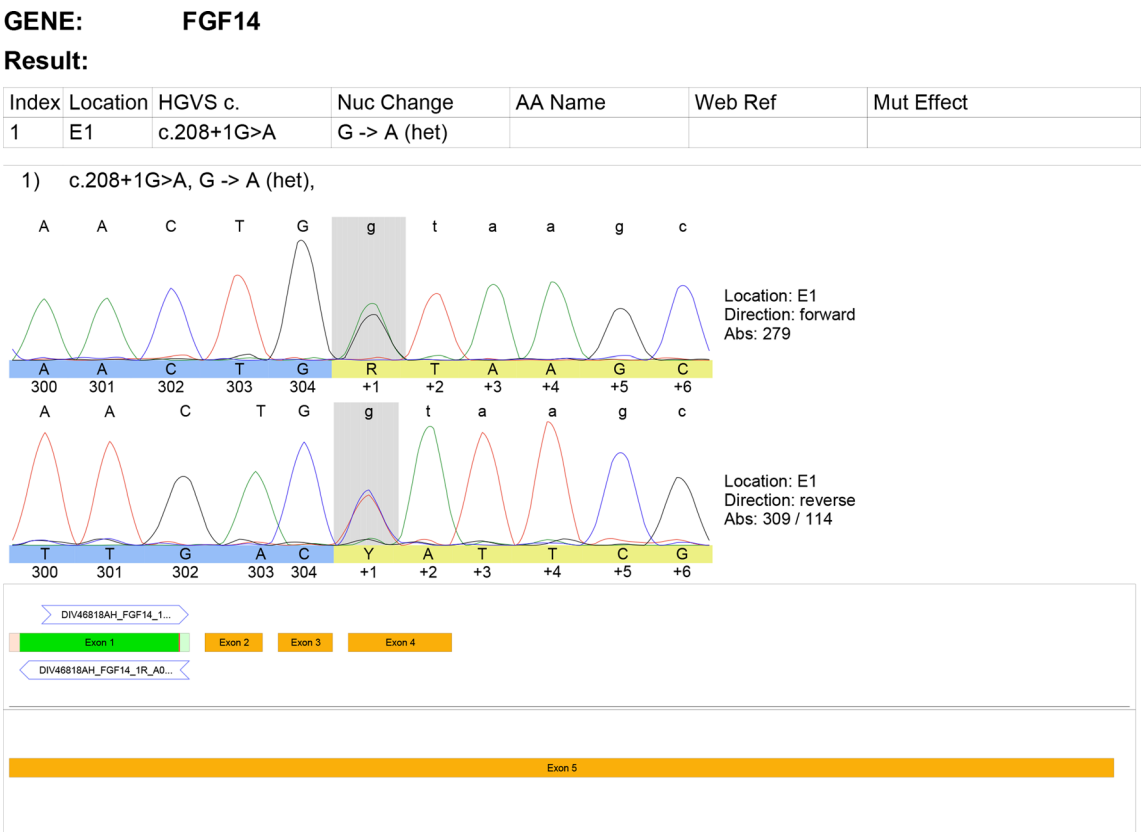

Fig. 2 Sequencing report of the FGF14 gene in our patient

exacerbations triggered by high fever, a large (424 kb) deletion on chromosome 13q33.1 including the *FGF14* gene was found [12]. A possibly pathogenic missense variant (c.31 A > G) in exon 1 of the *FGF14* gene was recently reported in a Korean patient presenting with episodic dizziness and headaches for hours [13]. In another family, a young boy presented with paroxysmal nonkinesigenic dyskinesia that was linked to reciprocal chromosomal translocation between chromosomes 13 and 20, disrupting the *FGF14* gene [14]. In other cases with SCA27 (not presenting with episodic deterioration), a single base pair deletion in exon 4 resulting in a frameshift was found in one out of 208 patients with a familial history of ataxia but exclusion of repeat expansion at the SCA loci [15] and in a daughter and her mother, a disruption of the *FGF14* gene due to translocation between chromosome 5 and 13 was discovered [5].

After the first descriptions of cerebellar ataxia being linked to the *FGF14* gene, patients with suspected SCA were genetically screened for *FGF14* variants. In a large series of 412 index cases with dominantly inherited cerebellar ataxias and no evidence for CAG/polyglutamine expansions in spinocerebellar ataxia genes, a single case with a pathogenic variant in the *FGF14* gene was found [16], suggesting that pathogenic *FGF14* variants are an infrequent cause of hereditary ataxia.

Based on the role of the *FGF14* gene in modulating voltage-gated sodium channels by the intracellular FGF homologous factor encoded [17, 18], drugs affecting the sodium channels seem most promising. Our patient showed a clear reduction in frequency and intensity of the attacks, indicating that acetazolamide should be considered as a treatment option in this new type of episodic ataxia. Treatment response to acetazolamide was also recently reported in a Korean patient with EA and a possibly pathogenic missense variant in the *FGF14* gene [13]. In contrast, the treatment response to chlorzoxazone in our patient was questionable and could not be reproduced later on.

Noteworthy, while we saw the patient several times in-between attacks, we never had the opportunity to perform a clinical examination during an attack; thus, we could not objectively confirm reported ictal symptoms. Whereas on clinical examination, vestibular function was normal, peak head-velocity values on video head impulse testing were borderline or below the target range in up to 25% of trials, and oVEMP responses were bilaterally absent. While also those head impulses with head-velocity values within the target range showed no abnormalities and lack of oVEMP responses is most likely related to technical limitations, we cannot fully exclude minor vestibular impairment in our patient.

Furthermore, no genetic testing in healthy relatives of the patient could be performed and no functional studies were obtained due to limited financial resources; thus, we could not further validate the described mutation.

In conclusion, the case described here adds further support to the notion that pathogenic variants in the *FGF14* gene may result in variable phenotypes, namely in progressive spinocerebellar ataxia (type 27), paroxysmal nonkinesigenic dyskenesia, or in episodic ataxia responsive to acetazolamide [3, 8].

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent The final version of this manuscript has been seen by the patient and written informed consent for publication has been retrieved from the patient.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Jen JC, Graves TD, Hess EJ, Hanna MG, Griggs RC, Baloh RW, et al. Primary episodic ataxias: diagnosis, pathogenesis and treatment. Brain. 2007;130:2484–93. https://doi.org/10.1093/brain/awm126.
2. Choi KD, Choi JH. Episodic Ataxias: Clinical and genetic features. J Mov Disord. 2016;9:129–35. https://doi.org/10.14802/jmd.16028.
3. McGovern EM, Roze E, Counihan TJ. The expanding spectrum of paroxysmal movement disorders: update from clinical features to therapeutics. Curr Opin Neurol. 2018;31:491–7. https://doi.org/10.1097/WCO.0000000000000576.
4. Brusse E, de Koning I, Maat-Kievit A, Oostra BA, Heutink P, van Swieten JC. Spinocerebellar ataxia associated with a mutation in the fibroblast growth factor 14 gene (SCA27): a new phenotype. Mov Disord. 2006;21:396–401. https://doi.org/10.1002/mds.20708.
5. Misceo D, Fannemel M, Baroy T, Roberto R, Tvedt B, Jaeger T, et al. SCA27 caused by a chromosome translocation: further delineation of the phenotype. Neurogenetics. 2009;10:371–4. https://doi.org/10.1007/s10048-009-0197-x.
6. Feil K, Claassen J, Bardins S, Teufel J, Krafczyk S, Schneider E, et al. Effect of chlorzoxazone in patients with downbeat nystagmus: a pilot trial. Neurology. 2013;81:1152–8. https://doi.org/10.1212/WNL.0b013e3182a55f6d.
7. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. https://doi.org/10.1038/gim.2015.30.
8. Groth CL, Berman BD. Spinocerebellar Ataxia 27: a review and characterization of an evolving phenotype. Tremor Other Hyperkinet Mov (N Y). 2018;8:534. https://doi.org/10.7916/D80S0ZJQ.
9. van Swieten JC, Brusse E, de Graaf BM, Krieger E, van de Graaf R, de Koning I, et al. A mutation in the fibroblast growth factor 14 gene is associated with autosomal dominant cerebellar ataxia [corrected]. Am J Hum Genet. 2003;72:191–9.
10. Choquet K, La Piana R, Brais B. A novel frameshift mutation in FGF14 causes an autosomal dominant episodic ataxia. Neurogenetics. 2015;16:233–6. https://doi.org/10.1007/s10048-014-0436-7.

11. Coebergh JA, Fransen van de Putte DE, Snoeck IN, Ruivenkamp C, van Haeringen A, Smit LM. A new variable phenotype in spinocerebellar ataxia 27 (SCA 27) caused by a deletion in the FGF14 gene. Eur J Paediatr Neurol. 2014;18:413–5. https://doi.org/10.1016/j.ejpn.2013.10.006.
12. Amado A, Blanco MO, Reparaz-Andrade A. Spinocerebellar Ataxia 27: clinical phenotype of twin sisters with FGF14 deletion. Neuropediatrics. 2017;48:131. https://doi.org/10.1055/s-0037-1598110.
13. Choi KD, Kim JS, Kim HJ, Jung I, Jeong SH, Lee SH, et al. Genetic variants associated with episodic Ataxia in Korea. Sci Rep. 2017;7:13855. https://doi.org/10.1038/s41598-017-14254-7.
14. Shimojima K, Okumura A, Natsume J, Aiba K, Kurahashi H, Kubota T, et al. Spinocerebellar ataxias type 27 derived from a disruption of the fibroblast growth factor 14 gene with mimicking phenotype of paroxysmal non-kinesigenic dyskinesia. Brain and Development. 2012;34:230–3. https://doi.org/10.1016/j.braindev.2011.04.014.
15. Dalski A, Atici J, Kreuz FR, Hellenbroich Y, Schwinger E, Zuhlke C. Mutation analysis in the fibroblast growth factor 14 gene: frameshift mutation and polymorphisms in patients with inherited ataxias. Eur J Hum Genet. 2005;13:118–20. https://doi.org/10.1038/sj.ejhg.5201286.
16. Coutelier M, Coarelli G, Monin ML, Konop J, Davoine CS, Tesson C, et al. A panel study on patients with dominant cerebellar ataxia highlights the frequency of channelopathies. Brain. 2017;140:1579–94. https://doi.org/10.1093/brain/awx081.
17. Laezza F, Lampert A, Kozel MA, Gerber BR, Rush AM, Nerbonne JM, et al. FGF14 N-terminal splice variants differentially modulate Nav1.2 and Nav1.6-encoded sodium channels. Mol Cell Neurosci. 2009;42:90–101. https://doi.org/10.1016/j.mcn.2009.05.007.
18. Laezza F, Gerber BR, Lou JY, Kozel MA, Hartman H, Craig AM, et al. The FGF14(F145S) mutation disrupts the interaction of FGF14 with voltage-gated Na+ channels and impairs neuronal excitability. J Neurosci. 2007;27:12033–44. https://doi.org/10.1523/JNEUROSCI.2282-07.2007.