REVIEW

Therapy of episodic ataxias: case report and review of the literature

Daniele Orsucci MD, Laura Maria Raglione MD, Monica Mazzoni MD, Marco Vista MD

Unit of Neurology, San Luca Hospital, Lucca, Italy

Abstract

Episodic ataxias (EAs) are characterized by recurrent, discrete episodes of vertigo and ataxia. EA1 and EA2 are the two most common forms. In the interictal interval, myokymia is typically present in EA1, whereas EA2 patients present with interictal nystagmus. Specific pharmacological therapies are available for EA1 and especially EA2. We briefly discuss the case of an Italian young man with EA2, with a novel *de novo CACNA1A* mutation, who in our opinion is particularly illustrative for introducing the therapeutic approach. Acetazolamide could fully suppress EA episodes in our patient. We also provide a perspective review of the topic. 4-Aminopyridine is another valid treatment option. For EA1 (and for rarer EAs), the therapeutic possibilities are more limited. Carbamazepine is probably the treatment of choice for EA1, but the optimal treatment plan is unknown. A better understanding of the molecular processes involved in the mediation of EAs will lead to more specific and efficacious therapies for this still elusive group of disorders.

Keywords: acetazolamide, ataxia, *CACNA1A*, episodic ataxia, episodic ataxia type 1, episodic ataxia type 2.

Introduction

The term 'cerebellar ataxias' comprises a wide spectrum of neurological diseases with ataxia as the pivotal feature.[1] Ataxia is characterized by imbalance (e.g. truncal ataxia, gait ataxia) or incoordination of a limb while executing a task (dysmetria).[1] Ataxia is usually caused by dysfunction of the cerebellum or its connections. However, patients can also have ataxia from peripheral sensory involvement.[1] Neurological examination allows a correct distinction of the two conditions. Furthermore, cerebellar ataxia is frequently associated with other signs of cerebellar dysfunction, including abnormal eye movements (e.g. nystagmus, saccadic pursuits, hypermetric or hypometric saccades), kinetic tremor, dysmetria, dysarthria, and/or dysphagia.[1]

Once acquired conditions leading to cerebellar ataxia have been ruled out, making a correct etiological diagnosis of ataxia may be a challenge, considering the overlap in phenotypes and the different presentations of cerebellar ataxias.[1]

Genetic ataxias are commonly progressive, chronic conditions.[1] Few rare genetic ataxias are episodic. In this paper, we present an illustrative case report followed by a perspective review. We focused our attention on the two most common genetic forms of episodic ataxia (EA). We searched PubMed in October 2018 for all articles about 'episodic ataxia', and we reviewed the abstracts to identify relevant publications on treatment of EAs. Furthermore, we briefly discuss the case of an Italian young man with EA, who in our opinion is particularly illustrative for introducing the therapeutic approach.

Episodic ataxias

EAs are characterized by recurrent episodes of ataxia and/or dizziness.[1] These diseases can be progressive or not. Most EA genes code for ion channels.[1] Intermittent neurological phenotypes are typical of most channelopathies. The differential diagnosis includes paroxysmal dyskinesias[2] and other paroxysmal motor disorders.[3]

EA type 1 (EA1) is clinically defined by brief episodes of ataxia. It is due to mutations in the *KCNA1* gene. In EA type 2 (EA2), attacks tend to last longer and there is usually ataxia on neurological examination; the causative gene is *CACNA1A*. In the interictal period, myokymia is present in hand muscles when analyzed by EMG in EA1, whereas EA2 patients present with interictal nystagmus (downbeat nystagmus, gaze-evoked nystagmus, and/or rebound nystagmus) (Table 1).[4]

Table 1. Episodic ataxia 1 (EA1) and 2 (EA2).

	EA1	EA2
Causative gene	*KCNA1*	*CACNA1A*
Protein	Potassium channel	Calcium channel
Interictal features	Myokymia	Nystagmus
Ataxic spell duration	Minutes (rarely hours)	Hours (rarely days)
Treatment of choice	Carbamazepine	Acetazolamide

There are other few rare forms. Many other different genes have been associated with an EA phenotype, including *CACNB4* (EA4), *SLC1A3* (EA6), *SCN2A42*, *SLC2A144*,[5] *FGF1443*,[6] *KCNA2*, and *PRRT2*.[7] With the exception of *CACNA1A* and *KCNA1*, leading to EA1 and EA2, the rest have been found mutated in only one or few patients[5] and will not be discussed here. Next generation sequencing (NGS) tools will allow a better understanding of the complexity and genetic heterogeneity of EA phenotypes.[3]

Episodic ataxia type 1

EA1 is caused by mutations in the potassium channel gene *KCNA1*, which encodes the Shaker-related channel Kv1.1. These channels have a major role in action potential repolarization at cerebellar basket cell terminals.[8] The mutant channels show accelerated decay of outward potassium current during prolonged depolarization of the membrane potential, leading to a reduction in Kv1.1 current amplitude in basket cells.[9] Interestingly, mutations underlying EA1 may also antagonize Kv1.1 RNA editing.[10]

EA1 is an autosomal dominant channelopathy characterized by persistent myokymia (with muscle twitching or intermittent cramps) and episodes of ataxia.[3] Neurological spells can include unsteady and wide-based gait, incoordination, dizziness/vertigo, dysarthria, and other manifestations (i.e. nausea and vomiting, headache, muscular weakness, and/or stiffness).[3] Myokymia may be misinterpreted as peri-ocular, peri-oral, or finger tremor.[3] Typical attack duration is in minutes though events may persist for hours. Episode frequency varies widely, and typical triggers include physical exertion, emotional stress, and environmental temperature extremes.[3] Neuroimaging is typically normal, though cerebellar atrophy has been reported.[3] The finding of deafness in some individuals raises the possibility of a link between Kv1.1 dysfunction and hearing impairment,[11] but further studies are needed.

Interestingly, it has been reported that about 20% of EA1 patients accumulate persistent cerebellar symptoms and signs, contrary to the perceived course of this condition.[12] The first episode of ataxia occurs before age 20 in nearly all patients, and quality-of-life score correlates negatively with attack frequency.[12] EA1 patients may improve on a modest dose of carbamazepine, which is probably the treatment of choice (even if valproic acid and acetazolamide may also be effective in some instances).[12]

Episodic ataxia type 2

The *CACNA1A* gene codifies a calcium-dependent voltage channel, expressed in neurons. Mutations in this gene lead to a broad clinical spectrum including EA2, spinocerebellar ataxia type 6, familial hemiplegic migraine, and more recently epileptic encephalopathy.[13] Even if different mutations tend to associate with different phenotypes, some families show a wide variability of the neurological manifestations associated with the same variant.[13] The calcium channels that are altered in EA2 are highly expressed in the central nervous system and are particularly present in cerebellar Purkinje cells and in axon terminals.[14] Cav2.1 dysfunction in episodic ataxia type 2 also has negative effects on axon excitability.[15]

Most EA2-associated variants in the *CACNA1A* gene cause loss of function of the channel.[5] Missense variants leading to decreased channel currents have also been reported, as well as deletions in *CACNA1A*.[5]

EA2 is characterized by recurrent spells of ataxia, lasting for several hours (sometimes days), which may be induced by stress or exercise.[5] Neurological findings between attacks include signs of central ocular motor and vestibular dysfunction, such as downbeat nystagmus. Acetazolamide frequently leads to significant improvement.[13,16]

Case report

We present the case of a 20-year-old man presented because of increasingly frequent spells of gait instability, dizziness, and dysarthria. The patient's identity may not be ascertained from this report.

These attacks began at age 10 and typically lasted 3–6 hours. He was having 2–4 episodes per month, mostly evoked by physical exertion (typically after amateur five-a-side football matches). He was empirically treated with valproic acid and subsequently levetiracetam with no improvement. Family history was unremarkable.

Interictal neurological examination was normal except for a congenital gaze-evoked downbeat nystagmus, impaired smooth pursuit, and for very mild axial ataxia only noticeable during tandem gait.

Brain MRI was normal (Figure 1). Diffuse slow waves with no epileptic spikes were observed on electroencephalogram. Laboratory assays, neurosonologic examination, and complete cardiologic screening were normal. The cognitive profile was normal.

Figure 1.   A brain MRI scan was normal (including brainstem and cerebellum) in our patient at age 20. T2 (left) and FLAIR sequences.
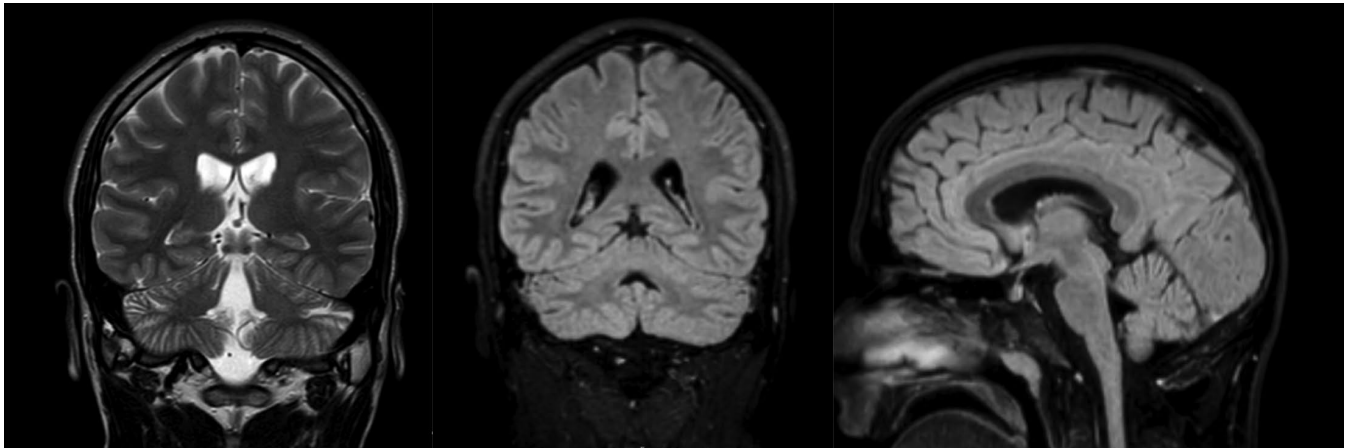
Given his history, highly suggestive of EA2, he was started on acetazolamide 250 mg/day with an excellent response. Our patient did not experience further EA spells in the 3 years following the introduction of acetazolamide, which was optimally tolerated. The very mild ataxia was no longer appreciable, whereas the nystagmus persisted.

Genetic testing showed a novel heterozygous variant in exon 6 of the *CACNA1A* gene, c.889G>A (p.G297R). The amino acid modified in our patient (glycine) is well conserved through the species, and *in silico* analysis (PolyPhen) showed that this missense variant is probably damaging, with the highest possible score of 1.00; the same results were obtained with other bioinformatic tools (Panther, Mutation Tester). This mutation was absent in both parents, who were examined and did not show any features of EA nor other neurological signs. This genetic finding confirmed the diagnosis of EA2 in our patient, who had a highly suggestive clinical picture. The excellent responsiveness to acetazolamide further supported the diagnosis of EA2 (see later).

Therapy of episodic ataxias

The mainstays of treatment of degenerative cerebellar ataxia (including EA patients with stabilized ataxia) are currently physiotherapy, occupational therapy, and speech therapy.[17] Specific pharmacological therapies are available for EA1 and especially EA2.

Episodic ataxia type 1

Several drugs could improve symptoms in some EA1 patients but, so far, no medication has been proven effective.[18] Furthermore, the responses are variable.[18] Responsiveness to acetazolamide treatment is only occasional in EA1 patients. The antiepileptic drug, phenytoin, is a modulator of voltage-gated Na+ channels that is also capable of decreasing ataxia

and myokymia in EA1 patients.[18] However, phenytoin can cause permanent cerebellar dysfunction and atrophy and should be used with extreme caution in these patients.[18] Carbamazepine stabilizes the inactivated state of voltage-gated sodium channels, making fewer of these channels available to subsequent opening.[18] It could significantly reduce the frequency of attacks in members of several large families.[18] Even if in some cases the initial response was not sustained,[18] carbamazepine is currently the treatment of choice for EA1.

Episodic ataxia type 2

Acetazolamide is the pharmacological treatment of choice for EA2; a dosage between 250 and 1000 mg/day is usually effective.[19] Acetazolamide 250 mg/day could fully suppress EA episodes in our EA2 patient. Alternatively, 4-aminopyridine can be used. Other drugs, including dalfampridine, have been proposed as potential treatment options, but further studies are still needed.[19]

As previously seen, EA2 is a dominant genetic disease caused by mutations in the *CACNA1A* gene encoding the CaV2.1 subunit of the PQ-type calcium channel, highly expressed in Purkinje cells.[16] The loss in the precision of Purkinje cell pacemaking likely contributes to EA2 symptoms.[14] In a mouse model, Purkinje cells exhibit high-frequency burst firing during attacks.[20] The changes induced by the mutation, resulting in a reduced calcium current, are considered to decrease the inhibitory effect of Purkinje cells. This may result in disinhibition of the deep cerebellar nuclei and therefore ataxia, and also in disinhibition of vestibular nuclei neurons receiving anterior semicircular canal pathways.[19] As aminopyridines (potassium channel blockers) improve nystagmus, their effects on the frequency of attacks in EA2 were evaluated.[16] Specifically, 4-aminopyridine was reported to reduce the frequency of attacks and improve the quality of life in EA2,[19] likely restoring the diminished precision of pacemaking in Purkinje cells, by

increasing the action potential after hyperpolarization and prolonging the action potential.[16]

A recent systematic review has concluded that for patients with EA2, 4-aminopyridine 15 mg/day probably reduces ataxia attack frequency over 3 months,[21] based on one randomized, double-blind, placebo-controlled, crossover, class 1 study performed on 10 patients.[22] This study showed that EA2 subjects receiving placebo had a median monthly attack frequency of 6.5, whereas patients taking this drug had a frequency of 1.65 (significant difference, $p<0.03$).[22] Considering that further controlled trials on 4-aminopyridine are still strongly needed,[23] the same review acknowledged that 'historical treatment approaches, such as the use of acetazolamide for the treatment of EA2, can have clinical value even in the absence of clinical trial evidence'.[21] Potential side effects of long-term acetazolamide use include kidney stones; therefore, ultrasound monitoring is warranted. Acetazolamide can be safely administered to patients with a history of antibiotic allergic reactions.[24]

Recently, an EA2 patient with poor response to acetazolamide has been reported to significantly improve with a combination of acetazolamide 750 mg/day and levetiracetam 750 mg/day.[25] Levetiracetam could be effective by inactivating calcium channels,[25] but further studies are needed.

Furthermore, the muscle relaxant agent, chlorzoxazone, has been proposed as a new potentially effective treatment of EA2.[14] In a mouse model of EA2, chlorzoxazone could restore the precision of Purkinje cell pacemaking in a dose-dependent manner.[14] Oral administration of chlorzoxazone could improve interictal motor performance and reduce the duration, severity, and frequency of spells of motor imbalance in this mouse model, with no adverse effects.[14] Studies in human patients are still needed.

Conclusion

We reported here an EA2 case with a novel *de novo CACNA1A* mutation. Eye movement disorders, including congenital nystagmus as in our patient, are an early manifestation of *CACNA1A* mutations[26] and may strongly help in the diagnostic approach of EA2 patients.

Acetazolamide and 4-aminopyridine are reported to decrease severity and frequency of spells in EA2,[27] and represent two valid and generally safe treatment options. A clinical trial focusing on the comparison of acetazolamide and 4-aminopyridine therapy in EA2 patients is ongoing in Munich (EAT2TREAT study). In fact, acetazolamide could fully suppress EA episodes in our patient. Further studies are needed to clarify the potentialities of acetazolamide and 4-aminopyridine in EA2 patients: for instance, can these two drugs be combined? Are their effects synergistic? Studies focusing on the possible utility of levetiracetam and chlorzoxazone are also needed.

For EA1 (and for rarer EAs), the therapeutic options are more limited. To date, carbamazepine is probably the treatment of choice for EA1, but this conclusion is based only on some case reports and case series,[18] and the optimal treatment plan is unknown.

EAs are still underdiagnosed. Therefore, improved recognition and understanding of EAs is necessary. NGS techniques will represent a useful, time-saving, and cost-effective diagnostic tool for the diagnosis of a patient with an EA phenotype.[28] An improved diagnostic approach may help determine early therapeutic intervention strategies and directly affect patient care.[29] A greater understanding of the molecular processes involved in the mediation of episodic ataxias (as well as of other paroxysmal movement disorders)[30] will lead to more specific and efficacious therapies for this still elusive group of disorders.[31,32]

Article URL: https://drugsincontext.com/therapy-of-episodic-ataxias:-case-report-and-review-of-the-literature

Correspondence: Daniele Orsucci, Unit of Neurology, San Luca Hospital of Lucca, Via Lippi-Francesconi, 55100 Lucca, Italy. orsuccid@gmail.com

Provenance: invited; externally peer reviewed.

References

1. Mancuso M, Orsucci D, Siciliano G, Bonuccelli U. The genetics of ataxia: through the labyrinth of the Minotaur, looking for Ariadne's thread. *J Neurol*. 2014;261(Suppl 2):S528–541. http://dx.doi.org/10.1007/s00415-014-7387-7

2. Gardiner AR, Jaffer F, Dale RC, et al. The clinical and genetic heterogeneity of paroxysmal dyskinesias. *Brain*. 2015;138(Pt 12):3567–3580. http://dx.doi.org/10.1093/brain/awv310

3. Zima L, Ceulemans S, Reiner G, et al. Paroxysmal motor disorders: expanding phenotypes lead to coalescing genotypes. *Ann Clin Transl Neurol*. 2018;5(8):996–1010. http://dx.doi.org/10.1002/acn3.597

4. Gasser T, Finsterer J, Baets J, et al. EFNS guidelines on the molecular diagnosis of ataxias and spastic paraplegias. *Eur J Neurol*. 2010;17(2):179–188. http://dx.doi.org/10.1111/j.1468-1331.2009.02873.x

5. Sintas C, Carreno O, Fernandez-Castillo N, et al. Mutation spectrum in the CACNA1A gene in 49 patients with episodic ataxia. *Sci Rep*. 2017;7(1):2514. http://dx.doi.org/10.1038/s41598-017-02554-x

6. Schesny M, Joncourt F, Tarnutzer AA. Acetazolamide-responsive episodic ataxia linked to novel splice site variant in FGF14 gene. *Cerebellum*. 2019. http://dx.doi.org/10.1007/s12311-018-0997-3

7. Gardiner AR, Bhatia KP, Stamelou M, et al. PRRT2 gene mutations: from paroxysmal dyskinesia to episodic ataxia and hemiplegic migraine. *Neurology*. 2012;79(21):2115–2121. http://dx.doi.org/10.1212/WNL.0b013e3182752c5a

8. Begum R, Bakiri Y, Volynski KE, Kullmann DM. Action potential broadening in a presynaptic channelopathy. *Nat Commun*. 2016;7:12102. http://dx.doi.org/10.1038/ncomms12102

9. Peters CJ, Werry D, Gill HS, Accili EA, Fedida D. Mechanism of accelerated current decay caused by an episodic ataxia type-1-associated mutant in a potassium channel pore. *J Neurosci*. 2011;31(48):17449–17459. http://dx.doi.org/10.1523/JNEUROSCI.2940-11.2011

10. Ferrick-Kiddie EA, Rosenthal JJ, Ayers GD, Emeson RB. Mutations underlying episodic ataxia type-1 antagonize Kv1.1 RNA editing. *Sci Rep*. 2017;7:41095. http://dx.doi.org/10.1038/srep41095

11. Tomlinson SE, Rajakulendran S, Tan SV, et al. Clinical, genetic, neurophysiological and functional study of new mutations in episodic ataxia type 1. *J Neurol Neurosurg Psychiatry*. 2013;84(10):1107–1112. http://dx.doi.org/10.1136/jnnp-2012-304131

12. Graves TD, Cha YH, Hahn AF, et al. Episodic ataxia type 1: clinical characterization, quality of life and genotype-phenotype correlation. *Brain*. 2014;137(Pt 4):1009–1018. http://dx.doi.org/10.1093/brain/awu012

13. Angelini C, Van Gils J, Bigourdan A, et al. Major intra-familial phenotypic heterogeneity and incomplete penetrance due to a CACNA1A pathogenic variant. *Eur J Med Genet*. 2018; pii:S1769-7212(18)30335-5. http://dx.doi.org/10.1016/j.ejmg.2018.08.011

14. Alvina K, Khodakhah K. Kca channels as therapeutic targets in episodic ataxia type-2. *J Neurosci*. 2010;30(21):7249–7257. http://dx.doi.org/10.1523/JNEUROSCI.6341-09.2010

15. Tomlinson SE, Tan SV, Burke D, et al. In vivo impact of presynaptic calcium channel dysfunction on motor axons in episodic ataxia type 2. *Brain*. 2016;139(Pt 2):380–391. http://dx.doi.org/10.1093/brain/awv380

16. Isaacs DA, Bradshaw MJ, Brown K, Hedera P. Case report of novel CACNA1A gene mutation causing episodic ataxia type 2. *SAGE Open Med Case Rep*. 2017;5:2050313X17706044. http://dx.doi.org/10.1177/2050313X17706044

17. Ilg W, Bastian AJ, Boesch S, et al. Consensus paper: management of degenerative cerebellar disorders. *Cerebellum*. 2014; 13(2):248–268. http://dx.doi.org/10.1007/s12311-013-0531-6

18. D'Adamo MC, Hasan S, Guglielmi L, et al. New insights into the pathogenesis and therapeutics of episodic ataxia type 1. *Front Cell Neurosci*. 2015;9:317. http://dx.doi.org/10.3389/fncel.2015.00317

19. Strupp M, Thurtell MJ, Shaikh AG, Brandt T, Zee DS, Leigh RJ. Pharmacotherapy of vestibular and ocular motor disorders, including nystagmus. *J Neurol*. 2011;258(7):1207–1222. http://dx.doi.org/10.1007/s00415-011-5999-8

20. Tara E, Vitenzon A, Hess E, Khodakhah K. Aberrant cerebellar Purkinje cell activity as the cause of motor attacks in a mouse model of episodic ataxia type 2. *Dis Model Mech*. 2018;11(9). http://dx.doi.org/10.1242/dmm.034181

21. Zesiewicz TA, Wilmot G, Kuo SH, et al. Comprehensive systematic review summary: treatment of cerebellar motor dysfunction and ataxia: report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. *Neurology*. 2018;90(10):464–471. http://dx.doi.org/10.1212/WNL.0000000000005055

22. Strupp M, Kalla R, Claassen J, et al. A randomized trial of 4-aminopyridine in ea2 and related familial episodic ataxias. *Neurology*. 2011;77(3):269–275. http://dx.doi.org/10.1212/WNL.0b013e318225ab07

23. Strupp M, Teufel J, Zwergal A, Schniepp R, Khodakhah K, Feil K. Aminopyridines for the treatment of neurologic disorders. *Neurol Clin Pract*. 2017;7(1):65–76. http://dx.doi.org/10.1212/CPJ.0000000000000321

24. Platt D, Griggs RC. Use of acetazolamide in sulfonamide-allergic patients with neurologic channelopathies. *Arch Neurol*. 2012;69(4):527–529. http://dx.doi.org/10.1001/archneurol.2011.2723

25. Lee H, Jang DH, Jang JH, Kim T. Effectiveness of levetiracetam in an acetazolamide-unresponsive patient with episodic ataxia type 2 by a novel cacna1a nonsense mutation. *Eur J Neurol*. 2017;24(7):e43–e44. http://dx.doi.org/10.1111/ene.13327

26. Tantsis EM, Gill D, Griffiths L, et al. Eye movement disorders are an early manifestation of cacna1a mutations in children. *Dev Med Child Neurol*. 2016;58(6):639–644. http://dx.doi.org/10.1111/dmcn.13033

27. Guterman EL, Yurgionas B, Nelson AB. Pearls & Oy-sters: episodic ataxia type 2: case report and review of the literature. *Neurology*. 2016;86(23):e239–241. http://dx.doi.org/10.1212/WNL.0000000000002743

28. Maksemous N, Roy B, Smith RA, Griffiths LR. Next-generation sequencing identifies novel CACNA1A gene mutations in episodic ataxia type 2. *Mol Genet Genomic Med*. 2016;4(2):211–222. http://dx.doi.org/10.1002/mgg3.196

29. Tacik P, Guthrie KJ, Strongosky AJ, et al. Whole-exome sequencing as a diagnostic tool in a family with episodic ataxia type 1. *Mayo Clin Proc*. 2015;90(3):366–371. http://dx.doi.org/10.1016/j.mayocp.2015.01.001

30. Silveira-Moriyama L, Kovac S, Kurian MA, et al. Phenotypes, genotypes, and the management of paroxysmal movement disorders. *Dev Med Child Neurol*. 2018;60(6):559–565. http://dx.doi.org/10.1111/dmcn.13744

31. Jen JC, Graves TD, Hess EJ, Hanna MG, Griggs RC, Baloh RW. Primary episodic ataxias: diagnosis, pathogenesis and treatment. *Brain*. 2007;130(Pt 10):2484–2493. http://dx.doi.org/10.1093/brain/awm126

32. Kalla R, Teufel J, Feil K, Muth C, Strupp M. Update on the pharmacotherapy of cerebellar and central vestibular disorders. *J Neurol*. 2016;263(Suppl 1):S24–29. http://dx.doi.org/10.1007/s00415-015-7987-x