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Intellectual Disability in Episodic Ataxia Type 2: Beyond Paroxysmal Vertigo and Ataxia

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Background and Purpose Episodic ataxia type 2 (EA2) is characterized by recurrent vertigo and ataxia due to mutations in *CACNA1A* that encodes the α_{1A}-subunit of the P/Q-type voltage-gated calcium channel. This study aimed to determine intellectual function in EA2.

Methods During 2019−2023, 13 patients (6 males, age range=10−52 years, median age=29 years) with a genetically confirmed diagnosis of EA2 had their intellectual function evaluated using the Korean versions of the Wechsler Intelligence Scales (version IV) for adults or children in 3 referral-based university hospitals in South Korea.

Results The full-scale intelligence quotients (FSIQs) among the 13 patients were below the average (90−109) in 11, low average (80−89) in 5 (38.5%), borderline (70−79) in 1 (7.7%), and indicated intellectual disability (≤69) in 5 (38.5%). These patterns of cognitive impairments were observed in all four of the following subtests: verbal comprehension, perceptual reasoning, working memory, and processing speed. The FSIQ was not correlated with the ages at onset for vertigo and ataxia (Pearson correlation: p=0.40).

Conclusions Patients with EA2 may have hidden intellectual disabilities even without a history of epilepsy or administration of antiepileptic drugs, and should be considered for genetic counseling and therapeutic interventions. Given the availability of medication to control episodic vertigo and ataxia, early diagnosis and management are important in preventing irreversible brain dysfunction in EA2.

Keywords vertigo; ataxia; episodic ataxia type 2; intellectual disability.

INTRODUCTION

Episodic ataxia (EA) type 2 (EA2) is an autosomal-dominant disorder characterized by recurrent vertigo and ataxia episodes that often begin in childhood or early adolescence at a frequency ranging from three to four times per week to once or twice per year.[1,2] The attacks are frequently triggered by emotional stress, fatigue, or exercise.[2] In addition to attacks, patients with EA2 often present with downbeat nystagmus, gaze-evoked nystagmus (GEN), positional nystagmus, impaired smooth pursuit, and saccadic hypermetria, which all indicate baseline cerebellar dysfunction.[1] Another characteristic of EA2 is dramatic responses to carbonic anhydrase inhibitor, acetazolamide, or 4-aminopyridine.[3,4]

EA2 is mostly caused by nonsense mutations in *CACNA1A* located on chromosome 19p that encodes the pore-forming α_{1A} subunit of the P/Q-type voltage-gated calcium channel Cav2.1.[5,6] EA2 is therefore allelic with familial hemiplegic migraine type 1 and spinocerebellar ataxia type 6, which are mostly caused by missense mutations and glutamine-encoding CAG-repeat expansion in *CACNA1A*, respectively.[5,7] Indeed, these allelic disorders share clinical features with epilepsy,[2,8] dystonia,[9] migraine,[2,10,11] and even intermittent coma additive to episodic or progressive cerebellar dysfunction.[1,12-14] This wide spectrum of phe-

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notypes can be well explained by the ubiquitous expression of the voltage-gated P/Q-type calcium channels in both the central and peripheral nervous systems, even though those expressions predominantly present in the Purkinje and granule cells of the cerebellum.[5] Previous studies have also described saccadic slowing and internuclear ophthalmoplegia in patients with EA2, indicating extracerebellar involvement.[15-17] However, clinical features other than episodic vertigo and ataxia have received little attention in relation to EA2.[2,16-22]

The interviews of the patients with EA2 impressed on the authors that these patients frequently have various degrees of intellectual disability. Cognitive impairments are often expected in patients with EA2 due to the roles of calcium channels in neural development and function.[18,23] However, no studies have systematically investigated the intellectual function of patients with EA2. The present study was the first to evaluate cognitive dysfunction in patients with EA2.

METHODS

Patients

During 2019−2023, 13 patients with a genetically confirmed EA2 diagnosis had undergone clinical, genetic, and imaging evaluations at 3 university hospitals in South Korea: 11 at Seoul National University Bundang Hospital, 1 at Chonnam National University Hospital, and 1 at Incheon St. Mary's Hospital (Table 1). The sample included six males, and were aged 30.5±13.7 years (mean±standard deviation [SD]; median age=29 years, age range=10−52 years).

The clinical diagnoses of EA2 were based on a combination of the clinical features of episodic vertigo and imbalance lasting hours to days, interictal eye-movement abnormalities indicative of cerebellar dysfunction, and response to acetazolamide. The presence of EA2 was genetically confirmed in all patients based on mutations found in *CACNA1A*. The clinical and genetic features of some of the included patients had been reported previously.[17,24-26]

Bedside evaluations

In addition to routine neurologic examinations, patients received bedside evaluations of ocular alignment, spontaneous nystagmus, horizontal and vertical GEN, horizontal and vertical saccades and smooth pursuit, head-impulse tests (HITs), and vergence while sitting.[27,28] For the bedside HITs, the patients were instructed to fixate on the nose of the examiner while their head was rapidly rotated to about 20° in the semicircular canal plane in a passive and unpredictable manner.[29,30] We then observed spontaneous nystagmus, head-shaking nystagmus (HSN), and positional nystagmus without visual fixation using video Frenzel goggles. Positional maneuvers included lying down from sitting, head turning to either side while supine, straight-head hanging, and the bilateral Dix-Hallpike maneuver.

Video-oculography

All patients had also undergone three-dimensional video-oculographic recording of their eye movements.[30] Spontaneous nystagmus was recorded both with and without visual fixation. GEN was recorded using target displacement in the horizontal (±30°) and vertical (±20°) planes. Vibration-induced nystagmus was observed while vibratory stimuli were applied to either the mastoid or brow.[30] Positional nystagmus was observed without visual fixation during serial changes in head position and during bedside evaluation. The presence of positional nystagmus was determined as described previously.[31] The examiner induced HSN by pitching the head of the patient forward by about 30° to bring the horizontal canal into the plane being stimulated. The head was then shaken horizontally sinusoidally at a rate of about 2.8 Hz at an approximate amplitude of ±10° for about 15 s. The head shaking was paced using computer-generated periodic tones, and the amplitude was controlled using online monitoring of the head motion. Patients were instructed to open their eyes after shaking their head and look straight ahead into darkness.[32] Saccades and smooth pursuit were stimulated as described previously and considered abnormal when they exceeded the reference ranges obtained from 50 normal controls.[33] We also quantified eye movements during HITs using video recording. Seven or more impulses were delivered in each direction. Improvements in the vestibulo-ocular reflex were measured in individual trials as the ratio of the mean eye velocity divided by the mean head velocity during a 40-ms window centered on the time of peak head acceleration.[34,35]

Intellectual-function evaluation

Intellectual function was evaluated using the Korean versions of the Wechsler Adult Intelligence Scale version IV (K-WAIS-IV) and the Wechsler Intelligence Scale for Children version IV (K-WISC-IV).[36,37] These comprise the following scales with subtests: verbal comprehension (core subtests: similarities, vocabulary, and information; supplemental subtest: comprehension), perceptual reasoning (core subtests: block design, matrix reasoning, and visual puzzles; supplemental subtests: picture completion and figure weights), working memory (core subtests: digit span and arithmetic; supplemental subtest: letter-number sequencing), and processing speed (core subtests: symbol search and coding; supplemental subtest: cancellation).[36] The full-scale intelligence

Table 1. Clinical and genetic characteristics of patients

Patients	Sex	Age (yr)	*CACNA1A* mutation	Age at onset (yr)	Attack frequency (per month)	Duration (hours)	Triggering factors	Interictal ocular motor findings	Response to acetazolamide	Other clinical features
1	M	52	Exon 37, c.5569C>T, nonsense	10	1	12	Exercise	GEN, DBN, pHIT	+	
2	M	18	Exon 37, c.5569C>T, nonsense	5	1	24-36	Exercise, concentration	GEN, DBN, convergence upbeat, pHIT	+	
3	F	23	Exon 37, c.5569C>T, nonsense	9	4	1	Exercise, menstruation	GEN, DBN	+	Tinnitus, earfullness
4	F	47	Intron 31, c.4953+1G>A, aberrant splicing	10	Almost resolved	0.5	Fatigue	GEN, DBN	+	Migraine
5	M	41	Exon 23, c.3871_3873delGAG, deletion	19	2	2–3	Exercise, fatigue, cold	GEN, DBN, pHIT	+	Febrile seizure
6	F	10	Exon 23, c.3871_3873delGAG, deletion	4	5–6	Several hours	Unknown	GEN, DBN, CPN	+	Febrile seizure
7	F	34	Exon 36, c.5509delG, deletion	9	2	24	Exercise	GEN, DBN, increased AC gain during HI	+	Migraine, tonic up-gaze, developmental delay, spasmus nutans
8	M	46	Exon 36, c.5455C>T, nonsense	30	0.5	2	None	GEN, DBN, CPN, impaired SP	+	Headache
9	M	17	Intron 31, c.4953+1G>A, aberrant splicing	13	4	1	None	GEN, DBN, vertical saccadic slowing	+	
10	F	39	Exon 21, c.3679_3680delCT, deletion	38	15	1	None	GEN, pHSN, increased AC gain during HI	+	
11	F	59	Exon 5, c.757C>T, p.His253Tyr, heterozygte	10	2	2–3	Stress	GEN, loss of torsional saccades	+	
12	M	17	Exon 20, c.3414dup, nonsense	1.2	2–3	0.5–1	Exercise, stress, overeating	GEN, DBN	+	
13	F	22	Intron 31, c.4953+1G>A, aberrant splicing	12	10–15	1	Exercise	GEN, DBN	+	

AC, anterior semicircular cans; CPN, central positional nystagmus; DBN, downbeat nystagmus; GEN, gaze-evoked nystagmus; HI, head-impulse; pHIT, perverted head impulse test; pHSN, perverted head-shaking nystagmus; SP, smooth pursuit.

quotient (FSIQ) was calculated based on these core subtests, and represents the overall intelligence level of an individual.[36] The FSIQ as measured by the K-WAIS-IV is defined as a mean score of 100±15,[36] meaning that 68% of subjects score within one SD of the mean (85–115). The K-WAIS-IV classifies intelligence quotients (IQs) into very superior (130 and higher), superior (120–129), high average (110–119), average (90–109), low average (80–89), borderline (70–79), and intellectual disability (≤69).[36] The K-WAIS-IV or K-WISC-IV was administered using paper and pencil or digitally, and the core subtests were typically performed in 70–100 minutes.[37]

Molecular analyses

Genetic analyses using direct and next-generation sequencing were applied to *CACNA1A* in eight and five patients, respectively.

Direct sequencing

We applied polymerase chain reaction (PCR)-based direct sequence analysis to *CACNA1A* after obtaining informed consent from all patients.[38] Genomic DNA from the peripheral blood of the patients were amplified using 52 primer pairs that covered all coding exons and intron–exon junctions of *CACNA1A*. PCR-amplified products were separated and purified using 2% agarose gels, cycle-sequenced with PCR primers using the BigDye Terminator Sequencing Kit (Applied Biosystems, Foster, CA, USA), and electrophoresed using an ABI PRISM 3730xl DNA Analyzer (Applied Biosystems). Sequence variations were identified by visually analyzing chromatograms. PCR primer sequences and conditions are available upon request. Mutation c.4391-1G>C was further verified using PCR restriction-fragment-length polymorphism analysis with the restriction enzyme HpyCH4 III (New England Biolabs, Ipswitch, MA, USA) and a primer pair (forward, 50-TTC CCT CTG TTC CTG TTC TGC-30; reverse, 50-GGG GTT CCT GGG TGT TGT G-30) in the DNA of patients and 100 control chromosomes. Since that mutation produces a new recognition site for HpyCH4 III, those with a mutated allele will produce 119- and 282-bp DNA fragments and those with the normal allele will produce one 402-bp fragment.

Next-generation sequencing

We adopted a stepwise approach to identify the genetic mutation responsible for EA.[26] We determined the presence of pathogenic variants in EA genes registered at the Online Mendelian Inheritance in Man (OMIM; https://www.omim.org/about) compendium. These included *KCNA1* (EA1, OMIM 176260), *CACNA1A* (EA2, OMIM 601011), *CACNB4* (EA5, OMIM 601949), *SLC1A3* (EA6, OMIM 600111), and *UBR4* (EA8, OMIM 609890). All variants detected were annotated for disease-causing variants previously reported in the Human Gene Mutation Database and Korean Personal Genome Project information.[39] The pathogenicity of nonsynonymous variants was analyzed using the following predictive software: Sorting Intolerant From Tolerant, Likelihood Ratio Test, Polyphen2, and MutationTaster.[40-42] Base-position conservation was evaluated using Genomic Evolutionary Rate Profiling.[43] All variants were further confirmed using PCR-based direct sequencing, and were screened against 150 South Korean controls.

Statistical analyses

The correlations of the K-WAIS-IV and K-WISC-IV scores with the ages at onset of vertigo and ataxia were quantified using Pearson's correlation coefficient. Statistical analyses were performed using R software (version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/), and $p<0.05$ was considered significant.

Standard protocol approvals

All experiments were in accordance with the Declaration of Helsinki, and informed consent was not required because this study was retrospective and did not affect subject care in any way. The Institutional Review Board of Seoul National University Bundang Hospital approved this study (IRB no. B-2406-907-102).

RESULTS

Clinical features

The age at the onset of episodic vertigo and ataxia ranged from 2–38 years was 13±10 years, with 11 (84.6%) patients experiencing symptom onset when younger than 20 years. Ataxic episodes occurred from once in 2 months to 15 times in 1 month, and lasted from 30 minutes to several days. Exercise was the most common triggering factor, occurring in 7 (53.9%) patients. Seven patients in three families had at least one family member with genetically confirmed EA2. All patients presented interictal ocular motor findings indicative of cerebellar dysfunction, which included downbeat, gaze-evoked, and positional nystagmus, impaired smooth pursuit, saccadic dysmetria, and the cross-coupled head-impulse sign (upward eye deflection and downward corrective saccades during horizontal head impulses). All patients also reported a response to acetazolamide. Two patients (patients 5 and 6) from the same family reported a history of febrile seizure, and two others (patients 4 and 6) had migraine. Tonic upgaze and developmental delay with spasmus nutans were reported in patients 6 and 7, respectively.

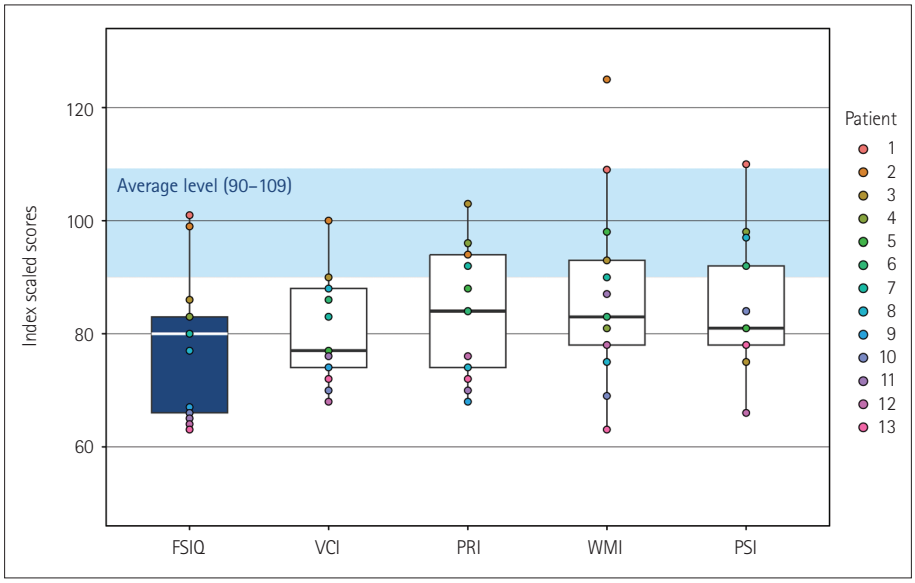

Fig. 1. The scales for intellectual function evaluated using the Korean versions of the Wechsler Adult Intelligence Scale and the Wechsler Intelligence Scale for Children (patient 6). Among the 13 patients, 11 (84.6%) had a FSIQ below the average (90–109; blue shaded area), at 77.8±12.2 (mean±SD). Patients also presented similar patterns of intellectual impairment in all subtests: VCI (80.8±9.1), PRI (84.3±12.0), WMI (86.8±16.1), and PSI (83.8±12.2). FSIQ, full-scale intelligence quotient; PRI, perceptual reasoning index; PSI, processing speed index; SD, standard deviation; VCI, verbal comprehension index; WMI, working memory index.

Intellectual function

The FSIQs of the 13 patients were below the average (90–109), low average (80–89), borderline (70–79), and indicated intellectual disability (≤69) in 11 (84.6%), 5 (38.5%), 1 (7.7%), and 5 (38.5%) patients, respectively (Fig. 1 and Supplementary Table 1 in the online-only Data Supplement). These cognitive impairment patterns were observed in all four subtests: verbal comprehension, perceptual reasoning, working memory, and processing speed. The verbal comprehension index was therefore below the mean minus 1 SD for the normal controls (<85) in 8 (61.5%), and below the perceptual reasoning index in 7 (53.8%), the working memory index in 7 (53.8%), and the processing speed index in 9 (69.2%) patients. The FSIQ and each subtest score were not correlated with the age at onset for vertigo and ataxia (Pearson's correlation coefficient, $p>0.05$).

DISCUSSION

This study was the first to document the underrecognized findings of cognitive impairments in patients with EA2. These impairments were found in most of our patients with EA2 despite their disabilities generally being of mild-to-moderate severity. The impairments were observed in all four subtests. These findings expand on the clinical phenotype of EA2 and necessitate the consideration of cognitive dysfunction in genetic counseling and therapeutic interventions for the disorder.

Genetic basis of intellectual disability and EA2

Intellectual disability has been defined as IQ<70 with accompanying adaptive behavior deficits, with mild and moderate-to-severe intellectual disabilities defined as IQ=50–69 and IQ<50, respectively. Intellectual disability affects 1%–3% of the general population.[44] Genetic factors play a key role in developing intellectual disability of a congenital origin despite it being caused by heterogeneous disorders.[45] Numerous genetic abnormalities have been found in patients with intellectual disability along with various hereditary patterns.[45] The responsible genes are mostly involved in neuronal differentiation and the formation and transmission of synapses in the developing brain.[46]

EA2 is caused by mutations in *CACNA1A*, more than two-thirds of which induce a premature stop owing to nonsense mutations or defects at splice sites.[2,26] *CACNA1A* encodes the pore-forming and voltage-sensing subunit Cav2.1 of P/Q-type voltage-gated calcium channels, which are ubiquitous in the central nervous system and abundantly expressed in the Purkinje and granule cells of the cerebellum.[5] P/Q-type calcium channels play roles in neuronal proliferation and differentiation, membrane excitability, signal transduction, gene expression, neurotransmitter release, and the outgrowth and synaptogenesis of neurites.[47-50] Calcium is a cellular messenger that also plays a role in synaptic plasticity and further regulatory processes in the central nervous system.[51] Indeed, mice with selective knockout of *CACNA1A* in the forebrain or cerebellum also presented marked deficits in memory,

spatial learning, and exploratory behaviors.[52,53]

Intellectual disability has occasionally been described previously in patients with familial or sporadic cases of paroxysmal ataxia despite the genetic abnormalities not being defined.[54-59] An autopsy study also found cortical microdysgenesis comprising nodular heterotopia and hypermyelination in the temporal lobe in addition to a marked loss of Purkinje and granule cells exclusively in the superior cerebellar vermis of a patient with mild intellectual disability and hereditary acetazolamide-responsive paroxysmal ataxia, but without mutation or CAG expansion in *CACNA1A*.[59] Indeed, more clinical phenotypes are being observed in variants involving *CACNA1A*,[23] now comprising developmental delay, intellectual disability, paroxysmal dystonia, epilepsy, and psychiatric disturbances in addition to episodic or progressive ataxia and hemiplegic migraine.[60-65]

Possible role of cerebellar dysfunction in cognitive impairment development

Since cognitive and limbic functions are controlled by the posterior cerebellum, cerebellar dysfunction may promote deficits in executive function, visual spatial procession, linguistic skills, affect regulation, and social interaction (cerebellar cognitive-affective syndrome).[66-68] The calcium currents passing through P/Q-type channels contribute to early cerebellum maturation. Dysfunction of this channel may therefore contribute to the development of cognitive-affective impairments early in life by altering how the cerebellum tunes cognitive cortical networks.[69]

The cognitive impairments observed in EA2 may be caused by recurrent episodes of vertigo and ataxia in early childhood. Indeed, children with vertigo are at a greater risk of cognitive dysfunction and psychiatric comorbidity.[70] Given the absence of descriptions for cognitive impairments in other primary episodic vestibular disorders, such as benign recurrent vertigo of childhood or vestibular migraine, recurrent episodes of vertigo and ataxia seem unlikely to cause cognitive dysfunction.

Genetic counseling and therapeutic interventions for intellectual disability

Patients with EA2 often exhibit dramatic responses to acetazolamide or 4-aminopyridine treatments aimed at inhibiting vertigo and ataxia episodes.[2-4] Even though the exact mechanisms have not yet been elucidated, these medications may work by changing the extracellular proton concentration and thus modulating ion permeation through either the calcium channels or a direct effect on the ion channels.[71]

It is essential for intellectual disability caused to genetic abnormalities to be recognized early, since this mostly develops during childhood and the early recognition of this condition is important for therapeutic interventions. Although intellectual disability can be formally diagnosed once a child is about 6 years old, most pediatricians can reliably diagnose cognitive impairments in younger children. Given their therapeutic effects on cerebellar dysfunction, acetazolamide or 4-aminopyridine should be administered as soon as the diagnosis is confirmed, although the preventive effects on intellectual disability still need to be established and considered alongside future side effects. Genetic counseling, education, and early diagnosis and management would therefore be important to prevent irreversible brain dysfunction in EA2.

In conclusion, patients with EA2 may have hidden intellectual disability, and so even those with no history of epilepsy or taking antiepileptic drugs should be considered for genetic counseling and therapeutic interventions. Given the availability of medication to control episodic vertigo and ataxia, early diagnosis and management are important to prevent irreversible brain dysfunction in EA2.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2024.0274.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

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Conflicts of Interest

Dr. J-S Kim serves as an Associate Editor of *Frontiers in Neuro-otology* and on the editorial boards of the *Journal of Clinical Neurology*, *Frontiers in Neuro-ophthalmology*, *Journal of Neuro-ophthalmology*, *Journal of Vestibular Research*, and *Clinical Translational Neuroscience*. Dr. J-S Kim is a technical director at SLMED. All remaining authors have declared no conflicts of interest.

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