Episodic Ataxia Type 2 : An Uncommon Inherited CNS Channelopathies

TEERATORN PULKES, MD*

Abstract

The author reports the first Thai patient with a rare inherited ataxic disorder characterized by intermittent episodes of ataxia, headache and vertigo. The patient was well between attacks despite persistent nystagmus on examination. Magnetic resonance imaging of the brain revealed cerebellar atrophy. All symptoms were ameliorated by acetazolamide therapy. This clinical syndrome was previously described as acetazolamide-responsive episodic ataxia which was subsequently shown to be associated with mutations in a α_{1A}-subunit of P/Q type voltage-gated calcium channel gene, known as 'episodic ataxia type 2'. Clinical and molecular aspects of episodic ataxia type 2 were also reviewed.

Key word : Episodic Ataxia, Channelopathies, Cerebellar Degeneration

PULKES T
J Med Assoc Thai 2003; 86: 376-380

Episodic ataxia (EA) is a rare hereditary neurodegenerative disorder characterized by early-onset acetazolamide-responsive intermittent ataxia[1]. Most families are inherited by autosomal dominant fashion but there are some clinical heterogeneous between families[2]. During the last ten years, several groups of research neuroscientists identified molecular defects of neuronal voltage-gated ion channel genes in association with EA[3]. To date two types of EA have been described which can be clinically differentiated. Patients with episodic ataxia type 1 (EA1) had typically brief episodes of ataxia and continuous myokymia (rippling of muscles) which may be clinically evident or only detectable by EMG. Linkage analysis revealed localization of an EA1 gene near the voltage-gated potassium channel gene, *KCNA1 (Kv1.1)*, on chromosome 12p13[4]. Browne et al subsequently described heterozygous missense

* Division of Neurology, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

point mutations in *KCNA1* gene in the EA1 patients [5]. In episodic ataxia type 2 (EA2) affected individuals had longer attacks of ataxia than EA1, lasting hours and often accompanied by nausea, vomiting and headache. Interictal nystagmus was almost invariably observed but there was no association with myokymia. EA2 subjects frequently develop progressive cerebellar ataxia and cerebellar atrophy[2]. Mutations in the α_{1A}-subunit of the P/Q-type voltage-gated calcium channel gene (*CACNA1A*) on chromosome 19p13 underlie EA2[6].

EA affected individuals almost always respond to acetazolamide treatment. Moreover, diagnosis could be made by clinical grounds alone. It is thus necessary that neurologists and internists should recognize this syndrome. The author reports herewith the first Thai patient with typical EA2 and the pertinent literature is reviewed.

CASE REPORT

A 34-year-old woman had suffered from recurrent episodes of severe headache, vomiting and ataxia for 5 years. Each episode lasted up to a few hours. Headache was dull-aching occipital pain often accompanied by vomiting. During the attack her gait was unsteady but she was completely well between the attacks. After the first attack she went to see a neurologist at a private hospital who observed persistent nystagmus on examination. Magnetic resonance imaging (MRI) of the brain showed a mild degree of cerebellar atrophy (Fig. 1). During the first year of the illness she had infrequent attacks about once a month. Attacks had been more severe and frequent, increasing to 3-4 times a week during the past year. For the last two years she also experienced oscillopsia and vertigo during the attacks and subsequently also had oscillopsia interictally. There was no family history of headache or other neurological disorders. Examination when she was 34 years old revealed several eye movement abnormalities including slow saccades in vertical gaze, hypometric saccades, impairment of pursuits and gaze-evoked nystagmus in both horizontal and vertical gaze, impairment of optokinetic nystagmus and a suppression of vestibulo-ocular reflex. Finger-to-nose and heel-to-knee tests were slightly impaired. Her gait showed only unsteadiness while she turned and tandem walk revealed some unsteadiness.

Episodic ataxia type 2 was diagnosed on the basis of over-an-hour of recurrent episodic attacks of ataxia, vertigo and headache accompanied by persistent eye movement abnormalities. She was treated with 250 mg of acetazolamide a day. Her attacks were less frequent immediately after commencing the medi-

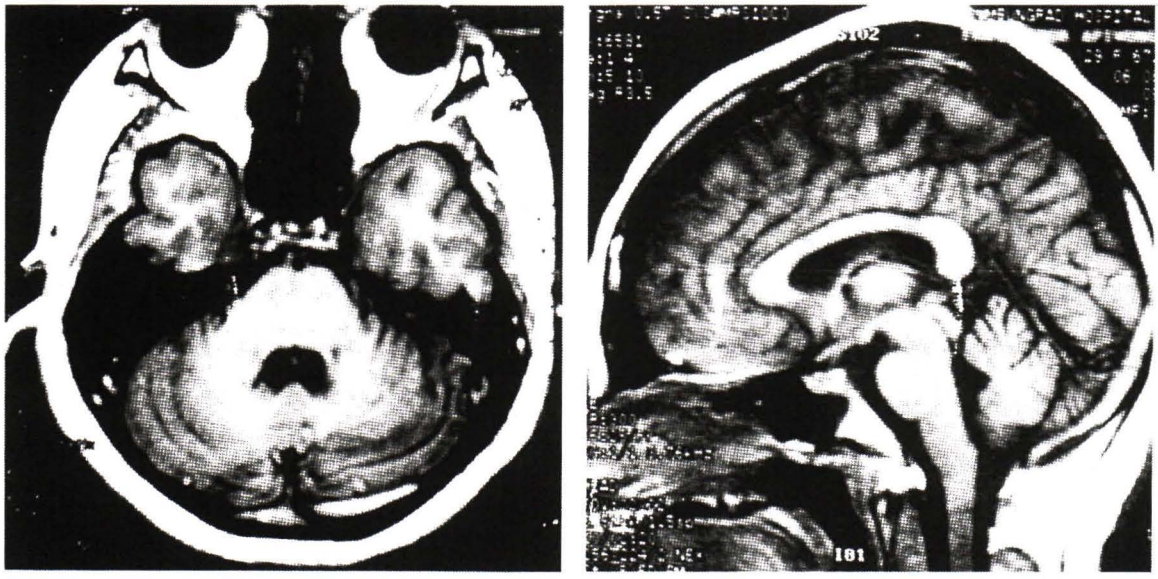

Fig. 1. MRI of the brain at the onset of the disease demonstrates mild cerebellar atrophy.

cation. Three months later she was free from attack of headache or unsteady gait, but occasional oscillopsia and persistent nystagmus were seen.

DISCUSSION

Long-lasting ataxic attacks and interictal eye movement abnormalities were consistent with episodic ataxia type 2 (Table 1). Intermittent attacks of headache, vertigo and ataxia respond well to acetazolamide as seen in the patient reported and medication has no beneficial effect on interictal nystagmus as previously described[7]. EA2 is invariably inherited in an autosomal dominant fashion. Although this patient had no family history of any neurological disease, there are two possibilities to explain this phenomenon. Firstly, clinical analysis of carriers of mutations in EA2 families showed the highly variable penetrance, which asymptomatic carriers were identified in association with some mutations[8]. Thus one of her parents may be an asymptomatic carrier or, secondly, the patient may have had de novo mutation occurring spontaneously in her parents' sperm or ovum before fertilization. A case of de novo mutation of *CACNA1A* gene associated with EA2 was previously reported[9]. Since the *CACNA1A* gene is enormously large, spanning in 47 exons and consisting of 300 kilobases, difficulty arises in attempting to identify a pathogenic single-base change in the whole gene by current technology. Until now only a few centers in the world perform analysis of this gene. Though genetic analysis was not done in this patient, the diagnosis was secured on clinical grounds[1].

Cells require regulatory systems to maintain a stable environment and mechanisms for controlling cell-specific processes. Ion channels are essential for such crucial functions as nerve and muscle excitability, epithelial transport, regulation of cell volume and acid-base equilibrium. They contain a family of transmembrane glycoproteins that are made up of two or more subunits. Each has a pore-forming subunit which has a central aqueous pore through which ions permeate. Most ion channels are extremely selective and show specificity for a particular inorganic ion. The channels can transform between an open or closed state, a process known as gating, which involves a conformational change in the 'pore-forming' region[10]. Each channel is therefore classified either in terms of its ion specificity or by its mode of gating. Channels may be gated by a change in membrane potential (voltage-gated), action of an extracellular ligand (ligand-gated) or in response to a mechanical stimulus. Many channels are also influenced by intracellular second messenger systems[10]. To date over one hundred mutations in various ion channel genes were associated with muscle and central nervous system disorders, known as 'inherited channelopathies'[10]. The disorders characterized thus far have variable natural courses. Some exhibit a paroxysmal course e.g. EA1[11], while others have a primarily progressive course such as in SCA6 [12]. A few disorders exhibit a combination of paroxysmal features and progressive interictal tissue dysfunction e.g. EA2 and periodic paralysis[13].

EA2 often manifests in late childhood or adolescence. Patients experience intermittent attacks of cerebellar disturbance with vertigo and headache and exhibit nystagmus, ataxia and dysarthria. About 50 per cent of patients develop headache and nausea during an attack leading to the diagnosis of basilar migraine. The attacks may be prolonged lasting for several hours and sometimes days. Common precipitants are stress, exercise or fatigue. Interictally, nystagmus may be present, and a progressive cerebellar disturbance may ensue[2]. Neuroimaging often demonstrates cerebellar atrophy since the early stage of the illness (Fig. 1). Fortunately, most patients res-

Table 1. Features of episodic ataxia.

	EA1	EA2
Onset	Childhood	Childhood
Duration of attack	Seconds to minutes	Hours to days
Precipitants	Startles, sudden movement and stress	Stress and exercise
Additional ictal symptoms	None	Headache and nausea
Interictal signs	Myokymia	Nystagmus and progressive ataxia
Interictal EMG	Continuous repetitive discharges	Normal
Response to acetazolamine	Variable	Consistently good
Channel affected	K+ channel	Ca+ channel

pond to acetazolamide therapy, although the precise mechanism is still unclear[7,14].

By linkage analysis two research groups simultaneously identified locus of EA2 on chromosome 19p13 in which the gene for familial hemiplegic migraine (FHM) was previously mapped to the same locus[15,16]. Ophoff et al characterized a brain-specific P/Q-type calcium channel α_{1A}-subunit gene, *CACNA1A*, covering 300,000 base pairs with 47 exons in this region. The voltage-gated calcium channel comprises a single transcript four domains (domains I-IV) in tandem, each with six transmembrane helical segments. The investigators analysed *CACNA1A* gene and identified different types of mutations in EA2 and FHM, missense mutations in patients with FHM and splice-site and frame-shift mutations in patients with EA2[6]. Subsequently small polymorphic CAG repeat expansions in the 3′-terminus in the same gene have been described in some inherited progressive cerebellar ataxia, namely SCA6[17]. The three allelic calcium channel disorders, SCA6, EA2 and FHM are now well-known to be associated with particular types of mutations but correlations between types of mutations and clinical syndromes are still imperfect. The EA2 phenotype has also been reported with an underlying trinucleotide repeat expansion characteristic of SCA6[17,18]. Similarly, a missense mutation in one family manifested as EA2 in two affected members but as a severe progressive cerebellar ataxia in six others[19]. Recently, Hanna et al described a novel nonsense *CACNA1A* mutation in a patient with absence epilepsy and ataxia which was the first description of epileptic syndrome in association with the calcium channel mutation in humans. Functional expression also provided direct evidence that this mutation impaired calcium channel function as a dominant negative effect[20]. This data further expands the heterogeneous clinical phenotypes of this calcium channel.

SUMMARY

The first Thai patient with EA2 was reported. Apart from Korea there has been no previous report of EA2 in Asia[18]. Characteristic clinical features are easily recognized. The patient has responded well to acetazolamide medication. Genetic counseling is possible from diagnosis on clinical grounds, although prenatal diagnosis could not be offered due to a lack of molecular diagnosis.

(Received for publication on September 28, 2002)

REFERENCES

1. Zasorin NL, Baloh RW, Myers LB. Acetazolamide-responsive episodic ataxia syndrome. Neurology 1983; 33: 1212-4.
2. Gancher ST, Nutt JG. Autosomal dominant episodic ataxia : A heterogeneous syndrome. Mov Disord 1986; 1: 239-53.
3. Bhatia KP, Griggs RC, Ptacek LJ. Episodic movement disorders as channelopathies. Mov Disord 2000; 15: 429-33.
4. Litt M, Kramer P, Browne D, et al. A gene for episodic ataxia/myokymia maps to chromosome 12p13. Am J Hum Genet 1994; 55: 702-9.
5. Browne DL, Gancher ST, Nutt JG, et al. Episodic ataxia/myokymia syndrome is associated with point mutations in the human potassium channel gene, KCNA1. Nat Genet 1994; 8: 136-40.
6. Ophoff RA, Terwindt GM, Vergouwe MN, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4. Cell 1996; 87: 543-52.
7. Baloh RW, Yue Q, Furman JM, Nelson SF. Familial episodic ataxia : Clinical heterogeneity in four families linked to chromosome 19p. Ann Neurol 1997; 41: 8-16.
8. Denier C, Ducros A, Vahedi K, et al. High prevalence of CACNA1A truncations and broader clinical spectrum in episodic ataxia type 2. Neurology 1999; 52: 1816-21.
9. Yue Q, Jen JC, Thwe MM, Nelson SF, Baloh RW. De novo mutation in CACNA1A caused acetazolamide-responsive episodic ataxia. Am J Med Genet 1998; 77: 298-301.
10. Felix R. Channelopathies : Ion channel defects linked to heritable clinical disorders. J Med Genet 2000; 37: 729-40.
11. Adelman JP, Bond CT, Pessia M, Maylie J. Episodic ataxia results from voltage-dependent potassium channels with altered functions. Neuron 1995; 15: 1449-54.
12. Geschwind DH, Perlman S, Figueroa KP, Karrim J, Baloh RW, Pulst SM. Spinocerebellar ataxia type

6. Frequency of the mutation and genotype- phenotype correlations. Neurology 1997; 49: 1247-51.
13. Davies NP, Hanna MG. The skeletal muscle channelopathies: Basic science, clinical genetics and treatment. Curr Opin Neurol 2001; 14: 539-51.
14. Griggs RC, Nutt JG. Episodic ataxias as channelopathies. Ann Neurol 1995; 37: 285-7.
15. Kramer PL, Yue Q, Gancher ST, et al. A locus for the nystagmus-associated form of episodic ataxia maps to an 11-cM region on chromosome 19p. Am J Hum Genet 1995; 57: 182-5.
16. Teh BT, Silburn P, Lindblad K, et al. Familial periodic cerebellar ataxia without myokymia maps to a 19-cM region on 19p13. Am J Hum Genet 1995; 56: 1443-9.
17. Jodice C, Mantuano E, Veneziano L, et al. Episodic ataxia type 2 (EA2) and spinocerebellar ataxia type 6 (SCA6) due to CAG repeat expansion in the CACNA1A gene on chromosome 19p. Hum Mol Genet 1997; 6: 1973-8.
18. Koh SH, Kim HT, Kim SH, Lee GY, Kim J, Kim MH. Spinocerebellar ataxia type 6 and episodic ataxia type 2 in a Korean family. J Korean Med Sci 2001; 16: 809-13.
19. Yue Q, Jen JC, Nelson SF, Baloh RW. Progressive ataxia due to a missense mutation in a calcium-channel gene. Am J Hum Genet 1997; 61: 1078-87.
20. Jouvenceau A, Eunson LH, Spauschus A, et al. Human epilepsy associated with dysfunction of the brain P/Q-type calcium channel. Lancet 2001; 358: 801-7.

Episodic ataxia type 2 : โรคทางพันธุกรรมในกลุ่ม Channelopathies ที่พบไม่บ่อย

*ธีรธร พูลเกษ, พบ**

ผู้นิพนธ์รายงานผู้ป่วยชาวไทยรายแรกที่มีอาการจากโรคสมองน้อยเสื่อม อาการประกอบด้วยการเดินเซ, เวียนศีรษะและปวดศีรษะเป็นพัก ๆ ในขณะที่ไม่มีอาการปวดศีรษะและเดินเซ ผู้ป่วยสบายดี ยกเว้นตรวจพบ nystagmus การตรวจสมองด้วย Magnetic resonance imaging พบมีสมองน้อยฝ่อ อาการทั้งหมดดีขึ้น เมื่อผู้ป่วยได้รับการรักษาด้วย acetozolamide กลุ่มอาการดังกล่าวเป็นผลจากความผิดปกติของยีน votage-gated calcium channel ใน alpha 1A subunit และมีชื่อว่า 'Episodic ataxia type 2' รายงานนี้ได้เสนอทบทวนความรู้ในด้านพันธุกรรมที่เกี่ยวกับโรคดังกล่าวด้วย

คำสำคัญ : อาการเดินเซ, โรคสมองน้อยเสื่อม

ธีรธร พูลเกษ
จดหมายเหตุทางแพทย์ ฯ 2546; 86: 376–380

* สาขาวิชาประสาทวิทยา, ภาควิชาอายุรศาสตร์, คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10400