Eye movement disorders are an early manifestation of *CACNA1A* mutations in children

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ABBREVIATIONS

EA2	Episodic ataxia type 2
PTU	Paroxysmal tonic upgaze
SCA6	Spinocerebellar ataxia type 6

AIM The alpha-1 isoform of the calcium channel gene is expressed abundantly in neuronal tissue, especially within the cerebellum. Mutations in this gene may manifest with hemiplegic migraine, spinocerebellar ataxia type 6 (SCA6) and episodic ataxia type 2 (EA2) in adults. There are reports of children with *CACAN1A* mutations presenting with paroxysmal tonic upgaze, abnormal saccades and congenital nystagmus as well as severe forms of hemiplegic migraine. The aim of this study was to review the clinical presentation and subsequent course of all children with a *CACNA1A* mutation who presented to a tertiary children's hospital.

METHOD We reviewed retrospectively nine children with a proven *CACNA1A* mutation who presented to the Children's Hospital at Westmead between 2005–2015. The initial and subsequent clinical presentation, radiological features and molecular genetic profile of each child was reviewed.

RESULTS Nine children presented to out institute over a 10 year period; six were female and three male. The median age of presentation was 1.2 years. Eye movement disorders were the presenting feature in eight children. Three of these children later presented with severe hemiplegic migraine episodes often requiring ICU care. Affected children also had developmental delay and developed classical hemiplegic migraine, episodic ataxia and seizures. Calcium channel blockers were used with some efficacy in preventing severe HM episodes.

INTERPRETATION Eye movement disorders are an early manifestation of *CACNA1A* mutations in children. Improved recognition of the *CACNA1A* phenotype in childhood is important for early diagnosis, counselling and appropriate emergency management. There is some early evidence that calcium channel blockers may be an effective prophylactic agent for the severe hemiplegic migraine episodes.

The *CACNA1A* gene encodes the alpha-1 subunit of the voltage-gated calcium channel. The alpha-1 isoform is expressed abundantly in neuronal tissue especially within the cerebellum. In adults, spinocerebellar ataxia type 6 (SCA6), sporadic and familial hemiplegic migraine, and episodic ataxia type 2 (EA2) have been linked to *CACNA1A* mutations.[1] *CACNA1A*-associated hemiplegic migraine in adults has a wide phenotypic spectrum including recurrent episodes of coma associated with minor head trauma,[2,3] stroke-like episodes,[4] delayed fatal cerebral oedema[5,6] episodic ataxia, and a progressive cerebellar syndrome.[6]

In comparison, the paediatric literature on *CACNA1A* disorders is relatively sparse, and the recognition of the range of presentations in childhood is still in its evolution. Investigators have reported children with episodes of 'coma',[2,7] 'stroke',[4] acute encephalopathy,[8] and fatal cerebral oedema[5] in association with *CACNA1A* mutations. Some of these cases have been identified as extreme episodes of hemiplegic migraine[2,5] and various authors have trialled medications previously used with some efficacy in adult hemiplegic migraine[9] in children with these presentations.[4,10]

Eye movement disorders including paroxysmal tonic upgaze (PTU),[11,12] abnormal (hypometric or hypermetric) saccades,[13,14] and congenital nystagmus with episodic or progressive ataxia[15,16] have been separately reported in patients with *CACNA1A* mutations. However, the regularity of these findings in children with a *CACNA1A* mutation is yet to be established.

Understanding the phenotype of *CACNA1A* in childhood will hopefully lead to earlier diagnosis and improved

counselling about the condition. Most importantly, it will prompt physicians to consider anticipatory emergency management for the more severe presentations of hemiplegic migraine.

CASE SERIES

We reviewed retrospectively all children with a proven *CACNA1A* mutation who presented to the Children's Hospital at Westmead over a 10-year period (2005–2015). This case review was approved by the hospital ethics committee (CCR.2015.07). We identified nine children with *CACNA1A* mutations. Their clinical, radiological, and molecular genetic profile is summarized in Table I. All nine children were born at term without perinatal or neonatal problems. There were six females and three males, and the median age of presentation was 1 year 3 months (range 2mo–10y).

Initial clinical presentation

Abnormal eye movements were a presenting feature in all but one patient (patient 3). The eye movement disorders diagnosed formally by either neurologists or ophthalmologists were PTU, hypometric saccades, and strabismus. The diagnosis of PTU (n=3) was based on the original description by Ouvrier and Billson.[17] Children with PTU presented at a younger age (<6mo) compared to those with hypometric saccades or strabismus (>18mo). The children presenting with an eye movement disorder had additional problems including hypotonia, cerebellar ataxia, or epilepsy at presentation.

Subsequent clinical course

Six patients were diagnosed with global developmental delay within 2 years of their initial presentation, including all three patients with PTU.

The clinical phenotypes of children with *CACNA1A* mutations broadly resembled those described in adults. Patients 1, 2, 5, 6, 7, and 9 had cerebellar ataxia which was static in all patients except patient 1. Patient 1 had a progressive cerebellar ataxia syndrome and by 13 years of age was no longer able to ambulate independently.

Patients 1, 2, and 9 had severe hemiplegic migraine. Patient 1 presented with recurrent episodes of hemiplegic migraine characterized by delirium, headache, vomiting, and overwhelming lethargy triggered by minor head trauma. These episodes started at 4 years of age. She had three major episodes annually. Each episode lasted up to 24 hours. Minor episodes were relieved by analgesia and sleep. One particularly severe hemiplegic migraine episode at 12 years of age was characterized by a dense left-sided hemiplegia that lasted for 4 weeks. Magnetic resonance imaging (MRI) demonstrated marked left hemispheric oedema but no accompanying diffusion restriction. She regained function over 3 months. Patient 2 presented with a severe hemiplegic migraine episode at 18 months of age after he fell from his high chair onto soft flooring. He did not lose consciousness. An hour later he had a left-sided hemiclonic seizure, then became progressively encephalopathic with a dense left-sided hemiparesis. Computed tomography (CT) was normal and an MRI performed 24 hours later was normal apart from pancerebellar atrophy. There was right hemispheric slowing on EEG. He made a full recovery and was discharged 5 days after the presentation. Patient 9 had three episodes of hemiplegic migraine characterized by a decreased level of consciousness following minor head trauma from 2 years of age. He had confusion and lethargy for several hours with each episode before making a full recovery. Brain CT performed after the first episode was normal.

Patient 3 is the only patient who presented with a 'classical' adult phenotype of *CACNA1A*-related hemiplegic migraine. He was also the only patient without abnormal eye findings and remains intellectually normal. He presented with episodes of right-sided hemiplegic migraine accompanied by confusion and difficulty with word finding from 10 years of age. EEG showed bilateral parietal-occipital slowing more marked over the left. He made a full functional recovery from each episode, albeit over several months. He subsequently developed chronic daily headache.

Patients 4 and 8 had recurrent episodes of ataxia exacerbated by acute illness and fatigue, similar to adults with EA2. Both also have migraine without aura. Patient 8 had an interictal EEG during an episode of ataxia that showed a diffuse alpha rhythm in both wakefulness and in sleep.

What this paper adds

- Eye movement disorders are an early manifestation of *CACNA1A* mutations in children.
- Coma-like episodes of hemiplegic migraine can be frequent in childhood and consideration needs to be given for appropriate acute and prophylactic management.

Family history

A positive family history was found in four families (Table 1). The underlying *CACNA1A* mutation had been previously identified in one family (Patient 4).

Neuroimaging

Patients 1, 2, and 9 had brain CT as described above.

Brain MRI was performed in eight patients (patients 1–8) during their initial presentation. Six were normal. Three patients with an initial normal MRI had a subsequent scan; two depicted progressive cerebellar atrophy (patients 1 and 2), and the other generalized mild cerebral atrophy (patient 3). In total 5 patients had an abnormal MRI brain.

CACNA1A mutations

There were seven mutations found in the eight families, three of which were novel (Table I). Patient 3 had a novel *CACNA1A* mutation and was negative for *ATP1A2* and *SCN1A* mutations also known to cause hemiplegic migraine. His asymptomatic father (60y old) carries the same mutation. Variable penetrance has been described in other families with a common *CACNA1A* mutation.[12,18,19]

Table I: Clinical presentation of nine children with *CACNA1A* mutations

Patient, Sex	Presenting feature (age)		Subsequent course (age onset)	Brain MRI: initial and subsequent (age)	Family history	Gene mutation	Previous report references
	Eye movement	Other disorder					
1, F	PTU (3mo)	Hypotonia	GDD, progressive cerebellar ataxia (1y), SHM (severe coma-like +/−mild head injury, hemiplegic) (4y)	Normal (1y), Pancerebellar atrophy (8y)	Nil	c.4046G>A Arg1349Gln NM_001127221.1	Severe HM, PTU, and progressive CA[4,7,11,25,27]
2, M	PTU (2mo)	Hypotonia	GDD, SHM (severe, coma-like with mild head injury, hemiplegic) (1.5y)	Normal (6mo) Pancerebellar atrophy (1.5y)	Nil	c.4046G>A Arg1349Gln NM_001127221.1	Severe HM, PTU, and progressive CA[4,7,11,25,27]
3, M	–	SHM (11y)	Recurrent SHM (>11y), chronic daily headache	Normal (10y) Mild global atrophy (15y)	Nil	c.1822C>T Leu608Phe NM_000068.3	–
4, F	Dysmetric saccades (10y)	Absence epilepsy, episodic ataxia	Learning difficulties, classical migraine (13y)	Normal (11y)	EA2 in father, paternal aunt, paternal grandfather	c.5260G>A Arg1666His NM_000068.3	EA2, FHM[28]
5, F	Dysmetric saccades and esotropic strabismus (3y)	GDD	Progressive cerebellar ataxia (3y), ADHD (8y)	Normal (6y)	Progressive cerebellar syndrome in father (SCA6-like)	c.1748G>A Arg583Gin NM_023035.2	FHM and SHM[3,29–31]
6, F	Dysmetric saccades (3y)	Cerebellar ataxia, GDD	Cerebellar ataxia (4y)	Cerebellar vermis atrophy (3y)	Strabismus, progressive cerebellar syndrome in mother, SCA6-like	c.4009G>T Asp 1337Tyr NM_01127222.1	–
7, F	Bilateral intermittent esotropic strabismus (14mo)		Cerebellar ataxia (6y)	Pancerebellar atrophy (7y)	Sibling of patient 6 (as above)	c.4009G>T Asp1337Tyr NM_01127222.1	–
8, F	PTU (4mo)		Episodic ataxia (18mo), GDD (4y), classical migraine (12y)	Normal (1y and 14y)	Nil	c.889G>A Gly297Arg NM_001127221.1	–
9, M	Alternating, non-accommodative esotropic strabismus (18mo)	GDD	Cerebellar ataxia, FHM (coma with mild head injury) (2y)	No MRI Brain CT normal	Strabismus, FHM (coma and hemiplegia) in mother	c.653C>T, Ser218Leu NM_001127221.1	HM[5,32]

MRI, magnetic resonance imaging; PTU, paroxysmal tonic upgaze; GDD, global developmental delay; F/SHM, familial or sporadic hemiplegic migraine; CA, cerebellar ataxia; EA2, episodic ataxia type 2; ADHD, attention-deficit–hyperactivity disorder; SCA6, spinocerebellar ataxia type 6.

Patients 6 and 7 are half-sisters and carry the same novel *CACNA1A* mutation, as does their mother who has SCA6. Patient 8 has a de novo mutation. The mutation was not found in 200 controls.

All detected mutations were missense mutations with details in Table I. For the novel mutations (patients 3, 6, 7, and 8) prediction of mutation effect was carried out using SIFT, PolyPhen, and Mutation Taster, and all their mutations were shown to be disease-causing. SIFT and PolyPhen predict mutational effect by reference to sequence conservation. Mutation Taster additionally includes determination of intron–exon splice site alterations, impact on the presence of regulatory features, histone binding sites, and other elements that may affect gene or protein function. In addition, we further investigated whether patients 3 and 6 carried expansions of the CAG sequence that is found in the carboxy terminal region of the *CACNA1A* protein in chromosome 19. Both patients had 13 CAG repeats when checked using the Integrative Genomics Viewer software.[20,21] This is within the normal range of 4–18 CAG units.[22] Therefore, a CAG elongation size was not responsible for the cerebellar ataxia phenotype in patients 3 and 6. Patient 7 underwent specific exon sequencing only, and no CAG repeat data is available.

Treatment

Hemiplegic migraine

The three patients with severe hemiplegic migraine were treated with various medications in an effort to decrease the severity and/or frequency of the episodes. Patient 1 was treated with IV methylprednisolone during the acute episodes and was prescribed daily verapamil following her severe hemiplegic migraine episode (12y). She has had no further severe hemiplegic migraine episodes in the 14 months of treatment. Her parents have found that her current migraines are less severe and respond to regular migraine treatment at home. Patient 2 was commenced on verapamil at the age of 3 years following three episodes of hemiplegic migraine with coma within a 2-year period. He has been on treatment for 8 months and has had no further episodes. Patient 3 had classic hemiplegic migraine and had four episodes over a 5-year period in early adolescence. Each episode was managed with intravenous corticosteroids followed by oral prednisolone. He has not had an episode over the past 2 years. He was also diagnosed with chronic daily headache for which he was treated with propranolol with no clear benefit. His headache is reasonably well controlled on dothiepin (tricyclic antidepressant), riboflavin, and pizotifen. Patient 9 was commenced on acetazolamide at 3 years of age following four episodes within 6 months of hemiplegic migraine associated with minor head trauma and coma. He has been on this treatment for 5 months with no further episodes.

Episodic ataxia

Patient 4 was treated for 2 years with acetazolamide, which decreased the frequency of ataxic episodes but was discontinued by the patient because she thought it was triggering her migraines. She has been on other medications for seizures (see below). Patient 8 has been on a number of medications including carbamazepine (CBZ), topiramate (TOP), acetazolamide (ACZ), and 4-aminopyridine (4-AP) which have either been ineffective, exacerbated the ataxia (CBZ, TOP, 4-AP), or had intolerable side effects (ACZ). She is not currently on treatment.

Seizures

Patient 4 has refractory absence epilepsy as well as episodic ataxia. She has been on topiramate, leveteracitam, and ethosuximide without benefit. She is currently on sodium valproate but has ongoing brief seizures.

DISCUSSION AND LITERATURE REVIEW

We have described the presentation and disease course of nine children with *CACNA1A* mutations from our institution. There was a wide range in the age of presentation (2mo–10y) though six of the nine children presented in the first 2 years of life.

An eye movement disorder was a common presenting feature seen in eight of the nine children, none of whom followed a 'benign' course. PTU, strabismus, and abnormal saccades have been previously reported in children with *CACNA1A* mutations.[11–13,15] This finding would suggest that an eye movement disorder may be a clue to the underlying diagnosis especially if there is evidence of developmental delay or cerebellar atrophy on MRI. The concept of a 'pre-symptomatic' eye movement disorder has previously been suggested by Christova et al. in adults diagnosed with SCA6.[14] It was suggested that the function of the posterior cerebellar vermis and flocculus is impaired early in patients with a *CACNA1A* mutation, accounting for the early manifestation of the eye movement disorder.[14] Our series and review of the literature suggests that the early presentation of an eye movement disorder is not limited to adults with SCA6, and may be an early manifestation of *CACNA1A* mutations in childhood.[3,4,12–14] Children with PTU have been described as following a relatively benign course;[17,23] however, more recently a number of neurological disorders including cerebellar ataxia, borderline intellectual abilities, delayed early motor development, and residual ocular motor apraxia have all been associated with the condition.[11,12,18,24] All three children with PTU in our cohort were diagnosed with global developmental delay in conjunction with other more significant paroxysmal disorders. A comprehensive genetic study of PTU will likely reveal that *CACNA1A* will account for a small yet significant proportion of cases.

Three of our patients with an eye movement disorder and global delay subsequently developed recurrent episodes of neurological impairment including coma with minor head trauma, 'stroke-like' episodes with hemiplegia, or seizures. These episodic disorders closely mimic the variable presentations of hemiplegic migraine associated with *CACNA1A* mutations described in adults.[1,2,16,25]

The combination of developmental delay and cerebellar atrophy on MRI is common and can be diagnostically challenging if the neuro-metabolic workup is unremarkable. Cerebellar atrophy has been reported in children with *CACNA1A* mutations[1,11,25] and is an important clue to the diagnosis. In a study by Ohba et al., whole exome sequencing identified an underlying genetic cause in 39% of children with cerebellar and/or vermal atrophy including a *CACNA1A* mutation in two unrelated children.[26]

There are no randomized control trials of hemiplegic migraine treatment. Anecdotal evidence suggests that verapamil is helpful in severe hemiplegic migraine, both acutely and as prophylaxis.[4,9,10] Some *CACNA1A* mutations including Arg1346Gln and Ser218Leu (patients 1, 2, 8) lead to a gain in function of the calcium channel by increasing the open probability of the channel and therefore increasing calcium influx[4,25] which may provide a pathophysiological basis for treating with a calcium channel blocker like verapamil. Our study reports only a short period of follow-up in a small number of patients. Further prospective trials are required to determine the true effectiveness of verapamil in *CACNA1A* disorders.

A weakness of our study is that it is retrospective. A multicentre research study with gene sequencing of all children with PTU would identify the true frequency of *CACNA1A* mutations in this cohort. It is our suggestion that all children with PTU, and an ocular motor apraxia or strabismus (when associated with developmental delay or cerebellar atrophy and without an alternative explanation) should be considered for *CACNA1A* genetic testing. Recognition of the wide phenotypic spectrum of *CACNA1A* is important in directing genetic testing, to inform families of the variable (and severe) presentations of hemiplegic migraine, and for providing a management plan for severe hemiplegic migraine episodes. Clues to the diagnosis of *CACNA1A* include an eye movement disorder in early infancy in conjunction with developmental delay with/without cerebellar atrophy on MRI. Children with a confirmed *CACNA1A* mutation are at risk of severe hemiplegic migraine episodes and consideration should be given to prophylactic treatment with verapamil.

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