

## TEACHING CASE REPORT

### A case of intermittent ataxia associated with migraine headaches

**The case:** A previously healthy 42-year-old woman had presented to our neurology service 1 year earlier with left-sided temporal headaches that she said typically lasted from a few hours to all day. They were associated with nausea but not with vomiting. Beginning at age 13 years, these headaches had occurred at a frequency of once a month to once every 2–3 months. The woman did not experience visual auras, such as scintillation photopsias (flashes of light), migrating scotomata (patches of blurred or absent vision) or fortification spectra (wavy linear “zig-zag” patterns that resemble the battlements of a medieval fort). She had no history of vertigo or seizures. The headaches tended to occur around the time of her menses. She rated the pain at 3 on a scale of 1–10 (10 being most severe), but she noted that on occasion the headaches could be severe enough to wake her from sleep and merit a pain rating of 8 or 9. Clinical examination was unremarkable during each of her visits. Ten years earlier, atypical migraine had been diagnosed and treated symptomatically; no migraine prophylaxis had been given in view of her infrequent and mild headaches. Magnetic resonance imaging scans of the brain were unremarkable. The diagnosis of atypical migraine was not altered at this time.

One year after her initial visit to our neurology service, the patient was admitted to hospital because of unsteadiness of gait, gaze-evoked nystagmus and truncal ataxia (see video of typical episode, available online at [www.cmaj.ca/cgi/content/full/177/6/565/DC1](http://www.cmaj.ca/cgi/content/full/177/6/565/DC1)). She did not report experiencing headaches at the time. Her condition resolved spontaneously after about 18 hours, and findings on clinical examination were normal. She had no hearing loss

or dysarthria and did not display any myokymia about the eyes, lips or fingers. She recalled experiencing similar mild attacks since the age of 25 that involved clumsiness and occasional falls and that lasted from a few hours to a day. These attacks were not associated with diplopia, hearing loss, weakness, choreiform movements, abnormal posturing, fatigable weakness, cognitive deficits, seizures, stiffness or myotonia. The attacks were not related to head position or change of posture. Her migraine headaches occurred both with and without episodes of ataxia. Similarly, ataxic episodes occurred without migraine headaches. An electroencephalogram appeared normal, as were the results of routine blood tests, including blood count, electrolyte levels and serum glucose level. The patient provided a detailed family history, describing intermittent clumsiness in her father and migraine headaches in 2 of 4 siblings.

A provisional diagnosis of episodic ataxia type 2 was made in view of the patient’s history of migraine, episodes of ataxia with normal examination between episodes and a strong family history.<sup>1,2</sup> The patient responded to acetazolamide, 250 mg 3 times a day, but experienced relapses of ataxia once or twice a year when she did not take her medication. With amelioration of her ataxic episodes, she became bothered by her migraine headaches, which responded to prophylaxis with amitriptyline and indomethacin for analgesia. Sumatriptan was efficacious for more severe migraine headaches.

The patient underwent genetic counselling and testing. None of the known mutations that cause episodic ataxia was detected in exons 23, 26, 28, 29, 32 and 35 of the calcium-channel gene (*CACNA1A*) on chromosome

#### Box 1: Possible diagnoses in a patient with ataxia

##### Primary intermittent ataxia syndromes (often not progressive) *With headaches*

- Episodic ataxia type 2
- Basilar migraines
- Episodic ataxia with paroxysmal choreoathetosis and spasticity
- Familial hemiplegic migraines

##### *Without headaches\**

- Episodic ataxia type 1
- Periodic vestibulocerebellar ataxia
- Spinocerebellar ataxia type 6

##### Secondary intermittent ataxias\* (often progressive)

- Hartnup’s disease
- Pyruvate decarboxylase deficiency
- Leigh’s disease
- Hereditary hyperammonemias

##### Primary ataxia syndromes\* (sometimes progressive)

- Spinocerebellar ataxia
- Multiple system atrophy
- Celiac disease
- Antiphospholipid syndrome
- Paroxysmal psychosis
- Seizures
- Drugs (e.g., anticonvulsants)
- Toxins (e.g., alcohol)

##### “Pseudoataxia”\*

- Paroxysmal kinesigenic dyskinesias

\*Headaches may occur incidentally.

19p13, which codes for the main transmembrane component of the neuronal calcium channel.<sup>2</sup>

Ataxia can be progressive, stable or episodic and can occur with or without headaches (Box 1). Our patient had migraine headaches and episodes of ataxia, with normal clinical findings between attacks. Her ataxic episodes and migraines may have been distinct but coincidental clinical entities or manifestations of a single disease. A

**Table 1: Clinical characteristics of the key forms of episodic ataxia with and without headaches**

Characteristic	Episodic ataxia with choreoathetosis and spasticity <sup>1</sup>				Episodic ataxia type 2 <sup>1,2</sup>		Episodic ataxia with paroxysmal cerebellar ataxia type 1 <sup>1,2</sup>		Episodic ataxia type 2 <sup>1,2</sup>		Episodic ataxia with paroxysmal choreoathetosis and spasticity <sup>1</sup>		Basilar type migraine <sup>3</sup>		Familial hemiplegic migraine <sup>1,2</sup>		Periodic vestibulocerebellar ataxia <sup>1</sup>		Spinocerebellar ataxia type 6 <sup>4</sup>		
	Childhood	Attacks of midline cerebellar disturbances lasting seconds to minutes	None	Attacks of midline cerebellar disturbances lasting hours	Childhood to second decade	Attacks of midline cerebellar disturbances lasting minutes	Occasional attacks lasting minutes	Occasional headaches	First to second decade	Attacks of midline cerebellar disturbances lasting hours	Emotional and physical stress	Emotional and physical stress	Myokymia uncommon. Subtle, slowly progressive interictal cerebellar signs, especially nystagmus	Myokymia prominent. May be associated with epilepsy, infantile contractions and neuromyotonia. Ictal dysarthria in some cases	Not applicable						
Onset	Childhood	Attacks of midline cerebellar disturbances lasting seconds to minutes	None	Attacks of midline cerebellar disturbances lasting hours	Childhood to second decade	Occasional attacks lasting minutes	Occasional headaches	First to second decade	Attacks of midline cerebellar disturbances lasting hours	Emotional and physical stress	Emotional and physical stress	Myokymia uncommon. Subtle, slowly progressive interictal cerebellar signs, especially nystagmus	Myokymia prominent. May be associated with epilepsy, infantile contractions and neuromyotonia. Ictal dysarthria in some cases	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Type and duration of ataxia	Attacks of midline cerebellar disturbances lasting seconds to minutes	None	Attacks of midline cerebellar disturbances lasting hours	Childhood to second decade	Attacks of midline cerebellar disturbances lasting minutes	Occasional attacks lasting minutes	Occasional headaches	First to second decade	Attacks of midline cerebellar disturbances lasting hours	Emotional and physical stress	Emotional and physical stress	Myokymia uncommon. Subtle, slowly progressive interictal cerebellar signs, especially nystagmus	Myokymia prominent. May be associated with epilepsy, infantile contractions and neuromyotonia. Ictal dysarthria in some cases	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Type and duration of headache	None	None	None	None	Occasional headaches	Occasional headaches	Occasional headaches	Occasional headaches	Occasional headaches	Occasional headaches	Occasional headaches	Occasional headaches	Occasional headaches	Occasional headaches	Occasional headaches	Occasional headaches	Occasional headaches	Occasional headaches	Occasional headaches	Occasional headaches	Occasional headaches
Triggers	Emotional (startle) and physical stress	Emotional (startle) and physical stress	Emotional and physical stress	Emotional and physical stress	Physical exertion, sleep deprivation, emotional stress, alcohol	Physical exertion, sleep deprivation, emotional stress, alcohol	Physical exertion, sleep deprivation, emotional stress, alcohol	Physical exertion, sleep deprivation, emotional stress, alcohol	Physical exertion, sleep deprivation, emotional stress, alcohol	Physical exertion, sleep deprivation, emotional stress, alcohol	Physical exertion, sleep deprivation, emotional stress, alcohol	Physical exertion, sleep deprivation, emotional stress, alcohol	Physical exertion, sleep deprivation, emotional stress, alcohol	Physical exertion, sleep deprivation, emotional stress, alcohol	Physical exertion, sleep deprivation, emotional stress, alcohol	Physical exertion, sleep deprivation, emotional stress, alcohol	Physical exertion, sleep deprivation, emotional stress, alcohol	Physical exertion, sleep deprivation, emotional stress, alcohol	Physical exertion, sleep deprivation, emotional stress, alcohol	Physical exertion, sleep deprivation, emotional stress, alcohol	Physical exertion, sleep deprivation, emotional stress, alcohol
Other neurologic manifestations	Interictal neuromyotonia and myokymia prominent. May be associated with epilepsy, infantile contractions and neuromyotonia. Ictal dysarthria in some cases	Interictal neuromyotonia and myokymia prominent. May be associated with epilepsy, infantile contractions and neuromyotonia. Ictal dysarthria in some cases	Interictal neuromyotonia and myokymia prominent. May be associated with epilepsy, infantile contractions and neuromyotonia. Ictal dysarthria in some cases	Interictal neuromyotonia and myokymia prominent. May be associated with epilepsy, infantile contractions and neuromyotonia. Ictal dysarthria in some cases	Choreoathetosis, dystonia, paresthesia, diplopia	Choreoathetosis, dystonia, paresthesia, diplopia	Choreoathetosis, dystonia, paresthesia, diplopia	Choreoathetosis, dystonia, paresthesia, diplopia	Choreoathetosis, dystonia, paresthesia, diplopia	Choreoathetosis, dystonia, paresthesia, diplopia	Choreoathetosis, dystonia, paresthesia, diplopia	Choreoathetosis, dystonia, paresthesia, diplopia	Choreoathetosis, dystonia, paresthesia, diplopia	Choreoathetosis, dystonia, paresthesia, diplopia	Choreoathetosis, dystonia, paresthesia, diplopia	Choreoathetosis, dystonia, paresthesia, diplopia	Choreoathetosis, dystonia, paresthesia, diplopia	Choreoathetosis, dystonia, paresthesia, diplopia	Choreoathetosis, dystonia, paresthesia, diplopia	Choreoathetosis, dystonia, paresthesia, diplopia	Choreoathetosis, dystonia, paresthesia, diplopia
Neuroradiology	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Treatment	Acetazolamide, carbamazepine, sulthiame, amphetamines	Acetazolamide, phenytoin	Acetazolamide, phenytoin	Acetazolamide, phenytoin	Acetazolamide, phenytoin	Acetazolamide, phenytoin	Acetazolamide, phenytoin	Acetazolamide, phenytoin	Acetazolamide, phenytoin	Acetazolamide, phenytoin	Acetazolamide, phenytoin	Acetazolamide, phenytoin	Acetazolamide, phenytoin	Acetazolamide, phenytoin	Acetazolamide, phenytoin	Acetazolamide, phenytoin	Acetazolamide, phenytoin	Acetazolamide, phenytoin			
Pathogenesis	Potassium channelopathy	Potassium channelopathy	Potassium channelopathy	Potassium channelopathy	Possibly potassium channelopathy	Possibly potassium channelopathy	Possibly potassium channelopathy	Possibly potassium channelopathy	Possibly potassium channelopathy	Possibly potassium channelopathy	Possibly potassium channelopathy	Possibly potassium channelopathy	Possibly potassium channelopathy	Possibly potassium channelopathy	Possibly potassium channelopathy	Possibly potassium channelopathy	Possibly potassium channelopathy	Possibly potassium channelopathy	Possibly potassium channelopathy	Possibly potassium channelopathy	Possibly potassium channelopathy
Inheritance; gene identified	Autosomal dominant; KCNA17 gene on chromosome 12	Autosomal dominant; linked to chromosome 1p	Autosomal dominant; linked to chromosome 1p	Autosomal dominant; linked to chromosome 1p	Autosomal dominant; linked to chromosome 1p	Autosomal dominant; linked to chromosome 1p	Autosomal dominant; linked to chromosome 1p	Autosomal dominant; linked to chromosome 1p	Autosomal dominant; linked to chromosome 1p	Autosomal dominant; linked to chromosome 1p	Autosomal dominant; linked to chromosome 1p	Autosomal dominant; linked to chromosome 1p	Autosomal dominant; linked to chromosome 1p	Autosomal dominant; linked to chromosome 1p	Autosomal dominant; linked to chromosome 1p	Autosomal dominant; linked to chromosome 1p	Autosomal dominant; linked to chromosome 1p	Autosomal dominant; linked to chromosome 1p			

Note: MRI = magnetic resonance imaging, SPECT = single-photon emission computed tomography, NSAID = nonsteroidal anti-inflammatory drug.

discussion of the differential diagnosis of recurrent and relapsing ataxia follows.

Episodic ataxias are characterized by spontaneous paroxysmal periods of ataxia that typically last from minutes to hours or days. Between episodes, the patient is normal, except for the presence of gaze-dependent or downbeat nystagmus.<sup>1,2</sup> Migraine is associated with episodic ataxia in a variety of conditions, such as basilar type migraine; episodic ataxia types 1 and 2; episodic ataxia with paroxysmal choreoathetosis and spasticity; periodic vestibulocerebellar ataxia; and familial hemiplegic migraine.<sup>1</sup> The clinical characteristics and distinguishing features of these conditions are summarized in Table 1.

Our patient likely had episodic ataxia type 2 in view of her history of migraine, fairly long ataxic episodes (lasting minutes to hours), good clinical response to acetazolamide therapy and relevant family history. *CACNA1A* encodes the  $\alpha$ -1A subunit of the voltage-dependent P/Q-type calcium channel, mainly expressed in the Purkinje cells of the cerebellum. Calcium channelopathy is thought to lead to alterations in intracellular pH, which alters the transmembrane potential. Acetazolamide is thought to normalize intracellular pH and thus restore Purkinje cell function.<sup>5</sup> The patient's negative genetic screen for episodic ataxia type 2 does not rule out the possibility that she has the condition, since we screened for only 6 of the mutations described to date. It is also possible, of course, that our patient carries a novel mutation in the *CACNA1A* gene or carries a mutation in some other gene. For example, a family whose members have the phenotype for episodic ataxia type 2 but who carry the genotype for episodic ataxia type 1 has been described.<sup>6</sup>

We ruled out basilar type migraine<sup>3</sup> on the basis of the temporal dissociation between migrainous and ataxic episodes, as well as the patient's favourable response to acetazolamide. We also excluded episodic ataxia with paroxysmal choreoathetosis and spasticity as well as familial hemiplegic migraine because of the absence of chorea, stiffness and hemiplegia during the headaches.

Channelopathies, such as paroxysmal kinesigenic dyskinesias, can be associated with migraine and can mimic episodic ataxias. Clinical examination during the attack (see online video, available at [www.cmaj.ca/cgi/content/full/177/6/565/DC1](http://www.cmaj.ca/cgi/content/full/177/6/565/DC1)) confirmed the presence of truncal ataxia rather than dyskinesia.

Migrainous headaches have also been reported to occur incidentally in patients who have ataxia because of other diseases, such as spinocerebellar ataxia type 6, celiac disease, antiphospholipid syndrome, paroxysmal psychosis and seizures. Similarly, they can occur in patients with cerebellar dysfunction or acutely from drugs (e.g., anticonvulsants) or toxins (e.g., alcohol).

Finally, ataxia may be seen intermittently as part of several recessively inherited diseases, such as Hartnup's disease, pyruvate decarboxylase deficiency, Leigh's disease and hereditary hyperammonemias. These conditions are usually associated with other signs, such as mental retardation, seizures and pyramidal dysfunction.

Episodic ataxia type 2 is treated with carbonic anhydrase inhibitors, such as acetazolamide, as well as migraine prophylaxis and therapy with analgesics. Magnetic resonance spectroscopy studies have demonstrated an increase in cerebellar pH in affected patients, which returns to normal on consumption of acetazolamide. The disease runs a relatively benign course, although progression to severe persistent cerebellar ataxia has been described in some cases.<sup>2</sup> Our patient has remained well 6 years after initiation of therapy.

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See an online video showing an episode of moderately severe truncal ataxia (available at [www.cmaj.ca/cgi/content/full/177/6/565/DC1](http://www.cmaj.ca/cgi/content/full/177/6/565/DC1)). The patient did not have a migraine headache during this episode.

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