carbonic anhydrase, which results in brain acidosis and reduction of brain lactate and pyruvate levels.¹ However, metabolic acidosis itself may give rise to several clinical manifestations, and there have been case reports describing drowsy mentality with metabolic acidosis by acetazolamide intoxication.^{2,3} We report on a patient with EA 2, who initially had a good response to acetazolamide for 2 years but later developed aggravation of ataxia with drowsy mentality caused by acetazolamide induced hyperammonaemia.

Case report

A 49-year-old man reported dizziness and ataxia which had started 4 days before admission. He had experienced several episodes of similar symptoms for the past 4 years. He had recurrent episodes of headaches, dizziness, nausea/vomiting, dysarthria and ataxia which had lasted for hours to days. Between the episodes, he showed gaze evoked nystagmus without spontaneous nystagmus. Horizontal head thrust tests were normal. Vibratory stimuli on both mastoids, horizontal head oscillation or hyperventilation did not induce nystagmus. Other findings of the neurological examination were normal. During the episodes, examination disclosed downbeat and aggravated gaze evoked nystagmus, rebound nystagmus, positional downbeat nystagmus, impaired smooth pursuit, hypometric saccades, slurred speech, and gait and limb ataxia. Vibratory stimuli on both mastoids, and horizontal head oscillation augmented downbeat nystagmus. Routine blood chemistry, EEG, CSF studies and brain MRI were normal. Genetic studies were unavailable. He denied any other diseases, including hypertension, diabetes, and liver or kidney disease. He did not have a history of seizure or inborn errors of metabolism, and did not take any medication or alcohol. He denied a family history of ataxia or other diseases. Based on the above findings, he was given acetazolamide 250 mg four times a day with a presumptive diagnosis of EA 2 from 2 years previously. The patient reported that the frequency and severity of attacks were significantly decreased after taking acetazolamide for 2 years.

With this attack he was found to have gaze evoked nystagmus, positional nystagmus, dysarthria and aggravated gait ataxia, which was similar to the previous attacks. This time, however, he was drowsy and was unable to speak unless painful stimuli were given. The Glasgow Coma Scale was measured as E3V4M6. His vital signs were normal. He was not taking any other medication except for acetazolamide 250 mg four times a day. He had suffered a mild upper respiratory tract infection 1 week prior to the event.

In view of the decreased mentality, routine blood chemistry, urinalysis, CSF studies and brain MRI were performed to exclude any other causes that might explain his decreased mentality. Again his brain MRI was normal, without any lesion or atrophy involving the cerebellum or brainstem. Laboratory data showed hyperammonaemia at 158 µg/dl (normal 8–48) and metabolic acidosis compensated by respiration with a pH of 7.39 (normal 7.38–7.46), pCO₂ of 23.4 mm Hg (normal 32–46) and HCO₃⁻ of 13.9 mmol/dl (normal 21–29). Other findings on blood chemistry, urinalysis and CSF studies were normal. Amino acid analysis in the serum and urine, and abdominal CT, which were performed to exclude

underlying liver disease or enzyme defects, showed no abnormality. He was maintained on acetazolamide but 3 days later ammonia levels increased to 660 µg/dl while ataxia and dysarthria were severely aggravated. After discontinuation of acetazolamide, his symptoms began to improve, and 10 days later serum ammonia had decreased to 122 µg/dl when his symptoms almost resolved. He was considered to suffer from acetazolamide induced hyperammonaemia and discharged without acetazolamide medication.

Comment

This is the first case showing an attack of ataxia due to acetazolamide induced hyperammonaemia in a patient with clinically diagnosed EA 2. Even though our patient denied a family history of ataxia and rejected genetic studies, the clinical manifestations and initial good response to acetazolamide suggest EA 2 as the most probable diagnosis. However, during the last episode, our patient had also developed a reduced level of consciousness, a rare manifestation of EA 2, which prompted us to search for causes other than EA 2. Laboratory data were normal except for hyperammonaemia which decreased markedly after discontinuation of acetazolamide, along with resolution of his symptoms. The level of arterial ammonia was proportional to the severity of his symptoms, and hyperammonaemia was normalised by discontinuing acetazolamide, without any further aggressive management such as haemodialysis. A recent history of upper respiratory tract infection might have influenced drug metabolism and caused hyperammonaemia but we failed to find any distinct cause explaining the acute adverse effect of acetazolamide.

The kidneys contribute to the acid-base balance by reabsorbing filtered HCO₃⁻ and excreting H⁺ in the form of titrate acid or ammonium. The ability to excrete H⁺ as ammonium contributes to the flexibility of the renal acid-base regulation as the rate of NH₄⁺ production and excretion can be modulated according to physiological needs. Acetazolamide, a carbonic anhydrase inhibitor that mainly acts on the proximal tubule of the kidney, induces metabolic acidosis by inhibiting bicarbonate reuptake. In metabolic acidosis, the kidneys increase NH₄⁺ excretion in two ways: by increasing proximal NH₄⁺ production from glutamine and by lowering urine pH, which would increase NH₃ diffusion into the lumen and result in NH₄⁺ production in combination with H⁺.⁴ The increased production of NH₃, caused by metabolic acidosis, and the relative decrease in H⁺ in the tubular lumen due to a carbonic anhydrase inhibitor, such as acetazolamide, give rise to hyperammonaemia, as in our patient.

Hyperammonaemia is an important cause of acute metabolic encephalopathy and a potentially lethal condition, and a differential diagnosis of hyperammonaemia must include liver disease, renal disease, critical medical conditions such as hypovolaemia or sepsis, and drug induced and enzyme defects (eg, urea cycle and organic acid disorders). Prompt management must be taken, which includes hydration with adequate urine output, removal of nitrogen by dialysis or medication, discontinuation of protein intake and minimisation of catabolism.

Acetazolamide was initially introduced as a diuretic but is now widely used in patients

with glaucoma, epilepsy, periodic paralysis and EA. Acetazolamide should be used with caution in patients with a previous history of hepatic or renal diseases. When a patient with EA 2 shows aggravation of ataxia with reduced alertness, emergent screening of arterial blood gas and serum ammonia is warranted to exclude acetazolamide induced hyperammonaemia even after an initial good response to acetazolamide. The potassium channel blocking agent, 4-aminopyridine, could be considered as an alternative medication.⁵

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doi: 10.1136/jnnp.2006.105353

This work was supported by a Korea Research Foundation Grant (KRF-2004-003-E00202).

Competing interests: None.

References

- Gordon N. Episodic ataxia and channelopathies. *Brain Dev* 1998;**20**:9–13.
- Baer E, Reith DM. Acetazolamide poisoning in a toddler. *J Paediatr Child Health* 2001;**37**:411–12.
- Watson WA, Garrelts JC, Zinn PD, et al. Chronic acetazolamide intoxication. *J Toxicol Clin Toxicol* 1984–1985;**22**:549–63.
- DuBose TD Jr, Good DW, Hamm LL, et al. Ammonium transport in the kidney: new physiological concepts and their clinical implications. *J Am Soc Nephrol* 1991;**1**:1193–203.
- Strupp M, Kalla R, Dichgans M, et al. Treatment of episodic ataxia type 2 with the potassium channel blocker 4-aminopyridine. *Neurology* 2004;**62**:1623–5.

Intralabyrinthine schwannoma affecting the low but not high frequency function of the vestibulo-ocular reflex: implications for the clinical diagnosis of chronic peripheral vestibular deficits

Peripheral vestibular hypofunction can be identified by asymmetric vestibular responses to caloric irrigation of the horizontal semicircular canal or by the head impulse test.¹ Whereas the first test investigates the low frequency function of the vestibulo-ocular reflex (VOR) the latter assesses the high frequency function. The high frequency VOR function is usually more persistently impaired in unilateral vestibular lesions (eg, vestibular neuritis) than the low frequency function and thus the more sensitive parameter to detect chronic peripheral vestibular deficits.²

Contrary to this current vestibular knowledge, we present a patient with a chronic

peripheral vestibular deficit showing normal high frequency but impaired low frequency VOR function. This unusual lesion pattern was caused by an intralabyrinthine schwannoma.

Case report

A 47-year-old patient presented with a 3 month history of repetitive episodes of vertigo, nausea and lateropulsion to his right side. The first episode lasted 1.5 h followed by short lasting (seconds to 15 min) episodes once a day. The patient reported a similar episode of vertigo 1 year previously, at that time associated with an acute hearing loss on the right side and persisting tinnitus ever since. Apart from moderate right sided hypacusis, neurological examination was normal in the asymptomatic stages during follow-up examinations over the next 2 years. Particularly, there was no spontaneous or head shaking nystagmus and no gaze evoked nystagmus.

After written informed consent was obtained according to the Declaration of Helsinki, cochlear functions were assessed by audiogram (including speech discrimination score) and brainstem evoked response audiometry, otolith function by click evoked myogenic potentials, funduscopy and the subjective visual vertical, semicircular canal function by caloric irrigation and scleral search coil recordings (Remmel Labs, Maryland, USA) with three dimensional coils (Skalar, Delft, the Netherlands).³ Eye-in-space and head-in-space position were used to

calculate eye-in-head position. High acceleration ($6000\text{--}9000\text{ s}^{-2}$), small amplitude ($15\text{--}25^\circ$) head thrusts in the horizontal canal planes were used to analyse individual semicircular canal function. Vestibular hypoexcitability was assessed by caloric irrigation using Jongkees's formula, and the directional preponderance is given in per cent.

Follow-up caloric irrigation tests ($n=4$) revealed a caloric hypoexcitability of the right side which remained largely stable over a course of 3 years (mean 55% (SD 8%); range 43–61% canal paresis). In contrast, scleral search coil recordings (fig 1A, B) during head impulse testing showed normal VOR gain to both sides (right 0.79 (0.07); left 0.78 (0.09)) compared with six age matched control subjects (right 0.86 (0.09); left 0.84 (0.08)).

Pure tone audiometry revealed a right sided sensorineural pancochlear hearing loss with a pure tone average of 60 dB. The patient's speech discrimination score was 50% (at 95 dB). Audiometry of the left ear was normal. Acoustic evoked potentials revealed slightly prolonged interpeak latencies I–III on the right side. Click evoked myogenic potentials, subjective visual vertical and funduscopy were normal.

High resolution MRI showed a small lesion in the right labyrinthine vestibule with typical features of an intralabyrinthine schwannoma. A contrast enhancing mass with a diameter of 3 mm was seen on the T1 weighted image (fig 1C). The tumour completely obliterated the

vestibule and partially grew into the ampulla of the horizontal semicircular canal, but largely spared the rest of the vestibular nerve and the cochlea, as depicted on the T2 weighted image (fig 1D). High resolution CT (slice thickness 1 mm) showed a normal bony labyrinth on both sides. Cranial MRI did not reveal intracranial lesions.

Discussion

The unusual finding is selective impairment of the VOR in the low frequency range whereas the high frequency VOR remained intact. Head impulses are small amplitude movements with high acceleration that are used to identify peripheral vestibular lesions. The head impulse test¹ can easily be conducted at the bedside and has a moderate sensitivity (35–45%) and high specificity (>90%). Sensitivity, however, can be improved by up to 100% when quantitative data of the VOR are obtained during the head impulse with the scleral coil technique.² Accordingly, we can exclude a false negative head impulse test in our patient.

The widely used caloric irrigation is usually sufficient to identify vestibular hypoexcitability in the acute stage but may fail to identify vestibular hypofunction in the chronic stage.² In vestibular neuritis, head impulses always reveal vestibular hypofunction at the time of caloric hypoexcitability but they remain capable of identifying this deficit in the chronic stage when responses to caloric irrigation may have become normal. This sign is probably related to the frequency dependence of dynamic vestibular imbalance after vestibular neuritis.

Conversely, high accelerating VOR was normal in our patient but caloric irrigation consistently revealed a unilateral vestibular hypoexcitability. This is the first report of selective impairment of unilateral low accelerating VOR in a vestibular schwannoma which grew from the schwann cell of the nerve. Evidence for an intralabyrinthine schwannoma came from the contrast enhancing mass with no signs of bony destruction in the CT scan of the temporal bone. These rare tumours arise from the proximal portion of either the vestibular nerve or the cochlear nerve. The patient's lesion involved the horizontal semicircular canal and the most proximal part of the vestibular nerve while sparing the largest portion of the nerve. A similar dissociation between low and high accelerating VOR function can occasionally be seen in Meniere's disease. Thus vestibular afferents conveying the high and low frequency VOR from the horizontal semicircular canal (ampulla) may be anatomically different and functionally dissociated before they enter the vestibular nerve. It cannot be deduced from this case whether the selective low frequency VOR deficit is related to (i) a frequency dependent vulnerability of type I hair cells,⁴ (ii) conduction loss of low frequency signals caused by damaged myelin or (iii) a compressive lesion of the primary vestibular afferents. A mechanical lesion might affect a subset of (eg, irregular) vestibular fibres possibly encoding the low frequency movements as high frequency responses are preserved after ablation of irregular afferents.⁵ Alternatively, the frequency dependence of vestibular compensation may be different in small chronic peripheral vestibular lesions of the semicircular canal which spare the vestibular nerve. The otoliths

Figure 1 (A) Horizontal head and eye (dotted lines, inverted for better comparison) velocity traces are plotted over time, as obtained during the head impulses to the right and left side. Vertical lines indicate head impulse onset. There was no vestibulo-ocular reflex (VOR) deficit. (B) Eye velocity is plotted against head velocity. Axial T1 weighted MRI scans of the temporal bones showing a contrast enhanced lesion (arrow) in the right vestibule with a diameter of 3 mm (C). The lesion is displayed as obliteration on the T2 weighted images (arrow, D).

probably do not contribute as our clinical test of saccular and otolithic function was normal.

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doi: 10.1136/jnnp.2006.106179

Competing interests: None.

References

- 1 Halmagyi GM, Curthoys IS. A clinical sign of canal paresis. *Arch Neurol* 1988;**45**:737–9.
- 2 Schmid-Priscoveanu A, Bohmer A, Obzina H, et al. Caloric and search-coil head-impulse testing in patients after vestibular neuritis. *J Assoc Res Otolaryngol* 2001;**2**:72–8.
- 3 Rambold H, Boenki J, Stritzke G, et al. Differential vestibular dysfunction in sudden unilateral hearing loss. *Neurology* 2005;**64**:148–51.
- 4 Angelaki DE, Perachio AA. Contribution of irregular semicircular canal afferents to the horizontal vestibuloocular response during constant velocity rotation. *J Neurophysiol* 1993;**69**:996–9.
- 5 Minor LB, Goldberg JM. Vestibular-nerve inputs to the vestibulo-ocular reflex: a functional-ablation study in the squirrel monkey. *J Neurosci* 1991;**11**:1636–48.

The syndrome of (predominantly cervical) dystonia and cerebellar ataxia: new cases indicate a distinct but heterogeneous entity

Patients displaying a slowly progressive syndrome combining dystonia and cerebellar ataxia are relatively rare and can cause considerable diagnostic uncertainty. The main differentials in these cases are the genetic spinocerebellar ataxias (SCAs), in which dystonia can be observed and can even be the presenting feature.¹ We recently reported five patients with mainly cervical dystonia (torticollis) and cerebellar ataxia in whom common SCA mutations were excluded and no definite cause was established.² Here, we report six further patients.

Case histories

Case 1

This 58-year-old man of Indian ethnicity presented with gait unsteadiness at age 54 years. Family history was negative. Symptoms were slowly progressive, but after 3 years (without neuroleptic exposure) blepharospasm developed and after 1 year involuntary movements of the jaw, lower face and neck developed. Examination at age 58 years showed blepharospasm, gaze-evoked nystagmus, hypermetric saccades, dystonic facial grimacing and tongue protrusion, cerebellar dysarthria, torticollis to the right, gait and

appendicular ataxia, hyper-reflexia and extensor plantar responses.

Cases 2 and 3

At age 24 years, this now 50-year-old woman developed posturing and jerky movements of her right shoulder. She subsequently developed unsteadiness of gait, episodic dizziness and slurred speech. Currently, examination reveals mild limitation of upgaze, jerky pursuit, hypometric saccades, slow tongue movements, marked cerebellar dysarthria, mild limb ataxia, ataxic gait and increased tone in all limbs but no pyramidal signs. She also has left torticollis with right laterocollis and dystonic posturing of the right shoulder/arm and leg.

Her 29-year-old son presented with a head tremor and tremulous speech at age 21 years. At age 29 years, he displayed mild gaze-evoked nystagmus to the left, hypermetric saccades, slow tongue movements, equivocal slurred speech, torticollis to the right with a high-frequency side-to-side tremor, mild dysidiadochokinesis on the left and hyper-reflexia. His gait was normal.

Further family history was negative.

Case 4

This 44-year-old woman developed balancing difficulties 5 years ago, followed by some falls. A cerebellar syndrome and laryngeal dystonia were noted, and the latter was treated with botulinum toxin injections. Family history was negative. Two years after onset, she had jerky pursuit, cerebellar dysarthria, torticollis to the right with left laterocollis, anteroposition of the left shoulder, mild dystonic posturing of the hands, gait and limb ataxia, mildly increased tone in all extremities, hyper-reflexia and extensor plantar responses.

Case 5

A 23-year-old man noticed the gradual onset of head turning at age 21 years. Family history was negative. He had recently developed balancing difficulties, loss of dexterity and slurred speech. A trial of levodopa proved ineffective. Examination revealed normal eye movements, a right torticollis, mild posturing of the right arm, cerebellar dysarthria, and mild gait and limb ataxia.

Case 6

This 58-year-old Ashkenazi Jewish woman, with a negative family history, first developed symptoms of writer's cramp and balance problems at age 8 years. Over the years, symptoms have been slowly progressive. A recent examination revealed jerky pursuit, gaze-evoked nystagmus, dysmetric saccades, cerebellar dysarthria, left torticollis with a side-to-side tremor, gait and limb ataxia, some choreo-athetoid movements of the hands, normal tendon reflexes and flexor plantar responses.

Auxiliary investigations

All patients tested negative for SCA1/2/3/6/7 mutations. In addition, negative investigations in most of the patients included acanthocytes, thyroid function, vitamin E, coeliac screen, copper studies and white cell enzymes. Additional negative investigations were the torsion dystonia gene DYT1, dentatorubropallidolusian atrophy and SCA12 genes (cases 2 and 3), SCA17 (cases 1 and 2), mitochondrial mutations 3243/8344/8993 (case 2),

Figure 1 T2-weighted craniocervical MRI of case 2 showing marked midline cerebellar atrophy with preserved brainstem structures (video supplement is available at <http://jnnp.bmj.com/supplemental>).

Huntington's disease gene (case 3), α -feto-protein (case 3), antineuronal antibodies (cases 1 and 6), bone marrow biopsy (case 2), and nerve conduction studies and electromyography (case 3).

Discussion

We have reported six new patients displaying a combination of dystonia and cerebellar ataxia, with age at onset varying from 8 to 54 years (table 1). Family history was negative in four cases, but indicated autosomal dominant or possibly mitochondrially inherited disease in two patients (cases 2 and 3). These six new cases resemble the five cases we reported previously.² Similar to these earlier reported cases, the dystonia mainly affected the cervical region. However, laryngeal adductor dystonia was the presenting feature in one patient, who only later developed neck and arm dystonia. In addition, severe cranial dystonia was observed in another patient, and in one, the dystonia was more generalised (case 2). Again, the cerebellar ataxia in these cases was relatively mild and always slowly progressive, particularly in the young-onset cases. In most patients, the dystonia was more prominent than the cerebellar ataxia.

Many diseases can cause a clinical picture of dystonia and cerebellar ataxia. However, except for the genetic ataxias, this particular combination as a pure mix seems to be rare in other sporadic/degenerative diseases, most of which can be distinguished by typical clinical, imaging or laboratory characteristics.

Dystonia, with occasional cervical predominance, has been observed in many of the dominant and recessive ataxias.¹ Although many of the recessive ataxias have not formally been excluded in the patients reported here, we consider that the known recessive ataxia genes are less likely to be the cause in these cases as they are usually characterised by additional distinctive features (such as oculomotor apraxia, overt peripheral neuropathy or spastic ataxia, which were all absent) and a more progressive disease course.

With new cases and families reported, new gene mutations will eventually be identified and may be more likely in the clearly dominant cases. In the "non-familial" young-onset cases, both recessive and dominant genes with incomplete penetrance are possible. Although most of the known SCA genes are thought to be fully penetrant, dystonia genes—for example, the torsion dystonia gene—can have low