

## LETTERS

### Task specific focal dystonia: a presentation of spinocerebellar ataxia type 6

Autosomal dominant cerebellar ataxias (ADCA) are characterised by clinical and genetic heterogeneity with a substantial overlap of clinical features and a variable degree of adherence to three distinct phenotypes according to Harding's clinical classification: ADCA type I, II, and III.<sup>1</sup> The availability of molecular genetic testing has provided increasing appreciation of a wider clinical spectrum than previously thought for each ADCA subgroup. In addition there is an increasing list of genes harbouring disease causing mutations which, to date, include spinocerebellar ataxia (SCA) types 1, 2, 3, 6, 7, 8, 10, 12, and 17.<sup>2</sup> SCA 6 is caused by unstable CAG expansion in the  $\alpha$ -1A calcium channel gene (CACNA1A).<sup>4</sup> We present a confirmed case of SCA 6 presenting with a task specific focal dystonia (writer's cramp) predated the onset of progressive gait ataxia by five years, which further widens the clinical spectrum of SCA 6.

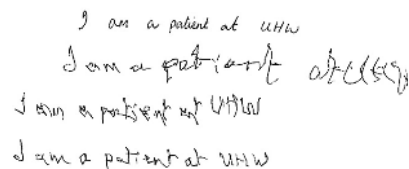
#### Case report

A 57 year old female pharmacist first presented at the age of 42 with a two month history of progressive difficulty in writing prescriptions as a result of writing induced cramp affecting the right hand. This task specific focal dystonia was aggravated by stress and fatigue. Her father was reported to have had Parkinson's disease on the basis of developing tremor and gait disturbance at age 40.

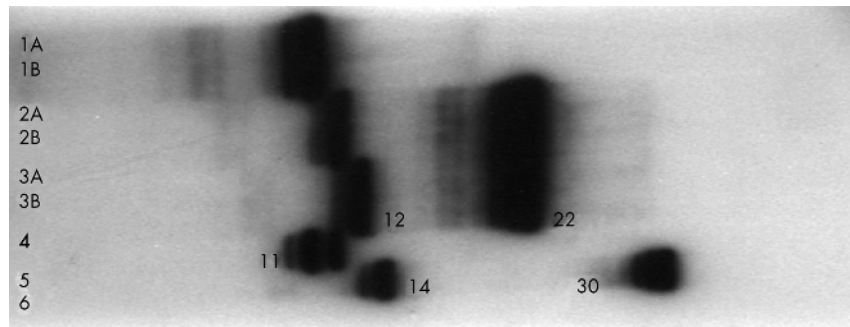
On examination, the patient's gait was normal and no focal neurological deficits were identified. Her writing, after a normal start, was interrupted by a semiflexed posture of the fingers to maintain the grasp of the pen, with the index finger and thumb appeared hyperextended and the wrist hyperflexed. This was accompanied by an ache in the hand. A working diagnosis of writer's cramp with a suspicion of familial dystonic disorders was made and she was started on the anticholinergic drug, trihexyphenidyl.

On annual follow up, she reported a satisfactory improvement in her symptoms. During this period and on more than one occasion, no cerebellar signs were identified.

Five years after the onset of focal dystonia, she developed an intention tremor in her right hand and upper limb ataxia but with a normal gait. A diagnosis of autoimmune hypothyroidism was made following a con-



**Figure 1** The patient's writing samples showing the use of the dominant right hand (line 2), the eventual use of the left hand (line 3), and the recent use of both hands (line 4), attempting to copy a short sentence (line 1).



**Figure 2** Autoradiography showing polymerase chain reaction products containing CAG repeats for SCA 6. Products were blotted and probed with a radiolabelled (CAG)<sub>n</sub> oligonucleotide. Lanes 2A/2B (loaded twice) showing patients with an allele of 22 CAG repeats. Results were confirmed with controls: lanes 3A/3B (12/22) and lane 5 (14/30). Lanes 1A/1B were another patient with ataxia; lane 4 was an unrelated healthy control, and lane 6 was blank.

firmary test results and thyroxine was started concurrently with propranolol to control the tremor. Two years later, at the age of 49, she began to experience difficulties with maintaining her balance when walking downhill, which later progressed to an increasing tendency to sway or trip. The writer's cramp had persisted with progressive tremor and clumsiness in both arms, forcing her to swap hands when writing (fig 1). A more detailed family history revealed additional information about paternal relatives who had a history of tremor and gait disturbance; however, none had developed writer's cramp.

Neurological examination now showed evidence of gait and limb ataxia, mild intention tremor, and horizontal gaze-evoked nystagmus, with mild dysarthria and no other neurological deficit. Ancillary tests to exclude acquired ataxias were also done, and brain magnetic resonance imaging revealed evidence of marked cerebellar atrophy with sparing of cortical and brain stem structures.

With informed consent, genomic DNA was extracted from peripheral blood leucocytes. Screening for trinucleotide repeat expansions for SCA 1, 2, 3, and 6 was done using polymerase chain reaction (PCR) amplifications of the genomic sequences containing each trinucleotide repeat expansion site. The PCR products were size fractionated by electrophoresis in a 6% polyacrylamide gel, which was then dry blotted. After hybridisation with a gamma-<sup>32</sup>P labelled (CAG)<sub>n</sub> oligonucleotide probe, allele sizes were visualised by autoradiography. Estimations of trinucleotide repeat size for each gene was made using well characterised positive control samples. A pathological 22 repeat expansion in the CACNA1A gene<sup>3</sup> and another allele of 12 repeats were detected (fig 2). Alleles within normal range were detected in the SCA 1, 2, and 3 genes.

#### Comment

We describe a case of SCA 6 with a focal dystonia preceding the onset of gait or limb ataxia by a period of at least five years. Recently, there has been a report of similar SCA 6 presentation but with a more progressive, disabling, and treatment resistant shoulder girdle and upper limb dystonia.<sup>3</sup> In the original description of SCA 6, the most common presenting feature was a progressive cerebellar syndrome, accompanied by involuntary movements, dystonic posturing, sen-

sory loss, and changes in the deep tendon reflexes.<sup>4</sup> Other presenting features have been reported as a result of direct molecular testing, including episodic ataxia and positional vertigo associated with downbeat nystagmus.<sup>5</sup> Our report provides further evidence of a wider clinical presentation of SCA 6, but may also be relevant to other ADCAs, which were previously considered to be relatively "pure" cerebellar ataxias.

This case also shows that, in the absence of a suggestive family history or presenting cerebellar features, it is unusual for clinicians to include ADCA in the differential diagnosis. Dystonia or extrapyramidal motor signs have often been associated with SCA 3, but are not specific, as overlap exists, though less frequently, with other subtypes in ADCA I.<sup>6</sup> With disease progression, the focal dystonia in our patient has partially resolved and has been predominantly replaced by a mild pancerebellar ataxia with very few extracerebellar signs and absence of other extrapyramidal features. The evolution of these signs and the partial resolution of the writer's cramp persuade us that the dystonia and ataxia are part of the same pathological process rather than separate disease entities.

Ten years after the onset of gait disturbance, the patient is walking using only one stick and remains employed, consistent with the mild disease course previously reported for SCA 6 phenotype. Increasingly, the availability of molecular investigations is indicating a need to revise the phenotype according to the underlying genotype. It is apparent that the majority of the inherited ataxias have a broader clinical spectrum than has previously been appreciated, particularly with ADCA.<sup>6</sup> Our experience highlights the wide range of syndromic presentations as well as advocating the clinical value of testing SCA 6 alongside SCA 1, 2, and 3 which constitute ADCA I. In addition, it may be useful to screen SCA loci in the ADCA I subgroup in cases of idiopathic focal dystonia who develop features of cerebellar dysfunction or who have a relevant family history.

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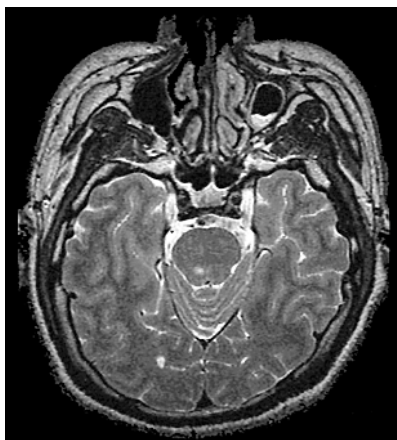
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## Bilateral cerebellar ataxia as the sole manifestation of a unilateral rostral pontine tegmental infarct

It has been reported that a small infarct of the pons can lead to various clinical syndromes such as pure motor hemiparesis, sensorimotor stroke, ataxic hemiparesis, dysarthria-clumsy hand syndrome, or ataxic tetraparesis.<sup>1</sup> However, bilateral, cerebellar ataxia as the sole manifestation of rostral pontine tegmental infarction has not been described. We report a patient with isolated bilateral cerebellar ataxia as the only sign of a rostral pontine tegmental infarct. This unique presentation reflected the selective involvement of part of the decussation of the superior cerebellar peduncle.

**Case report**

A 51 year old man with hypertension developed acute severe imbalance. On examination, he tended to fall to the right when standing unsupported with eyes open. He did not have dysarthria, limb weakness, vertigo,



**Figure 1** Brain magnetic resonance imaging: an axial T2 weighted image showing a right paramedian infarct of lacuna size situated in the tegmentum of the most rostral pons.

nystagmus, ophthalmoparesis, diplopia, sensory loss, or Horner's syndrome. The muscle stretch reflexes were normal and the plantar reflexes were flexor bilaterally. There was severe dysmetria on finger-to-nose and heel-to-shin testing on both sides. Dysmetria was worse on the right. The results of somatosensory evoked potentials, brain stem auditory evoked potentials, and pure tone audiography were unremarkable. There were no abnormalities of horizontal saccades, smooth pursuit, optokinetic nystagmus, or caloric responses.

Brain magnetic resonance imaging (MRI) showed a right paramedian infarct of lacunar size situated in the tegmentum of the most rostral pons, corresponding to part of the decussation of the superior cerebellar peduncle (fig 1). Magnetic resonance angiography (MRA) showed no abnormalities. An ECG and transoesophageal echocardiography with a bubble study revealed no abnormalities.

The limb coordination and gait improved steadily over several days, but there was mild dysmetria on the heel-to-shin test on the right side. On discharge, the patient complained only of mild unsteadiness when walking.

**Comment**

There have been several reports of bilateral cerebellar ataxia caused by a unilateral brain stem stroke.<sup>2-7</sup> However, previous reports have also described associated neurological symptoms such as mild hemiparesis, dysarthria, sensory change in an extremity, or multiple cranial nerve palsy.

Without pathological confirmation, it is difficult to be certain that the infarct affected only the structure identified (the superior cerebellar peduncle). However, in the rostral pons, the only anatomical structure responsible for bilateral limb ataxia is the superior cerebellar peduncle, which is situated in the dorsolateral side to the fourth ventricle and medial to the lateral lemniscus at the level of the most rostral pons—that is, at isthmus level.<sup>8</sup> From at this level, the fibres of the superior cerebellar peduncle move ventromedially towards their decussation. Serial neurological examinations over a period of days did not show any neurological signs except bilateral ataxia. These clinical data, when correlated with the known cross sectional anatomy of the most rostral part of the pons, suggest that the small lesion of our patient on brain MRI corresponded to part of the decussation of the superior cerebellar peduncle. Thus the isolated bilateral cerebellar ataxia in our patient may be explained by ipsilateral involvement of both efferent cerebellar pathways. These which include uncrossed fibres of the superior cerebellar peduncle ipsilateral to the lesion and crossed fibres arising contralateral to the lesion.

From the results of MRA and transoesophageal echocardiography, risk factor analysis, and the size of an infarct on brain MRI, small artery disease (that is, a lacunar stroke) was considered the likely pathogenesis.

In summary, our patient presented with isolated bilateral cerebellar ataxia caused by a small infarct situated in the rostral pontine tegmentum. This unique presentation may result from ipsilateral involvement of both efferent cerebellar pathways, before and after the decussation of the superior cerebellar peduncle. We have previously reported isolated ataxia as the sole manifestation of

lateral medullary infarction.<sup>9</sup> Together, these reports highlight the importance of sudden gait disturbance as the sole manifestation of brain stem stroke. Rostral pontine paramedian tegmental infarction should be considered in the differential diagnosis of sudden bilateral cerebellar ataxia, even when classic brain stem signs are absent.

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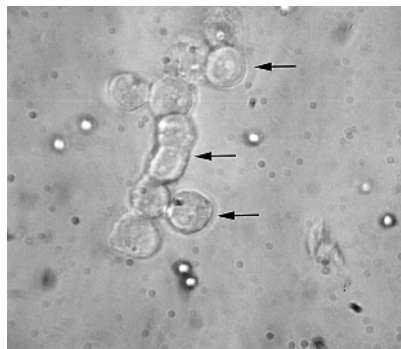
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## Identification of amoebae in the CSF in a patient with meningoencephalitis

Amoebae are amphi-zoic, ubiquitous, and opportunistic protozoa that can affect different organs including skin, lungs, eyes, and the brain.<sup>1,2</sup> In the central nervous system (CNS), two main, well defined disease entities have been described: primary amoebic meningoencephalitis, which is caused by *Naegleria fowleri* and is rapidly fatal, and granulomatous amoebic encephalitis, which is caused by *Acanthamoeba* spp and *Balamuthia mandrillaris* and is characterised by focal granulomatous lesions in the brain following a subacute or chronic course. CNS infections caused by free living amoebae are uncommon and, as of October 1996, for example, only 166 cases of granulomatous amoebic encephalitis have been reported from around the world.<sup>1</sup> Identification of amoebae in cerebrospinal fluid (CSF) samples is a rare event.<sup>1,2</sup>

We have recently seen a patient with meningoencephalitis in whom amoebic forms were identified in the CSF. She was a 48 year old woman who was admitted to our neurological clinic because of vertigo, headache, bilateral hypacusia, ataxia, diplopia, dysphonia, dysphagia, anosmia, ageusia, tetraparesis, occurrence of transient clonic fits in the right upper limb, and vomiting episodes. The onset of her illness dated from about six weeks earlier, when she began to



**Figure 1** Amoebic trophozoites directly observed in a sample of cerebrospinal fluid by light microscopy. The morphological characteristics (round or ovoid shape, abundant cytoplasm, nuclei with prominent nucleoli) are readily seen.

complain of a maddening noise, like a rustle, in the right ear, dizziness, difficulty in maintaining the erect posture, and vertigo. She was admitted to hospital. Computed tomography (CT) and magnetic resonance imaging (MRI) of the brain were normal, and analysis of CSF showed the following: cells, 60/mm<sup>3</sup> (white blood cells, primarily mononuclear lymphocytes); glucose, 1.7 mmol/l; protein, 95 mg/dl; and the presence of giant, atypical cells. After tumour pathology was excluded, the patient was admitted to our clinic. Her blood pressure was 170/95 mm Hg, pulse 125 beats/min, body temperature 36.5°C, and respiratory rate 22 breaths/min. She had a Glasgow coma scale score of 13. The main abnormal haematological findings (given as the range observed during her hospital admission) were as follows: white blood cells, 19 100 to 22 000/mm<sup>3</sup>, with modest neutrophilia of 79–81%; lactate dehydrogenase, 500 to 506 IU/l (normal range 150 to 460 IU/l); Katz index, 70 to 75. Other blood indices and analyses were normal. These included immunological assessment tests with differentiation of lymphocytic subtypes and haematological cultures for infective agents, including cat scratch fever and HIV.

Culture studies were negative for bacteria, fungi, viruses, and acid-fast bacilli. Direct examination of the CSF by light microscopy showed the presence of free living amoebae. The motile forms presented the characteristic morphological features of spherical (round or ovoid) shape, abundant cytoplasm, and nuclei with prominent nucleoli (fig 1). A CSF specimen cultured at 32°C and 37°C on non-nutrient agar culture plates covered with a dense lawn of the Gram-negative bacterium *Escherichia coli* was negative.

Serial EEG records showed diffuse delta and theta activity with occasional prevalence of this activity in the left sided anterior regions. Cranial CT and MRI revealed diffuse oedema with hydrocephalus and dilatation of the cerebral aqueduct. No focal lesions were observed.

Treatment included dexamethasone (4 mg intravenously twice daily), doxycycline (100 mg twice daily), rifampicin (600 mg daily), and amphotericin B, starting at doses of 20 mg intravenously per day with a progressive increase to 50 mg daily; simultaneous intrathecal amphotericin B was given at an initial daily dose of 0.012 mg, increasing progressively to a maximum daily dose of 0.250 mg.

Despite this treatment, the clinical situation rapidly worsened and the patient died after 11 days in hospital. A necropsy examination was denied.

### Comment

Free living amoebae of the genus *Acanthamoeba* are the causative agents of several infections usually occurring in immunocompromised, debilitated individuals and almost always resulting in death. Most cases, therefore, are diagnosed only at necropsy. Our patient was apparently immunocompetent and without any of the usual predisposing factors, such as a history of aquatic activities, treatment with immunosuppressive, chemotherapeutic, or steroid agents or broad-spectrum antibiotics, and so on.<sup>1</sup> The existence of extraneural infective foci in the skin, paranasal area, or lungs—a possible point of access for amoebae<sup>1</sup>—was also excluded. The most striking feature in our patient was that a firm diagnosis was made only through direct observation of the protozoon in the CSF. To our knowledge, this has not been described before in chronic amoebic meningoencephalitis and underlines the diagnostic value of CSF studies in this type of pathology. The main species reported as causing granulomatous amoebic encephalitis are *A polyphaga*, *A castellanii*, *A culbertsoni*, and *Balamuthia mandrillaris*.<sup>1</sup> The diagnosis is usually made by microscopic examination of stained slices of brain specimens obtained at necropsy or biopsy and cultivation of the causal organism in an appropriate medium. This usually consists of non-nutrient agar covered with bacteria for *Acanthamoeba* spp or mammalian cell lines for *B mandrillaris*. Discrimination among species may not be easy and requires experience and the use of different methods.<sup>1</sup> Morphological and ultrastructural analysis, for example, can help in discriminating acanthamoeba from balamuthia, as some differences in shape, dimensions, nuclei, and cytoplasm have been described for both cystic forms and trophozoites.<sup>2,3</sup> Physiological characteristics such as temperature tolerance, pH dependency, and

others—although they have proved useful—are not of definitive value in differentiating pathogenic from non-pathogenic strains.<sup>2</sup> More recently, molecular methods and the use of monoclonal antibodies for immunofluorescence microscopy have been developed; however, they have some limitations, such as their expense, laborious nature, and short lived reagents.<sup>2</sup> Nonetheless, in spite of these various diagnostic procedures, accurate species determination may prove problematic.<sup>3</sup> In our patient, we were unable to discriminate among the various species of amoebae that could have been involved in the infection. Culture tests on non-nutrient agar covered with bacteria were negative, and other cultures, serological tests, and CSF tests were not done because of the rapid progression of illness. Nonetheless, our case indicates that when an amoebic meningoencephalitis is suspected a careful search for the organisms in the CSF may be a decisive factor in the diagnosis.

In conclusion, this case report emphasises the importance of familiarising ourselves with this form of pathology and provides an example of how the identification of amoebae in the CSF may aid in making a firm diagnosis of this uncommon, underdiagnosed, life threatening, and difficult to treat CNS infection. As a successful therapeutic result may sometimes be achieved,<sup>4</sup> a timely diagnosis together with prompt and adequate treatment are essential.

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