

## SHORT REPORT

## Familial paroxysmal ataxia: report of a family

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**Abstract**

**Three cases from one kindred who suffer from dominant paroxysmal ataxia are described. This is a rare benign non-progressive disorder of childhood onset, characterised by bouts of ataxia with abrupt onset lasting minutes or hours. Cases may be identified on the basis of a suggestive history, nystagmus persisting between episodes, and dominant inheritance. Treatment with acetazolamide is often dramatically effective. This family is thought to be the first described in the UK but many more probably exist, mislabelled as epilepsy or migraine.**

Inherited episodic motor disturbances of the central nervous system are all rare and comprise three main varieties: periodic paralysis, paroxysmal choreoathetosis, and paroxysmal ataxia. I report here the last mentioned, as it has not been described in the British literature, is often unrecognised, and may respond dramatically to acetazolamide.

**Case reports**

*Case 1* was found to have mild concomitant squint at 3 years old but no nystagmus. She developed recurrent right otitis media at 5 years and became totally deaf on that side. Corrective eye surgery was performed at 6 years and just before this, nystagmus was noted for the first time. Subsequently four vessel arteriography and air encephalography were undertaken with negative results, and a provisional diagnosis of congenital nystagmus was made. Since then she had experienced fortnightly episodes of dysarthria, ataxia, and vertigo often accompanied by nausea and vomiting followed by headache with drowsiness. Onset was abrupt over the course of a few seconds. There were no obvious trigger factors except for exercise, and the attack duration varied from 2-24 hours. She was reassessed when 26 years old because the attacks were recurring up to five times a week. Pronounced spontaneous nystagmus was seen in all directions. Electroneystagmography confirmed normal saccades with distinct second degree gaze paretic nystagmus which was abolished in the absence of fixation. Rebound nystagmus occurred on recentering from both right and left. Pursuit was severely deranged in the horizontal plane. Optokinetic responses were disturbed and rotation responses revealed short cerebellar-

type reactions. There was no vestibulo-ocular reflex suppression. Pure tone audiograms and caloric tests were absent from the right ear. The left audiogram was normal but caloric tests showed large amplitude responses. Brainstem auditory evoked responses were normal on the left and absent on the right. No abnormalities were seen on EEG or visual evoked response. A provisional diagnosis of basilar migraine was made. At a further assessment one year ago, she was screened for the possibility of mitochondrial disease because of slight elevation of creatine kinase (150 units, normal < 120), but a muscle biopsy specimen was normal, and the diagnosis of familial paroxysmal ataxia was made. An MRI scan showed distinct atrophy of the superior cerebellar vermis. Institution of acetazolamide 250 mg twice daily in January 1990 resulted in a dramatic reduction of attacks over the first eight months' observation.

*Case 2* developed attacks at 1 year identical to his mother (case 1). They were initially suspected to be epileptic, and there seemed to be some response to carbamazepine. Some episodes were induced by physical exercise. He showed minor mental retardation with difficulty in articulation in early life. Neurological examination at 6 years showed numerous café-au-lait spots and slight clumsiness of the left arm but no evidence of neurofibromatosis. There was mild concomitant strabismus with nystagmus and jerky saccades on horizontal gaze. An EEG showed increased slow wave activity but a CT scan of the brain was normal. A provisional diagnosis of epilepsy was made once more, followed by treatment with sodium valproate without obvious benefit. The attacks continued about once every six weeks. When the diagnosis was made in his mother, acetazolamide treatment was started and completely abolished attacks over the first three months of observation. MRI scan showed striking atrophy of the cerebellum particularly in the superior vermis.

*Case 3* is another son of case 1. His episodes began when aged 6 weeks. According to his mother his head would flop and he would shake. When crawling at age 7 months he would inexplicably wobble. Subsequently episodes of imbalance, similar to his mother and older brother, recurred on a daily basis. Examination at 6 years revealed a mild convergent squint with nystagmus on horizontal gaze and jerky saccades. There were two very small café-au-lait spots. No lack of limb coordination was detectable. An EEG and CT brain scan showed

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no abnormality. Acetazolamide was started in May 1990 and again over the first three months of monitoring no more attacks were witnessed.

A urinary screen for abnormal amino acids in the mother and both sons was within normal limits. A further sibling aged 10 years (female) is quite healthy. A brother of the index case (aged 42) is educationally subnormal. Three other brothers and her sister are healthy. The father of the index case was initially ataxic then chairbound for 13 years and died aged 67. Her maternal grandmother died from "creeping paralysis", but no further particulars are obtainable.

### Discussion

Familial paroxysmal ataxia is an autosomal dominant disorder first described in 1946.<sup>1</sup> Since then some 17 families have been described, mostly from the United States, Canada, and France.<sup>2-9</sup> The basic cause is unknown. Onset is usually in early childhood, and the attacks of imbalance, which are frequent and disabling, do not seem to be associated with progressive neurological dysfunction, although exceptions are found.<sup>2,6</sup> Between attacks, many patients have spontaneous nystagmus (often in the vertical as well as horizontal plane) but little or no limb ataxia. Inconstant precipitating factors are described such as fatigue, emotion, exercise, change of position, or alcohol. Episodes typically consist of limb ataxia, dysarthria, nausea, vomiting, and oscillopsia occasionally with tinnitus and blurred vision. The duration is characteristically a few minutes, but episodes lasting seconds or days are documented.<sup>5</sup> There is one report of paroxysmal ataxia associated with episodic choreoathetosis;<sup>3</sup> another family member showed ataxia and interictal neuromyotonia. A further patient with associated neuromyotonia has been recently reported.<sup>10</sup> The neuromyotonia variety does not seem to respond to acetazolamide. The disorder is readily confused with other diseases, particularly epilepsy, especially (as in case 2) when the EEG is abnormal. Benign episodic vertigo of childhood is not familial and is self limiting. Basilar migraine is a seductive alternative diagnosis, especially in those complaining of headache after an attack, and was a provisional diagnosis in case 1. Some aminoacidurias may be episodic (for example, Hartnup or maple syrup urine disease), but these are readily identified by urinary examination and the presence of progressive mental deterioration.

The underlying cause of paroxysmal ataxia is presumably biochemical, and there are provisional reports of disordered pyruvate metabolism.<sup>8,9</sup> In a pedigree displaying probable X-index inheritance there was evidence of

pyruvate dysmetabolism and, at necropsy, one subject displayed features consistent with Leigh's disease.<sup>11</sup> MRI often shows atrophy (as in case 1 and 2) of the superior vermis.<sup>12</sup> This is of considerable interest as the pyruvate dehydrogenase activity relative to the rate of pyruvate oxidation is lowest in the superior vermis, hence defects of this enzyme too mild to impair carbohydrate catabolism in other parts of the brain may selectively cause dysfunction here.<sup>13,14</sup> The presence of pyruvate disorder in an X-linked family and not in the dominant form, implies a spectrum of pyruvate dysfunction which is genetically determined.

The first line of treatment is acetazolamide,<sup>15</sup> which is effective in at least half of cases. If acetazolamide fails, phenytoin may be helpful but sometimes worsens symptoms.<sup>3</sup> This is thought to be the first family with the typical, dominant form of disease to be described in UK but many other families must exist undiagnosed—mislabelled as epilepsy or migraine. Accurate diagnosis in one individual will usually reveal similarly affected family members, all of whom could benefit from effective treatment.

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