Short report

Sex-linked recessive congenital ataxia

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SUMMARY A family is reported in which three boys, two full brothers and a half brother, presented with marked delay in motor milestones, severe limb and truncal ataxia, nystagmus, speech delay and moderate global retardation. Autosomal recessive and sex linked recessive forms of cerebellar hypoplasia are reviewed and it is suggested that this family may have a rare, if not unique, form of sex-linked cerebellar ataxia.

Cerebellar ataxia may have many causes, both environmental and genetic. It has been estimated that congenital cerebellar ataxia accounts for up to 15% of all cases of cerebral palsy and that half of the patients with no history of perinatal asphyxia have a genetic disorder.¹ This illustrates the importance of establishing the family history when assessing a child with ataxic cerebral palsy and the difficulties involved in giving correct genetic advice. In this paper we report three boys, two full brothers and a half brother, who have presented with non-progressive cerebellar ataxia and moderate mental retardation in association with variable cerebellar abnormalities on CT scan. The family pedigree is consistent with sex-linked recessive inheritance.

Case reports

The family pedigree is shown in the figure. The three affected boys were the only sons of their healthy Caucasian mother. There was no parental consanguinity and the fathers of these boys were not related.

Case 1 (II 1) This boy weighed 3.53 kg following uneventful delivery at 41 weeks. During pregnancy his mother was treated with monthly hormone injections because of her history of previous miscarriage. No other medication was taken. He was tube fed in the neonatal period and feeding problems persisted throughout infancy. Motor milestones were delayed in that he first sat unaided at 18 months and walked holding on to furniture at 3½ years. By 6 years he could walk with a frame and he first walked alone, albeit very unsteadily, at 8 years. Speech was also

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Fig The family pedigree.

delayed with meaningful words first being used at 4 years. Formal assessment at 8.67 years yielded mental ages of 2.06 and 3.03 for expression and comprehension respectively. Hearing was found to be normal. Overall ability was assessed at ESN (M) level. General health was good during childhood with no convulsions or surgery other than removal of tonsils and adenoids.

General examination at age 13 years revealed a globally delayed pubertal male with no dysmorphic features. Height and head circumference were on the 50th centiles, weight on the 90th centile. Visual acuity was $\frac{6}{12}$ in the right eye and $\frac{6}{9}$ in the left. Fundal examination was normal. He showed marked nystagmus on lateral and upward gaze. Power and tone were normal but reflexes could be elicited only with difficulty. Plantar responses were flexor. Sensation to pin prick was intact; vibration could not be adequately assessed. The finger/nose test revealed marked ataxia and an intention tremor. His gait was very unsteady on a broad base and he could remain upright for only a few seconds with eyes closed.

Case 2 (II 2) This boy weighed 2.38 kg at birth at 34 weeks following an uneventful drug-free pregnancy. There were no major problems in the neonatal period and he was discharged from hospital to his mother's care at the age of 3 weeks. During infancy he was noted to be slightly floppy and to be a poor feeder. He was first referred for investigation at

the age of 1 year because of delayed development. He sat alone at 2 years and walked independently at 7 years. Meaningful speech was first achieved at 4 years. At the age of 6·7 years he scored at the 4 and 5½ year levels for verbal comprehension and expression respectively. Hearing was normal. Overall ability was assessed at ESN (M) level. General health was good during childhood, his only hospitalisation being for bacterial meningitis at 15 months and removal of tonsils and adenoids. He has had no convulsions.

General examination at age 12 years revealed findings almost identical to those present in his older brother. He showed no dysmorphic features and all growth parameters lay close to the 75th centiles. Fundal examination was normal and eye movements were full, but he showed marked nystagmus on lateral gaze. Speech was slow and slightly slurred. Tone and power were normal but reflexes were barely detectable. Plantar responses were flexor. Vibration, position and pin sensation were normal. He had a marked intention tremor on the finger/nose test with generalised ataxia and an unsteady broad based gait.

Case 3 (II 3) This boy was delivered by forceps because of foetal distress at 38 weeks. Apgar scores at birth were good. Birth weight was 2·67 kg. During pregnancy there was intermittent vaginal bleeding until 7 months. He fed well in infancy and was not noted to be hypotonic. He first sat at 9 months and crawled at 18 months, but was referred for investigation at 22 months because of generalised ataxia and suspected global delay. Formal assessment using the Bayley scales of infant development at chronological age 31 months yielded a mental age of 22 months. Expressive assessment using the Bayley scales of infant development at chronological age 31 months yielded a mental age of 22 months. Expressive and receptive language skills were estimated to be at the 20–22 month level. Fine motor skills scored at the 18 month to 2 year level; gross motor skill scored at the 9 to 10 month level. Hearing and vision were normal.

On recent examination at the age of 4 years height and weight fell on the 50th centiles and head circumference on the 90th centile. He had a small pit in front of his right ear and an overhanging upper lip with no other dysmorphic features. Fundal examination was normal as were visual fields and visual acuity. External ocular movements were full. There was fine horizontal nystagmus in both eyes. Muscle power was normal, but tone was reduced and reflexes could be elicited only with difficulty. Plantar responses were flexor. He showed a fine intention tremor with truncal ataxia and very unsteady supported gait. Speech was slightly slurred.

Sensation was normal. Apart from hyperextensible knees no other abnormalities were noted.

Investigations The following were normal in cases 2 and 3:— routine haematology and biochemistry, serum immunoglobulins, α -fetoprotein, cholesterol, creatine kinase, uric acid, thyroxine, phytanic acid and amino acids; urinary amino acids and organic acids; banded karyotype including fragile X studies. No acanthocytes were found in blood.

A CT scan in Case 1 at the age of 10 years showed an atrophic cerebellar vermis with normal cerebellar hemispheres. Motor and sensory nerve conduction velocities were normal at age 13. A CT scan in Case 2 at age 10 years showed generalised cerebellar atrophy with wide subarachnoid spaces between the hemispheres and between the occipital bone and cerebellum itself. A CT scan, which included good views of the cerebellum, was normal in Case 3 at age 3 years as were nerve conduction studies.

Discussion

The three patients described have presented a considerable diagnostic problem. Features in common include delayed motor and speech development, mild to moderate global retardation, sluggish reflexes, truncal and limb ataxia, intention tremor and nystagmus, with the most striking observation in all three boys being their very unsteady broad based gait. Two of these boys have had abnormal CT scans at age 10 years with atrophy of the cerebellar vermis in Case 1 and generalised cerebellar atrophy in Case 2. In contrast no abnormality was noted in the CT scan of Case 3 at age 3 years, an observation consistent with either subtle disease progression which was not clinically apparent, or failure of maturation.

There have been several familial reports of cerebellar hypoplasia, as outlined in the table. The findings in our patients most closely resemble those in the three sib pairs described by Wichman *et al*⁵ who showed variable combinations of motor and language delay with mild to moderate retardation and cerebellar and/or vermal dysfunction. Each of these sib pairs consisted of one affected male and one affected female, an observation clearly consistent with autosomal recessive inheritance, whereas the family we

Table Inherited forms of cerebellar hypoplasia

References	Mode of inheritance	Age of onset	Clinical and pathological features
Kvistad <i>et al</i> 1985 (1)	AR	1–2 years	Normal IQ. Atrophy of cerebellar vermis.
Riccardi and Marcus 1978 (2)	XR	Congenital	Hydrocephalus and cerebellar agenesis.
Sarrouy <i>et al</i> 1957 (3)	AR	1–2 years	Mental retardation. Cerebellar hypoplasia.
Jervis 1950 (4)	AR	First year	Severe retardation. Small cerebellum with degeneration of granular cell layer.
Wichman <i>et al</i> 1985 (5)	AR	First year	Mild retardation. Cerebellar hypoplasia
Joubert <i>et al</i> 1969 (6)	AR	Congenital	Episodic tachypnoea. Mental retardation.
"Joubert syndrome"			Agenesis of cerebellar vermis.
Sanner 1973 (7)	AR	First year	Moderate retardation. Cataract. Poor balance.
"Dysequilibrium syndrome"			Small cerebellar vermis.

AR—autosomal recessive; XR—sex-linked recessive.

report is strongly suggestive of sex-linked recessive inheritance. It may be relevant that when Lesny⁸ described 28 children with "symmetrical cerebellar hypogenesis" there was an excess of males (18 boys and 10 girls).

Sex-linked recessive inheritance has been noted in slowly^{9,10} and rapidly¹¹ progressive cerebellar syndromes, and in the condition first described by Paine¹² in which there is microcephaly, optic atrophy, spasticity and cerebellar hypoplasia. The clinical features in the boys now described, and in particular the absence of deterioration, make it unlikely that they have any of these disorders.

Thus we are prompted to conclude that in addition to the disorders listed in the table, there may also be a sex-linked recessive form of cerebellar hypoplasia of intermediate severity, characterised by lack of or minimal progression and mild to moderate global retardation.

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