X-linked sideroblastic anaemia with ataxia: another mitochondrial disease?

K D Hellier, E Hatchwell, A S Duncombe, J Kew, S R Hammans

Abstract

Objectives—The syndrome of X-linked sideroblastic anaemia with ataxia is rare, described only twice in the literature. The aim was to obtain clinical neurological and haematological data about this rare syndrome throughout adult life.

Methods—A family is described with two affected brothers and two affected maternal uncles. The family was evaluated clinically. Haematological investigations included full blood count, blood film, iron studies, free erythrocyte protoporphyrin (FEP) concentrations and a bone marrow examination where possible.

Results—Core neurological features included motor delay, ataxia evident from early childhood, and dysarthria. Neurological features were non-progressive until the fifth decade when slow progression became evident. Some family members showed mild spasticity. Patients usually have a mild asymptomatic anaemia or a borderline decreased mean corpuscular volume. Blood film examination showed Pappenheimer bodies. Bone marrow examination showed ring sideroblasts, indicating raised erythrocyte iron. Free erythrocyte protoporphyrin (FEP) concentrations were raised.

Conclusions—Haematological features are subtle and can be easily overlooked, and individual patients may not display all the abnormal features. X-linked ataxias are rare and incorrect genetic advice may be given if the diagnostic haematological features of X-linked sideroblastic anaemia are overlooked. Males with early onset ataxia should have a haematological evaluation including a blood film, with a bone marrow examination if abnormal blood count indices and measurement of FEP concentrations raise suspicion. The condition has parallels with Pearson's syndrome and Friedreich's ataxia. All three conditions are associated with mitochondrial iron handling defects and

ataxia. The human ATP binding cassette gene (hABC7) is a candidate gene and requires further investigation.

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The sideroblastic anaemias are a heterogeneous group of disorders, which may be inherited or acquired. Of the rare inherited forms, X-linked inheritance is the most common.¹ In a few pedigrees non-haematological features are also present which segregate with the anaemia, including ataxia and glucose-6-phosphate dehydrogenase deficiency.^{2–3}

Sideroblastic anaemia is characterised by ineffective erythropoiesis and marked iron loading of the red cell precursors. Sideroblasts are normal red cell precursors that contain granules of iron scattered throughout the cytoplasm; they can comprise up to 50% of normoblasts.⁴ Sideroblastic anaemias occur when abnormalities in the haem biosynthetic pathway produce iron accumulation in the mitochondrion. In the synthesis of haem, iron is inserted into the protoporphyrin IX as the final stage of the biosynthetic pathway—this occurs in the mitochondrion (fig 1).⁵

If not enough protoporphyrin is generated, or iron is not normally incorporated into protoporphyrin, then iron accumulates in the erythroblast mitochondria and tends to form the perinuclear pattern of the ring sideroblast. These siderotic mitochondria may also be retained in circulating erythrocytes as Pappenheimer bodies,^{6,7} more marked if there is absence or hypofunction of the spleen.^{6,8}

Clinically patients with inherited sideroblastic anaemias have an anaemia that may be identified at birth. Some pedigrees exhibit severe microcytosis and hypochromasia (mean corpuscular volume 50–60 fl), whereas others have such subtle anaemia that it is only manifest on close inspection of the complete pedigree.⁶ Iron loading is commonly present. Under normal circumstances slightly more protoporphyrin is produced by the red cell precursors than is actually required to make haem. The excess remains with the cell throughout its life and is detected as free erythrocyte protoporphyrin (FEP).⁹ The FEP concentration is usually low or normal in typical inherited sideroblastic anaemia.^{10–12}

Of the inherited ataxias, X-linked inheritance is rare.¹³ Only two families with the syndrome of X-linked ataxia with sideroblastic anaemia have been described, neither of which have affected members older than early adult life.²

Wessex Neurological Centre, Southampton General Hospital, Southampton SO16 6YD, UK
K D Hellier
S R Hammans

Wessex Human Genetics Institute, Duthie Building
E Hatchwell

Department of Haematology
A S Duncombe

Department of Neurology, The Princess Royal Hospital, Apley Castle, Telford, Shropshire, UK
J Kew

Correspondence to:
Dr S R Hammans
srh@soton.ac.uk

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Figure 1 Haem biosynthetic pathway (final stage).

Figure 2 Pedigree of the family.

We describe a new family with X-linked ataxia with sideroblastic anaemia with affected members in the sixth to eighth decades, with detailed neurological and haematological investigations (fig 2).

Case reports

PATIENT III.2

This man, aged 52, was the product of a normal pregnancy. Cognitive testing at 5 years of age showed that his IQ was normal. He did not walk until he was 11 years old and improved so that he could walk independently by the age of 17. His walking deteriorated since the age of 40, and he has been wheelchair bound for 12 years. Schizophrenia was diagnosed in his 20s and he has remained on phenothiazine medication since. After an assault at the age of 43 a splenectomy was performed. Examination showed a spastic and ataxic gait. He had a left abducens palsy, unchanged since childhood according to his mother. He had nystagmus on upbeat and lateral gaze. He had some mild restriction of upgaze. He was markedly dysarthric. Comparison with an examination 5 years previously showed some evidence of progression. He now has marked finger-nose ataxia and increased tone on his right side with

a mild right upper motor neuron VIIth nerve palsy. Sensory examination was normal. He had a stiff legged ataxic gait.

Haematological investigations are shown in the table. Of note he had a mild anaemia and raised FEP concentrations. Also Pappenheimer bodies were visible on his blood film (fig 3), especially prominent in view of his splenectomy. Brain MRI showed a markedly atrophic cerebellum, with some atrophy of the pons and medulla (fig 4). Supratentorial brain was within normal limits. Nerve conduction studies were normal. His karyotype was 46,XY. Genetic analyses for spinocerebellar ataxia mutations were negative.

PATIENT III.3

This man, aged 50, was the product of a normal pregnancy. He did not start walking until he was 3 years old, and was always below average in his motor abilities, although he was able to ride a bicycle. He worked as a toolmaker until the age of 48 when he retired. His walking deteriorated since the age of 45. He had double vision as a teenager; an operation failed to restore binocular vision. He had no swallowing or sphincter problems. Examination demonstrated broken pursuit eye movements and

Haematological findings

	III.3	III.2	II.5	II.2	II.1	Normal values
Sex	M	M	F	M	M	
Age (y)	50	52	74	63	78	
Genetic status	A	A	OC	A	A	
Packed cell volume (%)	42	36		41	29	0.39–0.50
MCV (fl)	77	84	93	74	83	78–98
FEP (μmol /litre)	4.9	3.1	1.4			0.4–1.7
Ferritin (μg /l)	125	95	135	38		14–200
Iron (μmol /l)	30	20	19			14–33
Ring sideroblasts	yes					
Hb (g/dl)	14.3	12.1	13.1δ	13.5	10.2	13–17
TIBC (μmol /l)	67	39	63			45–75
Blood film	Hypochromic red cells Pappenheimer bodies	Anisocytosis Poikilocytosis Target cells Howell-Jolly bodies Pappenheimer bodies	Pappenheimer bodies			

A=Affected; OC=obligate carrier; MCV=mean corpuscular volume; FEP=free erythrocyte protoporphyrin concentration; Hb=haemoglobin concentration; δ Female Hb range=11.5–16.0

Figure 3 Blood film. Smear showing Pappenheimer bodies in patient III.2.

some hypometric saccades. He had some perioral fasciculation. He had a concomitant divergent squint but no restriction of eye movements. He had finger-nose ataxia, more marked on the left side. Reflexes were symmetric and present, plantars downgoing. There was no sensory abnormality. He had a wide based gait and required no walking aids.

Haematological investigations are shown in the table. Key abnormalities include a low mean corpuscular volume, a raised FEP concentration, Pappenheimer bodies on the blood film, and ring sideroblasts in the bone marrow. Brain MRI showed selective atrophy of the cerebellum, with the pons and medulla of normal size (fig 4). A single tiny focus of high signal was seen in the anterior limb of the right internal capsule associated with the lenticulostriate arteries. This was thought to be ischaemic in origin. Nerve conduction studies were normal. His karyotype was 46,XY. Genetic tests as in patient III.2 were negative.

PATIENT II.5

This woman, aged 74, never had any unsteadiness or any known neurological symptoms, but was mildly disabled by osteoarthritis. Examination showed no neurological signs with impaired walking consistent with her joint problems. Haematological indices were normal except that she had Pappenheimer bodies on her blood film (table).

PATIENT II.1

This man, aged 78, lived in a nursing home, and was unavailable for examination. He was reported by his sister to have always had trouble walking, using a wheelchair to go out as a child but being able to walk until the age of 74. He is thought to have a moderate dementia.

PATIENT II.2

This man, aged 63, was the product of a normal pregnancy but did not walk until the age of 5 years. He wore callipers between the

Figure 4 MRI. (A and B) T1 weighted sagittal MR scans showing midline cerebellar atrophy (patients III.2 and III.3). (C) T2 weighted axial MR scan showing brainstem and cerebellar atrophy (patient III.2).

ages of 7 and 10 years. His gait was always ataxic and he was unable to ride a bicycle. He always had slurred speech. Since the age of 58 his balance started to deteriorate slowly and he had occasional falls. Examination showed that he was obviously dysarthric. He had hypometric saccades and nystagmus. Tone and power in the limbs was normal. Reflexes were brisk but plantars were flexor. He had bilateral finger, nose, and heel shin ataxia and bilateral dysidiadochokinesia. He had a wide based ataxic gait

and Romberg's sign was negative. There were no sensory signs. He had a low mean corpuscular volume with a normal ferritin concentration compatible with hereditary sideroblastic anaemia (table).

Discussion

This family is of interest for several reasons. X-linked forms of ataxia are very rare and the association with sideroblastic anaemia has been described only twice before.² The affected male patients described by Pagon *et al* had peripheral blood films and indices typical of sideroblastic anaemia and bone marrow examination on three patients confirmed ring sideroblasts. They had mild anaemias often only noted on routine blood testing with slightly low packed cell volumes and mean corpuscular volume. Iron, total iron binding capacity, and ferritin concentrations were normal and FEP concentrations were raised. The findings in our patients were similar although full haematological examination was not possible in all patients. Two out of four affected patients were anaemic; the other two were microcytic emphasising that these mild abnormalities on film blood counts could be easily overlooked. Blood films of patient III.3 and patient III.2 showed Pappenheimer bodies—these were particularly prominent in patient III.2 as a result of his previous splenectomy (fig 3); the splenectomy causes a higher mean corpuscular volume than otherwise would be expected. These patients also had raised FEPs and III.3 who underwent bone marrow aspiration showed ring sideroblasts. The obligate carrier also had Pappenheimer bodies in her blood film.

Whereas our haematological findings are concordant with the two other X-linked ataxia/sideroblastic anaemia families,² they differ from that of isolated classic sideroblastic anaemia in showing absence of iron overload and low FEP concentrations. Pagon *et al* described two families with a total of five affected members. The age range of those patients was 2 to 33. Our family has present ages ranging from 50 to 78. The affected family members described by Pagon *et al* all had neurological problems noted in the first year of life. They had truncal ataxia, problems walking, and incoordination. The three younger boys also had long motor tract signs shown by brisk reflexes in the legs and extensor plantars.

X-linked ataxias are rare in the literature. Shokeir *et al*¹⁴ described 16 affected patients in three families with dysarthria, nystagmus, ataxic arms, and spastic legs. Symptoms developed between 16 and 21 years and showed no progression after the age of 30, the oldest patient described being 68. No haematological data were given. By contrast, Spira *et al*¹⁵ described 10 males in five generations that, as our family, presented with delayed walking. However, one of the older affected family members was reported not to have had any problems until aged 13. Around puberty they developed progressive ataxia, cerebellar dysfunction including dysarthria, nystagmus (which was variable), and spasticity in their legs. The features resemble those of our family

but with the additional features of scoliosis, pes cavus, and slowing of both sensory and motor nerve conduction velocities. Unfortunately no haematological data were given. Harding¹⁶ saw two brothers with a syndrome similar to those described by Spira and Shokeir, but the pedigree was insufficient to define the mode of inheritance. No haematological data were given.

Johnston and McKusick¹⁷ described 15 males in seven generations who had delayed walking with an immediate scissors gait due to spastic paraplegia, talipes equinovarus, scoliosis, and then gradual development of cerebellar, posterior column, optic nerve and cerebral cortex involvement. Interestingly, when compared with our family, their oldest family member studied, aged 61, developed paranoia in his 40s, and then developed dementia, being in a mental hospital from the age of 46. These psychiatric problems obviously show similarities with our family. However, the presence of scoliosis, talipes, optic nerve problems, and severe spasticity probably make this family clinically distinct from ours. No haematological data were available for comparison. Malamud and Cohen¹⁸ described a much more disabling condition, where two male cousins, who had initial normal motor development, had deteriorated by the age of 1 year. They developed initial cerebellar signs of ataxia, dysarthria, and intention tremor, gradually being replaced by extrapyramidal signs. They also had mental deterioration, one had optic atrophy, and the other had probable myoclonic epilepsy. Their course was more severe than in our family with one of the boys dying aged 7 years. Farlow *et al*¹⁹ described a syndrome of ataxia and adult onset dementia. Some of the affected members had delayed motor milestones as in our family, with tremor described at a young age. Progressive development of cerebellar ataxia and spasticity occurred in their 20s, with signs of dementia beginning in their 30s and 40s. Death occurred in their 50s. Brain MRI of two of the patients showed cortical atrophy but no evidence of white matter disease, or olivary or cerebellar atrophy, by contrast with our two scanned patients who both had severe cerebellar atrophy. Lutz *et al*²⁰ described three affected males with olivopontocerebellar atrophy. They had delayed motor milestones, starting at 2–6 months of age, and had slowly progressive ataxia and dysarthria. Scoliosis was present in one, and there was no spasticity in any of them. All of them were considered to have mental retardation. Brain imaging showed cerebellar atrophy as well as atrophy of the pons and olive. One family member had a full blood count with anaemia and a normal packed cell volume and mean corpuscular volume.

We conclude that all these families differ clinically in some respect to our family. Because haematological investigations are often lacking, it is possible that some of the families represent X-linked sideroblastic anaemia with ataxia, with subtle haematological features being overlooked.

Core neurological features of our family include delayed motor milestones in childhood, ataxia from birth, truncal more than limb ataxia, dysarthria, and progression from the fifth decade. Our family showed no early dementia. Patient II.1 had become demented at a late age but we cannot be certain that this is genetically determined. Spasticity is variable in our family but ataxia and delayed walking were consistent findings. The families described by Pagon *et al*¹⁵ are said to have a non-progressive ataxia, but their oldest affected patient was 33. Our affected patients all show evidence of progression from the fifth decade; this progression is more in keeping with other X-linked spinocerebellar ataxias described.^{15–20} Pagon *et al* described delay in walking with ataxia and incoordination as seen in our family, and three of the affected boys also showed evidence of spinal tract involvement. There was no scoliosis, pes cavus, or muscle wasting in any of the families.

In 1991 Raskind *et al* reported linkage of X-linked sideroblastic anaemia with ataxia to the phosphoglycerate kinase (PGK1) locus at Xq13.²¹ In 1998 Shimada *et al* identified and cloned a novel ATP binding cassette gene (hABC7) at Xq13.1–q13.3.²² There is some homology with the yeast ATM1 gene, situated in the mitochondrial inner membrane. It is likely that this gene is involved in haem transport. Thus the hABC7 gene is a strong candidate for X-linked sideroblastic anaemia and ataxia. Mutational analysis is ongoing. If hABC7 proves to be the molecular basis of X-linked sideroblastic anaemia and ataxia, there are strong parallels with Friedreich's ataxia and Pearson's syndrome. Both of these disorders have the combination of mitochondrial iron handling defects with ataxia and may, with X-linked sideroblastic anaemia and ataxia, have elements of subcellular pathophysiology in common. Further genetic and biochemical investigation of X-linked sideroblastic anaemia and ataxia may increase our understanding of this group of ataxias.

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