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Karak syndrome: a novel degenerative disorder of the basal ganglia and cerebellum

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We report a Jordanian Arab family where two sibs developed the classical clinical and radiological features of pantothenate kinase associated neurodegeneration (PKAN, formerly known as Hallervorden-Spatz disease) but in addition had an early onset cerebellar ataxia.[1 2] Using polymorphic microsatellite markers we have shown that this family is not linked to the pantothenate kinase gene (*PANK2*) on chromosome 20.[2] We hypothesise that the disorder, Karak syndrome, is novel and a member of the growing family of neurological diseases involving excess cerebral iron accumulation, for example, PKAN, neuroferritinopathy, aceruloplasminaemia, and Friedreich's ataxia.[2–6]

Key points

- Two brothers are reported with early onset progressive cerebellar ataxia, dystonia, spasticity, and intellectual decline.
- Neuroradiology showed cerebellar atrophy and features compatible with iron deposition in the putamen (including the "eye of the tiger sign") and substantia nigra.
- Diagnosis was compatible with pantothenate kinase associated neuropathy resulting from pantothenate kinase 2 mutation (PKAN due to *PANK2*) but linkage to *PNAK2* was eliminated suggesting Karak syndrome to be a novel disorder.
- The "eye of the tiger" sign has previously only been reported to occur in PKAN due to *PKAN2*

CLINICAL STUDIES

Both affected members (fig 1, IV.1 and IV.2) were the product of a normal pregnancy and birth and had normal developmental milestones and progress at school until disease onset at the age of 6 years. They developed an ataxic gait that was slowly progressive, and was associated with decreased school performance. At 8 years of age they developed inverted feet (calcaneovarus), which was associated with frequent falls. Around the age of 9 years, both started to have choreiform movements of all four limbs, more marked in the upper limbs than in the lower limbs. By the age of 10 years the condition had progressed and they were unable to walk without assistance, and they left school soon after. Their mother found difficulty in feeding them because of swallowing problems after the age of 10 years and they were unable to dress, bathe, or feed themselves by their mid-teens. There were no visual or auditory symptoms or history of epilepsy. Both parents and four older sibs, two brothers and two sisters, were in good health. The parents were first cousins and came from an inbred family (fig 1). The family lived in Karak, a town in southern Jordan.

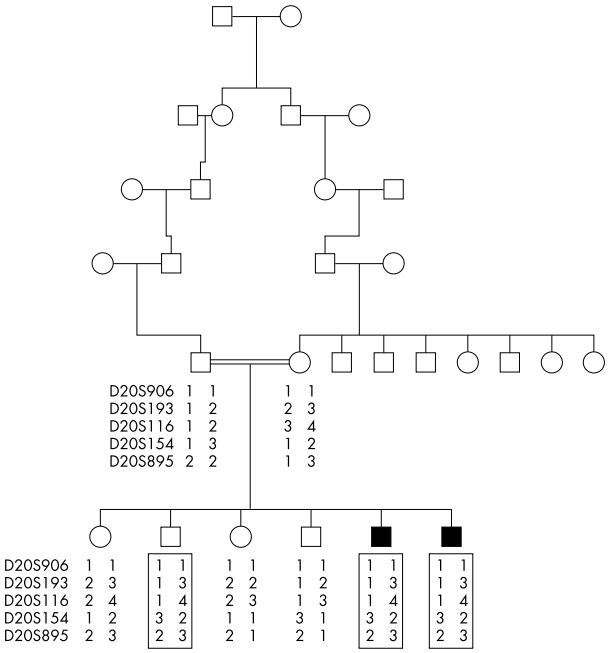

Figure 1 A simplified pedigree of the research family. Affected subjects with Karak syndrome are shown as shaded symbols. The closest link between family members is shown, although other more distant links also exist. The haplotype results for the polymorphic microsatellite markers tel-D20S906-D20S193-D20S116-D20S482-D20S895-cen are shown under each person who was genotyped. The *PANK2* gene lies between markers D20S193 and D20S116. The box highlights the allele results of the two affected males and an unaffected sib, all of whom have an identical heterozygous haplotype.

On examination at the ages of 12 and 14 years respectively, the patients were not dysmorphic and were well grown (height, weight, and head circumference between the 10th-50th centiles). No telangiectasia was found on skin or mucus membrane, nor were skeletal abnormalities detected. Pursuit eye movements showed bilateral limitation of upward gaze in both children; saccadic eye movements were abnormal with bilateral hypometric saccades. Visual acuity was normal, as were the pupillary responses, fundoscopy of the optic discs and retina, and slit lamp examination. Both affected children had dysarthric scanning speech with dystonic features. There was dystonic movement of the tongue and facial muscles and choreiform movement was present in both upper and lower limbs, being more marked in the lower limbs, along with dystonic posture of the distal feet. Significant bradykinesia was present in both upper and lower limbs. Muscle bulk was normal with no wasting or fasciculation. Generalised hypertonia was evident in both upper and lower limbs of a mixed spastic-rigid type. Motor examination showed normal strength testing throughout. Evaluation of the different sensory modalities showed no abnormalities. Deep tendon reflexes were +2 and symmetrical, with bilateral extensor plantar responses. Dysmetria, past pointing, dysdiadochokinesia, and intentional tremor were bilateral and symmetrical. The gait was wide based, swayed in all directions, and had a spastic

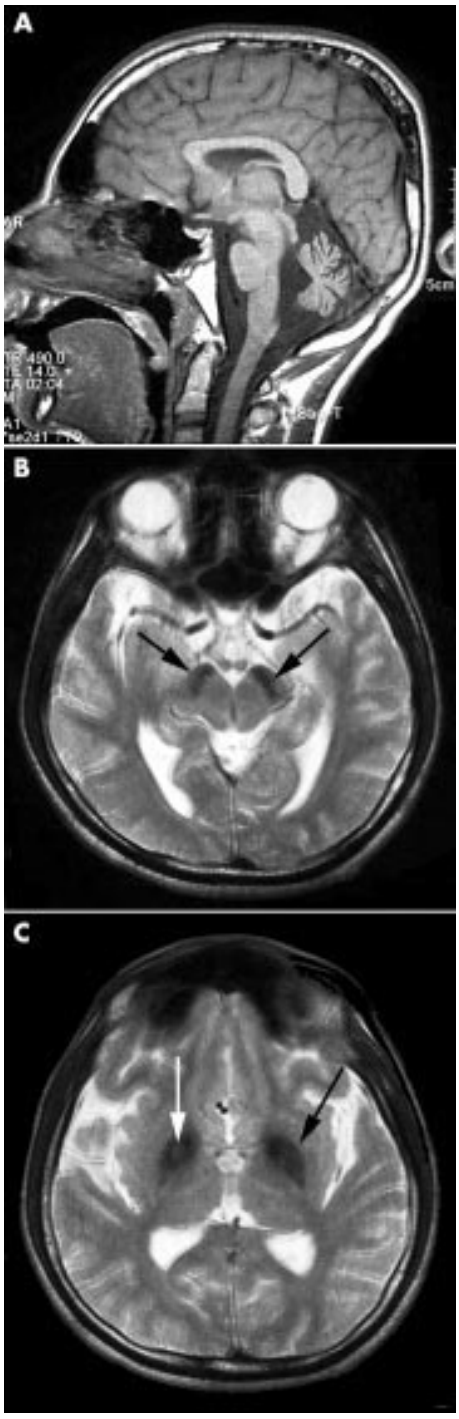

Figure 2 MRI T2 weighted images of the brain of the older affected sib. (A) A parasagittal view showing a moderate degree of pancerebellar atrophy. (B) Decreased signal intensity in the substantia nigra, indicated by a black arrow. (C) The "eye of the tiger" sign with decreased signal intensity in the globus pallidus, indicated by a black arrow, in the centre of which a small high signal spot was seen, indicated by a white arrow.

quality. Neurological examination showed evidence of impairment of cognitive functions and on the Wechsler Adult Intelligence Scale they both achieved less than 60 for verbal IQ.

The following investigations were normal in both children: blood count and film, haemoglobin electrophoresis, liver enzymes, lipid profile, urine testing, serum immunoglobulins, alpha-fetoprotein, serum B12, folate, copper, ceruloplasmin, creatinine phosphokinase, very long chain fatty acids, ferritin, urine organic acids (by gas chromatography and mass spectroscopy), audiogram, ECG, cardiac echo, chest radiographs, electromyography, motor and sensory conduction studies including studies of the late responses, and visual and brainstem evoked potentials. The potential differential diagnoses of PKAN, neuroferritinopathy, and aceruloplasminaemia were eliminated by these results. Muscle biopsy from the older affected child was normal with no evidence to suggest a mitochondrial myopathy. MRI studies of the brain of both affected sibs showed a moderate degree of pancerebellar atrophy (fig 2A). T2 weighted images showed markedly decreased signal intensity restricted to the substantia nigra (fig 2B) and the globus pallidus (fig 2C). In the centre of the globus pallidus a small high signal spot was seen ("eye of the tiger" sign) (fig 2C). There was no abnormal signal in the putamen, caudate nucleus, red nucleus, or dentate nucleus. T1 weighted inversion recovery images were not remarkable. The striking low attenuation on T2 weighted findings suggests an increased iron deposition in the globus pallidus, and is an obligatory radiological feature of PKAN caused by *PANK2* gene mutations.[7]

MOLECULAR GENETIC STUDIES

We performed linkage analysis between the family's disease and the *PANK2* gene that causes PKAN.[2] DNA was extracted using standard techniques from blood samples obtained from nuclear family members. Polymorphic microsatellite markers were sought that flanked the *PANK2* gene by scrutiny of the Marshfield Linkage Maps, the DeCode genetic map,[8] and the draft Human Genome Browser: D20S906-D20S193-*PANK2* gene-D20S116-D20S482-D20S895 (at the following distances from 20pter: 1.5 Mb-3.3 Mb-3.85 Mb- 4.05 Mb-4.5 Mb-5.05 Mb). PCR amplification of all markers was performed using a Roboseq 4200 (MWG BioTech Ltd). Amplified markers were pooled and electrophoresed on an ABI Prism 377 gene sequencer (Applied Biosystems) on 4.2% polyacrylamide gels, at 3000 V and 52°C, for 2.5 hours. Fragment length analysis was undertaken using the ABI Prism Genescan and Genotyper 1.1.1 analysis packages. Fig 1 shows the family genotyping results. The two affected subjects and one of the unaffected sibs all had the same heterozygous results for the informative markers surrounding the *PANK2* gene. This suggests that linkage of the disease to the *PANK2* gene is very unlikely. A further implication of the result is that the affected sibs do not have two separate conditions, one *PANK2* related and the other causing cerebellar ataxia. The results do not help determine if the condition is X linked or autosomal recessive. We also eliminated linkage to the mitochondrial ferritin gene on chromosome 5q23[9] (data not shown).

DISCUSSION

The disorder documented here presented at 6 years of age with cerebellar ataxia. Later, extra pyramidal motor features typical of classical PKAN due to *PANK2* gene mutation developed and intellectual ability declined. There have been a few case reports in which ataxia is associated with PKAN, but none with ataxia as a presenting feature.[10–12] However, in a large study of PKAN two groups were differentiated; firstly, cases with typical clinical symptoms (of what would have been once called Hallervorden-Spatz syndrome[13]) or atypical features with acanthocytosis, hypoprebetalipoproteinaemia and/or orofacial dyskinesia (known as HARP syndrome[14–16]) but all with the "eye of the tiger" sign on MRI brains scan and *PANK2* mutations; secondly, a group of clinically atypical cases which did not have *PANK2* mutations nor the "eye of the tiger sign" but did have hypodensity in the globus pallidus on T2 weighted MRI brain scans, cerebellar atrophy, and often evidence of iron deposition in the red nucleus and dentate nucleus.[7] The family we report appears to have a demonstrably different condition from these two phenotypes because of the

Table 1 Cerebral diseases in which excess iron accumulation is found on MRI scan

Disease title	Inheritance pattern	Age of presentation	Clinical features*	Intellect	Radiological features†	Cerebellar features‡	Gene§	Chromosomal location
Aceruloplasminaemia MIM 604290	Recessive	>30 y	Dementia, ataxia, chorea, dystonia	Declines	Caudate dentate, putamen, red, thalamus, on T1 + T2	Yes, normal	CP	3q23-4
Neuroferritinopathy MIM 606159	Dominant	40–55 y	Choreoathetosis, dystonia, spasticity, rigidity	Normal	Caudate, dentate, globus pallidus, putamen, substantia nigra	Normal	FTL	19q13.3-4
PKAN/PANK2 MIM 234200	Recessive	5–20 y	Rigidity, choreoathetosis, dystonia,	Often declines	"Eye of the tiger" and substantia nigra	Normal	PANK2	20p13
PKAN/PANK2 Atypical and HARP MIM 607236	Recessive	>15 y	Diverse extrapyramidal symptoms	Often declines	"Eye of the tiger"	Normal	PANK2	20p13
PKAN/not PANK2	Probably recessive	>15 y	Diverse extrapyramidal symptoms	Often declines	Dentate, globus pallidus, red	Often, atrophy	?	?
Karak syndrome	Recessive or X linked	6 y	Ataxia, chorea, dystonia	Declines	"Eye of the tiger" and substantia nigra	Yes, atrophy	?	?

Disease title and OMIM number, as described in McKusick's On-line Mendelian Inheritance in Man (OMIM).
PKAN/PANK2 and PKAN/not PANK2 is pantothenate kinaseassociated neuropathy with or without a pantothenate kinase 2 gene mutation.
*Clinical features, lists the presenting and major neurological features only.
†Radiological features lists the (consistent and major) abnormal findings reported on cerebral T2 MRI brain scans. Caudate, dentate, and red refer to the caudate nucleus, dentate nucleus, and red nucleus respectively. "Eye of the tiger" sign is of decreased signal intensity in T2 weighted images, compatible with iron deposits, and of a small area of hyper intensity in its internal segment (illustrated in reference 6).
‡Cerebellar features documents whether clinical findings have been reported followed by cerebellar MRI brain scan findings. Normal means that neither clinical cerebellar signs nor abnormal cerebellar scan findings are present.
§Gene abbreviations used, CP is ceruloplasmin, FTL is ferritin light chain, PANK2 is pantothenate kinase 2 and ? no identified gene.
Freidriech ataxia was not included in the table as there is no evidence on MRI brain scan of excess pathological iron deposition in the central nervous system.

clinical presentation and the neuroradiological findings. The "eye of the tiger" sign is present as is hypodensity in the substantia nigra, but with no abnormal signal in the putamen, caudate nucleus, red nucleus, and dentate nucleus. Exclusion of linkage to the *PANK2* gene provides further support that Karak syndrome is a distinct disorder. In the original paper mapping PKAN due to *PANK2*, family HS9 was the only unlinked family presented. However, insufficient clinical details are given to determine if this single Japanese male case was similar to the family we report.[17 18]

The highest concentration of iron in the brain is found within the basal ganglia (substantia nigra, putamen, caudate nucleus, and globus pallidus), red nucleus, and dentate nucleus. Cerebral iron accumulates with age, particularly in the basal ganglia.[19] While iron is essential for normal brain function, free iron ions impose an oxidative stress on cells, owing to the production of oxygen free radicals, leading to cell damage. Cerebral diseases in which excess iron accumulation is shown on MRI scan are summarised in table 1. All cause clinical features of basal ganglia disease and all exhibit excess iron deposition in some or all of the sites where iron concentrations are the highest in the disease free state. Iron is stored predominantly complexed with ferritin within brain cells, and dysfunction of the ferritin light chain causes neuroferritinopathy.[3] Ceruloplasmin is a ferroxidase with roles including ferric iron uptake by transferrin (which transports iron in the ferric state in the circulation) and dysfunction leads to aceruloplasminaemia.[6] How mutations in the *PANK2* gene, a brain specific CoA biosynthesis regulatory enzyme, cause pathological iron accumulation is unclear, but may relate to an accumulation of cysteine, which can chelate iron. A potential common pathogenic mechanism for neurological disease involving excess cerebral iron accumulation would be the release of free iron ions, either in excess or in a non-physiological situation or both.[20] Because of this we sought, but did not find, linkage between the mitochondrial specific ferritin gene and Karak syndrome.

The inheritance pattern of Karak syndrome may be autosomal recessive or X linked recessive. The lack of other affected males in the matrilineal line and parental consanguinity favour recessive inheritance but clarification awaits further reports of the condition. We hypothesise that the disorder is novel and a member of the growing family of neurological disease involving excess pathological cerebral iron accumulation. Potentially, the gene mutated in Karak syndrome could be involved in iron sequestration, transport, storage, ferrous/ferric status control, intercalation of iron into enzymes, and oxidative respiration.

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Electronic database information. For genetic linkage maps: Center for Medical Genetics, Marshfield Medical Research Foundation at http://research.marshfieldclinic.org/genetics/ For data on polymorphic markers: Genome Database (GDB) at http://gdbwww.gdb.org/ For physical contig information of the human genome: the draft Human Genome Browser at http://genome.cse.ucsc.edu/ For genetic disease details: McKusick's Online Mendelian Inheritance in Man at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM

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Myhre syndrome: new reports, review, and differential diagnosis

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Several conditions characterised by short fingers, reduced joint mobility, short stature, and muscular build with or without mental retardation have been delineated during the past 30 years: Moore-Federman syndrome, Myhre syndrome, acromicric dysplasia, geleophysic dysplasia, GOMBO syndrome, and LAPS (Laryngotracheal stenosis, Arthropathy, Prognathism and Short stature) syndrome. In 1980 Myhre *et al*[1] reported two unrelated males with mental retardation, facial dysmorphism (short palpebral fissures, maxillary hypoplasia, prognathism, short philtrum, small mouth), short stature, brachydactyly, muscle hypertrophy, decreased joint mobility, mixed hearing loss, and cleft lip and palate in one of them. *X* rays showed a thickened calvarium, hypoplastic iliac wings, broad ribs, and large, flattened vertebrae with large pedicles. Five further cases were reported. Mental retardation of variable severity was present in all patients. Three of the older patients had hypertension.

We report here four new unrelated patients who fit a diagnosis of Myhre syndrome, expanding the behavioural profile of the disorder, and discuss the differential diagnosis.

CASE REPORTS

Patient 1

Patient 1, a male, was the second child of healthy, non-consanguineous parents. The father was 181 cm tall and the mother was 165 cm tall. They were aged 40 and 34 years, respectively, at time of delivery. Birth weight was 2130 g, length 44.5 cm, and OFC 36 cm at 36 weeks' of gestation based on LMP (40 weeks based on morphological score of maturity). Recurrent hypoglycaemia requiring glucose infusion was recorded during the first weeks. Psychomotor development was normal, but dysarthria required long term speech therapy. He had bilateral deafness, with loss of 40 dB in low frequencies to 20 dB on the right side, and from 60 dB to 35 dB on the left side. MRI and CT showed bilateral dysplasia of the external semicircular canal. The stapedial footplate was bilaterally thick and, on the right side, fused with the oval window. This appearance was compatible with primary stapedial dysplasia or with otosclerosis. The absence of evolution of the hearing loss was considered as an argument for the dysplasia hypothesis. He wore a hearing aid. He had hypermetropia.

Progressive growth catch up occurred during the first year of life, reaching the 25th centile curve, then he slowly came back to the 3rd centile curve. OFC stayed around the 25th centile. Repeated bone age studies always showed skeletal maturation concordant with chronological age. Longitudinal skeletal survey showed generalised brachydactyly with brachyphalangy and brachymetacarpalia, large epiphyses (notably the femoral heads and proximal phalanges of fingers 2 and 3), and mild platyspondylic appearance of the vertebral