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ORIGINAL ARTICLE

First cases in the Czech Republic of the Hallervorden-Spatz Disease resulting from mutation in the Pantothenate Kinase 2 Gene

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Abstract

Hallervorden-Spatz disease (HSD) was and is known as a rare disorder primarily characterized by progressive extrapyramidal dysfunction and dementia alongside optic nerve atrophy or retinal degeneration and pyramidal signs. The rate of occurence of HSD is thus far unknown. Progress in DNA diagnostics stirred up a nomenclature and from HSD, or, perhaps better put, the Hallervorden-Spatz syndrome, crystallized the pantothenate kinase-associated neurodegeneration (PKAN) as a clearly defined entity on the level of DNA.
In this paper, we present our first results and experience in the diagnosis of PKAN in the Czech Republic and discuss questions related to differential diagnosis.

Abbreviation

CT– Computer Tomography
CNS– Central Nervous System
DNA – Deoxyribonucleic acid
ECG – Electrocardiogram
EEG– Electroencephalogram
ERG – Electroretinogram
HARP – hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration
HSD – Hallervorden-Spatz disease
HSS – Hallerworden-Spatz syndrome
INAD– Infantile Neuroaxonal Dystrophy
MRI– Magnetic Resonance Imaging
NBIA– 1-Neurodegeneration with Brain Iron Accumulation Type1
PKAN – Pantothenate Kinase-associated Neurodegeneration
SPECT – Single-photon Emission Computed Tomography

Introduction

Hallervorden and Spatz described what is now known as HSD in 1922 as a form of familial brain degeneration characterized by iron deposits in the brain [2]. They based their report on five girls from a family with 12 children in which three other siblings died and the remaining four were healthy. The disease manifested itself in gait difficulties which included rigidity of the legs, dysarthria, and the progressive loss of intellectual functions. All females died between the ages 16 and 27 and a brown discoloration of the globus pallidus and substantia nigra was observed at the time of autopsy.

A number of reports of similar symptoms were released under a variety of titles in the following ninety years. Names assigned to the disorder included the following: *progressive pallidum degeneration syndrome, pallido-reticular pigmentarry degeneration, late infantile neuroaxonal dystrophy, infantile, Seitelberger disease, and neurodegeneration with brain iron accumulation type1 (NBIA-1)*. As with many other so-called clinical diseases, HSD became a group of anticipated distinctive entities.

Clinical and pathological signs established distinct groups within Hallerworden-Spatz syndrome (HSS) [3], but it was only with the end of the last century that the development of magnetic resonance imaging has increased the number of reported cases of HSS and enabled more precise classification. In the same way, diagnostic criteria have gradually crystallized [6,7,11].

A turning point came with the 2001 research conducted by Zhou et al [14] in which a pantothenate kinase 2 gene (PANK2) on band 20p13 was identified in patients with typical HSD. Pantothenate kinase is an essential regulatory enzyme in CoA biosynthesis, catalyzing the cytosolic phosphorylation of pantothenate (vitamin B5), N-pantothenoylcysteine, and pantetheine. CoA is the major acyl carrier, playing a central role in intermediary and fatty acid metabolism. Mutations in the same gene cause the allelic disorder HARP syndrome [1,9].

The discovery of the gene defect in PKAN, among others, has enabled differentiation between two similar disorders – infantile neuroaxonal dystrophy (INAD) and pantothenate kinase-associated neurodegeneration. By sequencing in seven INAD families, Hortnagel et al [8] revealed no mutations in PANK2 or in other genes of CoA biogenesis and thus confirmed that they are genetically heterogeneous disorders.

In 2003, Hayflick et al proposed the use of the term *pantothenate kinase-associated neurodegeneration (PKAN)* for the majority of patients with Hallervorden-Spatz syndrome who have proven or suspected mutations in PANK2. The term *neurodegeneration with brain iron accumulation* was proposed for the remainder of cases.

Hallmark features of panthotenate kinase-associated neurodegeneration are summarized in table 1.

Diagnostics of mutations in the PANK2 gene have been seen in Neurogenetic Centre, Motol, Prague since 2003.

The diagnosis in the following 3 non-consanguineous patients was established by sequence analysis of exons 1b-7 of PANK2 gene (see case reports). The diagnosis of the sister of one patient was established early, at the time of autopsy.

CASE reports of patients hospitalized in the Department of Child Neurology, 2nd Faculty of Medicine of Charles University and Faculty Hospital Motol, Prague

Case Report No 1. Female, 1993–2000

Family history: The father of the patient has moderate psychomotor retardation and the mother is treated for thyreotoxicosis. The patient had no siblings. Further information is not known.

Personal history: The patient was from a first risk pregnancy and delivery was in the term with an Apgar score of 9–9. Normal early post partum development, 3500g/47 cm, head circumference 35 cm. At the age of 4 months physiotherapy was started due to increased muscle tonus.

Psychomotor data:

The patient rolled from prone to supine from 5 months, sat in tripod fashion without support from 7 months, walked with assistance from 10 months, and reportedly walked without assistance from 11 months. Speech was delayed, first 1–2 words at the age of 2 years. Walking grew worse and the patient walked with falls from 22 months of age.

Due to insufficient family care the patient was placed in an orphanage at the age of 3. At that time high negativity and hyperkinetic manners were observed; there was no verbal communication and walking was possible only with assistance. After living in the orphanage, the psychomotor regress subsided slightly and the patient learned to walk and to say a few words. Physiotherapy was prolonged.

There was no increase in morbidity but the patient was observed because of the vesicourethral reflux and dystopia and hypoplasia of the dexter kidney.

Pathological findings at 4 years of age included:

- pigmentary degeneration of retina
- CT CNS – small symmetrical calcifications in basal ganglia.

Table 1. Hallmark features of Panthotenate Kinase-Associated Neurodegeneration [4,10,13]

	typical clinical form	atypical clinical form
onset of symptoms	early, in the first decadeor early adolescence	second and third decade
progression/loss of ambulation occurring within:	10–15 years of onset	15–40 years of onset
neurological symptomatology	impaired gait;pyramidal + extrapyramidal signs including rigidity, dystonia, and choreoathetosis	speech disorders,pyramidal + extrapyramidal signs including rigidity, dystonia, and choreoathetosis
dementia	global developmental delay in some children	psychiatric disorders (dementia and emotional imbalance)
retinitis pigmentosa/ optic atrophy	often	rare
MRI of brain	"eye-of-the-tiger" sign	"eye-of-the-tiger" sign

Cerebral palsy was the primary diagnosis. In 1999 the patient was recommended to the Department of Child Neurology in Prague-Motol due to the fact that a neurodegenerative disorder was suspected.

Neurological examination (6 years of age):

spastic diparesis with sinister dominancy, extrapyramidal and paleocerebellar syndrome. Dysarthria, dyspraxia, dysgnosia. Patient is able to count to ten and to say nursery rhymes.

Investigations:

- Complete blood cell counts and routine chemistry test results were normal.
- The level of vitamins, carnitine, lactate, copper, and ceruloplasmine were normal.
- Psychological examinations revealed moderate mental retardation at approximately 4–5 years of age.
- Conduction studies on motor and sensory nerves (2003) were normal on lower limbs. f-ERG no response, flash visual, brain stem, and somatosensory evoked potentials, were normal.
- EEG with fotostimulation was normal, only lower amplitudes.
- ECG findings were normal.
- Examinations of cerebrospinal fluid (protein, glucose, cytology, virology) were normal.
- Ophthalmologic investigation revealed retinitis pigmentosa, hypermetropia, and anisometropia. No Kayser-Fleischer ring.
- Brain magnetic resonance imaging scans disclosed bilaterally symmetric hyperintense signal changes with surrounding hypointensity in globus pallidus on T2-weighted images.
- HSD was established as the most likely diagnosis due to the background in the case, neurological examination, and MRI finding. DNA was isolated and the diagnosis was verified on an implementation DNA testing for PANK2 gene in the end of 2003. At that time, we learned that our patient had unfortunately died of an intercurrent infection in the year 2000.

Case Report No 2. Female, 1993–2004

Family history: The father and mother, as well as two older sisters and one older brother of the patient are healthy. No other family members had movement disorders.

Personal history: The patient is from the fourth non-consanguineous pregnancy of her mother, aged 41. The pregnancy was without complications and the mother withheld an amniocentesis. The delivery was in the term and the patient weighed 4000 grams at birth. There was normal early post partum development and no increased morbidity.

Psychomotor data: Normal development until 3 years of age. At that time walking worsened, falls were reported, and a digitigrades stereotype appeared. Gradually communication ceased, as did nighttime bladder control.

The patient was observed by a child neurologist in the home due to psychomotoric regress of an unspecified etiology. CT of brain with suspicion of calcifications in basal ganglia. Screening of inherited metabolic disorders was normal, as well as DNA analysis for fragile X chromosome and Angelman syndrome. No thyreopathy.

At 8 years of age in March of 2003, the neurological picture of the patient dramatically worsened. Dyskinetic movements and postural abnormalities were observed. Loss of bladder control was noted during the day. Starting in August of 2003 the patient was not able to walk and a progression of postural abnormalities in the form of choreoathetosis was described. Major dysphagia. The patient lost 8 kilograms.

Hospitalization in the Department of Child Neurology Prague-Motol began in September of 2003.

Neurological examination (7,5 years of age):

spastic quadruparesis with dexter dominancy, choreoathetosis. Inarticulate cry. Whereas the patient appeared unable to perceive or respond to external stimulation, the mother was of the opinion that the patient was able to perceive.

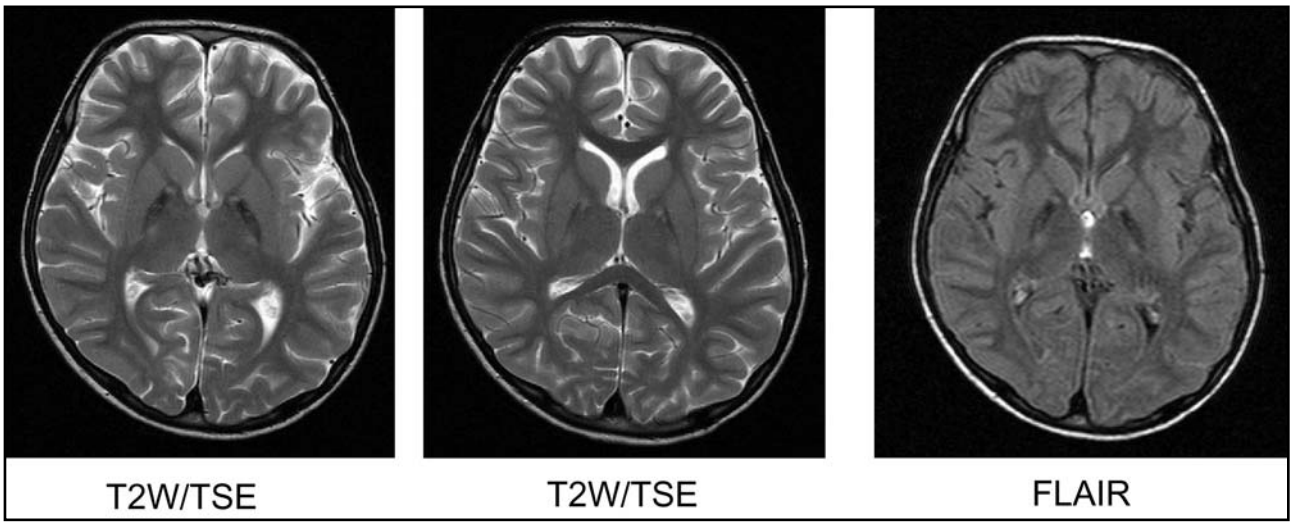

Figure 1: MRI scans of patient No. 2–7,5 years of age

Table 2. Summary of signs and results of investigations in our patients

	Patient 1	Patient 2	Patient 3	Patient 4
start of symptoms	*3 months of age:* ↑ muscular tonus, delayed of speech *since onset*	*3 years of age:* spastic diparesis	*9 years of age:* a gait difficulty	*6 years of age:* visual impairment (retinitis pigmentosa)
progression/loss of ambulation	*22 months of age:* rapid worsening of a gait, but latest partial improvement; she died in *7 years of age*	*8 years of age:* acute deterioration; loss of ambulation, choreoathetosis, weighted loss; she died in *11 years of age*	slowly; *41 years of age:* slow gait without support	*7 years of age:* spastic diparesis, extrapyramidal signs *12 years of age:* loss of ambulation, progressive dysarthria
neurological symptoms	*6 years of age*: spastic diparesis, dystonia, paleocerebellar syndrome	*8,5 years of age:* spastic quadruparesis, choreoathetosis, dysphagia, dysarthria	*41 years of age:* spastic quadruparesis, choreoathetosis, dystonia, dysphagia, dysarthria	*14 years of age:* spastic quadruparesis, rigidity, dysphagia, dysarthria
dementia	psychomotoric retardation since *first months of age*	? problems of testing due to neurological symptoms	mild; marked emotional lability	? problems of testing due to neurological symptoms
retinitis pigmentosa	found to be in *4 years of age*	no pathology	*12 years of age:* incipient retinopathy	*6 years of age* (a first sign)
CT/MRI of brain	CT (*4 years of age*): calcifications in basal gangliaMRI (*6 years of age*): "eye-of-the-tiger" sign	CT (8 *years of age*): calcifications in basal ganglia MRI (8,5 *years of age*): "eye-of-the-tiger" sign	was not made	was not made; the diagnosis was confirmed by autopsy

Investigations:

- Complete blood cell counts and routine chemistry test results, the level of vitamins, carnitine, lactate, copper, and ceruloplasmine, and examinations of cerebrospinal fluid were, as in the previous case report, normal. No Kayser-Fleischer ring, no retinitis pigmentosa, or optic atrophy.
- MRI scans confirmed small symmetric hyperintense signal changes with surrounding hypointensity in globus pallidus on T2-weighted images, and small arachnoideal cyst in the dexter fossa posterior (see Figure 1).
- Diagnosis was verified by sequence analysis of PANK2 gene.
- No effect of *biperidenum* (Akineton) was observed in therapy and there was a mild improvement with the use of *clonazepamum* (Rivotril). The patient progressively worsened and died in the year 2004 at the age of 11.

Case No. 3, Male, 41 years

Family history: Father and mother are healthy. The sister of the patient in Case No. 3 (Case No. 4, Table 2, 1957–1975) began experiencing problems with worsening sight and at the age of 6 retinitis pigmentosa was identified. From the age of 7, problems with motor control and repeated falls were observed. Extrapyramidal syndrome and spastic diparesis were neurological findings. The patient´s condition worsened progressively and the patient was unable to walk from the age of 12. Dysarthria progressed. In 1971 the patient was hospitalized in the Department of Child Neurology Prague-Motol.

The use of then-current examination methods excluded the possibility of stored disease, chronic inflammatory disease, morbus Wilson, and neuronal ceroid-lipofuscinosis. HSD was determined to be the most probable diagnosis and the diagnosis was confirmed after the death of the patient in 1975.

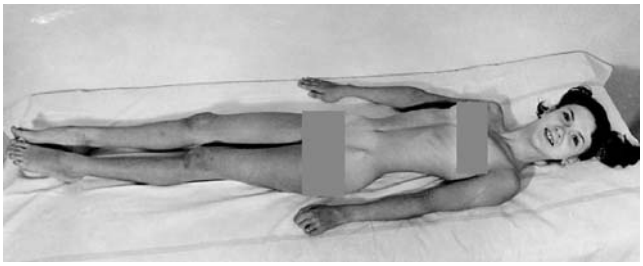

Figure 2. Patient No. 4: 14 years of age (with the agreement of her family)

Personal history:

The male patient was born at full term and developmental milestones were normal. A gait difficulty was observed by the parents when the patient was 9. In 1971, the patient and his sister were hospitalized in our department and neurological examination revealed only moderate spastic diparesis.

The condition of the patient worsened more slowly than in the case of his sister but at the age of 12 extrapyramidal signs appeared

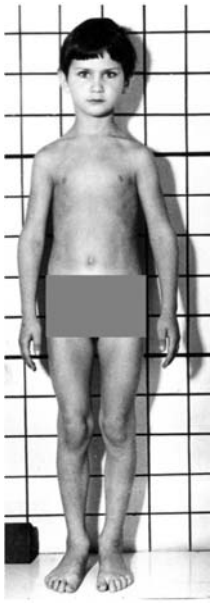

Figure 3. Patient No. 3: 7 years of age (with the agreement of his family)

Table 3. Basal ganglia calcifications – potential causes

BASAL GANGLIA CALCIFICATIONS	
PRINCIPAL GROUPS	***SPECIFICATIONS***
IDIOPATHIC	(accounts for greater than 50% of cases, normal (?) variant, familial or sporadic occurrence)
INFECTION	TORCHS infection *(esp. cytomegalovirus, toxoplasmosis)* Congenital HIV Tuberculosis Cysticercosis Measles, chickenpox, pertussis, coxsackie B virus, Systemic lupus erythematosus
POISONING or other EXTERNAL CAUSE	Lead Carbon monoxide Radiation therapy and chemotherapy Hypoxia (anoxia) Cardiovascular event Methaemoglobinopathy
ENDOCRINE	Abnormal calcium metabolism (Hypoparathyroidism, Hyperparathyroidism, Pseudohypoparathyroidism, Pseudopseudohypoparathyroidism)
METABOLIC	Nephrotic syndrome
NEURODEGENERATIVE (*seu* neurometabolicor neurogenetic) DISEASES	Fakomatoses (tuberous sclerosis, neurofibromatosis) Fahrs syndrome (familial cerbrovascular calcinosis) Cockayne's syndrome Down syndrome Hallervorden-Spatz disease (PKAN) Lipoid proteinosis (hyalinosis cutis) Mitochondrial cytopathies Carbonic anhydrase deficiency type II Hastings-James syndrome Carbohydrate-deficient glycoprotein syndrome Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL), or Nasu-Hakola disease

Figure 4. Patient No. 3: 40 years of age (with the agreement of his family)

and incipient retinopathy was detected. Since that time, the patient has been examined only during home care provided by his family. The patient has not suffered internal disorders of a more serious nature in addition to the basic illness. There are no neuroimaging investigation results at our disposal. Whereas the problem has gradually progressed, the patient is capable of walking by himself with minimal resistance at present. Drugs used in long-term therapy include *biperidinum* (Akineton), *selegilini hydrochloridum* (Jumex), *baclofenum* (Baclofen) and *alprazolamum* (Neurol).

At present, choreoathetosis and dysarthria precluded speech in neurological examination. Non-verbal communication, however, occurs promptly and effectively and without any difficulty provided that the patient does not move and is not under psychological stress. While emotional and behavioural deficits are undoubtedly present, the parents of the patient are not willing to subject him to problems associated with examination due to the fact that they are aware of the impossibility of the causal therapy of the patient. Nonetheless, the parents requested DNA verification of PANK2 gene mutation. As a consequence of the patient´s condition and anamnesis, an examination was carried out and the mutation was confirmed.

Discussion

PKAN is subtype of historic Hallervorden-Spatz disease and is characterized by progressive dystonia and basal ganglia iron deposits with an onset that usually occurs before the age of ten. Commonly associated features include dysarthria, rigidity, and pigmentary retinopathy. About 25% of affected individuals have an "atypical" presentation with onset after age ten years, prominent speech defects, psychiatric disturbances, and a more gradual advance of the disease.

The three patients presented exhibited confirmed mutations of the PANK2 gene and table 2 shows their results in the light of contemporary knowledge about hallmark features of Panthotenate Kinase-Associated Neurodegeneration (see table 2).

Our cases reports reflect that this similar subdivision is not in any case sufficient. The manifestation of diseases in patient No. 3, started before ten years of age and the course of the illness was typical in the early years. The question is how is it possible that the 41-year-old male patient is alive and able to walk with assistance while his sister died at the age of 18?

Further difficulties emerge over the course of investigation and differential diagnosis. The CT scan in both female patients has indicated calcifications in basal ganglia. The differential diagnosis of this sign is very large (see table 3). In addition, it leads to very misleading information. Calcifications in basal ganglia are most probably a result of storage of calcium in a disintegrating tissue but do not, as in the case of the main problem, display iron deposits.

In the event that a patient has a medical background which arouses the suspicion of HSD, it is necessary that it is indicated with an MRI or with a combination of CT and MRI. Single-photon

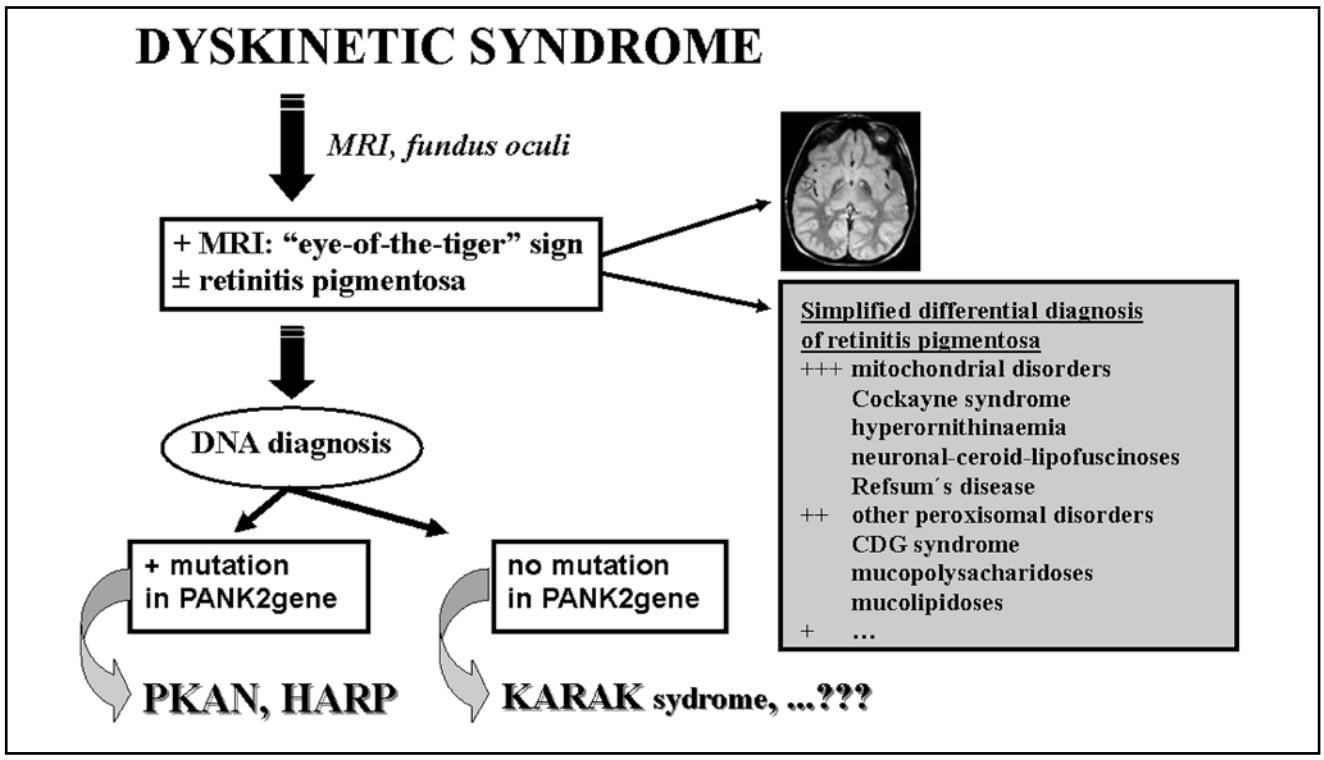

Figure 5. Scheme. PKAN diagnostic program – a simplified approach

emission computed tomography (SPECT) also has been used in differential diagnosis of HSD. When the *eye of the tiger* symptom is found in the MRI, three different illnesses or syndromes are diagnosed: HSD, Karak syndrome [12] and HARP (hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration) syndrome. It must be expected, however, that in the future more syndromes will be diagnosed (see Figure 5, scheme).

DNA diagnosis enables the verification of further illnesses included in the group of originally "neurodegenerative disorders." We face, at the same time, a range of other related questions and problems which need to be solved.

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REFERENCES

1 Ching KH, Westaway SK, Gitschier J, Higgins JJ, Hayflick SJ. HARP syndrome is allelic with pantothenate kinase-associated neurodegeneration. Neurology 2002; **58**:1673–4.
2 Hallervorden J, Spatz H. Eigenartige Erkrankung im extrapyramidalen System mit besonderer Beteiligung des Globus pallidus und der Substantia nigra: Ein Beitrag zu den Beziehungen zwischen diesen beiden Zentren. Z Ges Neurol Psychiat 1922; **79**: 254–302.
3 Halliday W. The nosology of Hallervorden-Spatz disease. J Neurol Sci 1995; **134** Suppl:84–91.
4 Hayflick SJ, Westaway SK, Levinson B, Zhou B, Johnson MA, Ching KH, Gitschier J. Genetic, clinical, and radiographic delineation of Hallervorden-Spatz syndrome. N Engl J Med 2003; **348**(1):33–40.
5 Hayflick SJ. Unraveling the Hallervorden-Spatz syndrome: pantothenate kinase-associated neurodegeneration is the name. Curr Opin Pediatr 2003; **15**(6):572–7.
6 Hayflick SJ. First scientific workshop on Hallervorden-Spatz syndrome: executive summary. Pediatr Neurol 2001; **25**(2):99–101.
7 Hickman SJ, Ward NS, Surtees RA, Stevens JM, Farmer SF. How broad is the phenotype of Hallervorden-Spatz disease? Acta Neurol Scand 2001; **103**(3): 201–3.
8 Hortnagel K, Nardocci N, Zorzi G, Garavaglia B, Botz E, Meitinger T, Klopstock T. Infantile neuroaxonal dystrophy and pantothenate-kinase-associated neurodegeneration: locus heterogeneity. Neurology 2004; **63**(5):922–4.
9 Houlden H, Lincoln S, Farrer M, Cleland PG, Hardy J, Orrell RW. Compound heterozygous PANK2 mutations confirm HARP and Hallervorden-Spatz syndromes are allelic. Neurology 2003; **61**(10):1423–6.
10 Morphy MA, Feldman JA, Kilburn G. Hallervorden-Spatz disease in a psychiatric setting. J Clin Psychiatry 1989; **50**(2):66–8.
11 Swaiman KF. Hallervorden-Spatz syndrome. Pediatr Neurol 2001; **25**(2):102–8.
12 Mubaidin A, Roberts E, Hampshire D, Dehyyat M, Shurbaji A, Mubaidien M, Jamil A, Al-Din A, Kurdi A, Woods CG. Karak syndrome: a novel degenerative disorder of the basal ganglia and cerebellum. J Med Genet 2003; **40**(7):543–6.
13 Swaiman KF. Hallervorden-Spatz syndrome. Pediatr Neurol 2001; **25**(2):102–8.
14 Zhou B, Westaway SK, Levinson B, Johnson MA, Gitschier J, Hayflick SJ. A novel pantothenate kinase gene (PANK2) is defective in Hallervorden- Spatz syndrome. Nat Genet 2001; **28**(4):345–9.