

ORIGINAL ARTICLE

Genetic, Clinical, and Radiographic Delineation of Hallervorden–Spatz Syndrome

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ABSTRACT

BACKGROUND

Hallervorden–Spatz syndrome is an autosomal recessive disorder characterized by dystonia, parkinsonism, and iron accumulation in the brain. Many patients with this disease have mutations in the gene encoding pantothenate kinase 2 (PANK2); these patients are said to have pantothenate kinase–associated neurodegeneration. In this study, we compared the clinical and radiographic features of patients with Hallervorden–Spatz syndrome with and without mutations in PANK2.

METHODS

One hundred twenty-three patients from 98 families with a diagnosis of Hallervorden–Spatz syndrome were classified on the basis of clinical assessment as having classic disease (characterized by early onset with rapid progression) or atypical disease (later onset with slow progression). Their genomic DNA was sequenced for PANK2 mutations.

RESULTS

All patients with classic Hallervorden–Spatz syndrome and one third of those with atypical disease had PANK2 mutations. Whereas almost all mutations in patients with atypical disease led to amino acid changes, those in patients with classic disease more often resulted in predicted protein truncation. Patients with atypical disease who had PANK2 mutations were more likely to have prominent speech-related and psychiatric symptoms than patients with classic disease or mutation-negative patients with atypical disease. In all patients with pantothenate kinase–associated neurodegeneration, whether classic or atypical, T₂-weighted magnetic resonance imaging (MRI) of the brain showed a specific pattern of hyperintensity within the hypointense medial globus pallidus. This pattern was not seen in any patients without mutations.

CONCLUSIONS

PANK2 mutations are associated with all cases of classic Hallervorden–Spatz syndrome and one third of cases of atypical disease. A specific MRI pattern distinguishes patients with PANK2 mutations. Predicted levels of pantothenate kinase 2 protein correlate with the severity of disease.

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THE DIAGNOSIS OF HALLERVORDEN–Spatz syndrome applies to a spectrum of disorders that share the common features of neurodegeneration and iron accumulation in the brain.^{1,2} Hallervorden–Spatz syndrome with early onset and rapid progression is the originally reported, classic form of the disease.³ It presents in childhood with dystonia, dysarthria, and rigidity and has a relentlessly progressive course, culminating in early death. Pigmentary degeneration of the retina may accompany this form of the disease, and iron deposition in the basal ganglia is evident on magnetic resonance imaging (MRI) and post-mortem examination.¹ In an atypical form of Hallervorden–Spatz syndrome, the onset of extrapyramidal defects is later and the progression of the disease is slower and more variable, with accumulation of iron in the basal ganglia. Atypical disease is clinically heterogeneous and is thought to encompass several disorders.^{1,4,5} In addition, the condition of some patients does not fit the diagnostic criteria for Hallervorden–Spatz syndrome, yet the atypical form of the disease remains the diagnosis that best fits their signs and symptoms.^{4,6,7}

Recently we discovered that many cases of Hallervorden–Spatz syndrome result from mutations in a gene located on chromosome 20p13.⁸ The culprit gene (*PANK2*) encodes a novel pantothenate kinase, a key regulatory enzyme in the biosynthesis of coenzyme A.⁸ We speculated that a deficiency of this enzyme could lead to neurodegeneration and iron accumulation, and we proposed a new descriptive term for the resulting autosomal recessive error of metabolism: pantothenate kinase–associated neurodegeneration (Online Mendelian Inheritance in Man number 234200).

In the current study, we determined the genotype of patients with classic and atypical Hallervorden–Spatz syndrome and reviewed their medical records to assess whether there was a correlation between clinical manifestations or radiographic findings and the presence of *PANK2* mutations.

METHODS

SUBJECTS

Subjects were recruited internationally by means of announcements posted in neurology and genetics journals, on a pediatric-neurology list server, and on the Web sites of the Hallervorden–Spatz Syndrome Association (<http://www.hssa.org>) and the National Organization for Rare Disorders (<http://www.rarediseases.org>).

We identified 186 patients from 145 families who had extrapyramidal defects and radiographic evidence of iron deposition in the basal ganglia. We examined 28 of the subjects. For the remainder, samples were sent by referring physicians and clinical and laboratory data were obtained from records and MRI scans. Detailed clinical information and DNA samples were collected from the patients after they had given written informed consent. The protocol was approved by the institutional review boards of the Oregon Health and Science University or the University of California, San Francisco. We gathered all possible clinical information, including the age at onset of disease and presenting symptoms; results of neurologic and ophthalmologic examinations; results of electrical studies, including electroencephalography, electromyography, electroretinography, and visual evoked potentials; and brain MRI scans. Clinical information was insufficient for 63 of the 186 patients, and our analysis is therefore based on the remaining 123 patients from 98 families.

Patients were classified as having either classic disease (66 patients) or atypical disease (57 patients). Early-onset, rapidly progressive (classic) disease was usually evident by the age of 10 years and was manifested by dystonia, progression to severe disability by 20 years of age, and radiographic changes indicating a high iron content in the basal ganglia. Those with atypical disease included all other patients with extrapyramidal dysfunction and radiographic evidence of iron accumulation in the basal ganglia. The atypical disease usually also had a later onset and a more slowly progressive course.

ANALYSIS OF MUTATIONS

Primers were designed to amplify each of the seven exons of *PANK2*. Polymerase-chain-reaction–amplified DNA was sequenced in both the forward and the reverse directions and compared with control DNA. Mutations were classified as null if they were predicted to result in premature protein termination (including frame shifts, nonsense mutations, and mutations altering splice-donor and acceptor sequences); missense mutations were defined as those causing the substitution of one amino acid for another.

STATISTICAL ANALYSIS

Chi-square analyses were conducted with the use of an online tool (http://www.georgetown.edu/cball/webtools/web_chi.html).

RESULTS

GENETIC FINDINGS

PANK2 mutations were found in 66 of the 98 families of patients with Hallervorden–Spatz syndrome

(Table 1). Of 49 families whose members had classic disease, all had mutations in PANK2. Of 49 families whose members had atypical disease, mutations were found in 17 (35 percent). Null mutations were found in 36 of 92 alleles in patients with classic dis-

Table 1. PANK2 Mutations Identified in Patients with Pantothenate Kinase–Associated Neurodegeneration.

DNA Mutation*	Protein Change†	No. of Alleles Found in Patients		DNA Mutation*	Protein Change†	No. of Alleles Found in Patients	
		Early-Onset, Rapidly Progressive (Classic) Disease	Late-Onset, Slowly Progressive (Atypical) Disease			Early-Onset, Rapidly Progressive (Classic) Disease	Late-Onset, Slowly Progressive (Atypical) Disease
1231G→A	G411R	24	7	416G→C	R139P	1	0
1253C→T	T418M	3	7	493–494del	Frame shift	1	0
1021C→T	R341X	4	1	503G→T	R168L	1	0
118C→T	Q40X	3	0	514C→G	L172V	1	0
1082G→A	S361N	3	0	606T→A	C202X	1	0
881A→T	N294I	0	3	635A→G	E212G	1	0
526C→T	R176C	2	2	700A→T	K234X	1	0
215insA	Frame shift	2	0	740G→A	R247Q	1	0
239insA	Y80X	2	0	755–758del	Frame shift	1	0
243del	Frame shift	2	0	794–822del	Frame shift	1	0
460C→T	R154W	2	0	862G→A	A288T	1	0
597–603del	Frame shift	2	0	908T→C	L303P	1	0
650C→T	T217I	2	0	943–945del	L315del	1	0
846–847del	Frame shift	2	0	953G→A	C318Y	1	0
993–996del	Frame shift	2	0	1009G→A	D337N	1	0
1169A→T	N390I	2	0	1160T→C	I387T	1	0
1171–1174dup	Frame shift	2	0	1201A→G	N401D	1	0
1196C→T	A399V	2	0	1358T→C	L453P	1	0
1264C→T	R422W	2	0	IVS1–1G→A	Aberrant splicing	1	0
IVS2+3A→G	Aberrant splicing	2	0	IVS6–2A→G	Aberrant splicing	1	0
IVS4–1G→T	Aberrant splicing	2	0	285del	Frame shift	0	1
IVS5–3C→G	Aberrant splicing	2	0	326G→T	G109V	0	1
370A→G	T124A	0	2	502C→T	R168C	0	1
721T→C	S240P	0	2	636G→T	E212D	0	1
71A→G	E24G	1	0	734A→G	N245S	0	1
206–228del	Frame shift	1	0	1172T→C	I391T	0	1
240C→G	Y80X	1	0	1379C→T	P460L	0	1

* Changes in the nucleotide sequence (GenBank accession number BK000010) are shown.
 † Changes in the amino acid sequence (GenBank accession number DAA00004) are shown.

ease, but in only 2 of 31 alleles in patients with atypical disease. All patients with two null alleles had the classic form of the disease.

Two PANK2 mutations, both of them missense mutations, accounted for one third of the disease alleles. G411R constituted 31 disease-related alleles in 27 families, and T418M occurred 10 times in 6 families. G411R was seen on a background of a shared haplotype derived from markers that spanned 1 cM and flanked PANK2, indicating a founder effect for this mutation (data not shown). The majority (81 percent) of the 27 families with the G411R mutation were of European descent. Neither of these sequence changes was seen in any of more than 100 control chromosomes.

An intriguing feature of the G411R mutation is that in six families harboring this mutation (four with classic disease and two with atypical disease), no mutation was detected on the other chromosome. Families with only one identified mutation were not distinguishable from those with two. With our current strategy, some mutations would be undetectable (e.g., promoter mutations). However, of nine families with single mutant alleles, six had an allele with a G411R mutation. This observation is striking because mutations in both alleles were detected in nearly all families, and it suggests that G411R might be semidominant, with one allele sufficient to cause disease given certain genetic backgrounds. Contrary to this hypothesis, no disease phenotype was observed in G411R-heterozygous carrier parents of affected persons. Environmental exposure or modifier effects of other genes, including those for enzymes downstream in the coenzyme A synthetic pathway, might also have a role in the pathogenesis of the disease, in concert with the G411R allele.

CLINICAL FINDINGS

On the basis of the existing clinical information, the 123 patients who were studied were not different from the 63 who were excluded because of insufficient clinical information. Information about each clinical characteristic was not available for every patient included in our study cohort.

The clinical features of our cohort of 66 PANK2-mutation-positive patients with classic disease were remarkably homogeneous. Pantothenate kinase-associated neurodegeneration usually presented before the age of 6 years (in 88 percent of cases), with a mean (\pm SD) age at onset of 3.4 ± 3.0 years (range, 0.5 to 12). The most common presenting symptoms

were gait or postural difficulties, which occurred in 40 of 51 patients for whom information was available (78 percent). These symptoms were much less common among patients who had the later-onset form of the disease or who did not have PANK2 mutations ($P<0.001$).

The predominant neurologic features were extrapyramidal and included dystonia, dysarthria, rigidity, and choreoathetosis (51 of 52 patients [98 percent]). Dystonia was a nearly constant early manifestation (45 of 52 patients [87 percent]). Early dystonia often involved the cranial and limb musculature, with axial dystonia predominating later. Involvement of the corticospinal tract, with spasticity, hyperreflexia, and extensor toe signs, was common (13 of 52 patients [25 percent]), as was cognitive decline (15 of 52 patients [29 percent]). Seizures were not reported in any patient with classic disease. Forty-five of 66 patients with classic disease (68 percent) had clinical or electroretinographic evidence of retinopathy. Optic atrophy was infrequent, occurring in only 2 of 66 patients (3 percent). Acanthocytosis was reported in 8 percent of patients with classic disease. Since acanthocytosis is not sought routinely, its true prevalence among patients with pantothenate kinase-associated neurodegeneration remains uncertain. We observed that classic pantothenate kinase-associated neurodegeneration progressed at a nonuniform rate, with periods of marked deterioration, often lasting one to two months, interspersed with longer periods of clinical stability. The majority of patients with classic pantothenate kinase-associated neurodegeneration (85 percent) became nonambulatory within 15 years after the onset of the disease.

The clinical features of the 23 patients with atypical Hallervorden-Spatz syndrome and PANK2 mutations were heterogeneous. These patients were significantly older at the onset of the disease than patients with classic disease (13.7 ± 5.9 years [range, 1 to 28] vs. 3.4 ± 3.0 years [range, 0.5 to 12], $P<0.001$). In rare cases, these patients had very early nonspecific problems (3 of 20 patients for whom information was available [15 percent]), including developmental delay (2 of 20 patients [10 percent]). Extrapyramidal defects developed in 16 of 22 patients with atypical disease (73 percent), but dystonia and rigidity were generally less severe and more slowly progressive than in patients with classic disease. Most of these patients (14 of 22 [64 percent]) continued to be able to walk into adulthood, but in many the disease eventually progressed

to loss of independent ambulation. Spasticity, hyperreflexia, and other signs of corticospinal tract involvement were common (3 of 17 patients [18 percent]) and progressive, eventually limiting ambulation. Freezing was reported in 3 of 20 patients with atypical disease (15 percent). Clinical evidence of retinopathy or optic atrophy was much less common than in patients with classic disease (3 of 15 patients [20 percent], $P < 0.001$).

An unexpected finding was that in 9 of the 23 patients with atypical pantothenate kinase-associated neurodegeneration (39 percent), difficulty with speech, including palilalia (repetition of words or phrases) and dysarthria, was either the sole presenting feature or part of the early disease. In contrast, no patient with classic pantothenate kinase-associated neurodegeneration presented with a speech defect (although dysarthria developed later in 16 of these patients). Psychiatric symptoms with cognitive decline, reminiscent of frontotemporal dementia, were prominent in patients with atypical pantothenate kinase-associated neurodegeneration (6 of 18 patients for whom information was available [33 percent]) and rare in patients with classic pantothenate kinase-associated neurodegeneration; these symptoms included personality changes with impulsivity and violent outbursts, depression, and emotional lability.

Additionally compelling is the clinical comparison between patients with a diagnosis of atypical Hallervorden-Spatz syndrome who had a PANK2 mutation and those who did not. Among the patients for whom the presenting symptoms were noted in the medical records, 6 of 18 with atypical disease and PANK2 mutations presented with speech difficulties, whereas none of the 17 with atypical disease who had no PANK2 mutations had this presentation ($P < 0.05$). Psychiatric symptoms developed in 6 of 18 patients with atypical disease and PANK2 mutations but in no patients with atypical disease without PANK2 mutations ($P < 0.05$). Otherwise, patients without PANK2 mutations were similar to those with mutations: they generally had extrapyramidal and corticospinal tract dysfunction; their mean age at onset of the disease was 7.0 ± 9.9 years (range, 0.5 to 38); and their family histories indicated that they had affected siblings or that their cases were sporadic, both findings that are consistent with autosomal recessive inheritance.

RADIOGRAPHIC FINDINGS

A striking correlation was found between the MRI findings and the presence or absence of PANK2 mu-

tations in patients with Hallervorden-Spatz syndrome. All MRI scans reviewed from 28 patients with PANK2 mutations (24 with classic disease and 4 with atypical disease) showed bilateral areas of hyperintensity within a region of hypointensity in the medial globus pallidus on T_2 -weighted images, a pattern known as "eye of the tiger"⁹ (Fig. 1). Moreover, reports of MRI scans from 41 additional mutation-positive patients (36 with classic and 5 with atypical disease) described them in detail as showing these specific changes. Indeed, no PANK2-mutation-positive patients lacking the eye-of-the-tiger sign have been found.

We also found the reciprocal to be true; that is, we found no evidence of the eye-of-the-tiger pattern on MRI in any mutation-negative patient. MRI films from 16 mutation-negative patients showed only hypointensity in the globus pallidus on T_2 -weighted images (Fig. 1). In this group of patients, cerebellar atrophy and iron deposition in the red nucleus and dentate nucleus were common features that were not seen in patients who had classic disease or in those who had atypical disease with PANK2 mutations. Thus, the eye-of-the-tiger sign is strongly correlated with PANK2 mutations ($P < 0.001$).

On the basis of this correlation, we assessed the value of the brain MRI alone in predicting mutation status. In a small subgroup of symptomatic patients with Hallervorden-Spatz syndrome who were not included in our study because of insufficient clinical information, we identified six patients solely by the presence of the eye-of-the-tiger sign and analyzed their DNA for PANK2 mutations. All six patients were found to have PANK2 mutations on both chromosomes, a result further supporting the correlation between the presence of these mutations and the eye-of-the-tiger sign.

DISCUSSION

We identified mutations in the PANK2 gene in a large subgroup of patients with Hallervorden-Spatz syndrome. All patients with classic disease had PANK2 mutations, suggesting that patients with early-onset, rapidly progressive disease will consistently prove to have inherited defects in pantothenate kinase 2. Among patients with atypical disease, those with PANK2 mutations were much more likely to have speech and psychiatric problems than were mutation-negative patients. Most compelling is our finding of a one-to-one correlation between the MRI eye-of-the-tiger pattern and the presence of a PANK2 mutation, regardless of the severity of the

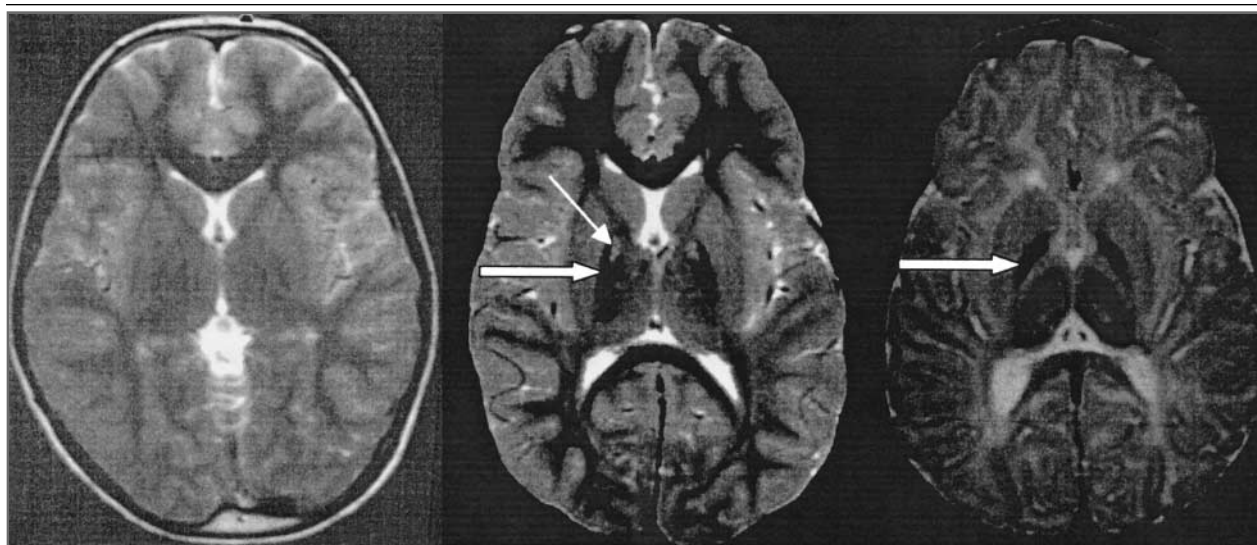


Figure 1. Patterns on T₂-Weighted Brain Magnetic Resonance Imaging.

The image on the left is of a normal patient. An image of a PANK2-mutation-positive patient with Hallervorden-Spatz syndrome (center) shows hypointensity (thick arrow) with a central region of hyperintensity (thin arrow) in the medial globus pallidus (the eye-of-the-tiger sign). In an image of a mutation-negative patient with Hallervorden-Spatz syndrome (right), only a region of hypointensity (arrow) is seen in the medial globus pallidus.

Table 2. Phenotypic Features of Pantothenate Kinase-Associated Neurodegeneration.

Feature	Early-Onset, Rapidly Progressive (Classic) Disease	Late-Onset, Slowly Progressive (Atypical) Disease
Age at onset	First decade	Second or third decade
Major neurologic features	Extrapyramidal dysfunction, corticospinal tract involvement	Speech disorders, psychiatric disorders, extrapyramidal dysfunction, corticospinal tract involvement
Pigmentary retinopathy	Very common	Rare
Rate of disease progression	Loss of independent ambulation within 10–15 years after onset	Loss of independent ambulation within 15–40 years after onset
Findings on brain MRI	Eye of the tiger	Eye of the tiger

disease. In Table 2, we propose clinical descriptions of the major forms of pantothenate kinase-associated neurodegeneration.

Our data have implications for the differential diagnosis of Hallervorden-Spatz syndrome and for treatment of pantothenate kinase-associated neurodegeneration. Patients with the classic form of Hal-

lervorden-Spatz syndrome should provisionally be given the diagnosis of pantothenate kinase-associated neurodegeneration, awaiting confirmation by DNA analysis. Patients with atypical Hallervorden-Spatz syndrome who present with speech and psychiatric disorders and whose brain MRI scans have the eye-of-the-tiger sign should undergo analysis for PANK2 mutations. The fact that almost all patients with atypical disease and pantothenate kinase-associated neurodegeneration have missense mutations indicates that many of them may have residual pantothenate kinase 2 activity. We speculate that supplemental pantothenate (vitamin B₅) could compensate for the partial enzymatic deficiency in these patients, possibly ameliorating or retarding the symptoms. Such treatment might even prove effective in patients with classic disease who have partial enzyme activity. However, these hypotheses require evaluation.

Two clinical observations warrant further discussion. First, although the profile of classic pantothenate kinase-associated neurodegeneration is consistent with that presented in the many reports of patients with early-onset Hallervorden-Spatz syndrome,^{1,3,10-12} pigmentary degeneration of the retina was much more common in our patients than has been reported in others.^{1,13} Retinopathy

develops early, though it may be recognized only when a full diagnostic evaluation is performed. As a corollary, we found it uncommon for retinopathy to develop later in patients with normal results on fundoscopic examination at the time of diagnosis.

Second, we have delineated the dominant neurologic features of patients with atypical pantothenate kinase–associated neurodegeneration, which differ from those seen in the classic form of the disease. These features, which include severe palilalia, dysarthria, dystonia (which may be intermittent and fluctuating), perseverative behavior and movements, and freezing, have not been widely recognized in this disease.¹⁴⁻¹⁶ Freezing during ambulation, especially when turning corners or encountering surface variations, is strikingly similar to changes seen in Parkinson's disease.¹⁵ Psychiatric symptoms, including depression and psychosis, were common in the patients with atypical disease in our study. In several patients with atypical disease whose first major symptom was palilalia, psychiatric abnormalities were misinterpreted as the cause of the speech defect. Progressive dementia occurs in atypical pantothenate kinase–associated neurodegeneration.

The one-to-one correlation between a specific radiographic finding, the eye-of-the-tiger sign, and mutations in a single gene, *PANK2*, is extraordinary. Clearly, the medial globus pallidus is especially sensitive to deficiency of pantothenate kinase 2, one of four pantothenate kinases encoded by the human genome. The eye-of-the-tiger pattern may reflect tissue necrosis and edema (seen on T₂-weighted MRI as hyperintensity) within a region of iron deposition (seen as hypointensity), but how a deficiency in pantothenate kinase 2 leads to these changes remains speculative. Previously, we suggested that accumulated cysteine, which would normally condense with phosphopantothenate, and cysteine-containing compounds may form complexes with iron and exacerbate oxidative damage in this brain structure.⁸

Pantothenate kinase–associated neurodegeneration is one of three extrapyramidal disorders associated with increased amounts of brain iron for which the molecular basis has been defined. The other two disorders, neuroferritinopathy, which results from mutations in the ferritin light-chain gene,¹⁷ and aceruloplasminemia, which results from mutations in the gene encoding ceruloplasmin,¹⁸ are of adult onset and can be distinguished from pantothenate kinase–associated neurodegen-

eration on the basis of the clinical presentation, MRI findings, and results of genetic testing.

Additional biochemical markers of pantothenate kinase–associated neurodegeneration may help us understand its pathologic effects and develop therapeutic targets. Acanthocytosis and a defect in plasma lipoproteins have been associated with mutations in *PANK2*.¹⁹ These systemic features will help focus future biochemical investigations. With better understanding of the metabolic perturbations in pantothenate kinase–associated neurodegeneration, we may be able to devise neuroprotective interventions to prevent exacerbations and thereby slow the progression of the disease.

Currently, however, we are left with no imaging or DNA-based tool for the definitive diagnosis of the disease in two thirds of patients with atypical Hallervorden–Spatz syndrome. Conceivably, pantothenate and coenzyme A metabolism may be perturbed in these patients or in patients with other neurodegenerative disorders. For example, patients with normal amounts of brain iron who have early-onset parkinsonism, severe speech impairment, perseverative movements, or pigmentary retinopathy may have alterations in these metabolic pathways. Indeed, the spectrum of diseases that are associated with inborn errors of pantothenate or coenzyme A metabolism is likely to expand.

The eponymous term “Hallervorden–Spatz syndrome” has fallen into disfavor in view of the unethical activities of the German neuropathologists Hallervorden and Spatz during World War II.²⁰ We encourage the use of the term “pantothenate kinase–associated neurodegeneration” for the majority of patients with Hallervorden–Spatz syndrome who have proved or suspected mutations in *PANK2*. For the remainder, we propose the term “neurodegeneration with brain iron accumulation.”

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