

Clinical and Neuropsychological Correlates in Two Brothers With Pantothenate Kinase–Associated Neurodegeneration

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Abstract: Adult-onset focal dystonia was the presenting sign of pantothenate kinase-associated neurodegeneration (PKAN) in a patient with a novel homozygous missense mutation (C856T). His brother shared the same mutation and showed similar, albeit minor, motor signs, but a different behavioral profile. Both brothers had an atypical form of PKAN. The neuropsychological assessment showed that, despite a normal Mini-Mental State Examination, both patients presented a deficit of executive functions and of attention. The profile of cognitive impairment in these cases was typically that of a subcortical dementia. Both patients fulfilled *Diagnostic and Statistical Manual for Mental Disorders* criteria for obsessive–compulsive disorder; however, paranoia was associated with depression and aggressive behavior in Patient 1, whereas Patient 2 had hyperactivity, disinhibition, and euphoria. Our findings suggest that these two brothers had a different pattern of involvement of motor and nonmotor basal ganglia–thalamocortical circuits. © 2004 Movement Disorder Society

Key words: neuropsychology; dystonia; Hallervorden-Spatz syndrome; obsessive-compulsive behavior

Pantothenate kinase-associated neurodegeneration (PKAN) is a rare autosomal recessive disease caused by mutations in the pantothenate kinase 2 (PANK2) gene, which encodes pantothenate kinase, an essential regulatory enzyme in coenzyme-A biosynthesis.¹ Patients with PKAN have dystonia, parkinsonism, and iron accumula-

tion in the brain.^{2,3} This disease was formerly called Hallervorden–Spatz syndrome (HSS); however, the fact that not all the cases clinically diagnosed as HSS harbor PANK2 gene mutations supports the existence of locus heterogeneity in this disorder.⁴ For cases with no detectable mutations in the *PANK2* gene, the term “neurodegeneration with brain iron accumulation” has been proposed.⁵

The identification of the genetic defect causing PKAN allows both antemortem diagnosis and detection of atypical or uncommon phenotypes that would otherwise remain unrecognized. We report the cases of two siblings who showed a mild course of PKAN and describe their neuropsychological and behavioral features.

PATIENTS AND METHODS

Patient 1

This 21-year-old man was referred to a neurologist in January 2002 after a 1-year history of a rapidly progressive clenching of his right hand. At onset, this involuntary motion was easily reducible and only showing in a desultory way; later, it progressively became a permanent posture. He was born full-term, had normal somatic and psychic development, and attended school until the eighth grade. His personal history was unremarkable. His parents were healthy, reportedly not consanguineous, Caucasians. Careful questioning only revealed an irritable character since the age of 5. He had one brother only, who was reportedly healthy.

Upon observation, his right upper limb was intrarotated with wrist flexion and clenched fist. This posture did not change with voluntary movements of the arm or while walking. Fist clenching was made worse by voluntary activity of the limb and could be counteracted, just for a few seconds, by the peculiar *geste antagoniste* of flinging the arm forward as if throwing the hand away from the body (see Video, Segment 1). Bilateral mild clumsiness in distal rapid movements of limbs, more severe on the right-hand side, as well as occasional oromandibular dystonia with forced smile were observed. Tendon reflexes were brisk, particularly in the right upper limb. Mental status was apparently normal, Mini-Mental State Examination (MMSE) was unremarkable; however, a detailed neuropsychological assessment could not be performed. The remainder of the neurological and general examination was normal.

Blood copper and ceruloplasmin, as well as dosage of beta galactosidase and hexosaminidase A, were unremarkable. There were no acanthocytes in the peripheral blood. The electroencephalogram was unremarkable.

This article includes Supplementary Video, available online at <http://www.interscience.wiley.com/jpages/0885-3185/suppmat>.

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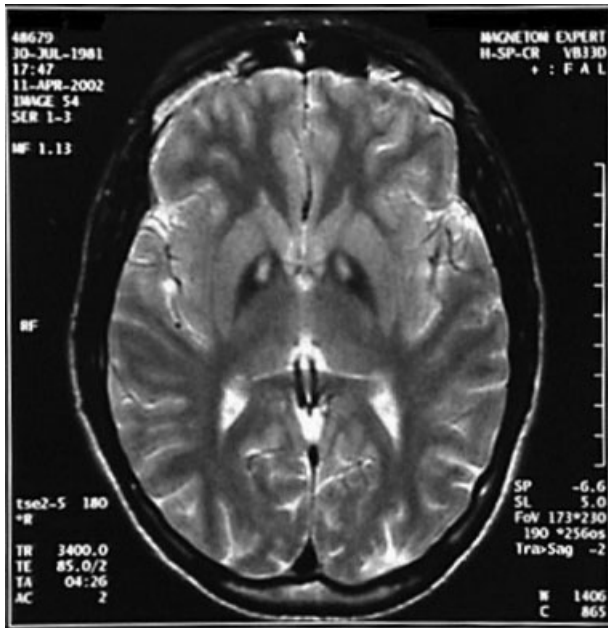


FIG. 1. Magnetic resonance imaging scan of Patient 1, performed 3 months after the first visit, shows the so-called "eye of the tiger" sign.

Neuro-ophthalmological examination revealed initial retinal degeneration. Electromyographic examination showed coactivation of the right finger flexors and extensors during voluntary activation, with high-frequency activity, consistent with upper limb dystonia.

Brain T2-weighted magnetic resonance imaging (MRI) showed a low signal intensity in the pallidum, with a slight anteromedial core of high signal intensity, as observed in PKAN (Fig. 1).^{6,7} Molecular analysis of the PANK2 gene revealed a missense mutation (C856T), resulting in an arginine-to-cysteine substitution at codon 286 (R286C). The patient was treated with pantothenic acid (vitamin B5) for 9 months and with levodopa for 14 months without appreciable benefit.

One year later, this patient developed moderate global slowing of movements, impaired balance with unsteady gait, progressive oromandibular dystonia, causing speech difficulties, and right foot dystonia. Although right hand dystonia progressed, the efficacy of the already described *geste antagoniste* persisted (see Video, Segment 1). A detailed neuropsychological evaluation was performed at this time²⁶ (Table 1). The Neuropsychiatric Inventory⁸ (NPI) revealed an abnormal profile (total score 69). The patient had no hallucinations, yet he suffered of aggressive behavior and irritability associated with depression and delusions of jealousy toward his mother. There were constant compulsions, such as touching and sniffing objects, or walking backward. He had poor insight of his

illness or of any associated problems and fulfilled the clinical criteria for obsessive-compulsive disorder (OCD).⁹

The patient also showed motor inertia and "kinetic blockade," without being able to account for his inactivity. Since the age of 18, he had recurrent blocks of activity during the day, each one lasting several minutes. Once, he spent 8 minutes staring in front of the open fridge, without being able to move in any way. The effect of external activation was remarkable, as this behavioral inertia could be immediately discontinued, for example, when his mother ordered him to move or asked him what it was about. These features, in combination with the results of neuropsychological testing (e.g., the modified card sorting test characterized by nonperseverative errors, reduced phonemic fluency), are reminiscent of autoactivation deficit (AAD).¹⁰

Patient 2

The brother of Patient 1 considered himself unaffected and was examined on the occasion of a follow-up visit of Patient 1. He was 2 years younger than his brother; at the age of 10, he developed difficulties in walking, with mild equinovarus deformity. Obsessive-compulsive personal-

TABLE 1. Neuropsychological profile of the patients

	Patient 1		Patient 2	
	RS	ES	RS	ES
MMSE Memory	28	Normal	30	Normal
Digit Span	6	4	7	4
Rey's 15 words learning task				
Immediate recall	48	Normal	31	Impaired
15 min. delayed recall	9	Normal	7	Impaired
Visuo-spatial span	3	0	4	0
Supra-span spatial learning	5.54	0	26.74	3
Information processing				
Raven's CPM	27	2	31	3
Attentional matrices	43	1	19	0
M.C.S.T. (Nelson)				
Categories	2/6		1/6	
Perseverative errors	1		NA	
Non-perseverative errors	6		NA	
Phonemic fluency	17	0	15	0
Language and apraxia				
Token test	36	4	35	4
Category fluency	33	2	39	3
Orofacial apraxia	20	4	18	0
Ideomotor apraxia	20	4	20	4

ES, equivalent score (0 indicates a performance below 5% of normal population and is the only definitively pathological score; 4 is equal to or better than normal population).²⁶

RS, raw score; MMSE, Mini-Mental State Examination; CPM, colored progressive matrices; NA, not available (test stopped because the patient was unable to identify global categories other than shape, as he focused only on details).

ity traits had been noted since childhood, because every day he carried in his school bag exactly 100 pens and 5 erasers. Since the age of 13, he developed attention deficit, resulting in inadequate performance at school; at 18, he had mild speech difficulties. All these features were mild and remained underestimated by the parents until Patient 1 developed upper limb dystonia.

At the age of 19, Patient 2 as well developed upper right limb dystonia. Dystonic posturing of fingers was absent at rest and was activated by voluntary movements of the hand or by arm swinging during walking. In this patient, dystonia was less disabling than in his brother. At the age of 20, the neurological examination showed dystonic gait, oromandibular dystonia with dysarthria, mild dysphonia, occasional stuttering, and palilalia. Rapid hand movements were bilaterally impaired, whereas dystonic posturing and mirroring occurred only in the right hand (see Video, Segment 2). Tendon reflexes were brisk.

There were no acanthocytes in the blood smear. Ophthalmological examination was unremarkable. The so-called "eye of the tiger" sign was found on brain MRI. As expected, genetic testing of the *PANK2* gene revealed the same mutation as his brother. MMSE was normal; a complete neuropsychological examination is reported in Table 1. His psychiatric profile was milder than his brother's (total NPI score, 47); there were neither hallucinations nor delusions, only euphoria, disinhibition, and aberrant motor behavior.

Daily life was filled with rituals; he had many repetitive behaviors and compulsory exploratory acts; a few months earlier he had also started sniffing objects. He had abnormal nighttime behavior and wandered at night disturbing the sleep of family members. He had no insight of his illness or of any associated problems and fulfilled the clinical criteria for OCD.¹¹

DISCUSSION

Typically, PKAN appears in childhood with dystonia, pyramidal tract signs, and parkinsonian features; alternatively, albeit in a less common way, first signs are seen in adulthood and consist of speech difficulties (such as palilalia or dysarthria), psychiatric symptoms and cognitive decline.⁵ Less common presentations of motor signs in genetically identified PKAN patients include bulbar amyotrophic lateral sclerosis-like syndrome,¹² or pure akinesia.¹³ In these two brothers, who shared a novel missense mutation in the *PANK2* gene, motor signs presented with focal upper limb dystonia. In Patient 1, in particular, upper limb dystonia remained an isolated mo-

tor sign for almost 1 year. In Patient 2, there was an earlier onset of a combination of motor and nonmotor signs; notwithstanding this finding, the patient was unaware of being ill; this was partially due to an overall milder motor disability.

The present report confirms that PKAN has a broad phenotypic spectrum, even among siblings with identical mutations, with a common set of fundamental features. Adult onset focal dystonia has been already reported to be the presenting phenotype of PKAN.⁵ Still, we were impressed by the long-lasting mild presentation associated with this novel mutation, in which dystonia remained an isolated motor sign for approximately 1 year and had features typical of primary torsion dystonia, such as the *geste antagoniste*.¹⁴ Missense mutations are thought to be associated with residual *PANK2* activity, but presently, there is no evidence of any strict genotype-phenotype correlates in PKAN.⁵

Dementia is reported in many individuals with HSS, and neuropsychological features of variable severity have been observed in most cases.² Neuropsychological abnormalities have been reported in few cases of genetically identified PKAN.^{5,13,15} Specifically, mild memory problems and executive dysfunction have been observed in 2 patients with PKAN,¹³ although the details are not reported. The present study provides a complete neuropsychological account showing that, despite a normal MMSE, impairment in information processing occurred in both patients and involved executive functions and attention. Cases of HSS with normal MMSE have been reported previously.¹⁶ The impairment in executive functions suggests a dorso-lateral prefrontal involvement as a consequence of fronto-subcortical disconnection. As concerns memory, spatial learning was impaired in Patient 1 but not in Patient 2, whereas the reverse occurred in verbal learning. The issue as to whether memory impairment in these brothers is due to memory or attention deficit cannot be solved based on the available evidence. Because episodic long-term memory was normal, and no everyday memory problems were reported, it may be argued that either an encoding or a retrieval problem, rather than an impairment in storage, occurred. Altogether, the profile of cognitive impairment in the present cases is typically that of a subcortical dementia.

Behavioral changes have been reported repeatedly either in HSS or in PKAN. Aggressive behavior, depression, nervousness, or irritability are common features, and psychotic disorders may also occur.¹⁷⁻¹⁹ Furthermore, a Tourette-like syndrome with behavioral features

(such as hyperactivity, obsessions, or compulsions) has been reported in patients with childhood onset.^{20,21} The present study shows that both patients fulfilled current Diagnostic and Statistical Manual for Mental Disorders criteria for OCD with different degrees of severity. Compulsions were prominent in both; however, they also presented diverging behavioral features: Patient 1 was depressed, aggressive, irritable, and had delusions; instead, euphoria with disinhibition was prevalent in Patient 2. These behavioral features suggest a common involvement of the lateral orbitofrontal circuit,²² with different patterns of dysfunction in the striatal thalamo-cortical circuits involved in regulation of behavior and affection. Different personality traits may also have influenced these features, as shown in monozygotic twins with Huntington's disease, who have differing cognitive and behavioral profiles, probably due to their premorbid personality.^{23,24}

An intriguing finding is the detection of AAD features in Patient 1 but not in Patient 2. These coexisted without overlapping with OCD features. The observed motor inertia differed from obsessional motor slowness,²⁵ as it could be immediately reversed by external cues, whereas compulsions were not. We consider this phenomenology as rather related to AAD features, although these have not been yet reported in patients with neurodegenerative disorders. As an isolated syndrome, AAD is mainly encountered after lesions of the basal ganglia, particularly the pallidum, and is thought to result from the disruption of passing fibers mediating the internal activation of mental processing¹⁰; therefore, it may also occur in a progressive neurodegenerative disorder of the basal ganglia, such as PKAN.

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Legends to the Video

Segment 1. Patient 1. October 2002: This patient presents focal right hand dystonia with wrist flexion and clenched fist; a dystonic smile is occasionally observed. He is capable of opening his right hand for a while, by means of a *geste antagoniste*. December 2003: Oromandibular dystonia is observed, and speech is impaired. Patient 1 is capable of opening his right hand with great difficulties; his smile is dystonic. The *geste antagoniste* is still present. Distal movements are hardly performed with the right hand and are

slowed in the left hand. Lower limbs are bradykinetic, as shown by foot tapping.

Segment 2. Patient 2. Dystonia is activated in the upper arm while walking; after moderate exercise, dystonia of the right lower limb becomes evident. Oromandibular dystonia impairs speech. Bilateral upper limbs dystonia is observed with outstretched arms. Mirror dystonic posturing occurs in the right hand while the left hand performs a motor sequence. Rapid distal movements are slowed bilaterally in the upper limbs.

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Hallucinations in Parkinson's Disease: A Follow-Up Study

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Abstract: To study prevalence of hallucinations in patients with Parkinson's disease (PD) during a 1-year period, and identify factors predictive of the onset of hallucinations in patients who were hallucination-free at baseline, 141 unscheduled outpatients with PD were evaluated prospectively for a set of demographic, clinical, and therapeutic variables and the presence of hallucinations during the previous 3 months. Patient groups were compared with nonparametric tests, and logistic regression was applied to significant data. Follow-up data were available for 127 patients. The hallucination prevalence rates (%) at the first and second evaluation were, respectively, 41.7 and 49.6 for hallucinations of all types (NS), 29.1 and 40.2 for minor hallucinations (i.e., presence or passage hallucinations, and illusions) ($P = 0.02$), 22.8 and 21.2 for

formed visual hallucinations (NS), and 8.7 and 8.7 for auditory hallucinations (NS). Hallucinations rarely started or ceased during the study. The most labile forms were minor hallucinations, which developed in 20% of patients and ceased in 9%. During follow-up, 15% of patients started to hallucinate. Three factors, all present at the first evaluation, independently predicted the onset of hallucinations in patients previously free of hallucinations at baseline (odds ratio; 95% confidence interval): severe sleep disturbances (14.3; 2.5–80.9), ocular disorders (9.1; 1.6–52.0), and a high axial motor score (5.7; 1.2–27.4). Hallucinations have a chronic course in most parkinsonian patients. Factors predicting the onset of hallucinations point to a role of extranigral brainstem involvement and a nonspecific, facilitating role of ocular disorders. © 2004 Movement Disorder Society

Key words: Parkinson's disease; hallucinations; sleep disorders; ocular disease

Hallucinations, mainly of a visual nature, affect about one-quarter of patients with Parkinson's disease (PD). The prevalence is higher when minor hallucinatory phenomena, such as "presence" or "passage" hallucinations, are included.¹ In most instances, hallucinations develop in a context of a clear sensorium, and seem to have a chronic, recurrent course.² However, few studies have investigated the long-term outcome of hallucinations in PD.^{3,4} The aim of this study was to determine if the prevalence and type of hallucinations remain stable at a 1-year interval in patients with PD. We also sought factors predictive of the onset of hallucinations in patients previously devoid of such phenomena. For this purpose, we prospectively followed 141 patients included in a previous study of hallucinations.

PATIENTS AND METHODS

Subjects

We conducted recently a prospective study of PD-associated hallucinations in two centers.¹ Among the 216 outpatients included in the original study, 141 were assessed in our center (mean age, 68.4 ± 9.8 years; mean duration of PD, 8.9 ± 6.2 years). They were consecutive patients who met the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria for PD. For the purpose of the present study, we reevaluated these 141 patients 1 year after initial enrollment. We could not assess 14 patients (10%): 4 had died; 2 had a severe intercurrent illness (stroke, esophageal cancer); follow-up data were unreliable in 3 cases; and 5 patients could not be located or declined participation. We report on the follow-up data of 127 patients. Of these 127 patients, 103 were reexamined by the neurologist who

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