Movement Disorders
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Letters to the Editor Related to New Topics

Parkinsonism in Polycythaemia Vera Probably Due to Manganism

Herrero Hernandez et al.[1] reported postural tremor in one patient with polycythaemia vera which was tentatively attributed to manganese deposits in the basal ganglia and improved after therapy with a chelating agent. Herein we report a patient with polycythaemia vera who developed persistent parkinsonism and in whom MRI showed features consistent with manganism.

In 1998 a 47-year-old man employee began to complain of headache and arterial hypertension that led to the diagnosis of polycythaemia vera, which were treated with repeated blood-lettings. The next year he began to complain of dysesthesia to the feet, nocturnal leg cramps, and unsteady gait. His wife reported that he was slightly confused. The neurological examination showed masked face, monotonous voice, rigidity of the neck and of the right upper arm, slightly ataxic gait with forward bent of the trunk and diffusely brisk tendon reflexes. The blood examination revealed an increase of the hematocrit (50.2%), and transferrin (504 mg/dL; NV 290-390 mg/dL) and a decrease of the sideremia (33 μg/dL; NV 50-150 μg/dL). The serum magnesium, copper and ammonium were within normal range. Serum or urine manganese was not assessed. Hepatic biopsy was negative for increased hepatic copper content. Cranial CT was negative. T1 weighted MR imaging revealed a symmetric hyperintensity of the basal ganglia, cerebral peduncles, red nucleus, quadrigeminal bodies, superior cerebellar peduncles, and dentate nuclei. He started levodopa therapy (100 mg/die) which was unsuccessful and interrupted few months later. Seven years later the clinical condition was substantially stable and the score of the Unified Parkinson's Disease Rating Scale subscale 3 was 16. A control MRI showed progression of the T1 symmetric hyperintensity in the cerebral peduncels and evidence of the same signal change also in occipital white matter (Fig. 1). There was only a mild diffuse cerebellar atrophy. SPECT examination, obtained by injection of 111-185 MBq of [^{123}I]FP-CIT, showed only a mild decrease of dopamine transporter (DAT) density in the right putamen. Manganese level was finally assessed in blood and urine and it was within normal limits.

The diagnosis of manganism in our patient was based on the clinical features, exclusion of Parkinson's disease and Wilson's disease, and on presence of the typical MRI appearance of symmetric hyperintensity in T1-weighted images of the basal ganglia and other brain structures caused by the paramagnetic properties of manganese.[1] Although a direct demonstration of increased manganese in the serum of our patient was not available, the normal manganese levels observed at follow-up do not exclude the diagnosis since it is well known that, serum or urine levels correlate with actual, but not previous, levels of exposure.[2]

Manganese intoxication is usually caused by professional exposure as it typically occurs in miners, welders, and workers in steel industry,[3] but it can also be observed in acute or chronic hepatic diseases and anemia.[4,5] In particular, increased level of serum manganese is observed in anemia since sideropenia increases the intestinal absorption of manganese.[6] We speculate that in our patient, the increased hematocrit[7] and the frequent blood-lettings associated with polycythaemia vera could have determined manganese intoxication though sideropenia.

Persistent parkinsonism is observed in chronic manganese exposure.[2] Although polycythaemia secondary to central hypoventilation can be observed in patients with Parkinson's disease,[8,9] in 1977 Herishanu and Rosenberg described occurrence of L-dopa responsive parkinsonisms in three patients with polycythaemia vera, but did not suspect a role for manganism.[10] Ours appears to be the first case of persistent parkinsonism in a patient with polycythaemia vera in whom manganism was documented by MRI and L-dopa was ineffective.

Inefficacy of the L-dopa therapy is common in patients with manganese intoxication and is in agreement with the DATscan results in our patient showing only a mildly decreased uptake in the right putamen, despite having the disease for 7 years. This indirectly supports a presumable predominant post-synaptic site of damage of the nigro-striatal pathway in manganism as supported by the normal 6[^{18}F]fluorodopa uptake observed with position emission tomography in patients with manganese intoxication.[11] However, our DATscan findings appear to be substantially at variance with the marked symmetric decrease of the 6[^{18}F]fluorodopa uptake recently reported in a further patient with parkinsonism due to manganism. However, the latter developed manganism on a background of chronic alcoholic hepatic disease, and it has been pointed out that different exposure mechanisms and factors related to the host metabolism might explain the heterogeneity of the nigro-striatal damage and its clinical expression observed in patients with manganism.[12] Chelating agents have been recommended in patients with chronic manganese exposure,[1] but they were not provided to our patient.

In conclusion our observation indicates that permanent extrapyramidal signs with striatal and extra-striatal manganese deposition can complicate polycythaemia vera, probably through increase of the intestinal manganese absorption secondary to sideropenia.

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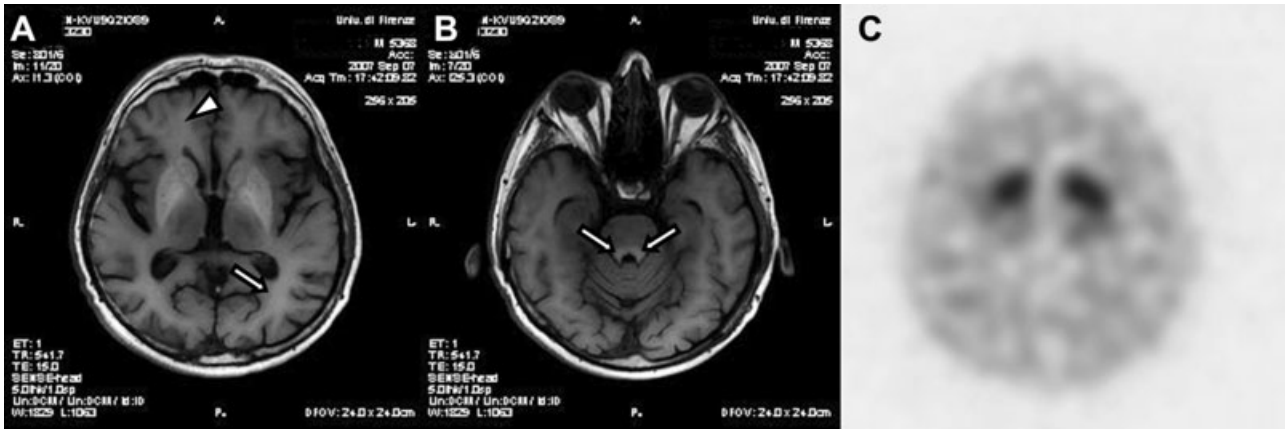

FIG. 1. A–C: Axial SE-T1 weighted MR images (A–B) showing signal hyperintensity in both the caudate and lentiform nuclei and in the occipital white matter (arrow) as compared with the frontal white matter (arrowhead) (A). Abnormal signal hyperintensity is also seen in the superior cerebellar peduncles (arrows) (B). Brain SPECT examination (C), obtained 7 years after onset by injection of 111–185 MBq of [^{123} I]FP-CIT for evaluation of striatal dopamine transporter (DAT) density, shows only a mild decrease of the uptake in the right putamen.

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A Case of Encephalitis Lethargica Associated with Relapsing Polychondritis

Since the first epidemic of encephalitis lethargica (EL),[1] cases with EL-like syndrome have been occasionally described in the literature. Herein we describe a case with clinical EL-like presentations associated with relapsing polychondritis (RP).

A 66-year-old woman had low-grade fever of unknown cause and general fatigue during the previous 6 months. Two

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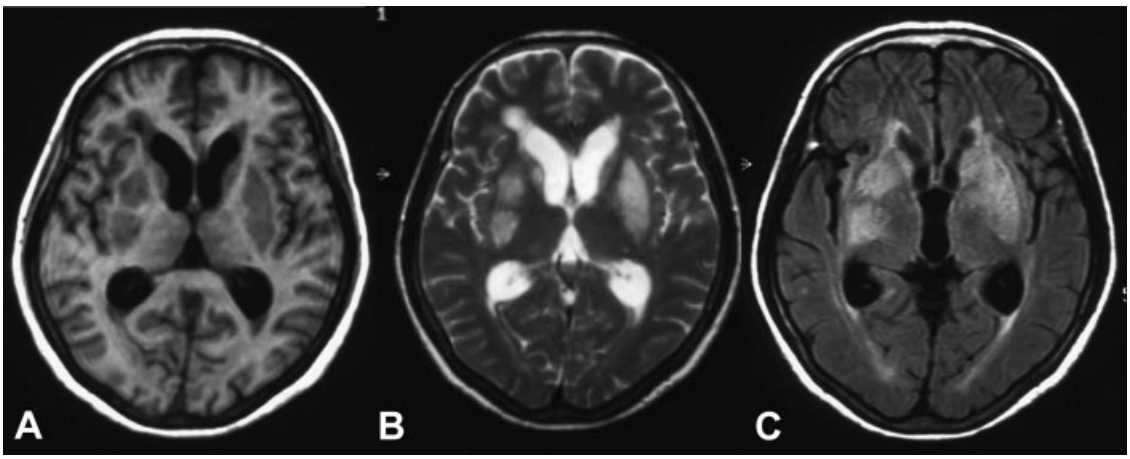

FIG. 1. Brain MRI with T1-weighted images revealing slightly low-signal intensity lesions in the bilateral basal ganglia (**A**). T2-weighted and FLAIR images show diffuse high-signal intensity lesions in the bilateral basal ganglia (**B**, **C**).

weeks before admission, she developed slowness of movement and difficulty walking because of bradykinesia and arthralgia in both legs. She also experienced daytime sleepiness and urinary incontinence. She was admitted at Fukuoka University Hospital because of progressive gait disorders and sleepiness. On admission, she had mildly elevated body temperature (37°C), and her blood pressure was 160/100 mm Hg. Other physical findings were normal. She was somnolent and her voice was monotonous. Neurologic examination revealed muscle weakness in her lower limbs with proximal predominance. She had bradykinesia and rigidity in her neck, trunk, and all four limbs with predominance in the right side. Postural tremor occurred in her hands bilaterally. Deep tendon reflexes were hyperactive in all extremities. Plantar response was flexor. Sensory system and coordination were normal. She had urinary incontinence. Memory disturbance and disorientation were also noted. Her Mini-Mental State Examination score was 16 (of 30), and her Frontal Assessment Battery score was 11.

Blood laboratory tests showed an increased white cell count of 10,500/μL, erythrocyte sedimentation rate of 30 mm/60 min. Serum viral antibodies were negative for herpes simplex virus Types 1 and 6, cytomegalovirus, and Japanese encephalitis virus. Cryptococcal antigen in the serum was within normal limit. Blood tests for immunological disorders were all negative including antinuclear antibody, rheumatoid factor, anticardiolipin antibody, anti-Jo-1 antibody: PR3-ANCA, MPO-ANCA, anti-AchR antibody. In addition, type II collagen antibody in the serum was within normal limit of 14.9 EU/mL (normal: <20 EU/mL). Cerebrospinal fluid (CSF) examination revealed elevated cell count of 90/μL, increased protein concentration of 147 mg/dL, and IgG index of 1.4. Brain MRI with T1-weighted images revealed slightly low-signal intensity lesions in the bilateral basal ganglia (Fig. 1A), whereas T2-weighted and FLAIR images showed diffuse high-signal intensity lesions (Fig. 1B,C). There were no enhanced lesions in T1-weighted images with gadolinium. Electroencephalography revealed diffuse slow waves in bilateral hemispheres.

On day 12 after admission, the patient's mental function deteriorated to akinetic mutism. She also developed bilateral auricular redness and swelling. Auricular biopsy showed marked polynuclear cell infiltration in the subcutaneous area surrounding cartilage, indicative of active-phase polychondritis. Because of relapsing polyarthritis in the medical history, her features filled criteria of RP. After receiving high-dose intravenous methylpreonisolone pulse therapy (1000 mg/day for 3 days), her consciousness and parkinsonism gradually improved. Two weeks after the steroid pulse therapy, her mental state improved except disorientation, and the auricular swelling disappeared. At the time, her gait was independent, but somewhat slow and shuffled. Three months after the treatment, abnormal signals on MR imaging in the basal ganglia decreased but still existed. Eight months later, she had no residual neurological and neuropsychological signs.

EL is a rare central nervous system disorder characterized by encephalitis with lethargy followed by sleep disorder, extrapyramidal syndrome, and neuropsychiatric sequelae. Clinical criteria for the diagnosis of EL should comprise at least three of the following: signs of basal ganglia involvement; oculogyric crises; ophthalmoplegia; obsessive-compulsive behavior; akinetic mutism; central respiratory irregularities; and somnolence and/or sleep inversion.[2] The present patient fulfilled these criteria since she had parkinsonism, akinetic mutism, and somnolence. The first EL epidemic occurred during the same period as the Spanish flu pandemic.[3] Recent observations have shown the presence oligoclonal bands in the CSF and successful treatment with corticosteroids, indicating that EL might be an autoimmune CNS disorder.[4]

RP is a rare autoimmune disorder characterized by relapsing inflammation of the cartilage in any part of body including auricles, nose, trachea, and joints. Although the etiology and pathogenesis of RP remain unknown, involvement of autoantibodies to cartilage and to type II collagen has been demonstrated in 33 to 50% of patients with RP.[5] The most common symptom of RP is pain and swelling of the bilateral external ear. Our patient fulfilled diagnostic criteria for RP proposed by Damiani and Levine.[6] There have been some reports of cases with encephalitis associated with RP[7,8] with suggestive links to CNS vasculitis.

In most cases, EL is difficult to diagnose. The results of the present case suggest that RP related autoimmunity may be related. To our knowledge, this is the first description of EL-like autoimmune disorder associated with RP, and therefore, supports an autoimmune or immune-mediated pathogenesis in EL. Our patient dramatically responded to early treatment with high-dose intravenous corticosteroids followed by an oral corticosteroid. Although RP is rare autoimmune disorder that involves multiple cartilage tissue, it should be considered in the differential diagnosis of EL, because early administration of steroids was beneficial in our patient.

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Unawareness of Head Tremor in Essential Tremor: A Study of Three Samples of Essential Tremor Patients

Patients with Huntington disease may be unaware of their chorea, and patients with Parkinson disease often do not recognize or endorse their medication-induced dyskinesias.[1,2] Head tremor occurs in essential tremor (ET),[3,4] yet patients in our experience are often unaware of it. While this phenomenon is anecdotally noted, it has not been formally documented or studied systematically.

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TABLE 1. *Demographic and clinical features of ET cases in each of the three ET case samples*

Tertiary-referral center (N = 320)	
Age in yr	67.4 ± 15.2
Women	165 (51.6%)
White race	301 (94.1%)
Total tremor score	18.9 ± 7.3
Tremor duration in yr	22.9 ± 18.7
Population-based study (N = 106)	
Age in yr	69.8 ± 18.4
Women	63 (59.4%)
White race	42 (39.6%)
Total tremor score	17.6 ± 6.5
Tremor duration in years	17.4 ± 19.7
Brain repository (N = 170)	
Age in yr	74.5 ± 9.5
Women	102 (60.0%)
White race	170 (100%)
Total tremor score	22.3 ± 6.9
Tremor duration in yr	39.2 ± 20.2

Values are means ± SD and number (percentages).

To broadly sample ET in different settings, we selected cases from three settings: a tertiary-referral center (largest sample),[5] a population-based study in Manhattan,[6] and a brain repository.[7] As expected, cases differed in several respects (Table 1). Using the same clinical questionnaire, each case was asked whether he/she sometimes has a head tremor. A 20 min videotaped tremor examination was performed, which included assessments of arm and head tremors (including sitting facing the camera, sustained phonation, reading aloud, finger-nose-finger maneuver, drinking, using a spoon, stand facing camera, and walking). The videotape was reviewed (E.D.L.); arm tremors were rated using a 0 to 3 scale.[8] Head tremor was rated as absent (0), mild or equivocal (1), intermittent yet clearly present (2), moderate (3), or severe (4).

In the tertiary-referral center, 119 of 320 (37.2%) ET cases had head tremor on examination (≥1); 46 of 119 (38.7%) did not report having head tremor. Most false negatives asked the interviewer, "do you see a head tremor now?" When told "*yes*", they uniformly commented that they were unaware of this (e.g., "*I do not notice it*"). By contrast to head tremor, of 298 ET cases with dominant hand tremor while writing on examination (rating ≥1), only 60 (20.1%) did not report having hand tremor while writing (OR: 0.40, 95% CI: 0.25–0.64; i.e., ET cases were 2.5 times less likely to report head tremor than handwriting tremor). Patients may under-report tremor because of embarrassment; however, when we restricted analyses to 129 ET cases who reported that they were *not* embarrassed by tremor, 21 of 43 (48.8%) with head tremor did not report their head tremor. When we restricted analyses to 78 ET cases who had moderate or severe head tremor on examination, approximately one-quarter (18 of 78 [23.1%]) did not report head tremor (as compared to only 12 of 150 [8.0%] cases with moderate to severe handwriting tremor who did not report their handwriting tremor, OR: 3.45, 95% CI: 1.56–7.61). On the basis of these findings, we consider that failure to report head tremor was not merely due to having mild head tremor.

In the population-based sample, 13 of 106 (12.3%) cases had head tremor on examination; 7 of 13 (53.8%) did not report having head tremor. In the brain repository, 92 of 170 (54.1%) cases had head tremor on examination, but 30 of 92 (32.6%) did not report having head tremor.

In each setting, one-third to one-half of ET cases did not report the presence of head tremor. These same cases were two to three times more likely to report their hand tremor than their head tremor. One possibility is ET cases failed to report head tremor because they were poor historians or were embarrassed. However, they reported hand tremor with reasonably high validity and, among those who were unembarrassed by their tremor, nearly one-half did not report their head tremor. A second consideration is cognitive impairment.[1] This is unlikely; in our largest sample (tertiary-referral clinic), cases with cognitive impairment (Telephone Interview for Cognitive Status[9] <31) were excluded. Third, even when head tremor impedes a skilled task (e.g., while shaving), patients are often unsure whether this is due to shaky hands or a shaky head. A final possibility is that cases were actually unaware of their head tremor. Indeed, when their tremor was pointed out to them, false negatives uniformly stated that they were unaware of it. A lack of internal feedback about a movement may lessen self-awareness of that movement.[1,2] Whether, from a proprioceptive vantage point, patients have a subjective experience of head tremor, is not always clear. For example, with some types of oscillatory cranial movements (e.g., patients with congenital nystagmus, who rarely experience oscillopsia[10]), perceptual stability (i.e., lack of awareness of nystagmus) may be achieved through a reduced sensitivity to the motion or the use of other signals to cancel the effects of the movements (i.e., a spatial constancy feedback loop).[11] Whether a similar mechanism is operative in ET cases with head tremor deserves future investigation.

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Normal Dopamine Transporter Single Photon-Emission CT Scan in Corticobasal Degeneration

A 65-year-old left-handed woman was presented with a 3-year history of a tremor involving her arms and head, general slowness, and small writing for 2 years in 2000. For 12 months, she felt that her right hand "did not belong to her," and it worked in opposition to her wishes when she was tying buttons or holding knives. Her balance had deteriorated, with occasional falls in this period. There was no family history of Parkinsonism.

On examination in 2000, she had a coarse bilateral postural upper limb tremor and a "no-no" head titubation. There was reduced arm swing and significant bradykinesia in the right upper limb, with mild rigidity. She had dinner forking dystonic posturing of the right hand, and her left hand had a very dystonic posture when holding a pen. Postural reflexes were impaired. Eye movements were normal. L-dopa was not beneficial at doses up to 800 mg/day, and was discontinued after 2 years. In the following 4 years, she had increasing right upper limb symptoms, including levitation, forced grasping, and intermanual conflict. A diagnosis of corticobasal degeneration (CBD) was made clin-

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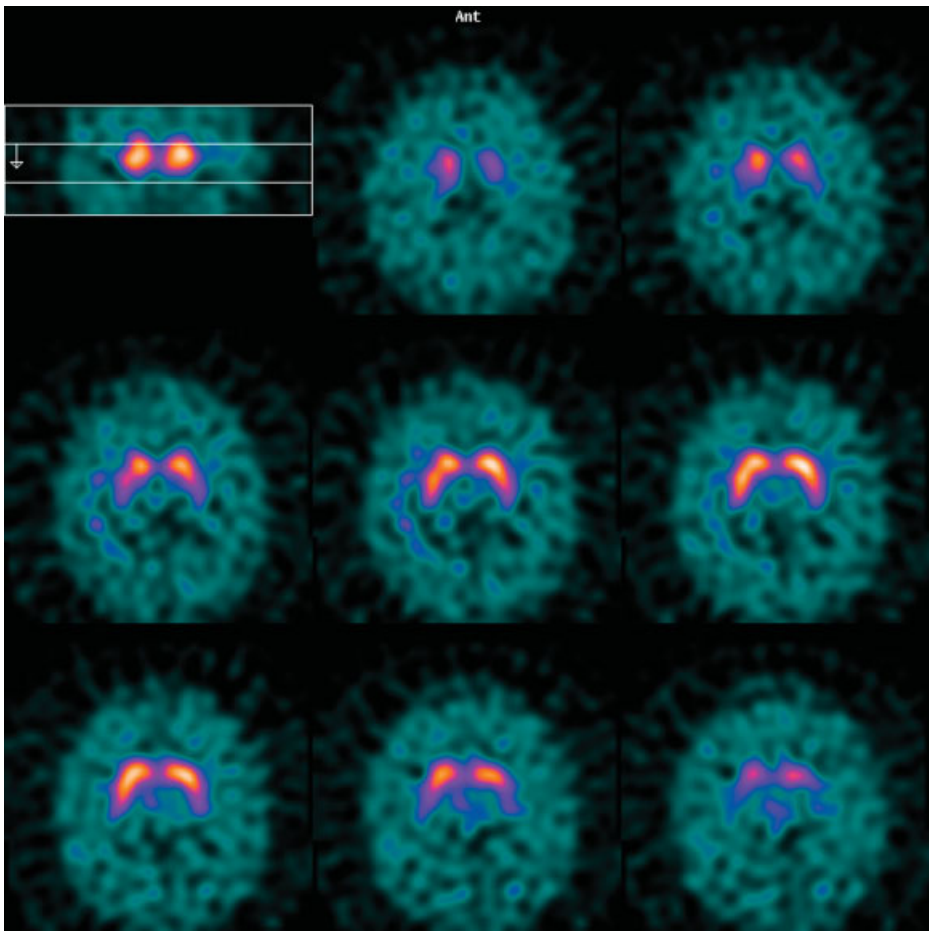

FIG. 1. DaTSCAN demonstrating symmetrical dopamine transporter activity, without evidence of degeneration of nigrostriatal dopaminergic pathways. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

ically. She died of bronchopneumonia in 2007 after an approximately 10-year disease course.

MRI of the brain showed only some cerebrovascular disease. Formal neuropsychometric testing showed no evidence of dementia. She had a dopamine transporter single photon-emission CT scan (^{123}I-FP-CIT DaTSCAN) in 2002, over 4 years after clinical onset, which was normal (Fig. 1). Neuropathological findings included very severe neuronal loss with gliosis in the substantia nigra, gliosis was considerable in the putamen and was less marked in the caudate. Immunohistochemical staining demonstrated neuronal and glial 4-Repeat tau pathology (neurofibrillary tangles, neuropil threads, and coiled bodies) affecting the frontal cortex, hippocampal formation, caudate, subthalamic nucleus, substantia nigra, midbrain tegmentum, locus coeruleus, pontine base, and the dentate nucleus. Astrocytic plaques were observed in small numbers in the frontal cortex. These findings confirmed the clinical diagnosis of CBD.

CBD remains a diagnostic challenge in many cases which can be confused clinically with Parkinson's disease, vascular Parkinsonism, MSA, and PSP.[1] Despite a high specificity of clinical diagnosis of CBD (nearly 100%), sensitivity is only about 35% at presentation, rising to about 48% at the last visit.[2]

Functional imaging studies using presynaptic dopaminergic tracers including ^{123}I-FP-CIT, ^{123}I-β-CIT, and ^{99m}Tc-TRODAT may be of use in the differential diagnosis of patients with suspected CBD particularly when the patient presents with frontal or parietal behavioral disturbances and have no definite bradykinesia. There have been few functional imaging studies in CBD, and these are based on clinically diagnosed cases. One study on 8 patients with a mean disease duration of 28 $\pm$ 11 months,[3] and another on 9 patients with a mean disease duration of 3.0 $\pm$ 1.6 years,[4] reported abnormal ^{123}I-FP-CIT SPECT tracer uptake in all CBD cases. A study on 6 patients with "early" clinically diagnosed CBD (mean disease duration $<$2 years) found that Fluorodopa (F-DOPA) PET uptake was reduced by 33% in the putamen, while uptake into the caudate was less markedly affected.[5]

We present a case of pathologically proven CBD, who despite having severe involvement of the substantia nigra at autopsy, had a normal ^{123}I-FP-CIT SPECT study over 4 years from disease onset. Although degeneration of the substantia nigra is characteristic of CBD,[6] the stage of the disease in which this occurs in unknown. Our patient clearly demonstrated bradykinesia in the presence of a normal dopamine transporter imaging, which may suggest that supranigral

lesions alone may be sufficient to cause bradykinesia in CBD. Large studies using pathologically confirmed cases of CBD are needed to define the role of presynaptic dopaminergic SPECT scanning in the diagnosis, and also to establish the rate of nigral degeneration at different stages of this condition.

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Reversible "Applause Sign" Secondary to Diffuse Large B Cell Lymphoma

Video 

The "Applause sign," in which a patient asked to imitate three claps shows a tendency to perseverate with continuous applause, is commonly seen in Progressive Supranuclear Palsy (PSP).[1,2] To our knowledge, the "applause sign" has not previously been reported in the context of non-neurodegenerative disease.

A 64-year-old man with an 8-year history of depression was referred to psychiatric services with worsening mood and inappropriate behavior. Treatment with venlafaxine and risperidone was commenced. He was referred to neurology 8 months later having developed transient episodes of confusion. Despite episodes of lucidity, there was persistent background confusion, and he had recently developed episodes of headache and right facial pain, associated with facial contortions, and episodic urinary incontinence. On examination, he was disorientated to time and place. There were bilateral grasp reflexes and evidence of marked perseveration with a positive "applause sign" on repeated, structured testing (Supp. Info. Video 1). There were extrapyramidal features including hypomimia, bradykinesia, general paucity of spontaneous movements, and slow gait. There was a mild right facial droop without objective weakness of facial muscles. The remainder of the neurological and general examination was normal.

Routine blood testing including inflammatory markers, HIV serology, and autoantibodies were normal or negative. Neuropsychometric assessment showed generalized cognitive impairment, with evidence for a frontal dysexecutive syndrome (including poor verbal fluency, sequencing and proverb interpretation), and temporal lobe dysfunction [including recognition memory for words (10–25th percentile) and faces (<5th percentile), and naming (5th percentile)]. There was evidence of dyspraxia and relative preservation of visual perception and visuospatial skills.

The electroencephalogram (EEG) showed no specific abnormalities. Magnetic resonance imaging (MRI) revealed diffuse white matter lesions, including involvement of the right anterior striatal and left supralenticular regions. There were scattered left posterior frontal and peri-insular white matter lesions (Fig. 1). Cerebrospinal fluid (CSF) examination showed elevated protein (1.58 g/L), 43 white blood cells (90% lymphocytes with atypical mononuclear cells); there were no oligoclonal bands. CSF viral polymerase chain reaction (PCR) was negative. Computed tomography of the chest was normal, but thoracic, abdominal and pelvic imaging demonstrated para-aortic and bilateral iliac lymphadenopathy, multiple low-density areas within the spleen, and an 8.7 mm lucent area within the body of the T3 vertebra. Ultrasound-guided obturator lymph node biopsy confirmed the diagnosis of T cell rich diffuse large B cell lymphoma (Fig. 1), and intensive treatment with idarubicin based chemotherapy regime was commenced, including intrathecal methotrexate and

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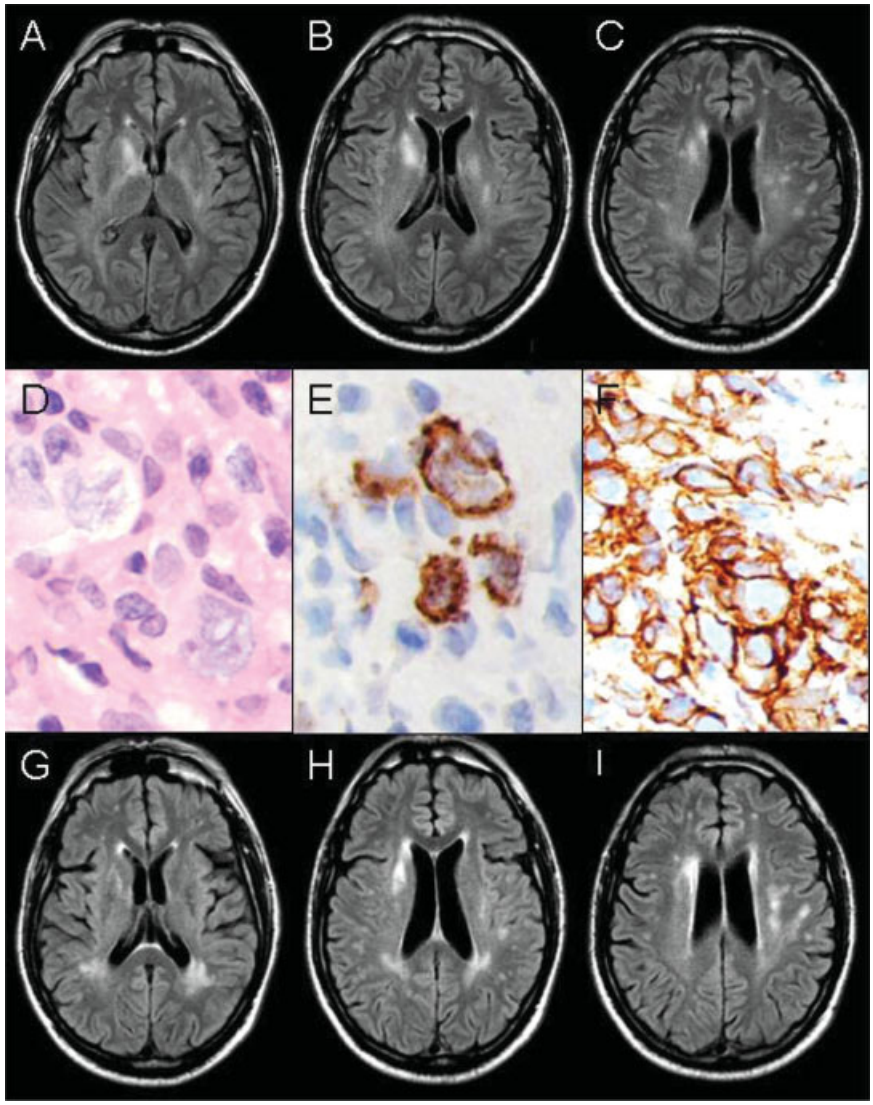

FIG. 1. Consecutive axial sections on MRI FLAIR (A,B,C) showing extensive white matter involvement, including right anterior limb of internal capsule with anterior striatal involvement (A,B), left supralenticular involvement (B) and scattered, predominantly posterior frontal, peri-insular and paraventricular white matter lesions (C). Obturator lymph node biopsy (D,E,F): Neoplastic large B Cells stained with haemotoxylin and eosin (D), and CD2O immunostaining (E). Small CD3 positive T cell lymphocytes (F). Corresponding axial sections on MRI FLAIR (G,H,I) ten months after presentation and following chemotherapy showing slight reduction of right pallido-capsular lesion (G), increased signal in the right anterior putamen (H) and persistent left frontal and peri-insular white matter changes (I). New bilateral peritrigonal white matter lesions are seen (G,H). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

cytarabine. The neurological disorder was thought to be consistent with lymphomatous meningitis (LM), with CNS involvement.[3,4]

He was reviewed 10 months after presentation. He continued to have extrapyramidal features including hypomimia; however, his gait and bradykinesia were much improved. He no longer exhibited the "applause sign" on repeated, standardized testing (Supp. Info. Video). On neuropsychological assessment, there was clear evidence of improvement. Frontal lobe function tests and praxis had improved, but were still weak, and he now performed within normal limits on recognition memory tests for verbal and visual material [50th percentile]. Repeat MRI showed subtle reduction of the right internal capsule and pallidal lesion, increased signal in the right anterior putamen, and persistence of the left posterior frontal white matter changes. New peritrigonal white matter lesions were seen bilaterally.

The "applause sign" is believed to reflect dysfunction of the basal ganglia and associated thalamocortical circuits resulting in impaired motor planning and an inability to stop an automatic activity once initiated.[5] Most commonly considered in the context of PSP, it has been shown to have diagnostic value in discriminating PSP from Parkinson's disease and predominantly cortical disorders such as frontotemporal dementia.[2] In this case, the presence of the "applause sign" provided clinical evidence for brain disease affecting frontal-

basal ganglia circuitry other than PSP. It may be argued that the "applause sign" may be due to a confusional state and difficulties in understanding the examiner's instructions. However, the patient did not have a diffuse confusional state at the time of testing, but had a partially reversible frontal-dysexecutive syndrome with temporal dysfunction and dyspraxia. We therefore suggest that the presence and subsequent disappearance of the "applause sign" signifies lesions in the fronto-subcortical pathways.

It is noteworthy that despite clear clinical improvement and disappearance of the "applause sign", the MR images show little definite improvement over time, with the exception of partial resolution of the right internal capsule and pallidal signal change, possibly implicating dysfunction of these anatomical regions or their connections in the etiology of the applause sign. Although a brain biopsy was not performed, the imaging and CSF in this case were thought to be in keeping with LM with CNS involvement. The basal ganglia lesions showed some response to chemotherapy and might have reflected direct invasion of lymphoma cells whereas the posterior frontal and peritrigonal lesions may represent a distinct pathological process. The new peritrigonal white matter changes might reflect either late sequela of LM or a cytotoxic microvascular phenomenon related to intrathecal chemotherapy. Although similar MRI changes can been seen in progressive multifocal leukoencephalopathy or in the context of paraneoplastic gliosis, the clinical presentation and improvement with chemotherapy make these diagnoses unlikely.

Although we routinely incorporate testing for the "applause sign" when assessing patients with atypical parkinsonism, this case demonstrates that the applause sign may be seen in non-neurodegenerative conditions, may disappear following appropriate treatment of the underlying pathological process, and may be a useful bedside test of frontal-subcortical involvement in a range of clinical contexts.

LEGENDS TO THE VIDEOTAPE

Segment 1. Patient demonstrating positive "applause sign".

Segment 2. "Applause sign" resolved following chemotherapy.

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Possible Post-Traumatic Paroxysmal Kinesigenic Dyskinesia

Video 

Paroxysmal dyskinesias are rare movement disorders characterized by recurrence of sudden involuntary movements. Attacks occur spontaneously at rest (paroxysmal nonkinesigenic dyskinesias) or induced by sudden voluntary movements (paroxysmal kinesigenic dyskinesias, PKD) or prolonged exercise (paroxysmal exercise-induced dystonia).[1,2]

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Standing up from a sitting or lying position is a very common precipitating factor. The attacks usually last from seconds to 1–2 min. There can be up to 100 attacks per day. Some patients refer a tingling sensation preceding the attack. Usually attacks are unilateral, but bilateral attacks have also been rarely described.[3] PKD affects men more than women (ratio 1.7:1). The onset usually occurs in late childhood or early adulthood, but can range from 6 months to 40 years.[3]

Idiopathic cases with a family history and sporadic cases have both been described. Some cases of secondary PKD have also been described, most frequently in association with multiple sclerosis, head injury, or stroke.[4,5] Moreover, some authors suggested that peripheral trauma may cause the occurrence of dystonia and other movement disorders.[6,7]

An 80-year-old man was referred to our service for abnormal movements of left hemibody, which had been present with increasing frequency during the last year. The patient had no significant previous medical history, except for a mild brain injury 52 years before, without overt consequences. He assumed medication for benign prostatic hypertrophy.

When he was 79-year-old, during a pedicure treatment, he felt intense pain caused by digging around his toe nail, which lasted weeks and was disabling. About 1 month later he began to present a dystonic posture of his left toe triggered when he moved especially after rest, the toe being stretched in plantar flexion. It lasted a few seconds and repeated several times up to 30 per day, with unimpaired consciousness. A stretching sensation usually preceded attacks.

In the following months, the paroxysmal dyskinesia spread to other body segments: first the whole left limb, and eventually the whole ipsilateral hemibody. Those episodes were precipitated by voluntary movements involving the left leg, lasted a few seconds and immediately after the patient could move normally. No movement disorders were present at rest; paroxystic episodes were always seen when patient started movements involving the whole body (as getting out of a chair), or the left leg (in Segment 2 the patient was asked to lift his left leg, and in Segment 3 to lift left arm and leg).

Neurological examination was normal; no signs of parkinsonism were present. Brain MRI showed mild diffuse cortical atrophy consistent with the patient's age, without any asymmetry or lesions in the basal ganglia or in cerebral hemispheres. Interictal EEG was normal. No hypoparathyroidism, hyperthyroidism, or diabetes was found.

During a video-EEG session, we recorded 12 attacks in 30 min.: the patient was able to induce them by voluntary movement of his left limb or rising up from the chair. Passive movements or the thought to move his limbs did not induce dyskinesias (videos 1–3). The EEG was normal during the episodes, while electromyographic polygraphy showed a cocontraction of both agonist and antagonist muscles of both left limbs. Patient refused EMG examination.

Attacks were significantly reduced with carbamazepine (300 mg bid), and completely disappeared with a daily dose of 400 mg bid. At 18 months follow-up, no recurrence was observed.

Pathophysiology of PKD is rather controversial: in the past many authors believed that this condition was a form of reflex epilepsy,[8–10] whereas more recently it has been considered a basal ganglia dysfunction.[3] Some authors emphasized similarity between PKD and other paroxysmal neurological disorders, as some forms of episodic ataxia, suggesting disorders of ion channels as possible cause of PKD.[2,11] PKD usually responds to anticonvulsant drugs, especially carbamazepine.[2,3] Very few sporadic cases of paroxysmal dyskinesias preceded by a peripheral trauma are reported in the literature.[5]

Jankovic suggested that some movement disorders, such as dystonia, could be induced by peripheral trauma, possibly resulting from some central reorganization in response to altered peripheral input.[12] He proposed the following three criteria for diagnosis of peripherally induced movement disorders: (1) the trauma is severe enough to cause local symptoms for at least 2 weeks or requires medical evaluation within 2 weeks after trauma; (2) the initial manifestation of the movement disorder is anatomically related to the site of injury, and (3) the onset of the movement disorder is within days or months after the injury.

Actually, hemidystonia has never been described as secondary PKD in association with peripheral trauma, and our patient is older than other cases reported in literature. Nevertheless, the onset of the movement disorder, with a strict temporal and spatial relationship with the described injury of the left foot, suggests that it could be a sporadic peripheral trauma-induced PKD.

Despite growing evidence supporting the relation between trauma and subsequent development of movement disorders, the physiological and biochemical mechanisms of peripherally induced dyskinesias are not well understood, deserving other pathophysiological studies.

Legends to the Video

Segment 1. Occurrence of brief dystonic movement when patient was asked to stand up.

Segment 2. Occurrence of brief dystonic movement when patient was asked to lift his left leg (despite the immediate involvement of left arm in the dystonic movement, the patient referred to feel the involuntary movement starting by the foot).

Segment 3. Occurrence of brief dystonic movement when patient was asked to move up his left limbs.

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Pisa Syndrome and Parkinsonism Secondary to Valproic Acid in Huntington's Disease

Pisa syndrome, also known as pleurothotonus, is an uncommon type of truncal dystonia manifested by persistent lateral flexion of the trunk. It is most commonly associated with prolonged treatment with typical antipsychotics and believed to represent a form of tardive dystonia. However, it has been also reported as occurring secondary to atypical antipsychotics,[1] including ziprasidona, olanzapine, aripiprazole, risperidone as well as sertindole, galantamina, and pergolide.

It has also been reported after unilateral pallidotomy in Parkinson's disease.

Here, we present the case of a patient with Huntington's disease who developed both parkinsonism and Pisa syndrome secondary to valproic acid treatment.

A 67-year-old male patient, with a history of phobias and depression, treated with clonazepam, developed behavioral disorders including increasing anxiety, irritability, and violent behavior at the age of 63. Progressively, choreic-like involuntary movements in his upper limbs, head, and trunk as well as motor tics became evident, associated with a weight loss of about 16 kg.

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His family history was positive; his father and four uncles on his father's side had a "psychiatric condition" and movement disorders with onset at about the age of 60; all of them had already died.

On neurological examination, he presented hypotonia, disarthria, generalized chorea, facial grimacing, slow saccadic eye movements, pendular deep tendon reflexes in his lower limbs, and moderate tandem gait disturbances.

Neurocognitive examination showed impairment in several domains of cognitive function including attention and memory, as well as visuo-spatial and executive function deficits.

The findings from the laboratory tests including complete blood count, liver and kidney function tests, blood sugar levels, serum protein electrophoresis, erythrocyte sedimentation rate, immune tests, thyroid hormonal tests, cupruria, and ceruloplamin levels were normal. He tested negative for HIV.

A brain MRI scan showed ventriculomegaly, cortical atrophy, and atrophic caudate nuclei. A DNA test for Huntington's disease tested positive (CAG expanded repeat of 41 triplets).

He was initially treated with olanzapine (10 mg), sertraline (50 mg) and clonazepam (1 mg), with improvement of his choreic-like movements, anxiety, and depression. After 1 year, sertraline was replaced by paroxetine. This therapeutic scheme lasted 2 years without modifications.

Because of progression of the cognitive impairment and psychiatric symptoms, more severe behavior disorders, impulsivity and disinhibition, rivastigmine (3 mg/day), and valproic acid (500 mg, twice a day) were added according to the psychiatrist's instructions; blood drug levels were within therapeutic limits.

Some days later, worsening of gait impairment was detected, and the patient often fell, face down and so had repeated face trauma.

On physical examination, he presented resting tremor in both upper limbs, mild bilateral rigidity, marked bradykinesia, anterior and right flexion of the trunk, both sitting and standing. He developed a festinating gait with short steps with an increased flexion of both the trunk and head leading to frequent falls. Walking without aid became extremely difficult. Choreic-like movements in the face became evident.

Because of the presence of a parkinsonian syndrome associated with axial dystonia, valproic acid was discontinued. A further brain MRI showed no significant changes. One week later, the patient's trunk posture dramatically improved, the right flexion disappeared, and he was able to walk without aid. However, parkinsonian symptoms improved slightly, and in 2 months they completely disappeared.

An association between cholinesterase inhibitors and Pisa syndrome has also been described,[2,3] and a cholinergic-dopaminergic imbalance has been proposed as the basis of this disturbance.[4]

To the best of our knowledge only 1 case of valproic acid Pisa syndrome has been reported,[5] and in this case, the patient was also on stable doses of risperidone and carbamazepine.

A further case of a mentally retarded 23-year-old woman with myoclonic epilepsy who developed camptocormia during valproate monotherapy has been reported. In this case, camptocormia was most likely a dose-dependent side effect of valproate.[6]

Here, we describe an additional case of a patient with Huntington's disease who developed drug-induced Parkinsonism and Pisa syndrome.

Our patient developed Parkinsonism and Pisa syndrome while on rivastigmine and valproic acid. Both rivastigmine

and valproic acid can cause or exacerbate parkinsonian motor signs or Pisa syndrome.[2,3,5,6] However, in our case discontinuation of valproic acid led to prompt recovery of both Pisa syndrome and Parkinsonism.

Our case further illustrates that valproic acid is apt to cause Pisa syndrome, and this should be borne in mind particularly when it is used to treat patients with Huntington's disease and not to ascribe it as a manifestation of this neurodegenerative disorder.

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