INTRODUCTION

Chorea-acanthocytosis is a rare autosomal recessive adult-onset neurodegenerative disorder due to VPS13A gene mutations, encoding chorein.\textsuperscript{1,2}

Clinical manifestations consist of a mixed movement disorder, seizures, neuropathy, myopathy, autonomic features, dementia, and psychiatric features.\textsuperscript{3} The differential diagnosis is wide. Acanthocytes are not always detected by the screening test of the peripheral blood smear. Hence, clinical clues and red flags are an important aid for clinicians.

In evaluating patients with chorea-acanthocytosis in our tertiary referral centers, we have observed typical flexions of neck (presenting as head drops) and trunk as a characteristic feature in advanced chorea-acanthocytosis which in our view have not been explicitly described before. We feel that these features may be a pathognomic clinical sign for chorea-acanthocytosis and a useful clue toward the diagnosis, particularly if self-mutilatory mouth movements or feeding-related tongue dystonia are also present. We illustrate our observations by videos including a series of videos over time for Case 1 showing that head drops become prominent late in the disease course. All patients gave written informed consent. A summary of the demographic and clinical details are shown in Table 1.

CASE 1

This 40-year-old patient developed slowly progressive frontal lobe dysfunction from age 32, followed by chorea and slurred speech from age 34. He developed falls at age 36. At age 38, he developed difficulty eating with tongue biting. On examination then he had generalized chorea, intermittent mild head drops, gait ataxia, and severe bruxism (Video Segment 1). At age 39, he presented with his first generalized tonic-clonic seizure and developed autonomic dysfunction with progressive loss of bladder control.

On last follow-up, aged 40, memory function was relatively preserved. He was depressed; however, aggression, self-injurious behaviour, or psychosis were absent. Saccades were hypometric. He had orobulbar involvement with marked dysarthria, slow tongue movements, and swallowing difficulties. Because of severe bruxism culminating in tongue biting and damage of his teeth, he wore a gum shield. He had...
generalized chorea and his head drops had become more severe resulting in head and face injuries (Video Segment 2). His gait was very unstable and lurching. Investigations demonstrated presence of 5% acanthocytes. The protein assay revealed absent chorein. Creatine kinase (CK) was raised to 224 at age 39 and to 429 on last follow-up, at age 40 (normal <150). Copper studies were normal. Genetic testing was negative for Huntington’s disease, DRPLA, SCA17, and junctophilin-3 (HD2). VPS13A testing was not performed. 

Electrophysiological studies suggested mild myopathy and mild chronic sensory motor axonal neuropathy. Tetrabenazine worsened his depression and had to be withdrawn. He continues to receive botulinum toxin injections in the masseter muscles to alleviate the bruxism, antidepressants, benzodiazepines and, for seizure control, valproate. In view of loss of bladder control, a catheter had to be inserted.

There was no family history of neurological disease. His sister was asymptomatic. She had normal (however, at the lower limit of the normal range) levels of chorein in the protein assay.

Case 2

This woman from an extended French-Canadian kined with VPS13A mutations presented at age 43 with a 6-year history of generalized abnormal movements. Her parents were first cousins. One sister and two cousins, also the products of a consanguineous marriage, were similarly affected. Examination at age 43 demonstrated moderate generalized chorea with dystonia of the trunk and legs, mild action hand tremor, and absent lower limb deep tendon reflexes. Mild “tic-like” behavior was noted including humming and mild swearing. At age 45, her trunk and knees began to “give-way”. While sitting unsupported her trunk would occasionally extend forwards or backwards involuntarily (Video Segment 2). Peripheral smear demonstrated 10% acanthocytes. CK levels were 3212. CT scans demonstrated caudate atrophy. Fluorodeoxyglucose positron emission tomography revealed absence of FDG uptake in the caudate-putamen area. Neuropsychological assessment showed only mild reduction in verbal fluency and procedural learning. She failed trials of multiple medications.

Case 3

This 32-year-old man, one of the affected cousins of Patient 2, was seen for consideration of bilateral globus pallidus internus (Gpi) deep brain stimulation (DBS) surgery. At age 22, he noted clumsiness in his hands and dysarthria. He developed involuntary movements of his tongue and jaw, with severe biting of his cheeks and tongue. He also developed facial tics, anterocollis, and opisthotonus. He fell while walking, due to imbalance and involuntary leg movements. When kneeling, there were involuntary backward trunk movements. His older brother was in a nursing due to the same disease and had exactly the same backward movements. His dysphagia and dysarthria progressively worsened. He had feeding dystonia needing to lie down to drink liquids and to push the food inside his mouth with his fingers or a fork. Genetic analysis at age 24 revealed he was compound heterozygous for the French Canadian founder mutation EX70_EX73del and a splice site (c.4242+1G>T) VPS13A gene mutation.

On exam, speech was dystonic and severely slurred. There was severe drooling. He had what were interpreted as tics involving blinks and shoulder shrugs. He had occasional simple vocalizations (“hmm” sounds). He also had compulsive nose picking and skin scratching to the point of bleeding and wore gloves to prevent him from this behavior. His head was held mostly flexed. He demonstrated prominent backwards trunk movements, which occasionally caused him to knock his head quite hard on the wall behind him and he wore a soft helmet as a protection (Video Segment 3). Hand movements were slow, but tone was normal.

A variety of medications provided only partial relief. Botulinum toxin injections of the masseters and pterygoid muscles markedly reduced cheek and tongue biting. Bilateral Gpi DBS surgery was performed at age 31 with clinical improvement.

Case 4

This 36-year-old male patient is taken from the archival video database of Professor David Marsden’s and was previously reported by Hardie et al. as Case 18. There was a 3-year history of progressive speech impairment, dysphagia, intermittent muscle spasms affecting the left-sided limbs, and difficulty walking with occasional falls. On examination, there were a fine slow tongue tremor at rest and action tongue dystonia and facial dystonia when speaking. His speech was dysarthric. He spontaneously made intermittent loud sucking and blowing noises and his head dropped intermittently (Video Segment 4). Optic fundi and eye movements were normal. Limb tone and power were normal, but rapid finger movements were mildly impaired in the left hand. There was leg dystonia when walking. Tendon reflexes were all reduced. 

Movement Disorders, Vol. 25, No. 10, 2010
responses were flexor. About 5% acanthocytes was present in peripheral blood. CK was elevated at 692. Mutation analysis revealed a $VPS13A$ mutation in exon 57.

**DISCUSSION**

Movements in chorea-acanthocytosis are often complex. Chorea, dystonia with prominent orofacial involvement, tics and parkinsonism have all been described.

We noted the occurrence of sudden and striking movements of the trunk and head, sometimes resembling sudden loss of tone as seen in negative myoclonus. In more severe Cases (#2 and 3), the trunk movements were profound causing drops from the waist downward so that the head would go into the lap. In less severe presentations, there were characteristic head drops with ballistic flexion of the neck as seen in two of our Patients (#1 and 4).

Case 3 had axial drops but also equally sudden and striking extensor movements. Thus, in addition to sudden loss of tone resulting in the head to drop, extension movements are equally possible. Interestingly, we noted intrafamilial homogeneity of the movement.

Patient 3 and his similarly affected brother showed exactly the same backward movements. Overall, these axial movements appeared to be a distinctive feature which may be a clue towards the diagnosis.

As a consequence, one of our patients (Case 1) had various injuries at the back of his head and the forehead. This was initially misinterpreted as self-injurious behaviour which may also occur in chorea-acanthocytosis. However, psychiatric assessment revealed no suggestion to support voluntary self-injurious tendencies in our case.

The type of myoclonus-like movements we describe here may also be seen in myoclonic disorders, for example Unverricht-Lundborg disease. However, psychiatric assessment revealed no suggestion to support voluntary self-injurious tendencies in our case.

The differential diagnosis of a mixed movement disorder with both myoclonic jerks and dystonia also includes myoclonus dystonia (DYT11). However, the onset of myoclonus dystonia is usually very early in life with "lightening jerks" in contrast to neuroacanthocytosis where onset is in adulthood. In addition, none of our patients had a beneficial response to
alcohol which is a characteristic feature DYT11 dystonia. Furthermore, inheritance in the latter is autosomal dominant in contrast to chorea-acanthocytosis where inheritance is recessive.

The differential diagnosis of sudden head movements furthermore includes tic disorders. Although two of our patients exhibited tic-like features like vocalizations (Cases 2 and 3) and motor tics (Case 3), Patients 1 and 4 had no tics and denied any inner urge to move. Also, tics can usually be suppressed, but Cases 2 and 3 had no control over their axial movements. Finally, there is phenotypic overlap with stereotypic “head banging” as seen in mentally disabled children for example those with Down syndrome, autism, or following amphetamine poisoning.

The classification of the movements we observed is not straightforward. As discussed earlier, there are similarities to myoclonus and tics; however, they could also represent a choreic movement especially as the direction included both flexion and extension. The movements could also be dystonic, in view of the prominent opisthotonus with dystonic arching present in Case 3. Interestingly and perhaps related, a pattern of trunk flexion (“feet-clasping posture”) is a characteristic feature in the R6/2 Huntington’s disease mouse model.

Treatment responses ranged from very good to unsatisfactory. In one Patient (#1), the head movements could be alleviated by botulinum toxin injections. Patient 2 failed trials of multiple medications. In Patient 3, bilateral GPi DBS markedly improved swallowing, axial dropping, and extensor movements.

We encourage physicians to look for these clinical signs, the spectrum of which ranges from mild to severe, and if present to screen for acanthocytes. A technically much simpler and more sensitive laboratory parameter in chorea-acanthocytosis, however, is determination of CK which generally is elevated. Protein assays or genetic testing can confirm the diagnosis.

**Legends to the Video**

Segment 1. Patient with chorea-acanthocytosis. The first part of the clip, shows the patient aged 38. While sitting there is generalized chorea with intermittent head drops (resembling a sudden loss of tone). The patient is also asked to shortly take the toothbrush out of his mouth which he uses to protect his teeth from clenching. After having done this, there is severe bruxism. The second part of the clip shows the patient at age 40 when walking. His forward head drops have become more severe. His gait is very unstable and with intermittent loss of tone in the legs.

Segment 2. The patient (shown at age 47) with chorea-acanthocytosis has generalized chorea. When sitting, she demonstrates involuntary sudden forward flexions of the trunk.

Segment 3. This patient with genetically proven chorea-acanthocytosis (compound heterozygous: EX70_EX73del and c.4242+1G>T VPS13A mutations) was recorded prior to GPi DBS surgery at age 32. When walking there is involuntary loss of tone in the legs and also sudden head drops. The postural stability is markedly impaired.

Segment 4. The patient aged 36 years with chorea-acanthocytosis makes loud sucking and blowing noises. Towards the end of the clip, there are intermittent involuntary forward head drops.

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Benign Hereditary Chorea: Clinical and Neuroimaging Features in an Italian Family

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Abstract: Benign hereditary chorea is an autosomal dominant disorder characterized by early onset nonprogressive chorea, caused by mutations of the thyroid transcription factor-1 (TITF-1) gene. Clinical heterogeneity has been reported and thyroid and respiratory abnormalities may be present. We describe 3 patients of an Italian family carrying the S145X mutation in the TITF-1 gene with mild motor delay, childhood onset dyskinetias, and subtle cognitive impairment. A child in the third generation presented with congenital hypothyroidism and neonatal respiratory distress. Imaging studies in 2 patients showed mild ventricular enlargement and empty sella at magnetic resonance imaging and hypometabolism of basal ganglia and cortex at 18-Fluoro-2-deoxy-glucose positron emission tomography. © 2010 Movement Disorder Society

Key words: benign hereditary chorea; thyroid transcription factor-1; congenital hypothyroidism; MRI; FDG-PET

Benign Hereditary Chorea (BHC) is an autosomal dominant disorder characterized by childhood onset chorea with little or no progression into adult life. Mental deterioration does not occur, but slightly lower I.Q. scores have been reported. Mutations in the thyroid transcription factor-1 (TITF-1) gene on chromo-

Additional Supporting Information may be found in the online version of this article.

Elena Salvatore and Luigi Di Maio contributed equally to the study, and both should be considered as first authors.

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Movement Disorders, Vol. 25, No. 10, 2010
some 14q have been identified as causative in several families, most of them recently reviewed.1,2 A second locus (8q21) for BHC has been recently mapped in two Japanese families with adult onset chorea.3

The TITF-1 gene is a homeodomain-containing transcription factor essential for the organogenesis of lung, thyroid, and basal ganglia.4 Thus, it is not surprising that the clinical spectrum in families carrying TITF-1 mutations includes thyroid and lung disorders, such as congenital hypothyroidism and respiratory distress. The putative mechanism of disease results from gene haploinsufficiency and reduced protein product.

We previously described molecular and functional data of the novel TITF-1 S145X mutation in an Italian pedigree.5 Here, we report in detail the clinical features and the neuroimaging data of the family.

CASE REPORTS

This three-generation family shows three affected individuals, one for each generation, all carrying a previously unreported mutation of the TITF-1 gene. The genetic defect and the molecular mechanisms have been described in the previous article.5 The index patient was Patient 1, who had been referred for exclusion of Huntington’s disease (HD). The information that her father (Pt. 2) had abnormal movements and that her son (Pt. 3) had congenital hypothyroidism led to the clinical suspicion of BHC and to the molecular analysis of the TITF-1 gene.

Patient 1, 26 years old, began walking at the age of 18 months, but she was clumsy and fell repeatedly. Her gait much improved around puberty. Mild generalized choreic movements appeared at the age of 7 years and remained stable thereafter. No mental or behavioral abnormalities were present, she did not encounter difficulties at school, and she was graduated at a Hotel school. During puerperium, when she was 19 years old, her chorea worsened and she presented with a postpartum psychosis, characterized by depression and aggressiveness toward the newborn and successfully treated with risperidone and lamotrigine.

At the age of 23 years she was admitted to our hospital. Neurological examination showed generalized choreic movements (video) and was otherwise normal. Neuropsychological evaluation demonstrated long term verbal memory deficit and low-normal score at Raven Matrices test.

Molecular analysis of HD gene and laboratory testing were normal, a part from elevation of thyroid-stimulating hormone.5 Thyroid hormone replacement was started. Brain magnetic resonance imaging (MRI) revealed ventricular dilatation, more marked in the posterior part of lateral ventricles (Fig. 1a–c) and partial empty sella (Fig. 1d). Brain 18-Fluoro-2-Deoxy-Glucose Positron Emission Tomography (FDG-PET) showed slight relative hypometabolism of the caudate nuclei and of the medial frontal and temporo-parietal cortices (Fig. 2). The patient was treated with tetrabenazine up to 75 mg daily, with mild improvement. At the age of 26 years she withdrew the therapy abruptly and presented marked worsening of chorea, irritability, emotional lability, poor sleep, inappropriate dress, and behavior. She was admitted to our hospital again, treated with quetiapine, 75 mg daily, and discharged improved after a week.

Patient 2, the proband’s father, 56 years old, had meningitis at the age of 6 months. Subsequent motor development was delayed with walking starting at the age of 5 years and normal language skills. His school performances were poor. Since childhood, slight, sporadic, hyperkinesias were present, which mainly involved the abdomen and had been stable over time. He did not report improvement by alcohol. He worked as a school-caretaker and had a normal social life. At examination jerky abdominal movements were evident; mild and rare choreic movements were present in other body regions (video). Neuropsychological evaluation showed short term verbal and spatial memory deficit, slight attentional deficit, and constructive apraxia.

Thyroid hormone screening showed primary hypothyroidism with increased TSH and mildly reduced FT3. Brain MRI evidenced slight, asymmetrical ventricular dilatation, more marked in the right side and in the posterior part of lateral ventricles (Fig. 1e–g), and complete empty sella (Fig. 1h). FDG-PET demonstrated relative hypometabolism of basal ganglia, more prominent in the caudate nuclei, and a slight relative hypometabolism of the left temporo-parieto-occipital cortex (Fig. 2). Tetrabenazine, up to 50 mg daily, was prescribed, but the drug was withdrawn for insomnia and nervousness.

Patient 3, the 5 years old proband’s son, born at term by cesarean delivery because of transverse position, received continuous positive airway pressure therapy for neonatal respiratory distress. The infant presented with multiple congenital anomalies: severe bilateral vesicoureteral reflux with pyelectasis and megabladder, patent foramen ovale, and congenital hypothyroidism for which thyroid replacement treatment was started.

Psychomotor development was delayed: sitting at 10 months, walking at 26 months, first words at 26 months, at present only few words in vocabulary and lack of sphincter control. His I.Q. was 76 at the age of

Movement Disorders, Vol. 25, No. 10, 2010
4 years. He is a pleasant boy, has no behavioral problem and developed normal social relationships. At the age of 4 years he developed slight, generalized choreic movements (video).

**Molecular analysis:** Direct sequencing of the TITF-1 gene showed, in all the 3 patients, the new heterozygous mutation C609A in exon 2, resulting in a substitution of serine at codon 145 for a stop codon (S145X). The mutation predicted a truncated protein of about 14.5 kDa that lacks the entire homeodomain and the carboxy-terminus portion.

**DISCUSSION**

BHC shows heterogeneity of the clinical presentation within and among the families. In the present family the neurologic presentation, characterized by mild motor delay, early-onset dyskinesias, and slightly lower intelligence, was quite similar in the 3 patients, although the abnormal movements are somewhat different among individuals. Although chorea is the movement disorder characteristic of BHC, dystonia, myoclonic jerks, and ataxia have been also described. The distinction among chorea, myoclonus, and jerky dystonia may be difficult. The diagnosis of chorea, which is characterized by a random flow of rapid, unpredictable abnormal movements, better applies to Patients 1 and 3, whereas the sudden, more predictable and repetitive abdominal jerks in Patient 2 seem to be more consistent with myoclonus. As described in other patients with BHC, dyskinesias, contrary to myoclonus-dystonia, were not worsened by action nor improved by alcohol.

Concerning extra-neurologic features subclinical hypothyroidism was present in Patients 1 and 2, whereas...
Patient 3 had congenital hypothyroidism and neonatal respiratory distress. Anticipation and more severe phenotype in subsequent generations have been suggested, but not demonstrated in BHC. Environmental factors and genetic background might also influence the clinical expression. A review of the reported cases reveals 11 cases of congenital hypothyroidism due to TITF-1 mutations in patients with de novo mutations or with no information about parental phenotype or genotype, 11 (including the present one) with maternal inheritance of the allele carrying the mutation, and one with paternal inheritance. However, there are also reports of maternal inheritance without congenital hypothyroidism. The predominance of maternal inheritance of congenital hypothyroidism in BHC may be due to chance or may be related to imprinting or maternal environment.

It remains unclear if some peculiar features of our patients, as postpartum psychosis in Patient 1 and urinary tract malformations in Patient 3, are related to the mutation. Psychosis occurred in two previously reported patients and hypospadias has been described before recognition of the molecular defect. We are not aware of a role of TITF-1 in urinary tracts organogenesis, although the gene is expressed in small cell carcinoma of the urinary bladder. We suggest special attention to urinary tract malformations in patients with BHC.

Imaging data also appear to be heterogeneous in BHC. CT/MRI findings are usually normal, but ventricular dilatation and other abnormalities have been also reported. A cystic mass in the posterior part of the sella turcica has been described in two cases. In the 2 patients investigated by us, MRI showed ventricular dilatation, more evident at trigone and occipital horn level, whereas in HD ventricular enlargement mostly affects the frontal horns. Empty sella was present in both patients, more marked in Patient 2, which has the longest disease duration. Haploinsufficiency of the TITF-1 gene could lead to congenital deficiency of the sellar diaphragm, which is a frequent cause of an enlarged sella. FDG-PET scan was reported to be normal in 4 patients with BHC, although a study performed when the molecular diag-

**FIG. 2.** Axial images of brain 18F-deoxy-glucose uptake obtained with PET in a 39 years control, in Patient 1 and in Patient 2. The images were spatially normalized into the Montreal Neurological Institute (MNI) space and normalized to globals. The scale shows values of highest uptake in red and lowest uptake in blue. In Patient 1 a mild reduction of tracer uptake is present in the caudate nuclei and in the medial frontal and temporo-parietal cortex, bilaterally. The basal ganglia hypometabolism is more marked in Patient 2, involving more the caudate than the putamen regions. In Patient 2 there is also a mild temporo-parietal metabolism reduction on the left side. L left, R right.
nosis was not available showed caudate hypometabolism. More recently reduction of technetium 99 m ethyl cysteinate dimer uptake has been demonstrated in the basal ganglia of two children studied by SPECT. Using FDG-PET we showed cortex and basal ganglia hypometabolism in both Patient 1 and Patient 2. These findings are consistent with the significant reduction of striatal and neocortical interneurons demonstrated by immunohistochemical staining in BHC and with the patients’ choreic syndrome and mild cognitive impairment. The pattern of metabolic changes is similar, but less severe than that found in HD, consistently with the milder, non progressive BHC phenotype.

Legends to the Videos
Segment 1. Patient 1 examination shows generalized, moderate to marked, choreic movements involving the face, the neck, the trunk, the limbs, both proximally and distally. Finger-to-nose and walking do not worsen the abnormal movements. Mild unsteadiness is also evident.

Segment 2. Slightly staggering gait and mild limb choreic movements, not worsened by action, in Patient 2. Brisk abdominal wall contractions are evident.

Segment 3. In Patient 3 mild choreic movements involved the trunk and the four limbs, both proximally and distally, not worsened by action. Brisk myoclonic-like movements are also evident. Tottering was probably too marked for his age.

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Long-Term Effect of Unilateral Pallidotomy on Levodopa-Induced Dyskinesia

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Abstract: Unilateral pallidotomy has been effectively used to treat parkinsonism and reduce levodopa induced dyskinesia (LID). We sought to determine the long-term effects of pallidotomy on LID in 10 patients who had initial benefit from pallidotomy but went on to require DBS surgery for symptom progression. The Dyskinesia Rating Scale (DRS) was used to rate and quantify LID in a blinded fashion. Though sample size was small, there was a trend towards a reduction in LID lasting up to 12 years suggesting that posteroventral pallidotomy may provide sustained benefit in reducing LID.

Patients and Methods

Patient Population

Ten patients (8 male) with PD and prior pallidotomy on average 7.3 years (range 2–12 years) earlier were evaluated for consideration of STN DBS. All patients were felt to have obtained an initial good response to pallidotomy with respect to parkinsonism and particularly LID. Not all patients had received pallidotomy at our center; pre and postoperative LID scores were available in 6 of the 10. Before DBS patients were evaluated under the protocol of the Core Assessment Program for Intracerebral Transplantation6 (CAPSIT) before STN DBS surgery. Dyskinesia was assessed using the Dyskinesia Rating Scale (DRS) (maximum score for unilateral limbs = 8). The dosage of anti-parkinsonian medication required by the patient was recorded; levodopa equivalent doses (LED) were calculated in a manner described elsewhere.7 Evaluations

In the era before DBS, as well as currently, in many countries around the world, unilateral postero-ventral pallidotomy as a treatment for Parkinson’s disease (PD) has been the surgical alternative of choice. Pallidotomy ameliorates parkinsonism and is particularly effective in reducing levodopa-induced dyskinesia (LID) most prominently in the contralateral hemibody.1 Despite initial control of disabling symptoms, parkinsonism generally worsens several years following pallidotomy and many patients have subsequently undergone STN DBS when their symptoms again became resistant to medical regimens.2–4 No long-term follow-up studies have blindly evaluated the persistent effects of unilateral pallidotomy on LID. It has been our personal experience that the antidyokinetic effects may be evident many years after the original surgery and Hariz reported that these effects could last up to 13.5 years.5

We sought to determine the long-term effect of pallidotomy on dyskinesia in a selected sample of patients who had previously undergone pallidotomy and were undergoing preoperative evaluation for STN DBS due to symptom progression. Given the extensive preoperative assessment for DBS, ON/OFF evaluations were available for review in these patients. We evaluated efficacy of pallidotomy on dyskinesia by comparing contralateral and ipsilateral dyskinesia at the STN-DBS preoperative evaluation. We postulated that there would be a difference between sides due to lasting effects of pallidal lesioning with less severe dyskinesia contralateral to the previous surgery.

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were made while the anti-parkinsonian medication was in effect (medication-on period) and following overnight withdrawal from medication (medication-off period). These assessments were video-taped and a blinded-rater (blinded to patient, side of previous pallidotomy, and medication state) quantified and identified the type of dyskinesia utilizing the DRS.

Statistical Analysis
Effectiveness of initial pallidotomy on dyskinesia was assessed comparing pre and postoperative DRS scores using the Wilcoxon sign-rank test. Pairwise comparisons were made between the limbs ipsilateral and contralateral to prior pallidotomy for “ON” dyskinesia and “OFF” dystonia using a paired t-test.

RESULTS
All patients had undergone pallidotomy contralateral to their most severely affected side (parkinsonism and LID). The available data demonstrated that at 12 months following pallidotomy patients had a significant reduction in dyskinesia: ipsilateral dyskinesia (mean reduction 1.25 points; minimum change 0 points, maximum change 2.5 points, \( P = 0.04 \)), contralateral dyskinesia (mean reduction 2 points; minimum change 1 point, maximum change 2 points, \( P = 0.04 \)), and axial dyskinesia (mean reduction 1.75 points; minimum change 0 points, maximum change 2 points \( P = 0.05 \)). Mean age at pallidotomy was 51.5 ± 5.9 with disease duration before pallidotomy of 9.5 ± 2 years. Mean LED at the time of pallidotomy was 754.3 ± 450 mg and at time of STN DBS was 1287.8 ± 419.2 mg.

The results of blinded assessment of dyskinesia before STN DBS are displayed in Table 1. There was a small difference in LID between sides with a trend toward less LID in the contralateral versus the ipsilateral limbs (\( P = 0.09 \)). In 5 of 8 patients, who demonstrated on-period LID, these were more severe (markedly in 3) on the side ipsilateral to the previous pallidotomy. There was no difference in OFF dystonia found between limbs.

DISCUSSION
Pallidotomy has a prolonged effect on contralateral dyskinesia with previous studies having reported benefit lasting up to 13.5 years even when akinesia and other PD symptoms had returned.\(^5\) Other studies have also reported sustained benefit from unilateral pallidotomy on contralateral dyskinesia.\(^1,8,9\) None of these studies evaluated LID in a blinded fashion. In this study, only patients who were undergoing subsequent DBS were included due to availability of data, and therefore, this may be a biased cohort of patients with suboptimal outcomes given the need for further intervention. There are other patients who underwent pallidotomy at our Center who have had sustained long-term improvement of LID (as evidenced by on-period clinical assessments demonstrating minimal or no dyskinesia contralateral to their previous surgery); however, video-taped CAPSIT evaluations of these patients were not available for blinded review. Our evaluated patients were all felt to have had an initial good effect on LID from pallidotomy; however, progression of parkinsonian symptoms necessitated consideration of DBS.

Although sample size in our case series was too small to achieve statistical significance, there was a trend toward significance lasting up to 12 years following the original surgery, consistent with previous reports of sustained benefit. This finding again suggests that postero-ventral pallidotomy remains a reasonable alternative therapy for disabling LID, especially in patients for whom DBS surgery is not a therapeutic option.

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### TABLE 1. Dyskinesia characteristics

<table>
<thead>
<tr>
<th>Yrs since pallidotomy</th>
<th>DRS (ON) ipsilateral</th>
<th>DRS (ON) contralateral</th>
<th>OFF dystonia (ipsilateral)</th>
<th>OFF dystonia (contralateral)</th>
</tr>
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<tr>
<td>1. 12</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>0</td>
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<td>2. 5</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3. 4</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>4. 10</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5. 9</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>6. 2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>7. 9</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8. 7</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9. 7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10. 8</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mean 7.3</td>
<td>3.1</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
</tr>
</tbody>
</table>

DRS, dyskinesia rating scale.
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Increased Reaction Time Predicts Visual Learning Deficits in Parkinson’s Disease

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Abstract: To determine whether the process involved in movement preparation of patients in the early stages of Parkinson’s disease (PD) shares attentional resources with visual learning, we tested 23 patients with PD and 13 healthy controls with two different tasks. The first was a motor task where subjects were required to move as soon as possible to randomly presented targets. The second was a visual learning task where targets were presented in a preset order and subjects were asked to learn the sequence order by attending to the display without moving. Patients with PD showed higher reaction and movement times, while visual learning was reduced compared with controls. For patients with PD, reaction times, but not movement times, displayed an inverse significant correlation with the scores of visual learning. We conclude that visual declarative learning and movement preparation might share similar attentional and working memory resources. © 2010 Movement Disorder Society

Key words: Parkinson’s disease; executive function; attention; motor control

Motor slowness in Parkinson’s disease (PD) is a general term that encompasses: akinesia, a poverty of movement production and delay in movement initiation; bradykinesia, a reduction in movement speed; and hypokinesia, a reduction in movement size.1 In experimental motor tasks, akinesia is reflected by increased reaction times, a finding often reported in patients with PD.1

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During the few hundred milliseconds between stimulus presentation and movement onset, many processes take place, including attentional and stimulus processing, decision making, and movement programming. Some of these processes and resources are also engaged during visuospatial learning that occurs without movement. In fact, activation of frontoparietal areas, the likely neural substrate of these processes, occurs during many tasks, independent of the modality and of the learning load.

It is now well known that PD impairs not only motor functions but also attentional and learning processes. However, the connection between the two deficits has not been explored.

Here, we hypothesize that if movement preparation shares neural resources with visual spatial learning, in patients with PD, abnormalities in reaction time and impairment of sequence learning that requires no movement should be correlated.

**PATIENTS AND METHODS**

Twenty-three patients with idiopathic PD (17 men and 6 women; mean age ± SE: 60.0 ± 6.8 years) in early stages of the disease (Hoehn and Yahr stages I–II) and 13 age-matched healthy controls (6 men and 7 women; 56.5 ± 2.7 years) participated in the study. All subjects were right-handed, underwent a clinical interview to determine that he or she did not meet the DSM-III-R criteria for depression or dementia, scored more than 27 at Mini-Mental State Examination, and had a normal brain MRI.

Mean UPDRS score (part 3) of patients with PD was 8.8 (1.8, SE). The most involved side was the right in 10 patients and the left in the remaining 13 patients.

At the time of testing, all patients were in stable conditions. Thirteen patients were drug-naïve; 4 had been treated with deprenyl alone, 4 with levodopa (L-dopa)/carbidopa, and 2 with a combination of dopamine agonists and L-dopa/carbidopa. However, all patients were drug-free for at least 12 hours before testing. Written informed consent was obtained from all participants under a protocol approved by the institutional review board of the participating institutions.

Detailed features of the tasks have been previously reported. Briefly, in both tasks, one of eight targets appeared on a screen with a common starting point, in synchrony with a tone at 1-second intervals. Each trial block lasted for 90 seconds.

The two tasks, which were presented in a randomized order, were:

1. Motor task: targets were presented in a pseudorandom and unpredictable order. Movements were performed on a digitizing tablet with the right dominant hand. Instructions were to reach each target as soon as possible, minimizing reaction time but avoiding target anticipation. Target distance was 1.8 cm.

2. Visual learning task: subjects were instructed to learn the order of a repeating sequence of eight targets that was presented in the 90-second block. At the end of the block, verbal reports about the sequence order were collected.

For each movement we computed: reaction time, movement duration, peak velocity, hand-path length, and spatial error. At the end of the visual block, declarative scores were computed from 0 (unawareness of a sequence) to 8 (complete correct sequence).

Factorial analysis of variance was performed to compare patients with PD and healthy controls’ values. Linear regression analyses were also performed to determine correlations between kinematic and other variables. Level of significance was \( P < 0.05 \).

**RESULTS**

There was no difference between the performance indices of treated and drug-naïve patients and between right and left hemiparkinsonian patients. Therefore, patients’ data were combined and compared with those of controls.

Data are summarized in Figure 1. On average, reaction times were prolonged in patients with PD when...
The declarative scores reflecting visual learning were significantly lower in patients compared with controls [F(1,34) = 5.6, P = 0.02]. Similarly, in patients with PD, movement durations were significantly longer [F(1,34) = 8.0, P = 0.008] and peak of velocity reduced [F(1,34) = 6.9, P = 0.01]. Spatial accuracy, expressed by spatial error, was similar in the two groups [F(1,34) = 1.9, P = 0.2]; however, hand-path lengths were reduced in patients with PD when compared with controls [F(1,34) = 9.0, P = 0.005].

The declarative scores reflecting visual learning were significantly lower in patients compared with controls [F(1,34) = 13.2, P = 0.0009], indicating impairment in visuospatial learning.

We then ascertained whether declarative scores in the visual task were associated to kinematic measurements. In patients with PD, declarative scores were negatively correlated with reaction times: the higher the reaction time, the lower the declarative score (r = −0.66, P = 0.0006). No significant correlations were found between declarative scores versus movement times (r = −0.23, P = 0.3), peak velocity (r = 0.05, P = 0.8), or hand-path length (r = −0.20, P = 0.4). In addition, there were no correlations between UPDRS (part 3) scores and either reaction times (r = 0.06, P = 0.8), movement times (r = 0.12, P = 0.7), hand-path length (r = 0.21, P = 0.5), or declarative scores (r = −0.13, P = 0.7). In patients with PD, there was no significant correlation between reaction times and movement duration or peak velocity (r = 0.29, P = 0.2). As expected, movement time and peak velocity values were instead highly correlated (r = −0.87, P < 0.0001).

Finally, in healthy controls we did not find any correlation between learning scores with either reaction time (r = 0.39, P = 0.2) or movement time (r = 0.004, P = 1.0).

**DISCUSSION**

This study shows that, in agreement with previous work, in patients with early stage PD increased reaction times and impaired visual sequence learning are significantly correlated; patients with higher reaction times are also more impaired in sequence learning, suggesting that movement preparation shares resources with learning of visuospatial sequences.

Increased reaction time in patients with PD is considered the experimental hallmark of akinesia. Our motor task also captured other characteristic features of PD: hypokinesia, with reduced hand-path length and bradikinesia, with significant increases in movement time and reductions of peak velocity. Interestingly, the clinical motor UPDRS scores did not correlate with any of the kinematic measures. This lack of correspondence is likely due to the fact that motor UPDRS scores reflect global motor impairment, as this scale embraces multiple motor aspects. Interestingly, in our PD population, reaction and movement time did not correlate, adding evidence that their respective neural mechanisms may not overlap.

As previously shown, our patients with PD display abnormal visual sequence learning, a learning that is declarative and explicit in nature, requires no motor involvement but loads working memory and attention buffers, possibly like movement preparation. Patients with PD also show alteration in visuospatial and central executive abilities. It has been suggested that all these deficits stem from malfunction of the frontoparietal network. In fact, this network is engaged in many and various facets of cognitive control, as it might be responsible for the active representation of attended and goal-relevant stimuli, and thus for promoting adequate domain-dependent information processing. In fact, even the simple shift between attended stimuli leads to an update of this network.

The exclusive correlation of declarative scores with reaction times, but not with other kinematic parameters, suggests that, first, the neural resources for movement preparation and those for visuospatial learning partly overlap and, second, PD significantly hampers such resources. Moreover, these data suggest that motor and cognitive functions are not completely independent processes but share similar resources, implying that some motor and nonmotor parkinsonian signs might have common neural bases. Such results are important in designing novel rehabilitative approaches to improve specific aspects of motor performance and the quality of life of patients.

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REFERENCES

Psychogenic Paralysis and Recovery After Motor Cortex Transcranial Magnetic Stimulation

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Abstract: Psychogenic paralysis presents a real treatment challenge. Despite psychotherapy, physiotherapy, antidepressants, acupuncture, or hypnosis, the outcome is not always satisfactory with persistent symptoms after long-term follow-up. We conducted a retrospective study to assess clinical features and to propose an alternative treatment based on repetitive transcranial magnetic stimulation (rTMS). Seventy patients (44 F/26 M, mean age: 24.7 ± 16.6 years) experienced paraparesis (57%), monoparesis (37%), tetraparesis (3%), or hemiparesis (3%). A precipitating event was observed in 42 patients, primarily as a psychosocial event or a physical injury. An average of 30 stimuli over the motor cortex contralateral to the corresponding paralysis was delivered at low frequency with a circular coil. The rTMS was effective in 89% of cases, with a significantly better outcome for acute rather than chronic symptoms. In conclusion, motor cortex rTMS seem to be very effective in patients with psychogenic paralysis and could be considered a useful therapeutic option. © 2010 Movement Disorder Society

Key words: conversion disorder; motor paralysis; transcranial magnetic stimulation; motor cortex

Psychogenic disorders imply that the patient has no voluntary control over the production of symptoms, with no known organic syndrome to explain the symptoms. Psychogenic disorders are frequently related to the motor system,1 as psychogenic paralysis,2–6 and present a real treatment challenge.

The initial aim of this study was to evaluate clinical features of patients with psychogenic paralysis. We performed a retrospective study of 70 adults and children. The second aim was to assess a promising new
treatment based on repetitive transcranial magnetic stimulation (rTMS), which is known to modulate cortical excitability, for patients with psychogenic paralysis characterized by a decreased activation of the primary motor cortex. Motor-evoked potentials have been suggested to be useful in the diagnosis of psychogenic paralysis, as they are normal. As some patients, before the onset of this study, had recovered immediately after several magnetic stimulations used for diagnostic motor-evoked potentials, we decided to apply rTMS to these patients.

PATIENTS AND METHODS

Patients
We retrospectively reviewed the medical records of 70 patients with psychogenic paralysis who received therapeutic rTMS between April 1999 and November 2008 in the Neurophysiology Department of the Rouen University Hospital. The rTMS was used for routine diagnostic purposes for each patient. The study was approved by the local Ethics Committee. The nature, onset, duration of the symptoms, and precipitating events were recorded. We defined symptoms as acute or subacute symptoms, <30-day or >30-day duration at the moment of the rTMS administration, respectively.

The diagnosis was explained to each individual patient, particularly regarding the nature of “functional” paralysis, i.e., a nervous system dysfunction without lesion. TMS was introduced principally as a diagnostic test and sometimes as a treatment that could possibly alleviate their symptoms. We tried to avoid suggestion in most cases. We spent 15 minutes explaining and performing the rTMS session.

Methods
An average of 30 stimuli delivered at low frequency (the device allowed stimulation every 4–5 seconds) and maximal intensity of 2.5 Tesla were attempted with a circular coil (P/N 9784-00) during 2 to 3 minutes. Another session of 30 stimuli was sometimes delivered a few minutes later in cases of incomplete improvement. The rTMS was applied to the motor cortex opposite from the corresponding paralysis or on both sides for bilateral paralysis. The rTMS efficacy was classified in two groups: effective (total recovery or dramatic improvement) or ineffective (mild improvement or failure). Patient follow-up was performed in most cases by the general practitioner, pediatrician, or neurologist.

Statistical Analysis
To assess the influence of certain characteristics on outcome, the comparison of rTMS efficacy between different situations (men versus women, etc.) was measured using the Fisher’s exact test. The accepted significance level was $P < 0.05$.

RESULTS
Seventy patients (44 women and 26 men) were referred by different units: the Department of Pediatrics ($n = 28$), Neurology ($n = 19$), Neurosurgery ($n = 11$), Orthopedics ($n = 7$), Rheumatology ($n = 3$), and Emergency ($n = 2$). They were aged $24.7 \pm 16.6$ years (mean ± SD; minimum–maximum: 8–79 years). The majority of patients (41 patients, i.e., 59%) were adolescents (Fig. 1).

All patients experienced an abrupt onset or rapidly progressive onset of the paralysis. At least one precipitating event was observed in 42 of 48 patients for whom information was available: a physically traumatic event ($n = 12$, in the affected limbs [$n = 5$] or in a diffuse way [$n = 7$], with a minor injury for six patients); a psychosocial precipitating event ($n = 21$, death of a relative [$n = 2$], family conflict [$n = 11$], work conflict [$n = 3$], and academic problems [$n = 4$]); cephalalgia ($n = 8$); malaise ($n = 8$); unusual physical effort ($n = 3$); and an infection ($n = 2$).

The symptoms were a paraparesis ($n = 40$, 57%), monoparesis ($n = 26$, 37%), tetraparesis ($n = 2$, 3%), and hemiparesis ($n = 2$, 3%). Paraparesis affected significantly more children than adults ($P = 0.0003$) and monoparesis more adults than children ($P = 0.01$).

The motor symptoms were isolated ($n = 24$, 34%) or were associated with sensory symptoms ($n = 27$, 39%), with pain ($n = 11$, 16%), or with both sensory
symptoms and pain (n = 8, 11%). The symptoms median duration at the time of the consultation was 5 days (minimum–maximum: 1–1080, Fig. 2). The symptoms were acute in 55 patients (median duration: 4 days) and subacute (even chronic) in 15 patients (median duration: 240 days).

The patients’ medical history revealed the following: a comorbid psychiatric disorder (n = 28, anxiety and depressive disorders [n = 21], eating disorders [n = 3], and posttraumatic stress disorders [n = 4]); physical injury history different from the precipitating event (n = 15, in the same area of the current paralysis [n = 13] or in a diffuse way [n = 2]); “back trouble” (n = 10, sciatica, spinal injury, or surgery); a personal neurologic pathology (n = 8 with 6 migraine); or a familial neurologic pathology (n = 4).

The rTMS was effective in 62 patients (89%), with a total recovery in 53 patients (immediately after rTMS [n = 43], quasi-immediately [within a few minutes or hours, n = 8], and a few days later [n = 2]) or a dramatic improvement in nine patients. The rTMS was ineffective in eight patients (11%), with a mild improvement (n = 5) or a failure (n = 3). It was significantly more effective for acute symptoms than subacute symptoms (P = 0.009). No significant difference of rTMS outcome was observed between children and adults, men and women, symptoms characteristics, concerning the precipitating events, or patients’ medical history.

The symptoms recurred in eight patients, always with the same paralysis, with a single recurrence of paralysis (n = 5) after a 160-day average delay and multiple recurrences (n = 3) after a 150-day average delay. The rTMS was applied again in six of the eight patients with recurrence and was effective for all patients.

**DISCUSSION**

**Description of a Population with Psychogenic Paralysis**

Although many studies have described adults with psychogenic paralysis, data are most limited in children. As previously reported, the majority of patients were women. Paraparesis appeared twice as less in the literature probably because of the adult population. Only two patients (two adults) experienced a hemiparesis, whereas this symptom occurred between 32% and 47% in the previously described adult population, probably because of our predominant pediatric population. As previously described, tetraparesis was a rare symptom.

At least one precipitating event was observed in 42 patients, mainly a psychosocial precipitating event (work or familial conflict) or a physical injury, although of a trivial nature that could be sufficient to produce psychogenic symptoms.

As previously described, medical history revealed the importance of psychiatric comorbidity and organic disease (physical injury in the paralyzed limb and previous back problems) as risk factors for psychogenic paralysis.

**Efficiency of Repetitive TMS on Psychogenic Paralysis**

Limited evidence exists regarding the optimal choice of treatment in psychogenic disorders. In some patients with mild symptoms, explanation and reassurance with encouragement may be sufficient. In patients with more resistant symptoms, a combination of psychotherapy and physiotherapy may be helpful. Cognitive-behavioral therapy, antidepressants, hypnosis, and acupuncture can also be effective. Despite all these treatments, outcome is not satisfactory in all patients; 37% to 83% of patients continue to experience symptoms 2 to 16 years after diagnosis.

In our study, rTMS applied over the motor cortex is associated with a very good outcome in 89%. As previously described, the factor significantly associated with a favorable outcome was acute onset of symptoms, but not the age or the sex. In contrast to previous studies, we did not find a significant good outcome for patients with a comorbid psychiatric disorder. Despite an improvement in paralysis, a psychologic follow-up is sometimes required in certain patients.

Three studies have reported a therapeutic benefit from diagnostic and rTMS in patients with psychogenic paralysis. Four patients were treated with 15-
Hz rTMS sessions of motor cortex for 5 to 12 weeks,\(^{22}\) with variable benefits (one total recovery, two marked improvement, and one failure). We have previously reported a spectacular recovery immediately after only one session of low frequency rTMS (50 stimuli) over the motor cortex in a psychogenic aphonia.\(^{21}\) Why has rTMS proved so effective? First, the possibility of a placebo effect cannot be ruled out because of symptom variability in psychogenic paralysis and the possible symptoms attenuation or disappearance with suggestion and persuasion. Nevertheless, 89% of rTMS efficacy is impressive and seemed specific to rTMS, without the same efficacy for other therapies usually used.\(^{2,3,6,12}\) Second, rTMS delivered over the motor cortex produces a muscular activation, allowing the patient to become aware of the movement possibility that could help in their management. Third, we suggest that rTMS may have the ability to restore an appropriate cerebral connectivity by activating a suppressed motor cortex. Functional magnetic resonance imaging studies have demonstrated a decreased activation of primary motor\(^{7}\) and an increased activation of prefrontal regions,\(^{23}\) suggesting an active inhibition from prefrontal areas to primary motor areas.\(^{23–25}\)

**CONCLUSION**

Our results suggest that motor cortex rTMS could be an effective treatment in patients with psychogenic paralysis, although further randomized controlled trial versus placebo is necessary. Nevertheless, the physiopathologic and rTMS efficacy mechanisms of psychogenic disorders remain unknown.

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