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Refractory Head Movements Secondary to Sandifer Syndrome Treated with Enteral Feeding

Video 

Sandifer syndrome is a paroxysmal movement disorder characterized by abnormal movements of the head, neck, and trunk in association with gastroesophageal reflux disease (GERD).[1] Most cases are neurodevelopmentally normal children with symptom onset in early childhood, although some cases have been reported in adults. Infants often have retrocollis and opisthotonic posturing, whereas older children have the side-to-side head movements.[1,2] The movements usually respond to anti-reflux medications and/or fundoplication.[3] We present a case of Sandifer syndrome caused by GERD and delayed gastric emptying that was refractory to fundoplication and improved with enteral feeding. To our knowledge, this is the first published case of Sandifer syndrome being treated with enteral feeding.

A four-year-old boy presented with a 3 month history of abnormal side-to-side head movements (see Video Segment 1). The movements lasted less than 1 min and occurred many times per day. Apart from the movements, his neurological exam was unremarkable. An EEG, head CT, and MRI were unremarkable. No Kayser-Fleischer rings were noted via slit lamp, and a 24-hour urinary copper was normal. With the hypothesis that the movements were tics, clonidine was initiated with no effect.

Eventually, an association was noted between the movements and gastrointestinal symptoms such as abdominal pain and regurgitation. The child was started on lansoprazole empirically, titrated to a maximum of 45 mg/day with no effect. An upper gastrointestinal endoscopy and a gastric emptying study revealed reflux esophagitis and delayed gastric emptying. An esophageal pH probe demonstrated acid reflux with regurgitation and long periods of pH less than 4. Thus, the movements were thought to be a manifestation of Sandifer syndrome. Treatment with domperidone (5 mg, TID) appeared to make the movements worse.

Laparoscopic fundoplication was performed to treat his GERD, as medical therapy failed and was followed by laparoscopic pyloroplasty to improve gastric emptying. However, the movements persisted after both surgeries.

Eventually a naso-jejunal (NJ) feeding tube was inserted which was associated with significant improvement in the patient's movements (see Video Segment 2). Attempts to wean the patient back to feeding by mouth resulted in the return of the movements. As his symptoms improved, the NJ tube was switched to naso-gastric feeding tube, which was well tolerated. A gastrostomy tube was inserted and, after follow-up 3 years after his initial presentation, the patient continues to be predominantly enterally fed with some oral intake.

The first symptoms of Sandifer syndrome often resemble torticollis or dystonia, thus early evaluation usually focuses on neurological etiologies.[1] EEG, CT, and MRI studies are all usually normal. Tics, unlike the movements in Sandifer syndrome, are suppressible, can wax and wane, and can be associated with an urge to perform the movements. Sandifer movements are often precipitated by meals, unlike other movement disorders. A psychogenic etiology in our case would be extremely unlikely considering the young age of the patient.

Why some children with GERD present with abnormal movements and others do not remains unresolved. Research supports the theory that the movements are learned behaviors used by children to reduce reflux. One study showed that head tilting results in an increase in esophageal motility and decreased reflux.[4] Another found that abnormal movements only occurred when the pH of the esophagus was less than.[3] Finally, most reports of Sandifer syndrome describe near complete cessation of abnormal movements with fundoplication, performed to reinforce the function of the lower esophageal sphincter and reduce reflux.[3]

In our patient fundoplication failed to stop the abnormal movements, nor did pyloroplasty, done to improve the patient's delayed gastric emptying. It was not until an NJ tube was inserted for enteral feeding that a decrease in abnormal movements was observed. Enteral feeding is an established treatment for children with refractory GERD.[5] Although previous case studies have investigated gastric emptying in patients with Sandifer syndrome, only one found delayed emptying and neither required enteral feeding.[6,7] It is still unclear as to when our patient will be able to tolerate full oral feeding again although it is possible that the symptoms will improve on their own with time.

This case report demonstrates that even when associated with GERD, other features such as delayed gastric emptying may also result in the abnormal posturing characteristic of Sandifer syndrome. If initial treatments aimed at reducing reflux are unsuccessful, physicians may need to explore other options such as enteral feeding.

LEGENDS TO THE VIDEO

Segment 1. Patient's abnormal head movements at presentation.

Segment 2. Patient demonstrating cessation of abnormal head movements after initiation of enteral feeding.

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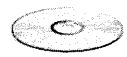
Chylomicron Retention Disease: Dystonia as a New Clinical Feature

Video 

Chylomicron retention disease (CRD) is a rare autosomal recessive disorder characterized by malabsorption, failure to thrive (FTT), developmental difficulties, mental retardation, abnormal vibration sense, and hyporeflexia.[1] Movement disorder has been reported only once.[2] Laboratory findings include fat-soluble vitamins deficiency, low cholesterol, and selective absence of chylomicrons. The diagnosis is made by electron microscopy of jejunal biopsy specimens demonstrating accumulation of lipid droplets in enterocytes. The majority of cases are caused by mutations of the *SAR1B* gene on chromosome 5.[3] We report 3 cases with biopsy proven CRD presenting dystonia as a new clinical feature.

The first patient was seen at age 49 for tremor in the context of CRD. Her family history is significant for consanguinity, an affected sister and the infantile death of 3 male siblings with prior history of FTT and developmental delay. She presented in early childhood with development delay, malabsorption, and FTT. Later, she was found to have learning difficulties and low average intellectual quotient. She developed a sensory polyneuropathy and a progressive cerebellar syndrome. She was diagnosed with CRD by small bowel biopsy at the age of 21 and started on fat-soluble vitamins. At the end of adolescence, she developed a slowly progressive dystonic tremor of the upper extremities, neck, and voice. The tremor was irregular in amplitude and frequency, with a sensory trick and zero position. A treatment trial with propranolol was performed with limited success.

The second patient was seen at age 50, also for tremor in the context of a known CRD. She is the sister of the first patient. Her clinical presentation, laboratory and jejunal biopsy results were very similar. She was less severely affected and developed a dystonic tremor of the head and upper extremities only in her early thirties.

The third patient was seen at age 47 for tremor in the context of CRD. His family history was significant for consanguinity. He presented in early childhood with malabsorption, slowly progressive cerebellar syndrome, and predominantly sensory polyneuropathy. He was diagnosed with CRD by jejunal biopsy at the age of 6. At the end of adolescence, he developed a slowly progressive and disabling dystonic tremor of the left more than right upper extremities (Supporting Information video 1a), head, and voice. Because of suboptimal response to several medications, a deep brain stimulator (DBS) was implanted in the right ventrolateral thalamus. Following surgery, both the proximal and distal components of his tremor were significantly reduced (Supporting Information video 1b) and the patient regained use of his left hand.

The pathophysiology of CRD is not well understood. The clinical manifestations may be secondary to malabsorption, which leads to deficiency in important vitamins and nutrients. Deficiency in vitamin E is the most likely cause of the cerebellar ataxia and sensory neuropathy, as seen in other conditions such as AVED (Ataxia with isolated Vitamin E Deficiency) and abetalipoproteinemia.[4] Dystonia has been reported as a clinical feature of AVED[5] but not of abetalipoproteinemia, suggesting that the pathophysiology of dystonia involves probably more than the vitamin E deficiency alone. We hypothesize that a dysfunction of the cortico-striato-pallido-thalamo-cortical circuits is implicated in the pathophysiology, as in other forms of secondary dystonia, and as supported by the improvement seen with stimulation of the ventrolateral thalamus.

Levy et al. postulated that CRD was secondary to a defect in the formation and secretion of chylomicrons, resulting from a defect in glycolysation.[6] In 2003, Jones et al.[3] identified mutations in the *SAR1B* gene in 10 cases. This gene encodes for a protein belonging to a family of small GTPases called the

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Sar1-ADP-ribosylation factor family.[7] This family of proteins is responsible for the intracellular trafficking of proteins in coat protein (COP)-coated vesicles. SAR1B is ubiquitously expressed; its expression has been demonstrated in several tissues including the brain. The relation between the defective gene and the clinical manifestations is not well understood.

This article is the first to report dystonia (dystonic tremor) as a clinical manifestation of CRD. Similarly to cases with essential and resting tremors, ventrolateral thalamus stimulation was effective and well tolerated.

Legends to the Video

Video 1a. Patient 3: important dystonic tremor involving more the left than the right upper extremity.

Video 1b. Same patient, after implantation of a deep brain stimulator in his right ventrolateral thalamus.

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Long-Term Suppression of Meige Syndrome After Pallidal Stimulation: A 10-Year Follow-Up Study

Video 

Meige syndrome is an adult-onset, idiopathic movement disorder that manifests as blepharospasm, facial and oromandibular dystonia, and frequently cervical dystonia.[1] This syndrome is often refractory to medication, and some patients do not adequately respond to botulinum toxin therapy. There is now an increased interest in the use of globus pallidus internus (GPi) deep brain stimulation (DBS) for medically refractory, generalized or segmental dystonia.[2] However, little is known about its effects in the treatment of other types of dystonias such as focal dystonia. In addition, the use of GPi-DBS for the treatment of Meige syndrome has rarely been reported.[3–7] Here, we report a long-term outcome of the patient in whom we first showed a striking impact of bilateral GPi-DBS on dystonia symptoms characteristic of Meige syndrome 10 years ago.[3]

The patient was a 71-year-old woman with no history of exposure to neuroleptics and no family history of dystonia. She experienced a gradual onset and exacerbation of blephar-

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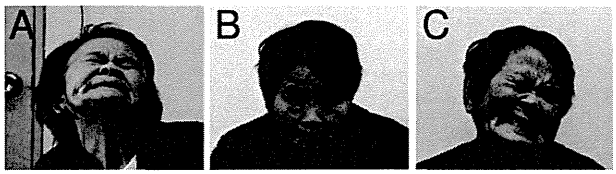

FIG. 1. Long-term effects of bilateral pallidal stimulation on Meige syndrome. A: Preoperative state. B: Postoperative state at the time of the 10-year follow-up: with bilateral GPi-DBS. C: Postoperative state at the time of 10-year follow-up: without bilateral GPi-DBS.

ospasm and oromandibular dystonia at age 43. At age 51, she was diagnosed with Meige syndrome at another hospital, and subsequently underwent two-stage operations for Vo complex (Voa + Vop) thalamotomy on the right and left sides. However, bilateral thalamotomy was not beneficial to this patient. In addition, multiple sequential pharmacological trials produced unsatisfactory results.

At the age of 61 years, she underwent bilateral GPi-DBS. Before the surgery (Fig. 1A and video segment 1), she manifested marked facial grimacing with excessive blinking and sustained forceful eye closure, and severe cervical dystonia characterized by turning and tilting of the head in the right and posterior directions. She also exhibited trunk bending toward the right and a mild dystonic tremor in the right arm. Her preoperative scores for the Burke-Fahn-Marsden Dystonia Movement Scale (BFMDRS) Movement and Disability Scales were 35 and 23, respectively (Table 1). Magnetic resonance images did not show any obvious abnormalities, except for the presence of previous surgical lesions in the thalamic nuclei on the right and left sides.[3] Under general anesthesia with propofol, quadripolar DBS electrodes (Model 3387; Medtronic, Minneapolis, MN) were implanted into the bilateral GPi. Furthermore, after confirming the beneficial effects of GPi-DBS, we implanted a receiver for the external transmitter (Mattrix Transmitter Model 3272; Medtronic). The postoperative course was uneventful. Optimal therapeutic results were obtained when the system was operated using the maximum pulse width of 500 μs, an amplitude of 3.6 V, and a frequency of 60 Hz.[3] Bilateral pallidal stimulation immediately improved the symptoms of mobile dystonia such as blepharospasm, facial grimacing, and phasic head movement. With continuous stimulation, the patient's fixed postural dystonias, such as cervical retrocollis and trunk bending, were gradually ameliorated and almost completely disappeared within a few months after the initiation of GPi-DBS (Table 1). The differential responses of the phasic and fixed dystonias to treatment with GPi-DBS in our patient supported the general thought that phasic hyperkinetic movements are ameliorated more rapidly than fixed tonic postures are after treatment with GPi-DBS.[2]

To avoid the inconvenience and troublesomeness caused by the use of external batteries, implantable pulse generators (IPGs; Itrel 3, Medtronic) were used instead of the Mattrix transmitter systems when the patient was 63 years old. In many trials wherein monopolar stimulation at an amplitude of less than 3.7 V was applied using IPGs, the results were unsatisfactory. Optimal benefits were derived when bipolar stimulation was applied using a pulse width of 450 μs, frequency of 60 Hz, and pulse amplitude of 3.9 and 3.6 V on the right and left sides, respectively (Table 1). After bilateral GPi-DBS, the patient's BFMDRS movement and disability scores were 5 and 4, respectively. Because continuous stimulation at an amplitude of 3.9 V shortened the battery life on the right side, the IPGs had to be replaced within 2 years. Bilateral pallidal stimulation resulted in sustained suppression of Meige syndrome until the time of the 10-year follow-up (Fig. 1B and video segment 2). Furthermore, we noted that dystonic symptoms, similar to those observed at the preoperative stage (Fig. 1C and video segment 3), were reproduced in this patient immediately after the IPGs were switched off.

GPi-DBS has emerged as the treatment of choice for patients with disabling dystonias; however, very little is known about its long-term effects in patients with different subtypes of dystonia. This study showed that in a patient with Meige syndrome, bilateral GPi-DBS resulted in a sustained, long-term improvement in both the movement and disability scores measured using the BFMDRS: these scores had improved by more than 80% at the time of the 10-year follow-up. We propose that bilateral GPi-DBS is an effective and a safe procedure that has long-lasting benefits in patients with Meige syndrome.

Legends to the Video

Segment 1. Preoperative state.

Segment 2. Postoperative state at the time of the 10-year follow-up: with bilateral GPi-DBS.

TABLE 1. *Deep brain stimulation status and impact on dystonia rating scale scores*

		DBS programming parameters (contacts/voltage/PW/freq)		BFMDRS	
Evaluation stage	DBS device	Right brain	Left brain	Movement score	Disability score
Preoperative state				35	23
Postoperatve 1 wk	Extrel with mattrix	1(−)3(+)/3.6 V 500 μS/60 Hz	1(−)3(+)/3.6 V 500 μS/60 Hz	7 (ON)	6 (ON)
Postoperative 3 mo	Extrel with mattrix	1(−)3(+)/3.6 V 500 μS/60 Hz	1(−)3(+)/3.6 V 500 μS/60 Hz	6 (ON)	4 (ON)
Postoperative 3 yr	Itrel 3	1(−)3(+)/3.9 V 450 μS/60 Hz	1(−)3(+)/3.6 V 450 μS/60 Hz	5 (ON)	4 (ON)
Postoperative 10 yr	Itrel 3	1(−)3(+)/3.9 V 450 μS/60 Hz	1(−)3(+)/3.6 V 450 μS/60 Hz	5 (ON) 36 (OFF)	4 (ON) 24 (OFF)

PW, pulse width (μS); freq, frequency (Hz); BFMDRS, Burk-Fahn-Marsden dystonia rating scale; wk, weeks; ON, on stimulation; mo, months; yr, years; OFF, off stimulation.

Segment 3. Postoperative state at the time of the 10-year follow-up: without bilateral GPi-DBS.

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Retraining and Transcranial Direct Current Stimulation in Musician's Dystonia — A Case Report

Focal dystonia in musicians (MD) is a task-specific movement disorder, which presents itself as a loss of motor control during instrumental playing.[1] Deficient inhibition at different levels of the CNS is involved in the pathophysiology.[2] MD is difficult to treat and retraining strategies aiming to establish non-dystonic movements have contradictory outcomes.[1,3] As acquisition of new motor skills is accompanied by changes of neuronal activity and excitability, transcranial direct current stimulation (tDCS) might be a tool to assist retraining. Anodal tDCS enhances, whereas cathodal tDCS reduces cortical excitability.[4,5] Hereby, anodal tDCS has been shown to facilitate motor learning, whereas cathodal tDCS improves performance in overlearned tasks.[4,5] Daily repeated application prolongs effects.[6] The aim of the study was to investigate whether repeated tDCS improves retraining effects in a pianist with MD either by anodal or by cathodal tDCS.

The patient was a male professional pianist aged 43. He had been suffering from a finger flexion dystonia of the right hand for 15 years. Other neurological disorders were excluded, and he was not under pharmacological treatment. Motor learning consisted of a retraining on the piano (20 min per day) based on following principles: (1) finger movements were limited to a tempo and force at which dystonic movements would not occur; (2) compensatory movements (e.g., of adjacent fingers) were avoided as far as possible. During retraining, the patient received tDCS. The study was placebo controlled and double blinded. Three treatment conditions were applied for 5 days consecutively with 6 weeks between conditions: 20 min retraining plus anodal tDCS, plus cathodal tDCS, or plus placebo stimulation. The stimulating electrode was placed over the left primary motor cortex (C3 according to the international 10–20 system) and the reference electrode over the right supraorbital area. Current strength was 2 mA for the active conditions and 0.2 mA (fading out after 20 seconds) for placebo. tDCS was induced through sponge electrodes (surface 35 cm^2) and delivered by a constant-current stimulator (eldith GmbH, Germany). Stimulation conditions were randomly assigned: 1. placebo, 2. anodal, and 3. cathodal tDCS. Motor control was assessed by MIDI-based scale analysis, a reliable and valid quantification of motor control in pianists with MD.[7] The patient played 10 C-major scales with the affected hand in a metronome-paced tempo over

Franziska Buttkus and Volker Baur contributed equally to this work.

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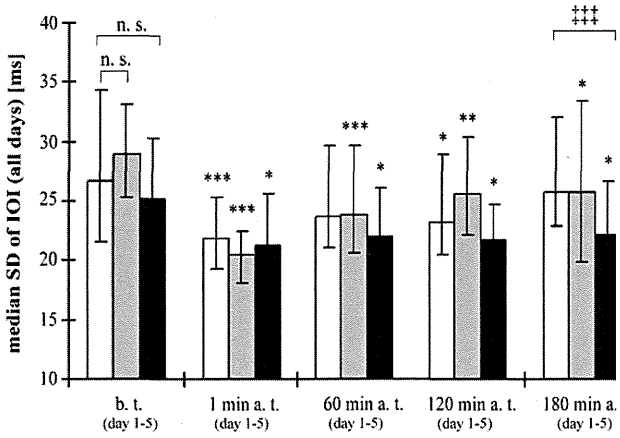

FIG. 1. Results of tDCS effects on retraining in a pianist with musician's dystonia. Bars show motor performance as the median SD of inter-onset intervals (IOI). High values indicate poor motor control and vice versa. Treatment condition is displayed as open bars for retraining and placebo tDCS, as light gray bars for retraining and anodal tDCS, as dark gray bars for retraining and cathodal tDCS. Whiskers depict the 25th and the 75th percentiles of data. b.t.: before treatment; a.t.: after treatment. The median SD of IOI of all performance tests of 5 days is displayed for each treatment condition and time. Asterisks depict motor performance after treatment vs. before treatment: $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ (Mann-Whitney-U, Bonferroni-Holm-corrected). Intertreatment comparisons between active and placebo conditions: $‡‡‡P < 0.001$ for cathodal vs. placebo (Mann-Whitney-U, Bonferroni-Holm-corrected).

two octaves (desired inter-onset interval 125 ms). Standard deviation (SD) of inter-onset intervals (IOI) was used as target parameter.[7] Motor control was assessed before and after treatment (1 min, 60 min, 120 min, and 180 min after end of treatment). Mann-Whitney-U tests were applied to analyze performance differences ($\alpha = 0.05$). Correction of multiple comparisons was done according to Bonferroni-Holm.

Treatment results were assessed by the median SD of IOI of respective time points of all days (Fig. 1). Baseline motor control did not differ between conditions. In the placebo condition, motor control was improved 1 min ($P < 0.001$) and 120 min ($P < 0.05$) after treatment as compared to before treatment. In the anodal condition, motor control was improved 1 min ($P < 0.001$), 60 min ($P < 0.001$), 120 min ($P < 0.01$), and 180 min ($P < 0.05$) after treatment. In the cathodal condition, motor control was improved 1 min, 60 min, 120 min, and 180 min after treatment (each $P < 0.05$). Intertreatment comparisons revealed a better performance outcome in the cathodal condition compared to placebo 180 min after treatment ($P < 0.001$).

We observed a beneficial effect of retraining on fine motor control in the reported patient, which was enhanced by cathodal tDCS. Improved motor control after treatment was found in all three conditions and was most pronounced immediately after retraining (Fig. 1). The intertreatment comparison suggests that cathodal tDCS may prolong retraining effects. In contrast, anodal tDCS did not enhance retraining effects beyond placebo stimulation. Inhibitory mechanisms related to movement preparation and execution are crucial for fine motor control and disturbed in patients with MD.[1] Thus, the inhibitory effect of cathodal tDCS might have facilitated physiological inhibition in this patient. A similar mechanism with improvement of visuomotor performance was seen after cathodal tDCS of V5 in healthy subjects, probably due to an increased signal-to-noise ratio.[5] As a limitation, cumulative retraining effects in the cathodal stimulation week (3rd week) might have influenced the outcome. In summary, retraining seems to be a promising tool with therapeutic potential. Repeated cathodal tDCS might facilitate retraining-based treatment. Studies on large numbers of patients are required to identify optimal retraining strategies and to clarify effects of repeated tDCS on retraining in patients with MD.

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Levodopa-Induced Belly Dancer's Dyskinesias in Parkinson's Disease: Report of One Case

Video 

Focal dyskinesias affecting the abdominal wall were first described by Iliceto et al.[1] and named "belly dancer's dyskinesias." So far, only a few cases have been reported, following an abdominal surgical procedure or local trauma,[1,2] prolonged antidopaminergic treatment,[3] central pontine and extra-pontine myelinolysis,[4] or as a result of spinal myoclonus[5,6] and spinal tumors.[7]

Herein, we report a 72-year-old woman with Parkinson's disease (PD) who developed belly dancer's dyskinesias in the context of dopaminergic therapy. To our knowledge, this is the first report of Levodopa (L-dopa)-induced belly dancer's dyskinesias in PD. Patient's consent was provided for the writing of this manuscript and video filming.

When she came to our attention, the patient had a six-year history of PD whose onset was characterized by bradykinesia and rigidity in the left upper limb. She was initially started on Ropinirole 0.5 mg twice a day, and L-dopa/Carbidopa 100/25 mg a day was then added to improve her motor performances. Six months prior to admission to our department, L-dopa was increased up to 200 mg a day in a controlled release formulation, and she was switched to Pramipexole 0.18 mg twice a day due to an unsatisfactory control of motor symptoms.

On admission, the examination showed continuous, not suppressible writhing movements of the abdominal wall which got worse while standing, causing a circular displacement of the umbilicus. They were not affected by respiration or breath-holding and ceased at night without being associated with local pain or abdominal discomfort. They started around 30 minutes after each L-dopa intake lasting about 3 hours. The neurological examination showed a short-step, shuffling gait with reduced arm swings bilaterally, moderate bradykinesia and rigidity in upper and lower limbs more marked on the left side, and cogwheel phenomenon in both elbows.

A magnetic resonance imaging of the spinal cord showed no structural abnormalities, and a computed tomography scan of the brain only revealed diffuse subcortical hypodense small lesions consistent with chronic vascular damage.

To investigate the neurophysiological features of the abdominal dyskinesias, an EEG-EMG recording was performed, and the back averaging technique did not demonstrate any time-locked correlate. Needle electromyography of both recti abdominis and external oblique muscles showed spontaneous bilateral synchronous bursts lasting 220 to 400 millisecond that occurred at variable intervals of 0.5 or 1 second.

To demonstrate the chronological correlation between L-dopa intake and the onset of abdominal dyskinesias, its administration was suspended for two consecutive days, with a complete cessation of abdominal movements. Pramipexole was increased up to 0.7 mg three times a day, and the patient

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was discharged with no abdominal dyskinesias. However, she resumed a single dose of L-dopa/Carbidopa 100/25 mg and developed end of dose deterioration and again abdominal dyskinesias with some mild distal dyskinesias in the lower limbs.

On readmission, an acute L-dopa challenge confirmed the onset of abdominal dyskinesias around 90 minutes after the L-dopa intake with duration of 3 hours. UPDRS III was 27 in the "off" phase, 20 one hour after L-dopa intake and 14 two hours later.

She was started on L-dopa/Carbidopa/Entacapone (50/12.5/200 mg) three times a day, Rasagiline 1 mg per day, and Pramipexole was maintained at the same dose. This therapy significantly reduced but did not entirely suppress the abdominal dyskinesias.

Peak dose and, less frequently, diphasic dyskinesias are a well-known motor complication of long-term L-dopa treatment, consisting of involuntary choreiform movements or dystonic postures usually involving neck, trunk, and upper limbs. Abdominal dyskinesias following L-dopa treatment have only been described in a patient affected by Multiple System Atrophy so far.

In our patient, belly dancer's dyskinesias were secondary to L-dopa exposure and intriguingly one case has been reported after chronic antidopaminergic treatment (Clebopride),[3] suggesting that a nonphysiological stimulation of postsynaptic dopaminergic receptors due to the use of exogenous L-dopa or antidopaminergic drugs may play a role in the genesis of abdominal dyskinesias. Interestingly, no cases of belly dancer's dyskinesias after chronic neuroleptic use have been reported so far.

In cases with no structural abnormalities of the spinal cord, the pathophysiology of belly dancer's dyskinesias has been explained with a dysfunction of inhibitory spinal interneurons or structural reorganization of local neuronal circuits.[1,2] In our case, given the clear temporal correlation between L-dopa intake and the onset of dyskinesias, these mechanisms are unlikely to have played a significant role.

LEGENDS TO THE VIDEO

Abdominal dyskinesias (belly dancer's dyskinesias) after acute L-dopa challenge. A partial spreading to the trunk and the lower limbs and some mild distal dyskinesias in the left foot are also visible.

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Parkinson's Disease Rehabilitation: A Pilot Study with 1 Year Follow Up

There is emerging evidence of the positive acute effects of intensive rehabilitation treatments to improve motor aspects of patients with Parkinson's disease (PD).[1] However, whether the effects of rehabilitation persist over time or not remains an open question.

In this pilot study, we tested in 20 PD patients whether the effects of our rehabilitation protocol are maintained over a 12 months follow up period, and investigated whether a second rehabilitation cycle administered after 1 year has the same efficacy as the first treatment. Inclusion criteria were: Hoehn-Yahr Stage 3, ability to walk without physical assistance and mini-mental state examination score ≥26.

All patients reported in the last year a deterioration of motor performance despite increase of Levodopa (L-dopa) dosages (average increase 90.18 mg/die).

The patients underwent an intensive 4-week cycle of physiotherapy that entailed 2 daily sessions, 5 days a week, in which standard physical therapy techniques were associated with treadmill training and auditory and visual cues.[1]

Clinical evaluation at baseline and at the end of the rehabilitation treatment was based on the Unified Parkinson's Disease Rating Scale II and III Section (UPDRS II and III), Berg Balance Scale (BBS), Timed "Up and Go" test (TUG), Comfortable Gait Speed (CGS), and Fast Gait Speed (FGS).

All patients were readmitted 1 year later, and underwent the same rehabilitation protocol and the same clinical evaluations. During this 1 year period, patients were managed by their own neurologists, with no indications from our Hospital. There was no patient attrition and compliance was good for all patients.

The time course of each clinical variable considered was assessed by repeated measurements analysis of variance with four repeated measurements: first admission, first discharge, second admission (after 1 year) and second discharge.

The demographic and clinical characteristics of studied patients are reported in Table 1. The performance of patients improved significantly by the end of the first rehabilitation cycle for all variables ($p < 0.0001$). At the second admission (after 11.8 ± 1.5 months) most parameters had returned to values similar to those of the first admission, but all improved again at the end of the second rehabilitation program.

L-dopa equivalent dosage at second admission was slightly reduced (588 ± 308 mg/die versus 633 ± 291 mg/die, $p = 0.12$).

The importance of these results can be appreciated considering the chronic-degenerative nature of PD. A recent study showed that, despite optimal treatment, UPDRS III score worsened after one year in 26% of PD patients and L-dopa dose had to be increased in 52%.[2] Also our patients reported a deterioration of motor performance in the year preceding enrolment, despite a documented significant increase of drugs dosage, which was >75 mg/die in 55% of them.

In this study, we have demonstrated that the beneficial effects of our intensive rehabilitation treatment persist over a 12 months follow up period, reducing the need for increasing L-dopa doses.

Both peripheral and central mechanisms are likely to be involved in the improvement of our patients. With regards to the first mechanism, exercise training is associated with pulmonary, cardiovascular, and skeletal muscle metabolic adaptations that have sustained beneficial effects on patients. Exercise training might increase muscle oxidative capacity, normalize skeletal muscle metabolism, and reduce oxidative stress. Moreover exercise reduces all peripheral risk factors, improving cardiovascular health, cholesterol levels, insulin sensitivity, and inflammation.[3]

The hypothesis of an involvement of central mechanisms is supported by data from clinical studies suggesting that high intensity exercise may be important in promoting activity-dependent neuroplasticity in the basal ganglia. Animal experiments provided evidence that exercise has a neuroprotective effect against neurodegenerative diseases.[4] A direct effect of exercise on the level of several growth factors has been shown,[5] and a beneficial effect of exercise on Parkinsonism in animal model was demonstrated.[6] Both central and peripheral effects of exercise improve brain health modulating growth factor signaling: exercise increase growth factor levels and reduce pro-inflammatory conditions, which impair

TABLE 1. *Demographic and clinical characteristics of the patients*

	First admission	First discharge	Second admission	Second discharge
Age (years)	71 ± 8			
Male/female	8/12			
Duration of disease (years)	7.8 ± 2.7			
L-Dopa equivalent (mg/die)	633 ± 291		588 ± 308	
UPDRS III score	22.8 ± 6.8	15.9 ± 5.5	22.0 ± 5.2	16.9 ± 3.8
UPDRS II score	14.6 ± 5.1	9.7 ± 5.1	13.9 ± 5.4	11.2 ± 5.0
BBS score	46.2 ± 6.9	51.0 ± 6.4	45.8 ± 7.5	50.8 ± 5.1
TUG score (s)	12.4 ± 2.3	9.7 ± 2.4	12.2 ± 2.5	9.5 ± 2.0
CGS score (s)	12.1 ± 2.3	10.2 ± 1.7	11.7 ± 2.3	9.5 ± 1.5
FGS score (s)	9.4 ± 1.7	7.8 ± 1.2	8.9 ± 1.4	7.5 ± 1.4

Demographic and clinical characteristics of the patients, at first admission, at first discharge after 4 weeks of in hospital rehabilitation programme, at second admission after about one year and at second discharge after another 4 weeks rehabilitation programme. Data were available for all of the participants at all of the time points.

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growth factor signalling.[7] However, further studies are needed to assess whether intensive treatment such as ours might determine significant and long-lasting changes in dopaminergic transmission.

In conclusion, our preliminary results suggest that the natural worsening of symptoms associated with PD can be effectively contrasted by a properly designed intensive rehabilitation protocol. If these findings will be confirmed in larger studies with proper experimental design, the association of periodic cycles of intensive rehabilitation with pharmacological treatment should be considered as a valid option to delay the increase in drugs dosage and the beginning of related adverse effects.

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