Movement Disorders
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Letters to the Editor Related to New Topics

Neurochemical Biomarkers in the Differential Diagnosis of Movement Disorders

Recently, Mollenhauer and Trenkwalder,[1] in an extensive and critical review of CSF biomarkers in the differential diagnosis of movement disorders, stated that differences of total tau (TT) between PD and PDD are only marginal, but elevated in both dementia with Lewy bodies (DLB) and multiple system atrophy (MSA), whereas CSF Aβ-42 in PD (no dementia) is normal or only slightly decreased, and regularly decreased in both DLB and MSA. These data can be confirmed by personal studies in a small cohort of patients, in whom both CSF Aβ-42 and total tau protein were measured.

The sample included (1) 10 patients who fulfilled the UK Parkinson Brain Bank criteria for clinically definite PD[2] (8 males, 2 females aged 46–76, mean 63.2 ± 7.8 years), all Hoehn & Yahr stages III or IV, none being demented; (2) 12 patients (6 males, 8 females, aged 71–88, mean 77.9 ± 8.3 years) with the clinical diagnosis of secondary parkinsonism related to vascular encephalopathy or suspected vascular parkinsonism[3]; (3) 3 patients with atypical parkinsonism fulfilling the diagnostic criteria of MSA-P[4] (2 males, 1 female aged 53–70, mean 61.3 ± 7.1 years); (4) 2 males (age 63 and 84, mean 73.5 years) fulfilling the criteria of probable DLB.[5] The control group consisted of 17 age-matched patients without neurologic or psychiatric disorders (mean age 60.7 ± 1.5 years), while 27 patients (mean age 68.7 ± 2.1 years) were diagnosed probable Alzheimer disease (AD) according to the NINCDS-ADRDA criteria.[6] Examination of lumbar CS was performed using ELISA methods for Aβ-42 and TT immunoreactivity (Innogenetics, Belgium)—for methods see Ref. 7.

The results are summarized in Table 1. In both PD patients without dementia and in those with vascular pseudoparkinsonism, both CSF Aβ-42 and TT levels were only insignificantly increased, but significantly differed from those in AD. The mild increase of CSF Aβ-42 is at variance to the findings by others (see 1), as were our findings in a small group of patients with atypical parkinsonism (MSA-P), indicating increased CSF Aβ-42 without considerable changes in TT immunoreactivity. These levels considerably differed from the 2 demented patients with DLB, where Aβ-42 was mildly decreased and TT-IR was significantly—around twofold—increased versus controls and PD patients ($P < 0.01$). This suggested additional AD-related changes, although CSF levels of both Aβ-42 and TT differed significantly from those in AD. The latter findings are in accordance with those by others, who either reported decreased Aβ-42 and normal tau levels in DLB or normal Aβ-42 and decreased phosphorylated tau (see 1). In conclusion, considering the variability in Aβ-42 and TT levels in CSF in various types of movement disorders, further prospective clinico-pathological correlative studies using modern proteomics are needed to further elucidate the validity and to increase the sensitivity and specificity of CSF markers in movement disorders.

TABLE 1. *Concentrations of CSF Aβ-42 and TT-IR in the study group of Parkinsonian disorders*

Diagnosis	n	Aβ-42 (pg/mL) (m ± SD)	TT-IR (pg/mL) (m ± SD)
PD without dementia	10	734.0 ± 61.3	274.0 ± 46.7
Symptom. parkinsonism (vascular)	12	718.1 ± 47.2	280.0 ± 34.6
Atypical parkinsonism (MSA-P)	4	836.3 ± 24.2[b]	260.3 ± 24.2
DLB/LBV/AS	2	598.0 ± 64.4[c]	558.0 ± 58.2[a,c]
Controls	17	658.0 ± 41.0	223.8 ± 19.6
Late onset AD	27	376.0 ± 22.7	760.5 ± 78.3

[a] $P < 0.01$ vs. controls.
[b] $P < 0.05$ vs. controls.
[c] $P < 0.01$ vs. AD.

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Identification of a De Novo Mutation in *SPG11*

Autosomal recessive spastic paraplegia with thin corpus callosum (MIM 604360) is a complicated form of HSP characterized by the degeneration of the pyramidal tract, the presence of an atrophied, thin corpus callosum (TCC), and white manner abnormalities (WMA) at brain MRI.[1] The disease is commonly associated with mutations in the *SPG11* gene (MIM 610844), encoding spatacsin,[1,2] on chromosome 15q.

We recently reanalyzed the case of a girl harboring two heterozygous mutations in *SPG11* (i.e., c.3075_3076insA/p.E1026RfsX1029 in exon 17 and c.5470C > T/p.R1824X in exon 30) to assess the segregation of the mutations within the family. The proposita showed deterioration in school performance and gait disturbance at age 10 and 14 years, respectively. The disease progressed insidiously to a severe disability at age 24 years (SPRS[3] score 32/52). EMG and nerve conduction velocity (NCV) studies showed mild axonopathy. Brain MRI disclosed TCC, periventricular WMA and cortical atrophy in frontal lobe regions.[4]

Whilst the variant in exon 17 was also heterozygous in peripheral blood DNA from the proposita's father, the c.5470C > T mutation was not detected in any other member of this family (Fig. 1A). A posteriori haplotype analysis with markers flanking the SPG11 locus confirmed the segregation of the first variant and suggested a de novo origin for the second mutation (Fig. 1B). Four genetic markers (*DXS1219*, *DXS8077*, *DXS8084*, and *DXS1185*) on chromosome X as well as polymorphic markers on chromosome Y were also used to exclude nonparenthood. Somatic mosaic in tissues other than blood from the mother was ruled out using an allelic discrimination assay of the exon 30 mutation with two allele-specific TaqMan MGB probes run on ABI 7500 real-time PCR (Applied Biosystems, Foster City, CA). As shown

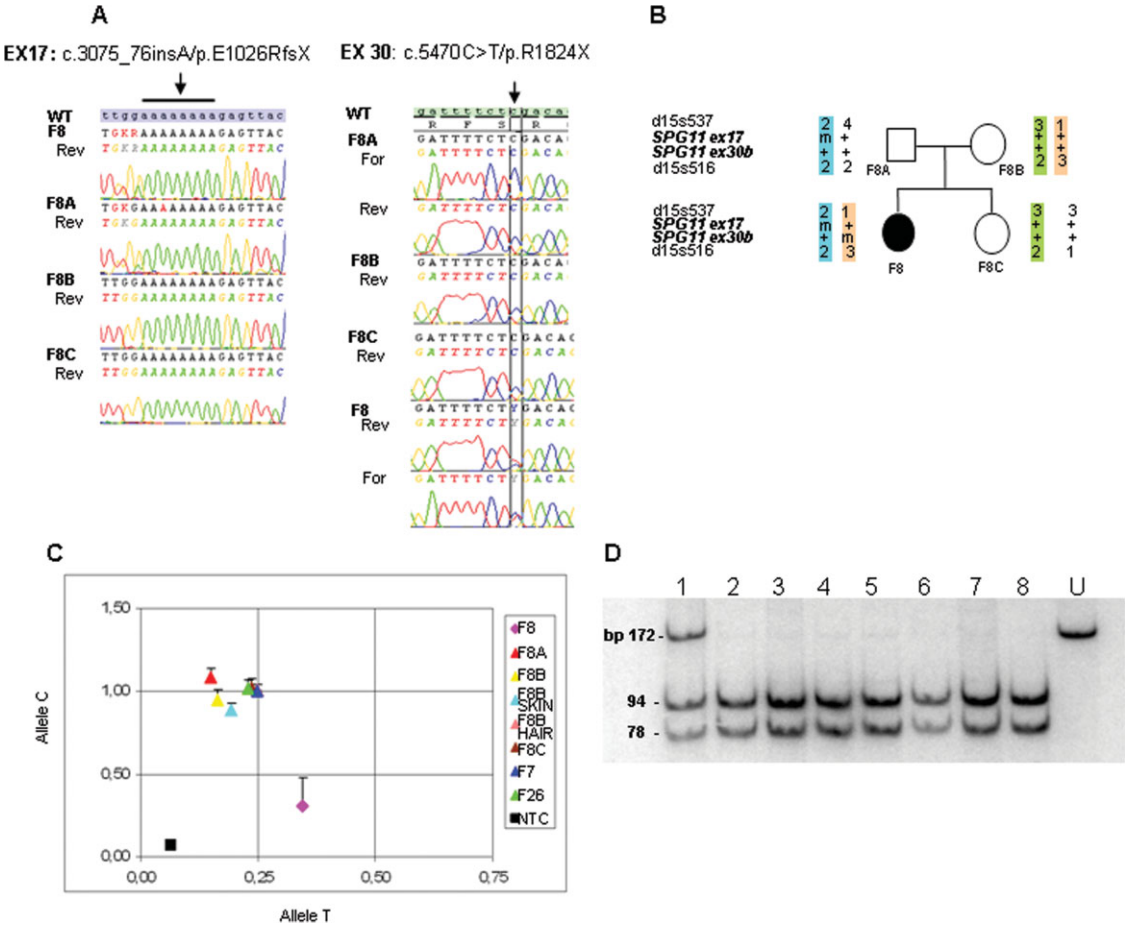

FIG. 1. (**A**) Electropherograms and (**B**) pedigree of the two *SPG11* mutations segregating within the family with the two flanking markers *D15S537* and *D15S516*. (**C**) Allelic discrimination assay plot. NTC, no template amplicon. (**D**) Radiolabeled-PCR-RFLP on exon 30. U, uncut PCR fragment.

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TABLE 1. *Primers (5′–3′) and probes sequence for allele-discrimination assay and PCR conditions for the semiquantitative determination of the c.5470C > T in exon 30 of the SPG11 gene*

		Annealing temperature (°C)
Taq Man assay		
Forward primer	TGGAAGAAATCA GGAGGAAACAG	65
Reverse primer	AAACTCACTGGCT AAACTATCAAAGG	65
Wild-type probe	CCCAGATTTTCTCGAC	65
Mutant probe	CCCAGATTTTCTTGACAG	65
PCR-RFLP assay		
Forward primer	TAAGCTGGAGGAGCTGGAGA	58
Reverse primer	GAGCAGCCAACTTGGAGAAG	58

in Fig. 1C, two healthy controls (F7 and F26), the father of the proposita (F8a), the healthy stepsister (F8c), and all the samples obtained from the mother (F8b) presented only the wild-type allele. On the contrary, the proposita (F8) harbored both the wild type and the mutant alleles. This finding was also corroborated by semiquantitative determination of the relative amount of wild-type and mutant alleles adopting a radiolabeled-*Taq* I-PCR-RFLP method.[5] As shown in Fig. 1D, in normal conditions the endonuclease *Taq* I cleaves the 172-bp PCR amplicon flanking the c.5470C > T mutation in fragments sized 94- and 78-bp. This pattern is observed in the control, the father, and the stepsister (lanes 8, 2, and 7, respectively) as well as in samples from the mother (lane 3: peripheral blood, lane 4: skin fibroblasts, lane 5: hairy roots, lane 6: urinary epithelial cells). In the proposita (lane 1), the presence of the heterozygous mutation removes the single site of cleavage and produces fragments sized 172-, 94-, and 78-bp. Table 1 shows sequences of oligonucleotide primers and probes and PCR conditions for both experiments.

As a whole, this case appears to be the first evidence of a de novo origin of mutations in *SPG11* but it is presently unclear how this happened.[6] The *SPG11* variant described affects a cytosine in a CpG dinucleotide, which is known to be more prone to mutate to thymine by spontaneous deamination.[7] Other factors could also been implicated such as sequence composition, repetition of DNA, ability to bind proteins important in pairing, or recombination. However, no repeated sequences surround nucleotide position c.5470 in *SPG11*. An age effect of the parents, eventually correlated with errors arising during mitotic oogonial or spermatogonial proliferation,[6] was also excluded in this family. On the other hand, the location of *SPG11* on a chromosome known to be prone to imprinting and frequent de novo origin of mutations such as in the case of the Prader-Willi/Angelman and Marfan syndromes,[8] or the large genomic region encoding spatacsin[2] could be possible explanations. Regardless of the mechanisms, we believe that the identification of a de novo variant in *SPG11* has two practical consequences. First, it expands the complexity of mutations detected in ARHSP-TCC. Second, it will alert neurologists when counseling at-risk individuals since most *SPG11* mutations are found in sporadic cases; this information might modify antenatal options of at-risk individuals to avoid recurrence of the disease.

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Psychogenic Chorea Associated with Family History of Huntington Disease

Video 

In contrast to other movement disorder phenotypes, psychogenic chorea has not been previously reported except in a brief description in 1951 in which "chorea," characterized as "marked jerking of her trunk and limbs," was attributed to a "conversion reaction.[1]" However, without actually examining the patient or at least viewing a video, it is difficult to be certain that the reported disorder is chorea or some other hyperkinetic movement disorder.[2] In the past, the term chorea was often applied to bizarre movements,[3] which may not fit today's definition of chorea, as involuntary, continual, abrupt, brief, and irregular movements that flow randomly from one body part to another.[4] In our series of patients with psychogenic movement disorders, 0.6% were classified as chorea.[5] We describe here a unique patient with psychogenic chorea who believes that she has Huntington disease (HD) like her affected relatives.

The patient is a 38-year-old right-handed Hispanic woman, who was laid off from her job as an administrator in human resources, referred for an evaluation of abnormal movements. These started 3 years ago with jerking movements of the head associated with grunting noises. Over the next year, she developed jerk-like, nearly constant movements in both upper and lower extremities, without any premonitory sensations, exacerbated during periods of stress. The movements were observed by her mother, her husband, as well as her child's pediatrician. Her mother felt that her symptoms closely resembled the movements of other family members diagnosed with HD. Except for depression, treated with fluoxetine, she has had no cognitive or other symptoms suggestive of HD, such as dysarthria, dysphagia, or loss of balance, and has been able to perform her daily activities without difficulties. She is convinced that her "involuntary movements" are due to HD (Video).

On examination, she exhibited head, arm, and leg movements that appeared choreic, but she had normal saccadic eye movements and was able to maintain tongue protrusion (Video). According to her, the movements were involuntary and could not be suppressed, although they markedly diminished or ceased when she was distracted during performance of voluntary repetitive movements.

The patient's father is currently in a nursing home because of HD, confirmed by genetic testing. Presenting with increased blinking about 15 years ago, he now has severe motor disability due to chorea and loss of balance, he also has hallucinations that are controlled with risperidone. Two of her paternal uncles also have been diagnosed with HD, one died and the other is currently institutionalized. The paternal grandmother and one stepsister also have HD-related symptoms.

On further questioning the patient admits several sources of stress. She has frequent and at times violent arguments with her husband who apparently yells at her and pressures her to go back to work. She has not been able to return to full employment because of lack of job opportunities and because her movements interfere with her job interviews, a view also expressed by her mother.

In light of her extensive family history of HD, her physicians performed MRI of the head, which was normal, as was HD DNA test, performed twice in two different laboratories, showing 16 and 17 CAG repeats in the HD gene. Because of the variable, distractible nature of her movements, which are incongruent with chorea, we conclude that she exhibits psychogenic chorea, supported by her negative DNA tests, excluding HD. We believe that the grunting vocalizations at onset of her symptoms, similarly present in her relatives with HD, are also of psychogenic origin, although tics and tourettism have been described as the presenting feature of HD.[6] The patient and her mother were very receptive to the diagnosis of psychogenic chorea and agreed to seek psychiatric treatment directed to insight-oriented psychotherapy, treatment of underlying depression, and stress management.[7]

Additional supporting information may be found in the online version of this article.

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Legends to the Video

Segment 1. Patient exhibits choreiform movements during the interview, which abruptly stop during performance of visual tasks. She can protrude her tongue for 10 seconds. Her difficulty with tandem gait is suggestive of astasia-abasia.

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TremAn: A Tool for Measuring Tremor Frequency from Video Sequences

Video 

Simple visual estimation of tremor frequency by a physician is a part of routine clinical examination in a patient suffering from tremor, allowing a rough differentiation between slow and fast as well as between apparently regular and irregular periodic movements. A more precise measure of the tremor frequency is provided by accelerometers[1] and electromyography,[2] however, specialized equipment must be attached to the patient's body. Although wearable devices have been recently introduced integrating accelerometers and gyroscopes to capture movement features,[3] these methods can still be viewed as being cumbersome and impractical for routine clinical use. As an alternative, we propose a method of tremor frequency analysis based on video recordings of the patients—Tremor Analyzing Tool (TremAn)*.

TremAn measures the visible periodicity of the tremor. This approach measures the changes in the image intensity (sum RGB components) of a selected area in the video sequence hence capturing movement of a specific body part in front of a background. From a theoretical perspective, the 3D movement of an object does not necessarily correspond to changes in image intensity. Our practical experience tells us that changes in image intensity correspond well to tremor motion. The image intensity from the selected area, collected over time, forms a one-dimensional periodic signal. The frequency of this signal is measured based on its Fourier transform power spectrum computed with the use of the implementation by Ooura.[4] Higher levels of precision are reached by collecting the signal at spatial points, which are regularly distributed within the area of interest. The movement of the body part is expected to be consistent; hence, the spectra of all the selected points are summed to produce one final spectrum. This approach eliminates accidental noise, however, if two dominant frequencies are present, two peaks can be seen in the resulting power spectrum, with the higher peak taken as the principal frequency.

TremAn allows for analysis of tremor recorded in most common video formats (.avi or .mpg). The assumptions made to ensure correct analysis are as follows: the tremor is visible in the video, the area of interest is stable (the video sequence was captured with a fixed camera, with no shifting, zooming or focusing of the shot and the body part captured was not moving markedly except for the tremor itself). The length of the analyzed video sequence should be at least 5 seconds and the sampling frequency should be at least 15 frames per second. To use the tool, users may simply open the video sequence in the application, select the area of interest (specific body part) with a single mouse click in the video sequence, and then initiate the analysis.

The output of the algorithm is the frequency of tremor for the selected body part. The progress of the frequency in time is also recorded and can be used to investigate whether the frequency was stable or changing. Several forms of visualization are offered: the signal progress, full frequency spectrum, or the frequency progress. These are all shown in graphs with the possibility to export the result as video, single image, or text file. Refer to Figure 1 for an example of the user interface.

Refer to Video 1 for examples of tremor analysis. The first segment shows a frequency measurement (3.22 $\pm$ 0.2 Hz) of the right hand rest tremor in a patient with Parkinson's disease. In the second patient with clinically probable psychogenic tremor, the frequency of postural tremor of the left hand varies with time and decreases by more than 1 Hz in 25 seconds. The third example analyses a recording of tremor

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

*The tool is available for free download at http://cmp.felk.cvut.cz/~uhrikz1/treman/.

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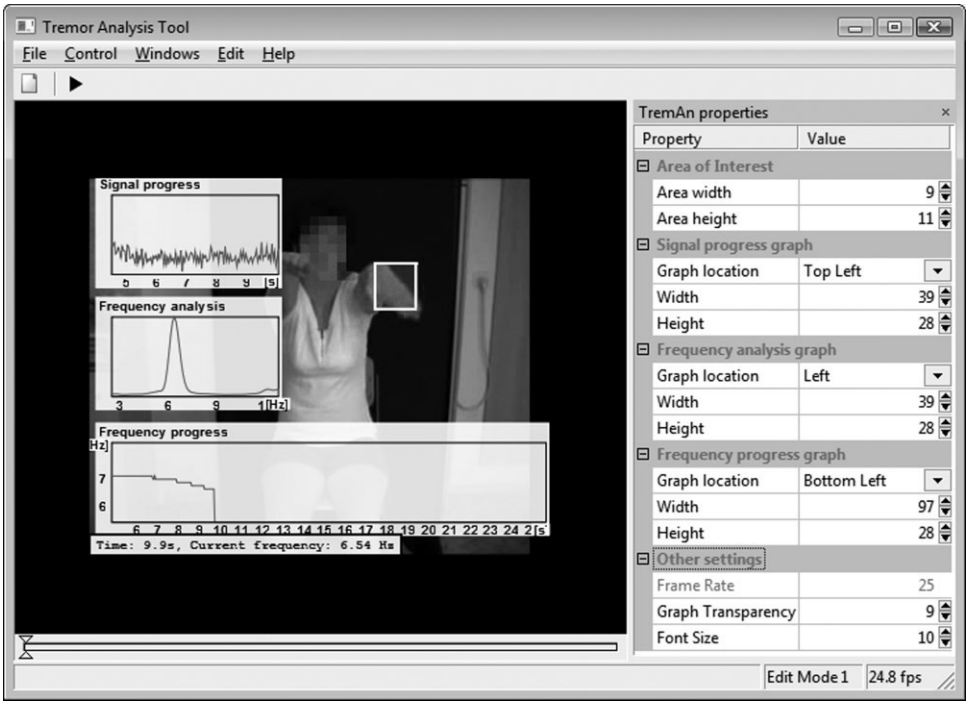

FIG. 1. User interface of TremAn containing the selected video (the area of measurement is highlighted by the square). Three graphs displaying the processed signal, the full frequency spectrum, and the principal frequency progress. Adjustable properties are listed on the right side.

taken from a previous publication in Movement Disorders Journal.[5] In line with the results of electromyography mentioned in the original article, the patient's head tremor frequency measured by TremAn is 5.3 Hz.

TremAn tool offers a convenient alternative to the common methods of tremor analysis. The patient does not need to wear any recording technology. The tool can be also used to analyze archived videos from various sources.

The results obtained by TremAn demonstrated a close correlation with tremor frequencies measured with accelerometers in the validation study with over 160 video sequences (manuscript in preparation, partly presented at the recent IEEE EMBC Conference[6]). Also the analysis of the aforementioned archived video showed that the results correspond well to tremor frequencies measured with electromyography.[5] However, care should be taken that the tremor is recorded in standardized positions. For example, here, video segment 1 probably does not show as nice a peak as the others, because the tremor of the hand is superimposed on the underlying leg tremor. Measuring other features, such as amplitude of the tremor might be feasible only under very strict conditions from calibrated videos and it is not practicable from ordinary video sequences.

Legends to The Video

Segment 1. Patient with Parkinson's disease rest tremor of right hand. The area of measurement is highlighted in green. In the bottom of the video frame, the current time and measured frequency is displayed. Graphs 1–3 demonstrate the progress of the signal, the full frequency spectrum and the progress of the measured frequency, as mentioned in the text and shown in Figure 1. At the end of the processed sequence the example of the image output with the principal frequency is shown.

Segment 2. Patient with probable psychogenic tremor. Same features of video analysis as in Video segment 1.

Segment 3. Patient with Parkinson's disease, with no-no head tremor (patient 5, segment 4, downloaded from Roze et al.).[5] Same features of video analysis as in previous segments.

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Psychogenic Movement Disorder After a Venlafaxine-Induced Dystonia

Video 

Psychogenic movement disorders are a huge diagnostic and therapeutic challenge for both neurologists and psychiatrists. A clear diagnostic is often difficult to establish, mainly because they can mimic a variety of neurological and psychiatric disorders, or even concur with these.[1]

A 29-year-old woman, with history of depression at the age of 18 and an abortion (fetal malformation) at age 24, was seen for acute onset of wave-like movements of the tongue with concomitant cervical torsion (Video, Segment 1), 2 hours after she had taken 75 mg of venlafaxine prescribed by her general physician due to complaints of sadness and anxiety. After a single 5-mg dose of biperiden, these movements subsided. In the following week, these symptoms recurred for three times and again remitted with 5 mg of biperiden. She remained asymptomatic for 1 year. At this time, her general physician prescribed her 50 mg of sertraline for depressive symptoms. Two hours after the first intake, an exuberant, irregular, arrhythmic, large-amplitude chin tremor developed (Video, Segment 2). This tremor persisted for several hours and was highly variable and responsive to both suggestion and placebo administration, the patient being remarkably indifferent to its occurrence. Both coactivation and entrainment signs could be elicited. Brain MRI, EEG, and a thorough lab work-up were normal. Electromyography of masseter muscles fulfilled Milanov proposed criteria for psychogenic tremor.[2] The diagnosis of psychogenic tremor could then be confidently made. Psychiatric evaluation elicited a conversion disorder. She is currently taking no medication. The frequency of the chin tremor episodes has diminished. The last occurred during child delivery and ceased spontaneously.

In the first episode, the movement disorder phenomenology, its clear-cut relation to drug administration, and its prompt response to anticholinergic medication strongly suggest a venlafaxine-induced dystonia, similar to those previously reported to occur with this antidepressant.[3]

In contrast, several features led us to label the second movement disorder as psychogenic. As previously described,[1] the chin tremor of our patient was highly variable and both distractibility and emotional indifference were remarkable. In addition, two of the most specific signs in psychogenic tremor, coactivation and entrainment, were found. Further supporting the diagnosis were symptom persistence after drug withdraw and the physiologic incongruent electromyographic pattern.

Of relevance is that citalopram-induced jaw tremor and several cases of bruxism due to SSRI drugs are well known, but with complete symptomatic relief after drug withdraw.[3,4] Furthermore, we could not find any report of such a tremor induced by sertraline use.

In our patient, the development of a psychogenic movement disorder after an iatrogenic one is particularly noticeable, as if she had learned how it could arise. This is supported by data showing that, in conversive patients, subsequent symptoms are rather similar to those of a past neurological disease, and as that, some kind of learning process appears to occur.[1]

Treatment of conversion disorder is rather complex. However, making an accurate diagnosis and allowing the acceptance of its psychogenic nature is essential for the treatment to be successful and to avoid unnecessary investigations and drug prescriptions.[5]

LEGENDS TO THE VIDEO

Segment 1. The patient was seen in the emergency room (ER) 2 hours after she has taken 75 mg of venlafaxine. As the video shows, she presented wave-like movements of the tongue and cervical torsion. These movements subsided with 5 mg of biperiden and she was discharged home.

Segment 2. The patient presented to the ER with an exuberant, atypical, and long-lasting chin tremor 2 hours after she has taken 50 mg of sertraline. The unusual clinical picture demanded the admis-

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sion to our inpatient unit for further investigation. The video images captured during inpatient care show the chin tremor features.

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Mortality in Parkinson's Disease

We read the article by Diem-Zangerl et al.[1] with interest. The study by Hoehn and Yahr[2] published in 1967 is regarded as representative of Parkinson's syndrome (PS) survival in prelevodopa era. It indicates markedly higher than expected mortality. This study included more malignant parkinsonian subtypes (progressive supranuclear palsy, multiple system atrophy, etc.). The symptomatic efficacy of levodopa (LD)[3,4] aroused interest in its impact on life expectancy, leading to a report on mortality in 238 patients with Parkinson's disease (PD) onset between 1974 and 1984.[1] They concluded that patients did not suffer significantly higher than expected mortality.[1] They noted "As PD is a slowly progressive disorder, disease-related mortality would be expected to be most increased in later stages ...."

We studied survival in 934 PS including 859 PD cases for a period of 22 years (1968–1990).[5] During the earlier years, most patients came to our clinic expecting to receive LD, as access to the drug was restricted. Many had long-duration symptoms and were at advanced stage of disease. After 1974, LD could be prescribed by any physician and was funded by a provincial drug plan.[5] Therefore, we divided the patients into two mutually exclusive subgroups, depending on the timing of LD access. Group one was 215 cases with onset and first assessment before January 1, 1974, and group two was 565 cases with onset and first assessment after January 1, 1974. 154 cases that did not fall in either group were excluded from this analysis (See Figs. 1 and 2).

In their study,[1] "Length of survival was estimated by calculating the difference between age at death or at the censor date (December 31, 2004) and age at symptom onset." They detected lower than expected mortality ratio during first 10 year of follow-up—0.6 at 5 and 0.9 at 10 year. We compared the observed to the expected survival starting with PS and PD onset. As in their report,[1] the survival was longer than expected (un published).

They did not clarify the duration of PD before the study entry or the treatment status at baseline.[1] Because no antiparkinsonian drug increases longevity in normal individuals, survival in PD would, at best be comparable to that in the general population.

Onset of PD is insidious and patients attend subspecialty clinics sometime later. Suppose 20 patients with PD onset at age 62 year were first evaluated at a Movement Disorder Clinic at age 65. The standardized general population mortality data tabulates fatalities in persons between age 62 and 65 year. Measuring the survival from the age of onset implicitly assumes that no PD patient would die between symptom (62 year) onset and presentation at subspecialty clinic (age 65) for study entry—but this is not the case for calculation of expected survival in the matched general population. This error can cause the observed survival to appear better than expected. Using date of PD onset as time zero for the comparisons of observed patient survival with the expected survival in general population is clearly an error to be avoided. The claim of greater than expected survival during the first 10 year[1] is, therefore, inappropriate as it assumed that 100% patients survived from symptomatic onset, to the study entry.

For comparison of survival in PS and PD cases with that expected in the regional matched population, we assigned the

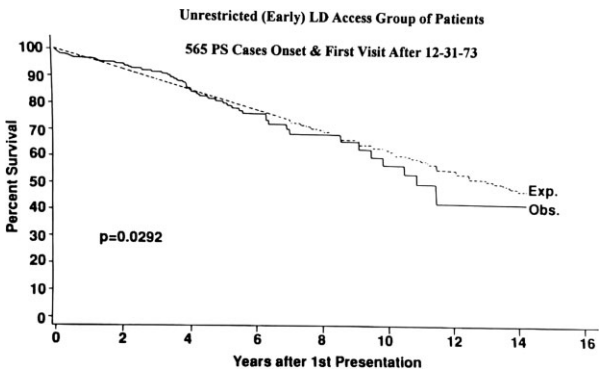

FIG. 1. Comparison of observed survival in Parkinsonism with that expected in the year of birth and sex matched regional general population, measured from date of first presentation at our clinic. This group of 565 cases had unrestricted access to levodopa. Exp = Expected survival in general population and Obs = Observed survival in Parkinsonism cases. Survival in Parkinsonism was reduced ($P = 0.029$). (Reproduced with permission of Elsevier Science Ltd.)

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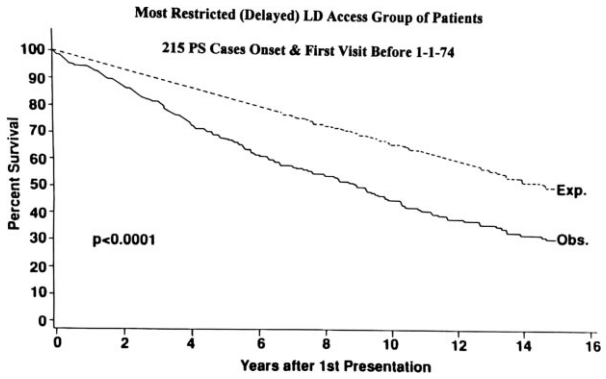

FIG. 2. Comparison of survival observed in Parkinsonism patients and that expected in the matched general population in 215 cases who had restricted and, in most cases, delayed access to levodopa, measured from the first presentation of the patients at our clinic. Survival in Parkinsonism is markedly reduced ($P < 0.0001$). (Reproduced with permission of Elsevier Science Ltd.)

date of first presentation of patients at our clinic as time zero. Survival in all PS cases (934) compared with the expected was markedly reduced ($P < 0.001$). The survival was also reduced in PD cases ($P < 0.001$). Figure 1 shows PS survival compared with that expected in general population, in those with onset and first visit after January 1, 1974 ($P < 0.029$). Figure 2 shows survival in cases with onset and first visit before January 1, 1974 ($P < 0.0001$). Observed survival was longer in the recent cases. Survival in more recent PD cases, as well, was longer than in the earlier patients. Only those patients who received LD before reaching Stage 2.5 modified Hoehn and Yahr Scale[6] experienced the survival benefit.

Survival in PD cases treated at Movement Disorder Clinics is now closer to expected in the general population but is not super-normal at any time during the course of disease.

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NMDA Antagonist Memantine Improves Levodopa-Induced Dyskinesias and "On-Off" Phenomena in Parkinson's Disease

The neural mechanism underlying levodopa (L-dopa)-induced dyskinesias (LIDs) is still poorly understood. Recent evidence suggests a major role of the overactive glutamatergic striatal circuit in the development of abnormal motor patterns.[1]

Memantine is a potent noncompetitive NMDA receptor antagonist.[2] It has been reported in Parkinson's disease (PD) to enhance the L-dopa efficacy[3] and to reduce the parkinsonian symptoms including motor fluctuations.[4] Although memantine is reported to improve severe LIDs resistant to other pharmacologic interventions,[5] this effect was not confirmed by a double-blind crossover study.[6]

We describe the effect of memantine in 3 patients with motor complications and their follow-up evaluations at 1–5 years.

Patient 1 is a 68-year-old woman with a 13-year history of PD. After 7 years of L-dopa treatment, she developed on-off phenomena and peak dose choreic LIDs. Amantadine (200 mg/day) was initially introduced to control the LIDs, but the drug could not be used above 100 mg/day because of hallucinations and livedo reticularis, and it was eventually discontinued after 3 years.

Before starting memantine 30 mg, the Unified Parkinson's Disease Rating Scale[7] (UPDRS) motor score (part III) was 23; her complications to therapy score (part IV) was 10, with on-phase dyskinesia score (items 32, 33) of 4 and clinical fluctuations (items 37, 38, 39, 40) of 4.

In the following months, the patient reported improvement of LIDs and almost complete resolution of unpredictable off periods. Two years later, her UPDRS part III score was 18 and part IV score was 4, with dyskinesia total score of 1 and fluctuations total score of 1.

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The discontinuation of memantine after 3 years resulted in worsening of patient's motor function and LIDs. The clinical evaluation showed a UPDRS part III score of 32 and part IV score was 11, with dyskinesia score of 5 and fluctuations score of 5.

Memantine was started again and increased up to 30 mg, with a significant improvement in the patient's motor complications. After 3 months the patient's dyskinesia score was 1 and fluctuations was 2, with a UPDRS part III score of 30.

Patient 2 is a 52-year-old woman with a 11-year history of PD. She poorly tolerates dopamine agonists, and thus, she was treated with L-dopa, entacapone, and amantadine from the disease onset. After 5 years of sustained improvement, the patients developed peak dose, dystonic and painful LIDs, and on-off fluctuations. When memantine was introduced, her UPDRS part III score was 26 and part IV score was 7, with dyskinesia score of 4 and fluctuation score of 4.

Adjustments in the L-dopa barely improved patient's condition, and thus, memantine was increased up to 30 mg/day. Over the following year, she had a sustained improvement of her LIDs. At the 1-year evaluation, patient's UPDRS part III score was 17 and part IV score was 7, with dyskinesia score of 2 and fluctuations of 4.

Patient 3 is a 75-year-old man with a 15-year history of PD, treated with L-dopa and entacapone. When the patient arrived to our observation, after 10 years of disease, he was suffering from on-off fluctuations and peak dose choreic LIDs. The UPDRS part III revealed a score of 36 and the part IV score was 9, with a dyskinesia score of 4 and a fluctuation score of 3. The L-dopa administration was optimized with minimal improvement.

Mild visual hallucinations and cognitive decline were major contraindications to the use of amantadine, and thus, memantine (20 mg/day) was introduced. At the 1-year evaluation, patient's UPDRS part III score was 34 and part IV score was 8, with dykinesia score of 2 and fluctuations score of 3.

When memantine was accidentally discontinued, the patient had a mild worsening of LIDs (dyskinesia score of 3) and a significant worsening of on-off phenomena (fluctuations score of 6), with no major change in the UPDRS part III score.

After 1 month from the resumption of memantine (20 mg/day), LIDs and on-off phenomena were completely suppressed (dyskinesia and fluctuations scores of 0), and the UPDRS part III score stabilized on 29.

All the 3 patients well tolerated memantine, and no side effects were observed. During the period of observation, none of the patients required new medications or major changes in dosing of the ongoing treatments.

An important aspect of the cases presented is that in 2 patients, the discontinuations of memantine led to significant worsening of the motor complications, with recovery after the drug was resumed.

In addition to its dopaminergic[8] and minimal anticholinergic activity,[9] which may contribute to the antiparkinsonian effects, memantine is a potent noncompetitive antagonist of the NMDA receptors.

In a short 2-week trial by Merello et al., memantine improved Parkinsonism in "on" and "off" state, but did not help dyskinesia.[6] In our subjects also, the improvement of dyskinesia was not observed during the first few weeks of treatment. It is therefore possible that different mechanisms may underline the beneficial effect of memantine on parkinsonian symptoms and motor complications. There is strong evidence that the chronic L-dopa therapy exerts a pulsed non-physiological stimulation of the dopamine receptors, resulting in the upregulation of the glutamatergic NMDA receptors in the striatum.[1,10] As a consequence, the glutamatergic transmission from the striatum to specific cortical areas, such as the supplementary motor area and the dorsolateral prefrontal cortex,[11,12] becomes overactive in PD, leading to the abnormal motor patterns of LIDs and motor fluctuations.

Considering the low side-effect profile and its putative neuroprotective effect,[11] we suggest that memantine may be a potentially effective drug for the treatment of L-dopa-induced complications in PD, particularly when other alternatives agents such as amantadine are contraindicated.

Our observation, along with previous cases, suggests that double-blind placebo-controlled studies are necessary to investigate the optimal role for memantine in the treatment of PD.

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The Use of Smell Identification Tests in the Diagnosis of Parkinson's Disease in Brazil

We read with interest the recent article by Silveira-Moriyama et al.[1] outlining the use of the UPSIT-40 and SS-16 in Brazilian patients with Parkinson's disease (PD) and controls. We have recently used Sniffin Sticks (SS) in Tanzanian patients with PD and controls. In sub-Saharan Africa (SSA), as in other developing regions, there is a lack of trained medical staff, particularly specialists such as neurologists (there are only 2 in Tanzania). There is a general lack of knowledge about "less common" conditions such as PD which particularly affect the elderly, both within the public and health professionals, which often leads to patients remaining undiagnosed with a condition for which there is effective symptomatic treatment available. It would be very helpful in these regions, where access to more sophisticated and expensive investigations such as dopamine transporter imaging is limited, to have a cheap, reproducible, and reliable test that would help in confirming the diagnosis in suspected individuals. The aim of our pilot study was to determine whether or not the SS test could be adapted for use in this population, and whether the adapted version was useful in discriminating between those with PD and those without.

Participants were asked to smell the "SS" pens with both nostrils and to identify the odor from a selection of four possible choices. The nostrils were not tested independently. To ensure that the choices were odors that were familiar to the Tanzanian population, the (Tanzanian) PD nurse specialist and local assistant medical officers reviewed all odors. For those that were familiar a Swahili translation was made. For those where the smell was not recognizable (e.g. blackberry), an alternative local smell was chosen. In total 14 substitutions were made. Only one correct answer, liquorice, was not applicable to the Tanzanian population, the other substitutions were for "distractors" or incorrect answers. However, a local cough medicine, "Kofta," is made with liquorice and the name of this brand was used instead.

These changes are similar to those made in the Brazilian study[1] for items where a direct translation did not exist. The SS test has previously shown good test–retest reliability.[2] The SS screening test has also previously been used, and demonstrated to be effective, in Taiwan with replacement of some "distractors" with smells that were similar, but common in Taiwan.[3] The SS test is not culturally applicable to all areas in its original form.

In our pilot study, 20 patients (13 male) previously identified in a prevalence study,[4] and 25 controls (6 male) were tested. Mean age of patients was 82.5 years, compared to 46.5 years for controls. As in another Brazilian study, the majority of patients had not been previously diagnosed.[5] Unlike the Brazilian patients, where the mean age at onset of disease was 49 years, the Tanzanian patients were much older at onset of disease, mean 69 years. Scores are shown in Table 1.

It was possible to adapt the SS testing kit for a rural Tanzanian population. The tests were acceptable and quick to perform. Silveira-Moriyama et al.[1] found their test took on average 5–10 minutes once translated into Portuguese. Patients with PD were more likely to have olfactory dysfunction than controls. For both groups, coffee was the easiest smell to identify and leather the most difficult. The fact that many controls were rated as hyposmic may relate to their educational background. The majority of the controls were female. Patients were significantly older than controls, and age may account for some of the decrease in olfactory function seen. However, bearing these limitations in mind, the potential usefulness of this test has been demonstrated by the fact that half of the patients with PD were anosmic as compared to only 8% of the controls. To test further in this population, it would be useful to compare age- and sex-matched controls to patients with PD and also include a larger sample size.

Using the prevalence rate from our Tanzanian study[4] and the United Nations predictions (Help Age International) for the number of people over the age of 60 years in developing countries by 2015 (597 million), there may be as many as 1.3 million people with PD living in the developing world who do not know that they have the disease and have no access to specialist diagnosis or treatment. We agree with the authors of the Brazilian study that the use of simple odor identification tests in those suspected to have PD is feasible

TABLE 1. *Sniffin Sticks results*

	Patients	Controls
Mean total score	5.5	8.2
Most frequently identified odor	Coffee	Coffee and peppermint
Least frequently identified odor	Leather	Leather
Number normosmic (>10 of 12)	2	5
Mean age (yrs)	82.7	46.6
Male: Female	1:1	2:3
Number hyposmic (6–10 of 12)	8	18
Mean age (yrs)	82.4	44
Male: Female	5:3	3:15
Number anosmic (<6 of 12)	10	2
Mean age (yrs)	82.5	47
Male: Female	7:3	1:1

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and may help in making the clinical diagnosis, and be a tool that is especially useful in resource poor settings.

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Sydenham's Chorea in a Girl with Juvenile Idiopathic Arthritis Treated with Anti-TNFα Therapy

Video 

Juvenile Idiopathic Arthritis (JIA) is the most common chronic rheumatic disease in childhood and results from an autoimmune disorder mediated by Th1 immune responses. The pathogenesis of JIA is still poorly understood, although several immunological abnormalities have been reported. T cells have been implicated in the pathogenesis of JIA, as have their related cytokines.[1] TNF-α is a cytokine that plays a crucial role in causing inflammation, and its inhibition has emerged as an effective treatment for JIA. Infliximab, Etanercept, and Adalimumab have been reported to be safe and effective, but adverse events of these drugs are being increasingly reported, including infections and autoimmune processes.[2]

Acute rheumatic fever (ARF) results from an autoimmune response to infection by group A streptococci. Sydenham's chorea is a major manifestation of ARF; its pathophysiology is unclear, but an inflammatory process of autoimmune nature has been proposed. Antibodies against the nucleus caudatus and nucleus subtalamicus in the sera of patients and increased levels of IgG in cerebrospinal fluid support the hypothesis that immunological mechanisms take a considerable place in the pathogenesis of Sydenham's chorea and the response to immunosuppressive therapy, such as corticosteroids, supports this theory.[3–5]

There have been reports of patients with JIA who had associated autoimmune disorders such as celiac disease or thyroiditis.[6,7] These associations suggest that different autoimmune phenotypes may share common susceptibility genes, which together may confer risk for autoimmunity. Table 1 summarizes the main reported associations between immunomediated neurological conditions and autoimmune diseases. In addition, there are a growing number of reports of development of autoimmune processes related to TNF-targeted therapies.[2]

We report a case of Sydenham's chorea in a 10-year-old girl with JIA who had been treated with two different TNF inhibitors.

A 10-year-old girl, born from a nonconsanguineous marriage, presented to our attention with nervousness, emotional lability and reduced attention span, abnormal movements of limbs with worsening writing ability, and dysarthria. History taken revealed that she had been diagnosed with JIA since the age of eight, and the disease had been complicated by uveitis. Therapy with nonsteroidal anti-inflammatory drugs, oral corticosteroids, methotrexate, and infliximab had been initially established. After several months infliximab was stopped and adalimumab was introduced. The patient's mother reported a febrile episode with pharyngodynia; a throat swab had been positive for group A beta-streptococcus a few months before admission to our unit.

On physical examination she was alert, well developed, and nourished and in no acute distress. On neurological examination, motor impersistence and choreiform movements were apparent in the four limbs, with facial grimacing, dysarthria, and gait abnormalities. Muscle tone was mildly reduced. The remainder of the physical exam was normal. (Supporting Information Video, Segment 1).

Laboratory data showed normal complete blood count, peripheral blood smear, liver, thyroid, and renal function. Fatty acyl carnitines, ceruloplasmin, copper, ANA, Lupus anticoagulant, anti-DNA, anticardiolipin, and anti-β2 auto antibodies were all negative or within normal limits, allowing us to exclude chorea associated with metabolic diseases, systemic lupus erythematosus, and antiphospholipid syndrome. The evidence of streptococcal involvement was confirmed by a raised antistreptolisin titer of 1190 IU/mL (normal range 0–200 IU/mL) and anti-DNAse B titer of 572 IU/mL (normal

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TABLE 1. *Main reported associations between immunomediated neurological conditions and autoimmune diseases*

Immunomediated neurological diseases	Co-occurring autoimmune diseases	Reference source
Rasmussen's encephalitis	Cerebral vasculitis, uveitis, SLE	8
Multiple sclerosis	Guillain-Barrè S., neuromyelitis optica, chronic inflammatory demyelinating polyradiculoneuropathy, myasthenia gravis, sarcoidosis, SLE, systemic sclerosis, Hashimoto thyroiditis, psoriasis, IBD, RA, bullous pemphigoid, diabetes, primary biliary cirrhosis, Goodpasture's S.	9,10,11,12,13,14,15,16,17,18,19,20
Acute disseminated encephalomyelitis	Inflammatory demyelinating polyradiculitis, cutaneous lupus	21,22
Neuromyelitis optica	Myasthenia gravis, Schilder's disease, SLE, APS, Sjögren S., celiac disease	23,24,25,26
Guillain-Barré syndrome	MS, opsoclonus, Vogt-Koyanagi-Harada disease, temporal arteritis, sarcoidosis, SLE, reactive arthritis, Hashimoto's thyroiditis, IBD, Henoch-Schönlein purpura, glomerulonephritis,	9,27,28,29,30,31,32,33,34,35,36
Chronic inflammatory demyelinating polyradiculoneuropathy	MS, myasthenia gravis, sarcoidosis, SLE, Sjögren S., Schnitzler's S., Graves' disease, diabetes, penphigus vulgaris, idiopathic hemochromatosis, thrombocytopaenia, glomerulonephritis	11,37,38,39,40,41,42,43,44,45
Myasthenia gravis	MS, neuromyelitis optica, chronic inflammatory demyelinating polyradiculoneuropathy, opsoclonus-myoclonus S., sarcoidosis, APS, RA, SLE, polymyositis and dermatomyositis, mixed connective tissue disease, Sjögren S., scleroderma, juvenile chronic arthritis, Graves' disease, Hashimoto's thyroiditis, primary biliary cirrhosis, IBD, coeliac disease, pemphigus, thrombocytopenia, hemolytic anemia, glomerulonephritis,	12,23,37,46,47,48,49,50,51,52 53,54,55,56,57,58
Lambert-Eaton myasthenic syndrome	Sarcoidosis, Sjögren S., dermatomyositis, discoid lupus erythematosus, RA, diabetes, thyroid disorder, psoriasis, vitiligo, Addison's disease, thrombocytopenic purpura, glomerulonephritis	59,60,61,62,63,64,65,66
Sydenham's chorea	APS, SLE, Henoch-Schönlein purpura	67,68

SLE, systemic lupus erythematosus; IBD, inflammatory bowel disease; RA, rheumatoid arthritis; APS, antiphospholipid syndrome; S, syndrome; MS, multiple sclerosis.

range 0–75 IU/mL). The echocardiogram showed minimal mitral regurgitation in the absence of heart murmur; an EKG was normal. Brain MRI and EEG were also normal.

Sydenham's chorea was diagnosed, and oral therapy with Haloperidol was given initially at 0.5 mg and progressively increased up to 3.4 mg (0.06 mg/kg/die). Prophylaxis with i.m. penicilline (1,200,000 IU every 3 weeks) was also started. During hospitalization clinical conditions improved; choreiform movements, dysarthria, and gait abnormalities became less prominent, and the patient was therefore discharged on haloperidol, adalimumab, and oral prednisone, as well as penicillin prophylaxis. After 9 months of follow-up her choreic movements had disappeared, though some minor distal twitching could still be detected (Supporting Information Video, Segment 2).

The occurrence of chorea in JIA is a rare event, and we cannot fully explain this unusual association. However, a common autoimmune background as well as the TNF-blocking treatment regimen might all have played a role.

Legends to the Video

Segment 1. On admission, choreiform movements of the four limbs, facial grimacing, and gait abnormalities were observed.

Segment 2. After 9 months of follow-up, abnormal movements were no longer apparent, with the exception of occasional twitching of the fingers of the left hand and an awkward gait.

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Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS) with Myoclonus

Video 

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disorder that can affect carriers of a premutation in the fragile X mental retardation 1 (FMR1) gene.[1] This gene normally contains fewer than 55 CGG triplet repeats. The full mutation (repeat number >200) is responsible for fragile X syndrome. Repeat lengths between 55 and 200 constitute a premutation which, besides being associated with FXTAS, also carries an increased risk of primary ovarian insufficiency (POI).[2,3] Symptoms of FXTAS usually begin in the seventh decade. Major motor abnormalities are action tremor, cerebellar ataxia affecting limbs and gait, and Parkinsonism. Other possible features include cognitive decline, neuropathy, and autonomic dysfunction.[4] The full phenotypic spectrum of FXTAS remains unclear. Although a broad range of neurological findings have been reported,[4]

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myoclonus has not previously been described in association with this syndrome. We describe a man with FXTAS who, besides known features of this syndrome, also has generalized reflex myoclonus.

A 60-year-old man presented with a 2-year history of mild gait and balance difficulties. Past medical history consisted of treated hypertension and prostate cancer. Family history was notable for two sisters who experienced ovarian failure before age 35, and for the absence of mental retardation, parkinsonism, tremor, ataxia, or dementia. Examination revealed mild memory impairment (Mini Mental State Examination score 28 out of 30), and symmetric limb coordination deficits that included mild irregularity of timing and amplitude of rapid alternating hand movements, mild dysmetria on finger–nose testing, and moderate dyssynergia, evident as impaired checking response. There was mild gait ataxia, which was manifest as unsteadiness on rapid turning and inability to tandem-walk. There was mild bilateral hand action tremor on finger–nose testing and spiral drawing, and there were no parkinsonian findings. Generalized reflex myoclonus was present: tapping deep tendons in the arms or legs with a reflex hammer resulted in single jerks of the neck, trunk, abdomen, and arms. The same movements could be obtained by gentle pinprick of the palms or by scratching the palms or soles with a key (Video, Segment 1). Quantitative movement analysis revealed jerks that caused backward head movement, forward and upward abdominal movement (indicating trunk extension and/or diaphragmatic contraction), and bilateral shoulder elevation and elbow extension, which were time-locked to the stimulus (Fig. 1A). Calculation of movement onset latencies after pinprick of the left hand showed that the hands moved first (80–100 milliseconds), followed by head (100–120 milliseconds), and abdomen/trunk (140–160 milliseconds). Note that these latencies do not inform on the point of origin of myoclonus (cortex vs. brainstem vs. spinal cord) because they do not necessarily correspond to electromyographic signal latencies, due to differences in biomechanical properties of the moving body parts. No spontaneous jerks were observed at rest or during posture or action. Neuropsychological assessment revealed dementia consistent with a frontal subcortical and cortical pattern, including poor encoding and retrieval, severely impaired visual confrontation naming, and significantly reduced psychomotor and processing speed. Brain MRI revealed marked atrophy of the cerebral hemispheres, moderate cerebellar atrophy, and bilateral increased T2 signal in the middle cerebellar peduncles (Fig. 1B,C). FMR1 gene analysis revealed CGG trinucleotide repeat length 114, that is, in the premutation range (55–200).

This report is the first description of myoclonus in association with FXTAS. The motor manifestations of FXTAS suggest involvement of cerebellar and striatonigral pathways. Therefore, generalized reflex myoclonus, which is typically of cortical or brainstem origin,[5] was unexpected. Whether myoclonus in this patient originates from the cortex or brainstem is unclear. His cognitive deficits fit the "frontal executive" pattern that has been described in FXTAS,[4] and include a cortical component. The reflex nature of the myoclonus (Fig. 1A) and the severity of cortical atrophy (Fig. 1B) are consistent with a cortical origin. Moreover, cerebral volume loss has been reported in FXTAS and is correlated with CGG repeat length.[6] Thus, diffuse cortical damage is a plausible substrate for myoclonus in FXTAS. However, volume loss in the brainstem also occurs in FXTAS,[6,7] and thus a brainstem origin for the observed myoclonus cannot be excluded.

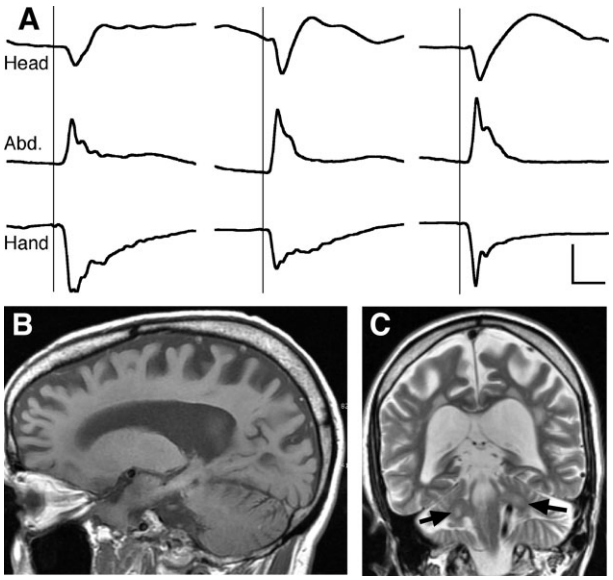

FIG. 1. A: Quantitative records of three examples of myoclonic jerks observed in the patient described in the present report. Position of head, abdomen, and left hand is plotted versus time. Traces show the response to three instances of pinprick stimulation of the hand (at times indicated by vertical lines), and illustrate generalized reflex myoclonus as time-locked jerks of the head (backward), abdomen (outward), and hand (down). Horizontal calibration bar: 0.5 seconds; vertical: 0.5 centimeters for head, 0.2 centimeters for abdomen, 1 centimeter for hand. Position was recorded at 110 Hz via an infrared motion capture camera (Proreflex MCU 500, Qualisys) with patient seated with arms flexed at the elbows. **B**: Sagittal T1-weighted magnetic resonance image illustrating cerebral atrophy out of proportion to cerebellar atrophy. **C**: Coronal T2-weighted image illustrating bilateral middle cerebellar peduncle hyperintensity (arrows).

FXTAS is a rare cause of ataxia with a reported prevalence of only 1.5% of men with ataxia.[4] However, clinical consideration and accurate diagnosis are essential because of the associated increased risk of fragile-X mental retardation syndrome and POI in family members. Besides demonstrating a new potential clinical feature of FXTAS, this case also highlights the fact that FXTAS can present with minimal tremor, and that family history of POI can be an important clue to the diagnosis. Establishing whether generalized reflex myoclonus is indeed a consequence of the FXTAS mutation, rather than indicating coincidence or a specific susceptibility in the patient described here, will require further clinical observation of individuals with this condition.

Legends to the Video

Segment 1. Selected examination findings in patient with FXTAS with reflex myoclonus. The video demonstrates generalized reflex myoclonus, dysdiadochokinesia (with mirror

movements in the other hand), mild intention tremor, dysmetria on finger step-tracking, impaired checking response, unsteadiness on turning, and impaired tandem gait.

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Stiff Person Syndrome as the Initial Manifestation of Systemic Lupus Erythematosus

Stiff person syndrome (SPS) is a rare neurological disorder characterized by the presence of fluctuating muscle rigidity and spasms of the trunk and proximal body parts.[1] In a significant number of cases, SPS is believed to be mediated by autoantibodies to glutamic acid decarboxylase (anti-GAD), limiting GABAergic activity and lowering the threshold for muscle spasms and other neuropsychiatric features of the disorder.[2] SPS with elevated serum anti-GAD levels may occur with other autoimmune disorders, specially insulin-dependent diabetes mellitus (IDDM).[3] Ten percent of cases with normal levels of this antibody may be related to autoantibodies against amphiphysin, representing commonly a paraneoplastic syndrome.[1]

Here, we report a case of SPS as the initial manifestation of systemic lupus erythematosus (SLE).

A 48-year-old woman with an 8-month history of painful bilateral thoracic and lumbar paravertebral muscles spasms. These spasms lasted from 10 to 30 seconds and were accompanied by severe pain that gradually disappeared over another 30 seconds. Contractions occurred spontaneously but were also elicited by anxiety and startle reactions. Symptoms occurred throughout the day and occasionally during sleep. In-between periods of exacerbation, she felt fluctuating discomfort and rigidity in the cervical, thoracic and lumbar axial muscles, including scapular girdle, leading to an almost persistent upright posture. During the previous 2 months, mild nonpainful facial spasms were noticed.

Past medical history was positive for depression, refractory to a 3-month trial of amytriptyline 75 mg qd and to current treatment with venlafaxine 150 mg qd. Family history was negative.

On examination, cranial nerves were normal except for increased startle responses after nose or facial tapping. Muscles were normotrophic and tone was normal in the limbs but moderately increased in the axial muscles. Strength was normal and deep tendon reflexes were brisk and symmetric. Cutaneous abdominal reflexes were decreased, plantars were flexor. Sensation was normal. Cerebellar signs were absent. Posture in the upright position showed the signs described above. Gait was slow with noticeable axial stiffness.

Routine laboratory exams included normal leucocytes count, with mild Coombs-positive anemia (Hb 10.3 g/dL) and thrombocitopenia (120,000/ml); normal fasting plasma glucose, hemoglobin A1C, creatinine, electrolytes, TSH and CK levels; erythrocyte sedimentation rate was 79 mm/h; negative syphilis, hepatitis B/C and HIV serologies; plasma anti-GAD levels were 12.6 U/mL (radioimmunoassay; normal 0–1 U/mL). Cerebral spinal fluid analysis was normal with no oligoclonal bands. Cranial and spinal cord MRI were unremarkable. Electromyography with nerve conduction studies revealed continuous activity of the lumbar paraspinal muscles.

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Screening for breast, lung, and ovarian malignancy was negative. She denied treatment during the 2 weeks period required for investigation. During this interval, she developed photosensitive rash on the forehead and upper extremities, metacarpo-phalangeal arthritis, fatigue, and brief episodes of confusion that interfered with job performance as a nurse. The patient was referred for assessment with a rheumatologist who requested additional inflammatory parameters: positive antidouble-stranded-DNA, anti-nuclear, anti-RP, anti-Scl-70 antibodies and IgM isotype of anticardiolipin antibodies titers; negative rheumatoid factor and mildly decreased C3 and C4 complement levels. A skin biopsy showed lymphocytic perivascular dermal infiltrates. Taken together, these findings led to the diagnosis of SLE.[4]

Treatment was initiated with oral prednisone (60 mg/day), hydroxychloroquine 400 mg/day, diazepam (up to 30 mg/day, maximum tolerated dose), and baclofen (20mg tid). This intervention brought significant improvement of mental status, dermatologic and joint symptoms, but only mild reduction in axial contractures. Intravenous immunoglobulin (1 mg/kg) for 2 consecutive days brought partial but significant relief of contractures.

The co-occurrence of additional immunogenic responses in patients with SPS and positive anti-GAD occur in up to 80% of such cases and include vitiligo, pernicious anemia, celiac disease, polymyositis, and endocrinopathies, such as Hashimota's thyroiditis, Graves' disease, adrenal failure, and IDDM.[1] Indeed, patients with anti-GAD positive SPS are particularly susceptible to develop IDDM as pancreatic beta cells are among the few cells outside the central nervous system that contain GAD.[5] Also, abnormal titers of a variety of antibodies have been described in these cases such as antiparietal cell, antinuclear, and antithyroidal antibodies, antibodies against gephyrin, Ri and Jo-1 antigens, ribonucleoprotein, and intrinsic factor.[1] Of importance, most of these antibodies are also found in SLE.[4]

SPS associated with SLE has been described in one previous report[6] of a 42-year-old man with symmetrical paraspinal and lower limb muscles stiffness, painful spasms, and asthenia. The patient also showed positive anti-GAD but levels are not reported. After 18 months, he presented clinical and paraclinical manifestations that led to the diagnosis of SLE. Except for this case, anti-GAD antibodies have not been reported in SLE, however, Dalakas et al.,[3] in a study of 20 cases of SPS, found a family history of SLE and rheumatoid arthritis in one case each.

The case presented here, of a patient who developed SPS with a tight temporal relationship with the clinical manifestations of SLE, reinforces the possibility of the pathological expression of a common immunogenetic background. Indeed, a very strong association with HLA phenotypes, often associated with SLE, has also been observed in SPS, including overlap of HLA DRB1*0301 and DQB1*0201 serotypes.[1,7] On the other hand, the lack of benefit on the SPS symptoms after prednisone and hydroxychloroquine were introduced suggests that SPS and SLE can co-occur with a frequency greater than chance alone, but may not share the same pathogenic processes.

Thus, we believe that our report provides valuable information to the growing amount of data on SPS with positive anti-GAD, guiding clinicians and broadening the spectrum of autoimmune disorders linked to this disorder.

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Pregabalin in the Treatment of Neuropathic Tremor Following a Motor Axonal form of Guillain–Barré Syndrome

We read with careful interest, the 2007 paper by Zesiewicz et al.[1] describing the efficacy and lack of undesired effects of pregabalin (PGB) in treating essential tremor (ET), a slowly progressive commonly hereditary disease.[2] Furthermore, in the last decade, a number of antiepileptic drugs have been shown to be effective for various types of tremor. Clinical trials have demonstrated that PGB can be used to control tremor due to peripheral neuropathy (neuropathic tremor, NT). This is most commonly observed during chronic demyelinating polyneuropathy,[3] dysgammaglobulinemic or hereditary diseases, and rarely following classical forms of Guillain–Barré syndrome (GBS).[4]

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TABLE 1. *Dose-dependent improvement of tremor with increasing doses of pregabalin*

	Right upper limb		Left upper limb	
TRS	Part A	Part B	Part A	Part B
TRS 0	A3	B2	A3	B2
TRS 300	A1	B0	A2	B1
TRS 450	A0	B0	A1	B1

TRS, Fahn–Tolosa–Marin tremor rating scale; A, assessment of tremor severity at rest, with posture holding and with action and maneuvers; B, tests action tremor while writing, drawing, and pouring liquids; A0, no tremor; B0, normal; A1, slight, barely perceivable, may be intermittent; B1, mildly abnormal, slightly untidy, tremulous; A2, moderate, amplitude <2 cm, may be intermittent; B2, moderately abnormal, legible but with considerable tremor; A3, marked, amplitude 2 to 4 cm; TRS 0, pretreatment; TRS 300, with pregabalin 100 mg three times per day; TRS 450, with pregabalin 150 mg three times per day.

This letter reports the case of a classical motor axonal form of GBS (AMAN) followed by a disabling NT that was successfully treated by PGB. Tremor severity was assessed using the first two parts of the Fahn–Tolosa–Marin tremor rating scale[5] before and after the introduction of increasing doses of PGB (see Table 1).

A 31-year-old previously healthy man presented with an acute ascending symmetric tetraparesis, without cranial nerve palsy and without respiratory failure, following a few days of gastrointestinal illness. Electromyographic studies were consistent with AMAN. Serology was positive for *Campylobacter jejuni*. With supportive care, neurological status improved and after a week the patient was transferred to the neurorehabilitation unit where he stayed for 3 months. Recovery was marked by a slow motor improvement, but also by the emergence of an appendicular, postural and kinetic 8 to 10 Hz tremor, predominant in the upper limbs. A detailed medical history, a complete physical examination, as well as routine and endocrine laboratory tests did not reveal any alternative cause for the tremor. Of note, the patient has no personal and familial history of tremor. Tremor relief by alcohol could not be evaluated as the patient does not drink alcohol.

Motor recovery was almost complete and the patient left the hospital with a mild paresis, predominantly proximal, associated with the persistent tremor. Six weeks later, he was reviewed in the outpatient clinic. At that time, the tremor was even more pronounced and required pharmacological intervention. Primidone and propanolol are first-line drugs for the management of ET but are usually unsuccessful in NT.[6] PGB rather than gabapentin was chosen because of its pharmacokinetic profile. We therefore started treatment with PGB 25 mg three times a day for a week and then progressively increased the total daily dose to 300 mg. At that time, a significant clinical improvement was noted in the right arm and to a lesser degree in the left arm (see Table 1). We further increased the dose to 450 mg daily and the tremor dramatically improved on both sides, after 3 weeks of monotherapy.

ET and NT share clinical features and are thought to be due to different pathophysiological mechanisms. Both conditions are characterized by pathological 5 to 10 Hz tremor with postural and kinetic components, and both involve neuronal systems that can cause rythmic or oscillatory activity under certain conditions.[2] In ET, this rythmic activity is thought to be due to a central functional disturbance, centered on the olivocerebellar circuit and cerebellocortical loop (involved in the feedforward control of movement), as well as cerebellothalamic and pallidothalamic bundles.[2,6] Unlike ET, with no neuroanatomic abnormalities, in NT, a peripheral slowing and possible distorsion of afferent and/or efferent signals seems to be the major underlying pathophysiology.[6]

$GABA_A$ receptors are the primary inhibitory receptors in the central nervous system that regulate motor function and several lines of evidence suggest that the GABAergic system is involved in the etiology of ET.[7] Importantly, inhibition of NMDA subtype of glutamate receptors decreases ET-like symptoms in animal models.[7] As gabapentin, PGB is an analog of GABA. PGB also decreases the release of some neurotransmitters such as glutamate, noradrenaline, and substance P.

In NT, the beneficial effects of PGB may be due to the modulation of feedback control of movement, of the somatic reflex arc and peripheral sensory afferents. In contrast, PGB effects in ET may be due to modulation of complex central neurotransmission (such as GABAergic and glutamatergic systems), and possibly modulation of feedforward control of movement.

We conclude that PGB could be a safe and useful treatment in NT after GBS and warrants future investigation by larger trials.

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Chorea Induced by Antihistamine Drugs

Video 

Chorea is an involuntary movement that flows from one place to another, being unpredictable in time and place. Chorea is not rare after exposure to drugs, such as neuroleptics, anticonvulsants, or psychostimulants.[1] Here, we described a patient showing chorea after antihistamine medications.

A 72-year-old man visited emergency room in our hospital because of involuntary movements sustained for 5 days. He had history of hypertension and diabetes mellitus treated with amlodipine and glimepiride. He intermittently used topical agents more than 2 years because of pruritus. About 4 weeks before admission, he had started to take regular oral medications for his skin lesions with diagnosis of allergic dermatitis; hydroxyzine HCl (25 mg), azelastine HCl (1 mg), and emedastine fumarate (1 mg). The patient complained of nausea and abdominal discomfort. Physical examination was not remarkable except for mildly increased bowel sounds. On neurological examination, nonrhythmic, unexpected flow-like movements were observed on his face, neck, and four extremities (Video, Segment 1). These movements were attenuated during rest and disappeared during sleep. Higher cortical, cranial nerve, motor, sensory, and cerebellar functions were not remarkable. His deep tendon reflexes were symmetrically decreased, which were thought to be associated with diabetics. Brain computer tomography and magnetic resonance imaging with T1-, T2-, or diffusion-weighted images showed unremarkable. A complete blood count showed mild normochromic normocytic anemia. Serum glucose was 63 mg/dl, and blood urea nitrogen (BUN) and creatinine (Cr) were slightly elevated (34.7 and 1.77 mg/dl, respectively), which were normalized 2 days after admission. Immunologic studies (antinuclear antibody, anti-DNA, lupus anticoagulant, and antiphospholipid antibodies) were negative. There was no expansion of CAG trinucleotide repeat in the huntingtin gene. With the discontinuation of antihistamine drugs, choreic movements lessened progressively and only minimal chorea was seen on the 7th day of admission (Video, Segment 2). Three weeks later, when he visited to outpatient clinic, his choreic movements were not observed any more.

According to study dealing with the etiology of nonhereditary chorea in patients who admitted to a hospital, vascular origin (68%) was the most commonly observed and, drug-related chorea (23%) and metabolic origin (9.6%) were main following causes.[2] In our case, there was no evidence of structural lesions on brain imaging as well as laboratory abnormalities except for slightly increased level of BUN and Cr. The possibility of uremic chorea could be excluded as there were no basal ganglia lesions on brain imaging and the patient had only mild azotemia.

The temporal relationship between introduction of antihistamine drugs and development of chorea as well as improvement of chorea after discontinuation of offending drugs suggests that chorea in our patient would be ascribed to complication of antihistamine medication. Antihistamine-induced chorea has been rarely reported. Samie and Ashton[3] reported a patient taking overdose of cyproheptadine (a H1-receptor antagonist), who developed generalized chorea and central anticholinergic syndrome. Klawans and Moskovitz[4] reported cyclizine-induced generalized chorea in a patient with mild lingual-facial-buccal dyskinesias. Lehmann[5] reported H2-receptor antagonist-associated related chorea.

The antihistamine drugs prescribed in our patients were all H1-recpetor antagonists; hydroxyzine (a first-generation antihistamine of the piperazine class), azelastine, and emedastine (a second generation antihistamine having less lipophilic and less affinity for cholinergic receptors). Regarding the mechanism of chorea, it has been suggested that anticholinergic property of antihistamine drugs can lower the threshold for appearance of chorea by disruption of balance between dopamine and acetylcholine activities in the striatum.[3,4] This hypothesis is also supported by a report of case series that chorea is induced by anticholinergics.[6] Even though our patient took a relatively large dose of antihistamines, central anticholinergic syndrome was not observed except for mild gastrointestinal symptoms of nausea and abdominal discomfort. Thus, other mechanisms beside the anticholinergic property may also play a role in the development of chorea by antihistamine drugs. There is in vivo evidence that H1-receptor antagonist increases the level of dopamine in the neostriatum[7] as well as clinical evidence that dopaminergic blocking agents suppress chorea.[1] In this regard, it is possible that antihistamine drugs acting mainly on H1 receptors may increase the level of dopamine in addition to decrease of cholinergic activity in the striatum and thus lead to development of chorea in our patient.

We believe that chorea in our patient is associated with antihistamine drugs. As antihistamines are used widely in allergies, it is worthy to note that antihistamines may induce chorea.

Legends to the Video

Segment 1. Chorea on the day of admission.

Additional supporting information may be found in the online version of this article.

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Segment 2. Improving chorea on the day before discharge.

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Ropinirole Diminishes Myoclonus and Improves Writing and Postural Balance in an ULD Patient

Video 

Unverricht-Lundborg disease (ULD) is a progressive neurodegenerative disease with cystatin-B pathology,[1] characterized by fragmentary and multifocal stimulus-sensitive myoclonic seizures. Treatment of myoclonus tends to be refractory and resistant to conventional antiepileptic medications. A common deficit in striatal dopaminergic inhibitory neurotransmission may play a role in myoclonus of PME.[2] A recent PET-imaging study of ULD patients demonstrated exceptionally high D2-like dopamine receptor binding activity in the striatum and thalamus,[3] suggesting dopamine depletion or upregulation of the receptor density/affinity.

We hypothesized that dopamine D2-receptor agonism could alleviate myoclonic jerks by modulating neurotransmission at thalamo-striatal level. As a part of our undergoing project to further characterize ULD, we evaluated the effect of a dopamine D2-receptor agonist, ropinirole, on symptoms of an ULD patient. The patient's clinical picture was profoundly characterized by stimulus-sensitive myoclonic jerks with clinical features of positive and negative myoclonus. Quality of life was significantly diminished by severe postural instability with frequent falls, decreased competence to look after own bodily needs, and inability to eat and write due to myoclonus. The patient had had no generalized epileptic seizures for years. Patient's daily antiepileptic medication was levetiracetam 3,000 mg, valproate 3,800 mg, and clonazepam 11 mg. The patient underwent a 10-week add-on treatment with a titrated daily dose of 4 mg of slow-release ropinirole. The patient also gave her informed consent for a video recording to objectively evaluate the possible effect of add-on ropinirole on myoclonic jerks and well-being of the patient. At the end of the 10-week treatment period, the patient felt improvement in the quality of life based on her opinion on the improved ability to walk, to eat without assistance, and to keep diary in handwriting. Fear of falls also decreased concomitantly. The patient's caregiver reported the same observations. The patient tolerated add-on 4 mg slow-release ropinirole well without any side effects.

In the accompanied video recordings before and during the add-on ropinirole, we observed diminished positive and negative myoclonic jerks, improved writing capabilities, and decreased unsteadiness in gait. The patient also underwent a separate placebo-controlled trial of ropinirole, during which EEG recordings were also available. These demonstrated marked decrease in myoclonic discharges during ropinirole treatment in comparison to baseline and placebo period (unpublished observation). After the study period, the patient was willing to continue on ropinirole treatment, thus strengthening the concept that the treatment is of benefit for the

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patient. In previous studies, dopaminergic therapy has either improved[4] or worsened myoclonus,[5] depending on the pathophysiology of the disease. Levodopa and apomorphine treatments have been reported to alleviate myoclonus in ULD.[3,6,7]

LEGENDS TO THE VIDEO

In the first part of the video, the patient is on her regular medication. On the second part, the patient has received a 10-week additional once daily add-on slow-release ropinirole of 4 mg. The patient tolerated the medication well without any side effects. She reported improved gait, writing, ability to keep diary in handwriting, and ability to eat independently. In the video, the patient performs drawings according to a Unified Myodlonus Rating Scale test.

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