Musician’s Dystonia and Comorbid Anxiety: Two Sides of One Coin?

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ABSTRACT

Background: Psychological abnormalities, including anxiety, have been observed in patients with musician’s dystonia (MD). It is unclear if these conditions develop prior to MD or if they are psychoactive phenomena.

Methods: Psychological conditions were studied in 44 professional musicians with MD, 45 healthy musicians, and 44 healthy nonmusicians using the State-Trait Anxiety Inventory (STAI) and NEO Five-Factor Inventory (NEO-FFI).

Results: Musicians with MD had significantly higher STAI state and trait anxiety scores than healthy musicians (P = .009 and P = .012, respectively) and nonmusicians (P = .013 and P = .001, respectively) and significantly higher NEO-FFI neuroticism scores than healthy musicians (P = .018) and nonmusicians (P = .001). Duration of dystonia did not correlate with anxiety or neuroticism scores.

Conclusions: Musicians with MD display increased levels of anxiety and neuroticism. The lack of correlation between anxiety and the duration of dystonia suggests that anxiety may not be a psychoactive phenomenon and is consistent with the hypothesis that anxiety and MD share a common pathophysiological mechanism. © 2011 Movement Disorder Society.

Key Words: zydystonia; musician; psychology; anxiety; State-Trait Anxiety Inventory; NEO-Five-Factors Inventory

Focal dystonia (FD) in musicians, also called musician’s dystonia (MD), is a task-specific movement disorder characterized by painless muscular incoordination of extensively trained movements.¹⁻⁴ Involuntary flexion or extension of individual fingers or loss of control of the muscles involved in the embouchure in affected musicians can lead to impaired technical performance on the instrument.¹⁻⁴ Musicians with FD are therefore often unable to continue their careers as performing artists.⁵,⁶

Several published studies have examined psychological conditions in patients with FD. Increased prevalence of anxiety, social phobia, and depression has been reported in patients with cervical dystonia, blepharospasm, and writer’s cramp.⁷⁻¹¹ Obsessive compulsive disorder (OCD) has been reported to be more common in patients with idiopathic focal dystonia and myoclonus-dystonia than in controls.¹²⁻¹⁵ Increased odds of social phobia, agoraphobia, panic disorder, and OCD was found in patients with cervical dystonia and blepharospasm compared with population-based controls.¹⁴ Based on a comparison of self-reported age of onset of psychiatric abnormalities and of FD, the authors concluded that most psychiatric abnormalities were present prior to the onset of FD.¹⁴

Only 2 studies have focused specifically on psychological conditions in musicians with FD, reporting that musicians with FD more commonly exhibited specific phobias, anxiety, and perfectionism than did controls.¹⁵,¹⁶ However, these studies were limited by their relatively small sample size and lack of use of validated questionnaires to evaluate the mentioned psychological characteristics.

The present study was designed to investigate psychological abnormalities in a larger group of musicians with FD compared with healthy musicians and healthy nonmusicians, using validated questionnaires. We hypothesized that a significantly higher degree of anxiety and other psychological conditions are present in musicians with FD.

Patients and Methods

Patients

Patients were recruited from the outpatient clinic of the Hannover Institute of Music Physiology and Musicians’ Medicine. All patients underwent complete neurological evaluations and were diagnosed with MD by at least 1 of the authors (E.A.). Patients with other neurological disorders or secondary dystonias or psychiatric diseases were excluded from the study.
Forty-four professional musicians (26 men, 18 women; mean age ± SD, 40.2 ± 9.2 years; age range, 23–64 years) with MD were enrolled in the study. MD presented as hand dystonias in 40 and as embouchure dystonia in 4 musicians. At the time of the study, the mean duration of the disorder was 9.3 years (SD, 8.1 years; range, 0–37 years).

**Controls**

Two control groups were enrolled in the study. The first control group consisted of healthy professional musicians recruited from German orchestras and music schools, and the second group consisted of healthy nonmusician university graduates. Potential controls were excluded if they reported a history of neurological or psychiatric diseases. All groups were matched for age and sex.

The healthy musician group consisted of 45 professional musicians (27 men, 18 women; mean age ± SD, 41.5 ± 12.6 years; age range, 20–68 years). This group was also matched by instrument family to the MD group. The healthy nonmusician group consisted of 44 university graduates (27 men, 17 women; mean age ± SD, 41.7 ± 16.2 years; age range, 21–76 years).

Details of all 3 groups are given in Table 1. Informed consent was obtained from all subjects before study participation. The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Psychological Assessment**

Assessment of personality and anxiety was performed using the revised German version of the self-administered NEO Five-Factor Inventory (NEO-FFI) and the State-Trait-Anxiety Inventory (STAI), respectively. Questionnaires were distributed and collected by mail and were accompanied by detailed written instructions in the German language. All subjects were able to speak, read, and write German fluently.

The NEO-FFI is a multidimensional personality inventory that consists of 12 items (descriptions of behaviors), scored on 5-point Likert scales in each of 5 personality domains: (1) extraversion, (2) agreeableness, (3) conscientiousness, (4) neuroticism, and (5) openness to experience. The NEO-FFI has been shown to be reliable, valid, and consistent.

The STAI is designed to distinguish chronic, or trait, anxiety (a general propensity to be anxious), from temporary, or state anxiety. The STAI consists of 20 trait and 20 state anxiety statements, scored on 4-point Likert scales, that assess how respondents feel “generally” and “right now, at this moment.” The STAI has been shown to be reliable, valid, and responsive to clinical change.

**Table 1. Patient and control characteristics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MD</th>
<th>HM</th>
<th>NM</th>
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</thead>
<tbody>
<tr>
<td>Number</td>
<td>44</td>
<td>45</td>
<td>44</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>26/18</td>
<td>27/18</td>
<td>27/17</td>
</tr>
<tr>
<td>Age, y (mean ± SD)</td>
<td>40.2 ± 9.2</td>
<td>41.5 ± 12.6</td>
<td>41.7 ± 16.2</td>
</tr>
<tr>
<td>Age, y (min/max)</td>
<td>23/64</td>
<td>20/68</td>
<td>21/76</td>
</tr>
<tr>
<td>Woodwind instruments (n)</td>
<td>16</td>
<td>15</td>
<td>—</td>
</tr>
<tr>
<td>String instruments (n)</td>
<td>14</td>
<td>14</td>
<td>—</td>
</tr>
<tr>
<td>Brass instruments (n)</td>
<td>4</td>
<td>6</td>
<td>—</td>
</tr>
<tr>
<td>Plucking instruments (n)</td>
<td>5</td>
<td>5</td>
<td>—</td>
</tr>
<tr>
<td>Keyboard instruments (n)</td>
<td>4</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>Drums (n)</td>
<td>1</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Age at onset of dystonia, y (mean ± SD)</td>
<td>30.9 ± 8.9</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Duration of dystonia, y (mean ± SD)</td>
<td>9.3 ± 8.1</td>
<td>—</td>
<td>—</td>
</tr>
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</table>

MD, musicians with dystonia; HM, healthy musicians; NM, healthy nonmusicians; y, years; SD, standard deviation.

**Statistical Analyses**

Comparison of NEO-FFI and STAI scores between the dystonia and control groups was performed using the Kruskal–Wallis test and the post hoc Tamhane’s T2 test. The Kruskal–Wallis test was chosen because of heterogeneity of variances demonstrated for age and the NEO-FFI extraversion subscale using the Levene test. Correlation was determined using Spearman’s $r$. $P < .05$ was considered statistically significant.

**Results**

All components of the questionnaires were completed by all subjects. Musicians with dystonia had significantly higher NEO-FFI neuroticism subscale scores than healthy musicians ($P = .018$) or nonmusicians ($P = .001$); see Figure 1. There was no significant difference in neuroticism scores between healthy musicians and nonmusicians ($P = .790$) or between subject groups on any of the other NEO-FFI subscales.

Musicians with dystonia had significantly higher STAI state and trait anxiety subscale scores than healthy musicians ($P = .009$ and $P = .012$, respectively) or nonmusicians ($P = .013$ and $P = .001$, respectively); see Figure 1. There was no significant difference in state and trait anxiety scores between healthy musicians and nonmusicians ($P = .997$ and $P = .614$, respectively).

There was no significant correlation between the duration of dystonia and NEO-FFI neuroticism subscale scores (Spearman’s $r = 0.005$, $P = .976$). Negative correlation was found between the duration of dystonia and the openness subscale (Spearman’s $r = -0.268$), and this correlation approached statistical significance ($P = .079$). There was a negative correlation between age and openness in musicians with
dystonia (Spearman’s $r = -0.363$, $P = .016$) but no correlation between age and openness in the control groups. There was no correlation between duration of dystonia and state or trait anxiety.

**Discussion**

In this study of psychological conditions in MD, affected musicians showed a higher degree of state and trait anxiety and neuroticism than did healthy musicians and nonmusician controls. Our results showing increased anxiety in musicians with MD are supported by conclusions of prior publications that reported significantly greater anxiety in musicians with MD compared with healthy musicians. Increased anxiety has also been reported in patients with other dystonias.

The cross-sectional nature of this study precludes a definitive determination of whether or not anxiety or neuroticism was present before the onset of MD. However, trait anxiety and neuroticism scores were significantly elevated in MD patients, and there was no correlation between neuroticism or anxiety scores and duration of MD. These results are consistent with studies of nonmusician patients with anxiety and other forms of FD, which reported that anxiety did not develop after the onset of FD, suggesting that anxiety is not a psychoreactive phenomenon.

A shared underlying mechanism for the development of MD and anxiety may exist, as reported for some forms of monogenic dystonia such as myoclonus-dystonia. Transcranial magnetic stimulation and electroencephalogram studies have provided evidence of decreased cortical inhibition in FD. Decreased cortical inhibition has also been observed in subjects with trait-related anxiety. It has been suggested that reduced cortical inhibition may play a role in the pathophysiology of both FD and anxiety. Specifically, abnormal neural activity in motor loops linking the basal ganglia to the frontal cortex via the thalamus may additionally influence limbic loops, resulting in both altered motor and affective processing.

Strengths of this study include a relatively large sample size and use of reliable and valid questionnaires for the evaluation of personality and anxiety. Limitations include the cross-sectional nature of this study and the resultant difficulty in characterizing temporal associations between psychological disorders and FD. The relatively low prevalence of FD in musicians presents a barrier to the study of FD in musicians in a prospective manner.

**Conclusions**

Musicians with FD showed significantly higher values of neuroticism, state anxiety, and trait anxiety than did healthy musician and non-musician controls. There was no significant correlation between neuroticism or anxiety and duration of focal dystonia, but...
there was a negative correlation between openness to experience and duration of focal dystonia that approached statistical significance. These results raise the possibility that openness to experience is a psychoreactive phenomenon as a consequence of MD, whereas other psychological conditions, including neuroticism and anxiety, do not represent psychoreactive phenomena. The hypothesis of a potential common pathophysiological mechanism of anxiety and MD should be further investigated.

References

Cysteinyl-Glycine Reduction as Marker for Levodopa-Induced Oxidative Stress in Parkinson’s Disease Patients

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\textbf{ABSTRACT}

Oxidative stress is influenced by the thiol homeostasis, which determines the redox milieu. One of its components is Cysteinyl-glycine (Cys-Gly) generation, as its metabolic precursor is the free radicals scavenging glutathione. Levodopa is under suspicion to promote oxidative
untreated, 9 were on a chronic drug regimen for treatment of PD (L-dopa/DDI [monotherapy, N = 1] plus various dopamine agonists [8]). Exclusion criteria were prior exposure to neuroleptics or any other drugs, which aggravate motor symptoms in PD patients, clinical signs of dementia, any electrophysiological or morphological evidence of additional CNS pathology exceeding PD. Patients fulfilled clinical diagnostic UK Brain bank criteria for PD.4

Table 1. Clinical characteristics

<table>
<thead>
<tr>
<th>Age</th>
<th>60.7 ± 11.1, 41 – 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>12 men, 3 women</td>
</tr>
<tr>
<td>Hoehn and Yahr stage</td>
<td>2.3 ± 0.9, I–III</td>
</tr>
<tr>
<td>UPDRS I</td>
<td>2.1 ± 1.9, 0 – 6</td>
</tr>
<tr>
<td>UPDRS II</td>
<td>14.8 ± 12.2, 5 – 52</td>
</tr>
<tr>
<td>UPDRS III</td>
<td>22.3 ± 11.6, 7 – 42</td>
</tr>
<tr>
<td>UPDRS IV</td>
<td>0.8 ± 0.8; 0 – 2</td>
</tr>
<tr>
<td>Duration of disease</td>
<td>5.8 ± 5.48; 0 – 13</td>
</tr>
</tbody>
</table>

All data are shown as mean ± standard deviation, range; UPDRS = Unified Parkinson’s disease rating scale; I (mentation, behavior, and mood), II (activities of daily living), III (motor examination), IV (complication of therapy) = various parts of the UPDRS; duration of disease, respectively interval since definite clinical diagnosis of PD, is given in months.

Results

Cys-Gly concentrations decreased following L-dopa/CD intake (F(df 2, df 14) = 9.15, P < 0.0009; Fig. 1A). L-dopa (F(df 2, df 14) = 16.88, P < 0.0001; Fig. 1B) and 3-OMD levels (F(df 2, df 14) = 4.92, P < 0.015; Fig. 1C) increased. There were inverse relationships between computed differences of Cys-gly and 3-OMD appearance ([Baseline – 120] R = −0.52; P = 0.046; [60 – 120] R = −0.74; P = 0.0001). Sex, age, body weight, duration of disease, and UPDRS-scores did not influence our results.

Discussion

We show a decay of free Cys-Gly plasma concentrations following one oral L-dopa/CD tablet intake under standardized conditions. As a result, a rise of L-dopa and 3-OMD plasma levels also took place. Hypothetically, these reactions may also occur within the brain, as L-dopa is converted to dopamine in tyrosine hydroxylase-containing dopaminergic neurons and then is further metabolized in glial cells by MAO-B after leaving the synaptic cleft. This metabolic pathway of dopamine degradation is associated with free radical generation.5 The observed, inverse correlations between computed differences of the Cys-Gly and 3-OMD levels between various assessments moments support this putative link between L-dopa metabolism with associated excessive dopamine synthesis and related oxidative stress.5,6 This increased ROS
synthesis may particularly occur in locally degenerated neuronal areas, like in the nigrostriatal system of PD patients. In these areas, higher oral \( \text{L-dopa/DDI} \) intake may result in a dopamine related elevated ROS synthesis. As a consequence, an altered regulation of redox processes, which also involve the GSH system, may occur.

In contrast to our present outcomes, which demonstrate a decrease of free Cys-Gly after acute \( \text{L-dopa/CD} \) intake, earlier trials showed no variation of total Cys-Gly levels compared with normal controls. In one study, blood samples were drawn in the morning only once following an overnight withdrawal of all prior antiparkinsonian medication and before an acute oral \( \text{L-dopa/DDI} \) application. Another study also showed no differences of total Cys-Gly levels in relation to previous chronic \( \text{L-dopa/DDI} \) exposure. However, Cys-Gly in plasma was again measured only one time after an overnight withdrawal of \( \text{L-dopa/DDI} \) administration. However, in our present trial, we measured Cys-Gly in a repeated fashion to investigate the effects of an acute, oral \( \text{L-dopa/DDI} \) application. Similar to the outcomes of the correlation analyses in these earlier studies, we found no relationships to the clinical parameters of participating PD patients in this investigation. Moreover, we included a relative low number

**FIG. 1.** Cys-Gly (A), \( \text{L-dopa} \) (B), and 3-OMD (C) plasma levels after oral intake of 200 mg \( \text{L-dopa} \) intake combined with 50 mg carbidopa. * = \( P < 0.05 \); ** = \( P < 0.01 \); *** = \( P < 0.001 \); \( \text{L-dopa/3-OMD} \) plasma concentrations are given in \( \mu \text{g/mL} \), free Cys-Gly levels are reported in \( \mu \text{mol/L} \); * = \( P \)-values of the post hoc analysis with the Tukeys HSD test; \( \text{min} = \) minutes.
of participants, who were rather homogenous particularly in terms of prior chronic drug treatment. Nevertheless, we suggest that this study outcomes allow no conclusions on the effect of continuous L-dopa/DDI application on the free Cys-Gly synthesis, as adaptive oxidative stress reducing processes may occur with repeat oral L-dopa/DDI application.

We assume that the demonstrated free Cys-Gly reduction is predominantly caused by the redox property of mitochondrial dopamine synthesis after a single L-dopa/CD application. Therefore, it will probably also occur during repeated L-dopa/DDI application and makes the enzyme COMT, which metabolizes L-dopa. But this hypothesis has to be investigated in future trials. A further shortcoming of the present trial is the fact that our study conclusions are based on plasma and not on CSF levels. The value of our trial would also improve with additional assessment of free radical occurrence.

In conclusion, we show that acute L-dopa/DDI application reduces free Cys-Gly in plasma. This Cys-Gly decline may be linked to prior appearance of oxidative stress with concomitant consumption of antioxidants like GSH and subsequent conversion of this molecule to GSSG. Appearance of free radicals in not physiological concentrations is known to be involved in irregular harmful cellular metabolism, altered communication between cells and progression of neuronal degeneration in the brain of PD patients.

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References

Phenotypic Spectrum of Musician’s Dystonia: A Task-Specific Disorder?

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ABSTRACT

Background: Musician’s dystonia (MD) is traditionally considered a sporadic and task-specific movement disorder. Methods: The phenotypic spectrum of the disorder was studied in 116 patients suffering from MD including videotaping. Results: Based on the movement disorders observed, we categorized our patients into two different groups: (i) 65 patients with isolated MD, that is only present when playing the instrument and (ii) 51 patients with MD and one or more additional features of primary dystonia independent of MD (complex MD). Patients with a positive family history of movement disorders had an increased risk to develop complex MD [odds ratio = 4.80; 95% confidence interval: 1.94–11.92; P = 0.001]. Discussion: In previous studies, we recently identified 22 relatives with different types of movement disorders in the families of 28 MD patients. Taken together, our results further support a genetic contribution to MD with a broad individual and familial phenotypic spectrum consisting of MD, other dystonias and even other, non-dystonic movement disorders.
Dystonia is characterized by sustained muscle contractions causing twisting and repetitive movements and abnormal postures. Musician’s dystonia (MD) has the hallmark features of dystonia and may present with painless muscular incoordination when a musician is playing his instrument. It has been associated with intensive training regimes and thus traditionally been considered a sporadic and focal task-specific form of dystonia (FTSD). However, we have recently observed an aggregation of different types of movement disorders in professional musicians suffering from MD followed at the Hanover Institute of Music Physiology and Musicians’ Medicine. This video report aims to illustrate the broad phenotypic spectrum of MD is summarized in Table 1. Multivariate logistic regression analysis revealed an increased risk to develop complex MD for patients with a positive family history of movement disorders [odds ratio (OR) = 4.80; 95% confidence interval (CI): 1.94–11.92; P = 0.001] and patients with upper limb dystonia [OR = 3.57; 95%CI: 1.12–11.39; P = 0.031].

Patients and Methods

After obtaining written informed consent, MD patients were consecutively included in the study. Based on history and clinical features, all were classified as having primary dystonia. They underwent a detailed videotaped neurological examination by a movement disorder specialist (AS, EA). Our patients were categorized into two different groups on clinical grounds: (i) patients with isolated task-specific MD that is only present when playing the instrument and (ii) patients with MD and one or more additional features of primary dystonia independent of MD (other types of dystonia or tremor in the same or other body parts) (complex MD). Statistical multivariate logistic regression analysis adjusting for gender, age of onset, family history of movement disorders, and type of MD was performed to identify significant risk factors for the development of complex MD using SPSS (SPSS Inc, Chicago).

Results

A total of 116 MD patients (81 men, 35 women; age: 43.26 ± 12.04 [18–75] years; age of onset: 33.77 ± 10.92 [15–66] years; duration of dystonia: 9.50 ± 8.83 [0–42] years) were included in the study. Of these, 94 (81.0%) were affected with upper limb dystonia, mostly hand dystonia and 22 (19.0%) with embouchure dystonia. A positive family history of movement disorders was reported by 38 patients (32.8%). The GAG deletion in the DYT1 gene and mutations in THAP1 (DYT6) were absent in all probands. Isolated MD was present in 65/116 patients (56.0%, video segments 1, 2, 5, and 6), complex MD with one or more additional FTSD (e.g. writer’s cramp (WC)), other dystonias (e.g. blepharospasm, brachial dystonia; segments 3 and 4) or tremor in 51/116 patients (44.0%). In some of the complex cases, additional dystonias were the consequence of spread; conversely, some patients experienced dystonia outside the initially involved segment over the course of the disease. The observed phenotypic spectrum of MD is summarized in Table 1. Multivariate logistic regression analysis revealed an increased risk to develop complex MD for patients with a positive family history of movement disorders [odds ratio (OR) = 4.80; 95% confidence interval (CI): 1.94–11.92; P = 0.001] and patients with upper limb dystonia [OR = 3.57; 95%CI: 1.12–11.39; P = 0.031].

Discussion

The traditional concept of MD as a simple task-specific disorder that is solely “environmentally” acquired needs to be reconsidered. About 50% of our patients showed additional types of dystonia or tremor as shown in video segments 3 and 4. A recent detailed clinical examination of 101 MD patients revealed a similar number of patients (54%) suffering from secondary motor abnormalities in activities other than playing the instrument. Also, in about half of patients presenting with other forms of focal dystonia (e.g. blepharospasm), dystonia spreads during the first 5 years after disease onset.

In addition to the described individual aggregation of movement disorders in our patients, we recently also reported a familial clustering. The families of 28 MD index patients were examined using a standardized telephone screening interview for dystonia and videotaped neurological examinations. Besides the 28 index patients, we identified 22 relatives from 21 families with one or more different types of dystonia or even other, non-dystonic movement disorders or abnormalities (MD: n = 8, other FTSD: n = 9, other
dystonias: n = 2, other movement disorders: n = 3; video segments 5–8). In light of the observed familial aggregation of movement disorders and the association of a positive family history with the risk of spread of symptoms, a careful evaluation of the family history with possible examination of relatives may help to identify musicians at risk to develop (complex) MD. Our results further support a genetic contribution to MD with a broad individual and familial phenotypic spectrum consisting of MD, other dystonias and rarely even other, non-dystonic movement disorders.

Legends to the Video

Segment 1. Right-handed 47-year-old pianist with flexion dystonia of the right third finger and compensatory intermittent extension of the second and fourth finger when playing scales (age of onset: 42 years), more pronounced at increased tempo (here and in the following descriptions, the fingers one to five refer to thumb, index, middle, ring, and little finger, respectively). Playing scales with the left hand appears to be normal. Octaves and alternating chords played with the right hand cause hyperextension of the second finger and an abnormal, flexed posture of the third and fourth finger. Dystonic movements and postures improve when playing with a special ring on the third finger of the right hand (sensory trick).

Segment 2. Tubist with embouchure dystonia while playing the main theme of the prelude of Richard Wagner’s Mastersingers (age: 41 years, age of onset: 20 years). There is some pulling and also locking of the upper lip and some facial grimacing involving the orbicularis oris muscle, and there are also extra movements of the chin involving the mentalis muscle.

Segment 3. Right-handed 63-year-old pianist with MD and additional other dystonias (age of onset: 35 years). When holding out the arms in front of him, there is right-sided brachial dystonia with a slightly flexed posture of the fingers four and five. In addition, blepharospasm is present with excessive blinking and occasional cramping of the orbicularis oculi bilaterally. There is possibly also cervical dystonia with some abnormal tilt of the head to the left. While playing scales with the right hand, he shows flexion dystonia of fingers four and five and compensatory extension of finger three.

Segment 4. Right-handed 48-year-old pianist with severe bibrachial dystonia affecting the left arm both at rest and during different tasks associated with dystonic movements and the right hand during writing. At the age of 31 years dystonia first affected the performance of the patient, over the course of the disease dystonic symptoms spread. When playing piano there is a grossly abnormal posture of the left hand with hyperflexion at the wrist, flexion of the proximal and also the distal interphalangeal joints of the fingers. He is hardly able to use individual fingers, whereas the right hand is unaffected. When holding out the arms in front of his face, the left hand immediately adopts a similar hyperflexed dystonic posture, and there are occasional rapid piano-playing-like dystonic movements of all fingers. There is also some overflow activity involving the upper and the lower arm. When spreading his arms apart, there are again dystonic movements in the left arm/hand increasing during voluntary movements, e.g., finger-nose testing. Writing with the right hand is abnormal with some ulnar deviation at the wrist and overflow activity affecting the upper and lower arm and also the right shoulder which is elevated and brought forward. Also, he holds the pen between the second and the third finger. Writing and pouring water into a mug with the left hand are also hampered by dystonic posturing and movements.

Segment 5. Ambidextrous 43-year-old flutist, with slight flexion dystonia of the left third finger (age of onset: 35 years). When he is playing very fast, the third finger adopts a hyperflexed posture in the distal finger segments leading to subtle rhythmic changes and squalidness.

Segment 6. Monozygotic twin brother of the patient shown in segment 5, a right-handed flutist with the same type of flexion dystonia of the left third finger when playing scales at increased tempo (age of onset: 26 years).

Segment 7. Sister of a guitarist’s cramp patient, 46-years-old, ambidextrous, with right-sided WC and additional task-specific dystonias of the right hand and arm (age of onset: 33 years). There is dystonic posturing of the right thumb and index finger and intermittent extension of the wrist that become more severe with increasing time of writing. Dystonic movements and posturing are also present when typing on the keyboard or when cutting food. Hypertrophy of the wrist extensor muscles are observed on the right hand side.

Segment 8. Mother of a MD patient, 69-years-old, right-handed, with unusual dyskinesias and choreic movements involving facial muscles (age of onset: 40 years). When sitting on a chair and during rapid finger movements of both hands, there are involuntary mouth opening and closing movements and also pouting (mirror movements). Voluntary hand movements are slow, more pronounced on the right side. There is also slight postural instability and when walking slightly reduced right-sided armswing.

References

The C.-237_236GA>TT THAP1 Sequence Variant Does Not Increase Risk for Primary Dystonia

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DYT6 dystonia is an autosomal dominant primary dystonia causally associated with sequence variants in THAP1, which encodes the DNA-binding transcription factor THAP1.1–3 DYT6 dystonia shows reduced penetrance and variable expressivity.2–8 In contrast to DYT1 dystonia, DYT6 more commonly remains focal in distribution and often affects the cervical and laryngeal musculature.1,4,5 Over 30 sequence variants have been localized to the coding regions of THAP1 and associated with focal, segmental, multifocal, or generalized dystonia with age of onset ranging from 2 to 62 years.1–8 In addition, several asymptomatic carriers have been identified in the relatives of probands. The genotypic and phenotypic heterogeneity of DYT6 dystonia and variable penetrance of known coding variants suggest that noncoding variants in THAP1 could contribute to the risk of developing adult-onset primary dystonia.1,5,7 Given that THAP1 is a

ABSTRACT

Background: Sequence variants in coding and noncoding regions of THAP1 have been associated with primary dystonia.

Methods: In this study, 1,446 Caucasian subjects with mainly adult-onset primary dystonia and 1,520 controls were genotyped for a variant located in the 5′-untranslated region of THAP1 (c.-237_236GA>TT).

Results: Minor allele frequencies were 62/2892 (2.14%) and 55/3040 (1.81%) in subjects with dystonia and controls, respectively (P=0.202). Subgroup analyses by gender and anatomical distribution also failed to attain statistical significance. In addition, there was no effect of the TT variant on expression levels of THAP1 transcript or protein.

Discussion: Our findings indicate that the c.-237_236GA>TT THAP1 sequence variant does not increase risk for adult-onset primary dystonia in Caucasians. © 2011 Movement Disorder Society

Key Words: dystonia; DYT6; high-resolution melting; untranslated region; THAP1
transcriptional repressor, it is conceivable that non-coding variants which cause minor quantitative changes in the temporal or spatial patterns of THAP1 expression could have broad effects on the transcriptome.

Djarmati et al. identified a noncoding sequence variant (c.-237_236GA > TT) near the transcriptional start site of THAP1 that might increase the risk of developing primary dystonia. The relative frequency of this polymorphism in their subjects with dystonia (20/320) relative to controls (7/355) was noteworthy (P = 0.0054). Extrapolation of their findings to a broad population of late-onset primary dystonia is problematic given that the subjects with dystonia were relatively young (mean age of onset = 38.5 years) and predominantly were Northern German individuals whereas the control group was composed of Caucasian individuals of more diverse European ancestry. Another, relatively small case–control study with heterogeneous control and dystonia populations did not find an association between the TT allele and risk for dystonia.

Herein, we present the results of a large case–control study of c.-237_236GA > TT in primary, mainly adult-onset dystonia. All subjects were Caucasians. Moreover, the effects of the TT variant on overall gene expression (transcript) were interrogated in leukocytes and replicated in lymphoblastoid cell lines (transcript and protein) derived from distinct cohorts of cases and controls.

### Patients and Methods

#### Participants

All human studies were conducted in accordance with the Declaration of Helsinki with formal approval from the institutional review boards at each participating study site. All subjects gave written informed consent. Recruitment of patients with primary dystonia and neurologically normal controls is described in the study of Xiao et al. Additional Caucasian control samples were obtained from Sigma-Aldrich (Human Random Control DNA Panels 1, 3, and 4), Emory Center for Neurodegenerative Disease Tissue Bank Core, Washington University in St. Louis School of Medicine Neuroscience Blueprint Core, and Coriell Institute for Medical Research (Control Panels NDPT020 and NDPT024). All normal controls except those from Sigma-Aldrich were examined to exclude dystonia and other neurological disorders. Demographics for dystonia and control subjects are

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### Table 1. Clinical diagnoses, demographics, genotypes, and allele frequencies in dystonia and controls

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Number</th>
<th>Age of onset</th>
<th>Family history</th>
<th>Minor allele frequency (TT)</th>
<th>Genotypes</th>
<th>P value</th>
<th>M</th>
<th>F</th>
<th>All</th>
<th>GA/GA</th>
<th>GA/TT</th>
<th>TT/TT</th>
<th>M</th>
<th>F</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spasmodic dysphonia</td>
<td>464</td>
<td>(64.6 ± 16.0, 4–75)</td>
<td>7.2%</td>
<td>4/214 (1.9%)</td>
<td>25/714 (2.9%)</td>
<td>439/464 (94.6%)</td>
<td>25/464 (5.4%)</td>
<td>0/464 (0%)</td>
<td>0.501</td>
<td>0.082</td>
<td>0.064</td>
<td></td>
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<tr>
<td>Cervical dystonia</td>
<td>490</td>
<td>(64.5 ± 15.9, 4–70)</td>
<td>6.8%</td>
<td>4/230 (1.7%)</td>
<td>12/750 (1.6%)</td>
<td>474/490 (96.7%)</td>
<td>16/490 (3.3%)</td>
<td>0/490 (0%)</td>
<td>0.554</td>
<td>0.359</td>
<td>0.581</td>
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<tr>
<td>Blepharospasm</td>
<td>197</td>
<td>(64.3 ± 11.6, 20–72)</td>
<td>9.5%</td>
<td>3/122 (2.5%)</td>
<td>4/272 (1.5%)</td>
<td>190/197 (96.4%)</td>
<td>7/197 (3.6%)</td>
<td>0/197 (0%)</td>
<td>0.356</td>
<td>0.17</td>
<td>0.619</td>
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<tr>
<td>Hand-forearm dystonia</td>
<td>52</td>
<td>(64.6 ± 15.9, 4–70)</td>
<td>15.9%</td>
<td>2/46 (4.3%)</td>
<td>2/58 (3.4%)</td>
<td>50/52 (96.2%)</td>
<td>2/52 (3.8%)</td>
<td>0/52 (0%)</td>
<td>0.435</td>
<td>0.197</td>
<td>0.581</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Oromandibular dystonia</td>
<td>17</td>
<td>(64.5 ± 11.6, 20–72)</td>
<td>16.2%</td>
<td>0/8 (0%)</td>
<td>0/26 (0%)</td>
<td>17/17 (100%)</td>
<td>0/17 (0%)</td>
<td>0/17 (0%)</td>
<td>0.571</td>
<td>0.359</td>
<td>0.42</td>
<td></td>
<td></td>
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<tr>
<td>Other primary dystonia</td>
<td>36</td>
<td>(64.6 ± 16.0, 4–75)</td>
<td>13.9%</td>
<td>1/28 (3.6%)</td>
<td>1/44 (2.3%)</td>
<td>34/36 (94.4%)</td>
<td>2/36 (5.6%)</td>
<td>0/36 (0%)</td>
<td>0.385</td>
<td>0.58</td>
<td>0.382</td>
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<tr>
<td>Segmental dystonia</td>
<td>140</td>
<td>(64.5 ± 15.9, 4–70)</td>
<td>13.2%</td>
<td>1/92 (1.1%)</td>
<td>6/188 (3.2%)</td>
<td>134/140 (95.7%)</td>
<td>5/140 (3.6%)</td>
<td>1/140 (0.7%)</td>
<td>0.546</td>
<td>0.263</td>
<td>0.537</td>
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</tr>
<tr>
<td>Multifocal dystonia</td>
<td>24</td>
<td>(64.5 ± 11.6, 20–72)</td>
<td>22.2%</td>
<td>0/16 (0%)</td>
<td>2/32 (6.3%)</td>
<td>22/24 (91.7%)</td>
<td>2/24 (8.3%)</td>
<td>0/24 (0%)</td>
<td>0.476</td>
<td>0.197</td>
<td>0.292</td>
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<tr>
<td>Generalized dystonia</td>
<td>26</td>
<td>(64.6 ± 15.9, 4–70)</td>
<td>13.3%</td>
<td>1/24 (4.2%)</td>
<td>0/28 (0%)</td>
<td>25/26 (96.2%)</td>
<td>1/26 (3.8%)</td>
<td>0/26 (0%)</td>
<td>0.342</td>
<td>0.581</td>
<td>0.571</td>
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<td></td>
</tr>
<tr>
<td>Dystonia totals</td>
<td>1446</td>
<td>(64.5 ± 15.9, 4–70)</td>
<td>9.1%</td>
<td>14/780 (1.8%)</td>
<td>48/2112 (2.3%)</td>
<td>62/2892 (2.1%)</td>
<td>1385/1446 (95.8%)</td>
<td>60/1446 (4.1%)</td>
<td>0.476</td>
<td>0.26</td>
<td>0.29</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologically normal controls</td>
<td>1520</td>
<td>(64.5 ± 15.9, 4–70)</td>
<td>NA</td>
<td>22/1320 (1.7%)</td>
<td>33/1720 (1.9%)</td>
<td>55/3040 (1.8%)</td>
<td>1465/1520 (96.4%)</td>
<td>55/1520 (3.6%)</td>
<td>0.476</td>
<td>0.26</td>
<td>0.29</td>
<td></td>
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</tbody>
</table>

**M**: male; **F**: female.

*Mean age at study enrollment ± standard error of the mean (SEM), range (yr).

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presented in Table 1. Of note, Table 1 does not include family members of probands.

**High-Resolution Melting**

High-resolution melting (HRM) analyses were performed with the LightCycler 480 Real-Time PCR system and High-Resolution Master Mix (Roche Indianapolis, IN) in accordance with manufacturer’s instructions and our laboratory protocol using forward (acctggctcgcaaatag) and reverse (ctgccccttggtggtg) primers designed to amplify the 3′-untranslated region (UTR) of THAP1. Melting curves and difference plots were analyzed by three investigators (J.X., Y.Z., and M.S.L.) blinded to phenotype. All samples were unambiguously assigned to genotypes by Gene Scanning Software (Roche). For samples with shifted melting curves, PCR products were cleaned using ExoSAP-IT (United States Biochemical, Cleveland, OH) and sequenced in the forward and reverse directions. To evaluate the sensitivity and specificity of HRM, amplicons from 400 neurologically normal controls and 400 subjects with dystonia were subjected to Sanger sequencing. Fisher’s exact test was used to evaluate association of the c.-237_236GA sequence variant with dystonia. The Genetic Power Calculator, case–control discrete traits module, was used for power analysis.

**THAP1 Expression**

Ambion’s LeukoLOCK Total RNA Isolation System and TRI Reagent (Ambion, Inc., Austin, TX, United States) were used to isolate RNA from peripheral blood leukocytes of dystonia subjects and controls. Leukocyte RNA was used to evaluate the effects of the TT allele on THAP1 expression in dystonia subjects with the TT allele (n = 20) and controls without the TT allele (n = 24). RNA and protein were also extracted from lymphoblastoid cells derived from another 5 patients with the TT allele and 10 normal controls without the TT allele. Sanger sequencing was used to exclude coding, splice-site, 3′-UTR, and previously reported intronic sequence variants (c.71+9C>A, c.71+126T>C) from the control and dystonia groups. Detailed protocols for maintenance of lymphoblastoid cell lines, quantitative real-time PCR, and quantitative Western blotting are provided in Supporting Information Methods. Student’s t-tests were used to compare RNA and protein expression between dystonia and control samples. G*Power 3 was used for post hoc power analysis.

**Results**

As depicted in Supporting Information Figure 1, melting curves robustly discriminated GA/GA homozygotes from heterozygotes (GA/TT) and homozygotes of the minor allele (TT/TT). Furthermore, different plots clustered these genotypes into three discrete groups. Based on follow-up sequencing of samples exhibiting shifted melting curves and sequencing data from 400 neurologically normal controls and 400 subjects with dystonia, HRM showed 100% diagnostic specificity and sensitivity.

As detailed in Table 1, only one subject with dystonia was homozygous for the TT allele whereas 60 were GA/TT heterozygotes. TT allelic frequencies were 62/2892 (2.14%) in subjects with dystonia and 55/3040 (1.81%) in controls. A one-tailed Fisher’s exact test failed to confirm nonrandom associations between the TT allele and dystonia (P = 0.202). Subgroup analyses for laryngeal dystonia, cervical dystonia, blepharospasm, hand-forearm dystonia, segmental dystonia, multifocal dystonia, and generalized dystonia also failed to attain statistical significance in both male and female subjects (P > 0.06, for all). Of note, with a Bonferroni correction for multiple comparisons, a P value less than 0.05/12 (0.0042) would be required to maintain a type I error rate (α) of 0.05 for the subgroup analyses. Using a conservative population prevalence for primary dystonia of 1/10,000 and an α of 0.05, our case–control cohort had over 95% power to detect a twofold relative risk of the TT allele. As seen in Table 2, there was no effect of the TT allele on THAP1 mRNA expression levels in either leukocytes or lymphoblastoid cell lines. Moreover, there was no statistically significant effect of the TT allele on expression of THAP1 protein (Supporting Information Figure 2). Post hoc power analysis

### Table 2. Effect of the c.-237_236GA>TT sequence variant on relative THAP1 expression levels in leukocytes and lymphoblastoid cells

<table>
<thead>
<tr>
<th>Genotype/phenotype</th>
<th>RNA leukocytes</th>
<th>RNA lymphoblastoid cell lines</th>
<th>Protein lymphoblastoid cell lines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterozygous c.-237_236GA &gt; TT</td>
<td>1.043 ± 0.036&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.973 ± 0.065</td>
<td>0.811 ± 0.146</td>
</tr>
<tr>
<td>Primary dystonia</td>
<td>(n=20)</td>
<td>(n=5)</td>
<td>(n=5)</td>
</tr>
<tr>
<td>Homozygous GA allele</td>
<td>1.011 ± 0.032</td>
<td>1.020 ± 0.065</td>
<td>1.000 ± 0.074</td>
</tr>
<tr>
<td>Neurologically normal controls</td>
<td>(n=24)</td>
<td>(n=10)</td>
<td>(n=10)</td>
</tr>
<tr>
<td>P value*</td>
<td>0.508</td>
<td>0.617</td>
<td>0.292</td>
</tr>
</tbody>
</table>

<sup>1</sup>All values are means ± SEM.
<sup>*</sup>Difference between dystonia and control samples.
with an effect size (d) of 0.20 showed that our comparison of leukocyte mRNA expression levels was weakly powered (1 - β = 0.10).

Discussion

THAP1 encodes a 213-residue transcription factor, which contains a highly conserved DNA sequence-specific zinc-dependent THAP domain (1-81aa), a proline-rich region, a nuclear localization signal (146-162aa), and a coiled-coil domain. Overexpression of THAP1 in endothelial cells was used by Cayrol et al. as an indirect means of identifying THAP1 targets. Downregulated genes were concentrated in classes related to cell-cycle/cell proliferation and the majority were also regulated by the pRB/E2F pathway. THAP1 knockdown was associated with decreased expression of eight pRB/E2F cell-cycle target genes. These data suggest that THAP1 promoter, UTR, and intronic sequence variants associated with alterations in THAP1 expression may exert deleterious effects on neural function and/or neural development and serve as risk factors for dystonia. However, based on the data presented herein, the c.-237_236GA>T variant does not appear to exert important effects on either transcription or translation in leukocytes and lymphoblastoid cell lines.

In contrast to previous investigations of the c.-237_236GA>T THAP1 sequence variant, our study was much larger and focused on late-onset dystonia. The previously described cohorts from Germany and England contained a higher percentage of subjects with generalized, segmental, and multifocal dystonia. Although the GA>T variant did not increase overall risk in our cohort of Caucasian subjects, we did not eliminate the possibility that this variant could contribute to dystonia risk in other populations. Similarly, several of our anatomical subgroups may have been underpowered to detect a small effect. Moreover, it is possible that the effect size of the TT allele on THAP1 expression is developmentally regulated in a tissue-specific fashion. Ideally, RNA and protein expression should be examined in several regions of human brain from individuals with GA/GA and GA/TT genotypes at several time points during development. Given the important role for THAP1 in primary dystonia, other sequence variants in promoter, UTR, and intronic regions of THAP1 are also worthy of investigation.

References

Novel Mutations in SPG11 Cause Hereditary Spastic Paraplegia Associated with Early-Onset Levodopa-Responsive Parkinsonism

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ABSTRACT

Background: Autosomal recessive hereditary spastic paraplegia with thin corpus callosum is a neurodegenerative disorder characterized by spastic paraparesis, cognitive impairment, and peripheral neuropathy. The neuroradiologic hallmarks are thin corpus callosum and periventricular white matter changes. Mutations in the SPG11 gene have been identified to be a major cause of autosomal recessive hereditary spastic paraplegia with thin corpus callosum and recently also proven to be responsible for juvenile parkinsonism associated with spastic paraplegia.

Methods: We describe one Italian autosomal recessive hereditary spastic paraplegia with thin corpus callosum patient who unusually presented at onset, 16 years, with parkinsonism-like features, responsive to dopaminergic therapy. Then the clinical picture evolved and became more complex. A brain magnetic resonance imaging scan showed thin corpus callosum and hyper-intense T2-weighted lesions in periventricular regions, and the 123I-ioflupane single-photon emission coupled tomography was abnormal.

Results: Genetic analysis detected two novel mutations, a c.3664insT variant in compound heterozygosity with a c.6331insG mutation, in SPG11.

Discussion: This case confirms the high genetic and clinical heterogeneity associated with SPG11 mutations. It also offers further evidence that parkinsonism may initiate autosomal recessive hereditary spastic paraplegia with thin corpus callosum and that parkinsonian symptoms can have variable dopaminergic response in these patients.

Key Words: parkinsonism; levodopa; spastic paraplegia; SPG11; thin corpus callosum

Hereditary spastic paraplegias (HSPs) are heterogeneous neurodegenerative disorders characterized by a wide clinical and genetic heterogeneity.1,2 Both pure and complicated forms are recognized, depending on whether the spastic paraplegia occurs in isolation or is combined with other neurological or extraneurological features.3

Among the rare recessive HSP forms, autosomal recessive (AR)-HSP with thin corpus callosum (TCC) (MIM 604360) presents with early-onset involvement of corticospinal tract and muscle stiffness followed by a slow development of progressive paraparesis, cognitive deterioration, and predominantly axonal motor or sensorimotor peripheral neuropathy.4 Thinning of the anterior corpus callosum (TCC) and white matter abnormalities are the most useful neuroradiological criteria to propose a diagnosis of AR-HSP-TCC.5 So far, mutations in SPG11 on chromosome 15q (MIM610844) represent the most common cause of AR-HSP, with or even without TCC,6 with a higher than expected frequency in the Mediterranean area.7,8 In AR-HSP-TCC, learning disabilities or stiff legs or both represent the commonest symptoms at onset, but atypical presentations,9 also including juvenile parkinsonism,10 have been recently described.

Here we present the clinical features and the molecular genetic data of a patient affected by SPG11 who initially displayed a juvenile levodopa-responsive parkinsonism in association with HSP.

Patients and Methods

Case

The patient, a 32-year-old Italian woman, offspring of a second-degree consanguineous marriage, was born by spontaneous delivery and had a normal, early psychomotor development. Her parents report poor scholastic performances even since primary school.
At age 14, the patient was referred to a neurologist because of abnormal gait and progressive rigidity in her lower limbs. Later on, she presented dysarthria, bilateral resting tremor, and mild bradykinesia in her upper limbs. The disease rapidly progressed, so that 2 years from onset she could no longer walk without support.

At age 16, she started a treatment with levodopa (titrated up to 100 mg t.i.d.) with significant improvement of parkinsonism. A year later, the patient developed the wearing off phenomenon and “peak-dose” dyskinesias, featuring facial, particularly lingual, truncal and limbs choreo-dystonic movements.

At age 23, when the patient was referred to our center, neurological examination revealed moderate hypomimia, pseudobulbar dysarthria, parkinsonism [unified Parkinson’s disease rating scale (UPDRS) III 55/108 “off” med], postural instability, severe spastic paraparesis (she was unable to walk without assistance), generalized brisk reflexes, and bilateral pes cavus with extensor plantar response. She also presented mild cerebellar signs (ataxia, dysmetria, nystagmus), mild dysphagia, and urinary urgency. At this time, she had no sensory symptoms or distal muscle atrophy. Neuropsychological tests documented a moderate impairment of memory and executive functions.

A brain magnetic resonance imaging (MRI) revealed pronounced TCC, diffuse cortical cerebral and mild cerebellar atrophy (Fig. 1), and hyperintense T2-weighted lesions in periventricular regions (Fig. 2). Electroneuromyography was consistent with an axonal sensorimotor peripheral neuropathy of the lower limbs.

A deltoid muscle biopsy ruled out a mitochondrial disorder, only showing features indicative of chronic neurogenic muscle damage. The 123I-ioflupane single-photon emission coupled tomography (SPECT) was consistent with severe, bilateral symmetrical nigrostriatal neuron loss. Motor-evoked potentials showed a delayed central motor conduction time, whereas somato-sensory-evoked potentials were normal.

Extensive laboratory investigations, also including DNA testing for spino-cerebellar ataxia 1,2,3,6,7,17, and for the most common mtDNA mutations, were all negative.

Over the next 9 years, both pyramidal (at age 31, spastic paraplegia rating scale score was 41/58 11) and parkinsonian symptoms progressively worsened. The neurological deterioration was accompanied by a progressive reduction of response to dopaminergic drugs. Levodopa doses were increased and other drugs (i.e., lisuride, cabergoline, pramipexole, ropinirole, apomorphine, amantadine, entacapone, and tolcapone) were included in the therapeutic cocktail, with moderate improvement of parkinsonism achieved in particular by apomorphine. Nevertheless, as a consequence of the progression of the disease, the patient became wheelchair bound at age 27.

At age 30, the patient was totally dependent, and a severe deterioration of her cognitive performances was documented by neuropsychological tests, which showed a severe mental retardation with total intelligent quotient = 44, verbal intelligent quotient = 52, and performance intelligent quotient = 40.

At age 31, 18 years after the onset of the symptoms, the patient presented a severe atypical fluctuating parkinsonism, still partially responsive to levodopa. The quality of the “on state” deteriorated, but there was a clear-cut difference from the “on” and “off” state. The on state was complicated by severe choreodystonic dyskinesias, particularly severe in the bucco-lingual district (See Supporting Information Video Segment 2). In the off state, the patient presented painful dystonia and severe akinetic symptoms (See Supporting Information Video Segment 1). At the latest clinical evaluation, the
UPDRS motor score improved from 77 to 69 following treatment with 250 mg levodopa.

Molecular Genetic Analyses

Genomic DNA from peripheral blood samples was extracted using a common salting out procedure. The 40 coding exons of SPG11 and at least 50 base pairs of flanking intronic sequence were PCR-amplified and subjected to d-high-performance liquid chromatography analysis using described oligonucleotide primer pairs.12 Amplicons showing abnormal elution profiles were agarose gel purified and directly sequenced using a BigDye 3.1 chemistry protocol on a 3130XL Genetic Analyzer (Applied Biosystems, Foster City, CA; http://www.appliedbiosystems.com).

Results

Direct sequencing of SPG11 in blood DNA from the proband detected a c.3664insT (p.K1222HisX13) in compound heterozygosity with a c.6331insG (p.E2111GfsX36) mutation. Segregation of the new mutations in peripheral blood DNA from the healthy parents was performed by direct sequencing. The two novel mutations were not found in 200 Italian control chromosomes.

Discussion

We report a sporadic Italian case with early parkinsonism and AR-HSP-TCC associated with two novel mutations in SPG11. SPG11 encodes spatacsin, a protein with still unknown specific biological function. Spatacsin is expressed ubiquitously, including the basal ganglia, and it appears to be essential to the function and the survival of many neurons.13 Patients with SPG11 most commonly present clinical involvement of the pyramidal tract in association with axonal polyneuropathy, mental retardation, or moderate cognitive impairment. Some patients also develop pseudobulbar dysarthria, cerebellar ataxia, urinary incontinence, or cataract. However, unusual phenotypes are increasingly been recognized, including pure spastic paraplegia14 and juvenile, slowly progressive motor neuron disorder.15

The patient described in this article presented a complex neurological phenotype dominated by parkinsonism at its onset, with dopaminergic denervation documented by 123I-ioflupane SPECT, which is quite unusual for SPG11-related phenotypes.10,14,16–18

An extensive diagnostic panel had ruled out other etiologies, such as hereditary SpinoCerebellar Ataxias (SCAs), mitochondrial encephalomyopathies, and disorders of copper metabolism.

We also considered neurodegeneration with brain iron accumulation type 1, due to mutations in PANK2 gene, that can present with parkinsonism, pyramidal signs, and cognitive impairment.19 Mutations in other genes, characterized by AR inheritance, ATP13A2 (PARK9, Kufor-Rakeb syndrome), PLA2G6 (PARK 14), and FBX07 (PARK 15) also produce clinical similar phenotype with rapidly progressive parkinsonism, transient response to levodopa, pyramidal signs, and cognitive decline.20–23

Most of these conditions present radiological signs of neurodegeneration with progressive cortical atrophy.

As in our patient, brain MRI showed the presence of TCC and periventricular white matter changes, typical, albeit not exclusive, features of AR-HSP linked to SPG11 mutations, we oriented the molecular study on SPG11 gene, and indeed two novel heterozygous mutations have been found.

This is the second report of a molecularly-proven SPG11-linked AR-HSP-TCC associated with atypical juvenile parkinsonism and abnormal 123I-ioflupane SPECT. Our patient, who carried different mutations from the cases initially reported by Anheim et al.,10 showed some distinctive features compared with these patients. Indeed, unlike them, she still conserves a levodopa response after 18 years since the onset of the disease; moreover our patient presents symmetrical nigro-striatal neuron loss and showed good tolerance and positive response to levodopa and other dopaminergic drugs. However, she soon developed the “wearing off” phenomenon and dyskinesias, that complicated therapy management.

Taken together, these findings suggest that different mutations in SPG11 may affect dopaminergic neurons in a distinct way. In conclusion, our report confirms that SPG11 mutations may cause early-onset parkinsonism. Other two descriptions14,17 closely resemble our patient: in one of them, a clinical response to levodopa was reported, in the other one complicated by peak-dose dyskinesias.14 However, SPG11 gene testing was not performed in these patients.

Therefore we suggest that (1) mutations in SPG11 should be considered in patients with atypical juvenile-onset parkinsonism accompanied by limited or good response to levodopa and (2) in similar cases treatment with dopaminergic drugs should be attempted as parkinsonian symptoms and so the quality of life can be improved.

Legends to the Video

Segment 1. (1) Off-state evaluation. A severe parkinsonism is evident: marked dysarthria, hypomimia, bradykinesia with very slow finger tapping, plastic rigidity in the upper limbs, upper limb resting tremor, more severe on the right side. (2) Patient is unable to walk and to stand without assistance for severe spastic paraparesis.

Segment 2. On-state evaluation. After a standard dose of levodopa/carbidopa (250/25 mg), the neurological examination reveals a mild improvement of parkinsonian symptoms with “peak-dose” lingual dyskinesias.
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References