Neuropsychiatric Assessment of Gilles de la Tourette Patients: Comparative Study with Other Hyperkinetic and Hypokineti c Movement Disorders

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Abstract:

The role of the basal ganglia in conditions with co-occurring movement disorders and neuropsychiatric symptoms is not well known. It has been hypothesized that hyperkinesia - disinhibited behaviors and hypokinesia-inhibited behaviors result from an imbalance between the direct and indirect striatal output pathways, and that differential involvement of these pathways could account for the concurrent abnormalities in movement and behavior observed in these disorders.

This study aimed to evaluate whether the pattern and the extent of the neuropsychiatric manifestations of patients with GTS, a hyperkinetic movement disorder of basal ganglia origin, differs from that of patients with other basal ganglia hyperkinetic (e.g., HD) or hypokinetic (e.g., PSP) movement disorders, and to determine whether patients with GTS show a greater frequency of hyperactive behaviors (e.g., agitation, irritability, euphoria, or anxiety) than PSP patients, and are comparable to patients with HD.

The Neuropsychiatric Inventory (NPI), a scale with established validity and reliability, was administered to 26 patients with GTS (mean age, 30.2 ± 2.2 years), and the results were compared with that of 29 patients with HD (mean age, 43.8 ± 2 years) and 34 with PSP (mean ± S.D. age, 66.6 ± 1.2 years).

There was no difference between the groups in the total NPI scores. However, there was a double dissociation in behaviors: patients with hyperkinetic disorders (HD and GTS) exhibited significantly more agitation, irritability, anxiety, euphoria, and hyperkinesia, whereas hypokinetic patients (PSP) exhibited more apathy. Patients with GTS showed greater scores than HD patients in all those scores differentiating HD and GTS from PSP patients (e.g., agitation, irritability, anxiety and euphoria), and were differentiated in a logistic regression analysis from both HD and PSP patients in having significantly more anxiety. We found that patients with GTS manifested predominantly hyperactive behaviors similar but more pronounced than those presented by patients with HD, while those with PSP manifested hypoactive behaviors.

Based on our findings and the proposed models of basal ganglia dysfunction in these disorders, we suggest that the hyperactive behaviors in GTS are comparable to those observed in HD, being both secondary to an excitatory subcortical output through the medial and orbitofrontal cortical circuits, while in PSP the hypoactive behaviors are secondary to hypostimulation of these circuits. Abnormalities of other brain structures (e.g., amygdala, brainstem nuclei) may account for the significantly higher anxiety scores differentiating GTS from HD patients.

Key words: Gilles de la Tourette syndrome; basal ganglia; neuropsychiatric symptoms

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Patients with basal ganglia disorders manifest cognitive and neuropsychiatric disturbances in addition to motor dysfunction. These disturbances may reflect damage to one or more of the frontal-subcortical circuits that subserve cognition and behavior rather than motor functions. While much has been written about the role of the basal ganglia in motor and cognitive functions, less is known about their role in neuropsychiatric conditions. Differential involvement of the frontal–subcortical circuits may lead to contrasting patterns of neuropsychiatric symptoms in patients with hyperkinetic (e.g., Huntington’s disease [HD] or Gilles de la Tourette Syndrome [GTS]) compared with those with hypokinetic (e.g., progressive supranuclear palsy [PSP] or Parkinson’s disease) disorders. In a previous study, Litvan and colleagues demonstrated that patients with HD evidenced a higher frequency of hyperactive behaviors (e.g., agitation, irritability, euphoria, and anxiety) than those with PSP, who manifested hypoactive behaviors (e.g., apathy). To further verify the hypothesis that hyperkinetic movement disorders are associated with a greater frequency of hyperactive behaviors, we investigated whether patients with GTS, another hyperactive disorder, and patients with HD show different patterns of behavioral abnormalities compared with those with PSP, and whether there are differences in the abnormal behavioral patterns that may distinguish GTS patients from those with HD.

SUBJECTS AND METHODS
The patients with GTS were 26 consecutive Spanish-speaking outpatients (Table 1) regularly attending the Movement Disorders Section at Sant Pau Hospital (Autonomous University of Barcelona) and the Neurology Service of the Clinic University Hospital of Málaga, Spain. The diagnosis of GTS was made by a senior staff neurologist on the basis of the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). None of the GTS patients had antecedents of childhood Attention Deficit Hyperactivity Disorder. The patients with HD were 29 participants in the Huntington’s Disease Clinical Research Program at the University of California at San Diego (Table 1). A senior staff neurologist made the diagnosis of HD on the basis of positive family history of the disease, typical choreiform movements and dementia according to DSM-IV criteria, and evidence of reduced volume of caudate nuclei on magnetic resonance imaging studies (when available). All HD diagnoses were molecularly confirmed with expanded CAG repeat lengths in IT15 on chromosome 4.

The patients with PSP consisted of 34 consecutive outpatients (Table 1) presenting to the National Institutes of Neurological Disorders and Stroke (NINDS), Bethesda, Maryland, for evaluation and participation in research studies, and who fulfilled the research criteria of the NINDS Society for Progressive Supranuclear Palsy for the diagnosis of PSP. Patients with HD and PSP were included in previous studies and were reported elsewhere. All patients gave their informed consent to participate in the study.

Motor and Cognitive Evaluation
The chorea of the patients with HD was scored according to the Unified Huntington’s Disease Rating Scale. The hypokinesia of patients with PSP was scored by adding the motor items (i.e., speech, limb rigidity, and neck rigidity) assessed using the Unified Parkinson’s Disease Rating Scale. The phenomenology and severity of tics in GTS was scored according to the Yale Global Tic Severity Scale (YGTSS). In all three groups, the overall degree of cognitive impairment was evaluated using the Mini Mental State Examination.

| TABLE 1. Characteristics of patients with progressive supranuclear palsy (PSP), Huntington’s disease (HD), and Gilles de la Tourette’s syndrome (GTS) |
|-----------------|-----------------|-----------------|-----------------|
| Characteristics | PSP (n = 34) | HD (n = 29) | GTS (n = 26) |
| Age (yr)        | 66.6 ± 1.2     | 43.8 ± 2.1     | 30.2 ± 2.2     |
| Sex (M/F)       | 22/12          | 14/15          | 21/5           |
| Education (yr)  | 14.4 ± 0.5     | 13.4 ± 0.4     | 10.6 ± 0.5     |
| Disease duration| 4.4 ± 1.5      | 5.6 ± 1.6      | 20.3 ± 1.7     |
| Mattis Dementia Rating Scale | 115.6 ± 5 (n = 27) | 121.2 ± 3.5 (n = 28) | NA |

Data are expressed as mean ± S.E.M.

*P < .001 (one-way analysis of variance [ANOVA]).
GTS, pairs of means that are significantly different (Turkey Kramer).
NA, not available; n.s., not significant.
Neuropsychiatric Evaluation

The neuropsychiatric evaluation was carried out using the Neuropsychiatric Inventory (NPI), a caregiver-based rating scale of established validity and reliability, whose items have also been shown to be valid and reliable in cross-cultural comparisons. The NPI contains 10 subscales designed to rate various psychiatric domains, including delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behavior. The NPI scores are based on abnormal behaviors present in the past month. Since the GTS patients did not have caregivers, other informants (usually a first-degree relative) were interviewed using the Spanish version of the NPI, which has established validity and reliability. A training video was used to ensure standardized administration by all raters. The three patient groups were interviewed with the NPI, as previously described. Briefly, screening questions for each behavior were posed first, and if a positive response was obtained for any of the 10 behavioral domains, this aspect was then further explored with scripted questions. The caregiver rated the behaviors using a 1 to 4 scale for frequency (1, occasionally; 2, often; 3, frequently; and 4, very frequently) and a 1 to 3 score for severity (1, mild; 2, moderate; and 3, marked). The composite score for each behavioral domain was the product of the frequency and severity subscore for that particular behavior (maximum, 12). The NPI is fully scripted to require standardized interview procedures by all raters. The total score of the NPI is the sum of the subscale scores. In previous studies, agitation, irritability, euphoria, and anxiety subscales were considered hyperactive behaviors, while apathy was considered a hypoactive behavior because depression is observed in many neurological conditions. The GTS patients also were administered the 17-item Hamilton Rating Scale for Depression and obsessive-compulsive behavior was rated with the Leyton Obsessional Inventory.

Statistical Analysis

Differences between data sets were evaluated by one-way and two-factor analyses of variance (ANOVA). Planned comparisons for all pairs of data were made using Tukey-Kramer analyses. Additional statistical tools included nonparametric Spearman correlation coefficients and logistic regression analysis. Statistical significance was considered at $P < 0.0025$ after Bonferroni correction for multiple comparisons.

RESULTS

There were no statistically significant differences between HD and PSP patients in either years of formal education or symptom duration. Patients with GTS were significantly younger than the other two groups. They had also significantly fewer years of education and longer symptom duration than subjects with HD and PSP (Table 1).

Over 79% of HD patients were taking no medications. Four patients were taking a selective serotonin reuptake inhibitor (SSRI) and a typical neuroleptic, although dosages of the neuroleptic were very low in every case (< 5 mg). One patient was taking an atypical neuroleptic. Four patients were taking an SSRI only and one patient was taking trazodone at bedtime for sleep. No patients were taking tetrabenazine. Among PSP patients, 17 were receiving levodopa treatment with unclear or no motor benefit, no patient was receiving neuroleptic treatment, two patients were taking trazodone, two patients amitryptiline, two nortryptiline, and other two sertraline. Regarding GTS patients, 12 (46%) were receiving pharmacological treatments to control motor and phonic tics, associated conditions, or both. Fourteen patients received no medication. To control tic symptoms, three patients received tetrabenazine (50 mg/day), other three risperidone (1 to 3 mg/day), one tiapride (400 mg/day), and another patient received clonazepam (0.5 mg). To control associated psychiatric conditions (i.e., depression, obsessive-compulsive disorder, generalized anxiety disorder) six patients were receiving sertraline (50 to 150 mg/day), another patient clomipramine (150 mg/day) and alprazolam (1 mg/day), whereas another received carbamazepine (400 mg/day) to control hypomania.

The mean HD score of the HD patients was $1.93 \pm 0.15$ (range, 1 to 3) and the mean total score of the HD patients on the Unified Huntington’s Disease Rating Scale (maximum 60 points) was $13.25 \pm 7.5$ (range, 2 to 26). The mean total score of the PSP patients on mainly axial measures of the Unified Parkinson’s Disease Rating Scale (maximum 24 points) was $12.3 \pm 3.7$ (range, 7 to 24).

Patients with GTS had significantly higher Mini-Mental State Examination scores than those with PSP and HD (Table 1). There were no significant differences in the scores obtained in the Mattis Dementia Rating Scale between PSP (115.6 ± 25.9) and HD patients (121.2 ± 18.5). Table 2 shows the NPI values of the patients and normative data of the NPI. There were no significant differences between groups in the total NPI scores (Table 2). However, both GTS (0.73 ± 0.09) and HD (0.56 ± 0.08) patients exhibited significantly higher ($P < 0.0001$) hyperactive behavior scores than PSP patients (0.12 ± 0.08). Conversely, patients with PSP exhibited significantly higher ($P < 0.0001$) hypoactive behavior scores (mean, 0.83 ± 0.08) than those
with HD (0.35 ± 0.09) and GTS (0.35 ± 0.09). On individual subscales, patients with GTS and HD had higher scores on the assessments of anxiety (GTS significantly different from both PSP and HD), irritability (GTS significantly different from PSP), agitation (GTS and HD significantly different from both PSP and HD), and depression (GTS significantly different from both PSP and HD), while patients with PSP had significantly higher apathy scores than both HD and GTS patients (Table 2).

In the patients with GTS, anxiety was associated with depression (r = 0.78; P < 0.0001) and agitation (r = 0.58; P < 0.0001). Similarly, euphoria was associated with disinhibition (r = 0.71; P < 0.0001) and agitation (r = 0.53; P < 0.0001), and irritability was associated with apathy (r = 0.70; P < 0.0001), anxiety (r = 0.67; P < 0.0001), agitation (r = 0.64; P < 0.0001), and euphoria (r = 0.58; P < 0.0001). The severity of depression according to the Hamilton Depression Scale was associated, as expected, with depression (r = 0.86; P < 0.0001) and anxiety (r = 0.76; P < 0.0001) and with the total NPI score (r = 0.64; P < 0.0001). Similarly, the complexity of the motor tics according to the YGTSS was strongly associated with the total NPI (r = 0.75; P < 0.0001) and anxiety scores (r = 0.71; P < 0.0001), and the intensity of the tics was associated with irritability (r = 0.56; P < 0.0001) and anxiety scores (r = 0.51; P < 0.0001). No association between the Leyton Obsessional Inventory and the NPI scores was found.

Logistic regression analysis performed on the total data set revealed that patients with GTS exhibited high anxiety scores (χ² = 21.6; odds ratio, 5.0; P < 0.0001) compared with those with HD and PSP.

### DISCUSSION

We investigated the relationship between three different types of movement disorder (GTS, HD, and PSP) and their associated neuropsychiatric behaviors using the NPI. Our main interest was to examine whether the pattern of behavioral disturbances associated with GTS compared with the profile of behaviors occurring in other hyperkinetic movement disorders with a proposed excitatory basal ganglia output (HD), and differed from that of an hypokinetic movement disorder with a proposed hypostimulation of basal ganglia circuits (PSP). We found that hyperactive behaviors such as agitation, irritability, euphoria, and anxiety predominated among patients with GTS and HD, whereas patients with PSP more frequently displayed hypoactive behaviors (apathy).

Some methodological limitations of this study should be pointed out. First, the geographic origin of the patients with GTS (Spain) was different than the PSP and HD (US) groups and cultural differences in the clinical expression of psychopathology and in coping with it could account for some of the behavioral discrepancies. However, the phenomenological characteristics of these differences was not random and followed the expected direction, as patients with GTS behaved in relative similar fashion than patients with HD (except for anxiety), and abnormal behavior in both groups significantly differed from the PSP group. Moreover, the NPI has been used previously to assess neuropsychiatric symptoms in patients in European and Spanish-speaking cultures and has been shown to be valid and reliable in these settings.19,20

### TABLE 2. Neuropsychiatric Inventory (NPI) composite scores of patients with progressive supranuclear palsy (PSP), Huntington’s disease (HD), and Gilles de la Tourette’s syndrome (GTS)

<table>
<thead>
<tr>
<th>Behavior</th>
<th>PSP (n = 34)</th>
<th>HD (n = 29)</th>
<th>GTS (n = 26)</th>
<th>Significance</th>
<th>Normative data (#)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apathy</td>
<td>6.03 ± 0.7 (82)</td>
<td>2.28 ± 0.7 (34)</td>
<td>0.85 ± 0.7 (25)</td>
<td>PSP with both HD and GTS* 3.1</td>
<td>0.14 (1.01)</td>
</tr>
<tr>
<td>Agitation</td>
<td>0.06 ± 0.06 (3)</td>
<td>1.66 ± 0.5 (45)</td>
<td>2.23 ± 0.5 (19)</td>
<td>GTS and PSP* 2.8</td>
<td>0.11 (0.84)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.24 ± 0.1 (12)</td>
<td>1.2 ± 0.3 (34)</td>
<td>4.12 ± 0.5 (50)</td>
<td>GTS with both PSP and HD* 5.6</td>
<td>0.14 (0.85)</td>
</tr>
<tr>
<td>Irritability</td>
<td>0.15 ± 0.09 (9)</td>
<td>1.31 ± 0.4 (38)</td>
<td>2.30 ± 0.4 (42)</td>
<td>GTS and PSP* 4.5</td>
<td>0.1 (0.64)</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>1.79 ± 0.6 (35)</td>
<td>0.69 ± 0.3 (24)</td>
<td>1.35 ± 0.6 (35)</td>
<td>n.s. 9.0</td>
<td>0.03 (0.50)</td>
</tr>
<tr>
<td>Depression</td>
<td>0.50 ± 0.3 (18)</td>
<td>1.41 ± 0.4 (41)</td>
<td>3.00 ± 0.5 (61)</td>
<td>GTS and PSP* 7.0</td>
<td>0.2 (1.03)</td>
</tr>
<tr>
<td>Euphoria</td>
<td>0</td>
<td>0.93 ± 0.5 (17)</td>
<td>1.61 ± 0.5 (61)</td>
<td>GTS and PSP* 0.3</td>
<td>0.00 (0.50)</td>
</tr>
<tr>
<td>Delusions</td>
<td>0</td>
<td>0.66 ± 0.4 (10)</td>
<td>0.46 ± 0.3 (19)</td>
<td>n.s. 2.4</td>
<td>0.08 (0.75)</td>
</tr>
<tr>
<td>Abnormal motor behavior</td>
<td>0.47 ± 0.4 (6)</td>
<td>0.41 ± 0.3 (7)</td>
<td>0.43 ± 0.4 (46)</td>
<td>n.s. 0.4</td>
<td>0.02 (0.35)</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>0</td>
<td>0</td>
<td>0.08 ± 0.02 (15)</td>
<td>n.s. 0.6</td>
<td>0.01 (0.1)</td>
</tr>
<tr>
<td>Total NPI score</td>
<td>9.23 ± 0.12 (88)</td>
<td>10.55 ± 1.9 (83)</td>
<td>16.43 ± 2.5 (81)</td>
<td>n.s. 15.8</td>
<td>0.76 (2.89)</td>
</tr>
</tbody>
</table>

Patient data are expressed as mean ± S.E.M. NPI composite scores (frequency of changes in percentage). The maximum composite score is 12. *P < 0.001.

( #) Normative data (mean scores and % present for the NPI items) obtained from 673 non-dementia individuals 65 years or older in a community-based epidemiologic study.24

n.s., not significant.
Similarly, it is unlikely that the different raters may have influenced our findings, as the NPI appears as a reliable instrument when used by different raters.19 Nevertheless, future studies should include patients of similar cultures. Second, another major limitation of this study is the age difference between the GTS group and both the HD and PSP groups. For instance, the fact that younger people (i.e., the GTS group) are expected to be more impulsive than older ones raises the possibility that some results of our study are not genuine. However, matching these three groups by age may also pose several problems and on designing the study we reasoned that attempts to match the three patient’s groups by age could likewise yield confounding results. It is well known that in GTS behavioral problems are highly symptomatic during adolescence and early adulthood, tending to decline in old age, whereas the opposite pattern is true for HD. The comparison between young adults with GTS and cases of juvenile HD may have been the gold standard, but unfortunately the former condition is rare.

The present findings agree with previous observations. Obsessive–compulsive disorder (OCD) is frequently found both in HD and GTS, and mania, psychosis, and intermittent explosive disorder are all described in HD and GTS25 as well as in other hyperkinetic disorders such as neuroacanthocytosis, Sydenham’s chorea, basal ganglia calcifications, Wilson’s disease,5,26–28 subcortical hyperkinetic movements disorders associated with stroke lesions29 and even in the “on” phase (hyperkinesia) of Parkinson’s disease.30

While prominent subcortical and brainstem pathologic changes can induce apathy in PSP by decreasing dopaminergic stimulation of frontosubcortical circuits,31–33 we hypothesize that in GTS as well as in HD,11 hyperactive behaviors result from an excitatory subcortical output through the medial and orbitofrontal circuits to the pallidum, thalamus, and cortex. This occurs in parallel with the excitatory stimulation of premotor-motor and supplementary motor cortices, resulting in tics. Functional neuroimaging studies in GTS34– 37 and HD38–40 suggest an altered relationship between limbic-related cortical regions and striatum-mediating complex cognition and behavior with other nonlimbic cortical regions implicated in the generation of hyperkinetic movements. In fact, positron emission tomography (PET) studies revealed decreased metabolic rates in basal ganglia (caudate and putamen in HD and ventral striatum in GTS) that coexisted with normal or increased metabolism in various cortical regions.34–37 Our clinical findings of hyperactive behaviors in GTS and HD concur with previous speculations that disinhibited behavior and hyperkinesia in HD and GTS may result from an excitatory subcortical output through the medial and orbitofrontal circuits to the pallidum, thalamus, and cortex.11 Future functional neuroimaging studies are necessary to examine the relative contribution of different frontosubcortical circuits in disinhibited behavior and hyperkinesia in these disorders.

A biological basis for GTS is widely supported by genetic, biochemical, neuropharmacological, neuroimaging and electrophysiological studies,41–45 yet its anatomic substrate, pathophysiology, and neurochemical abnormalities are uncertain.46 Although only a small number of GTS brains have been evaluated pathologically and histochemically, 45–47 clinical investigations suggest that the basal ganglia are a primary site of dysfunction in GTS. Our findings are consistent with these views. We found a significant association between the complexity of tics and the total NPI score and the anxiety subscale score. In addition, the intensity of tics was associated with the irritability and anxiety scores. Because the various hyperactive behaviors were significantly related in our patients with GTS, it is possible that they share common mechanisms.

The two groups with hyperkinetic disorders (HD and GTS) shared the same pattern of behavior in virtually all subscales of the NPI, but anxiety was more common and severe among patients with GTS. Indeed, anxiety was the best behavioral predictor of GTS. Because the NPI rates anxious symptoms related to conditions such as generalized anxiety, panic, phobias (agoraphobia, social, or other specific phobias) and separation anxiety, the finding of heightened anxiety levels in this group should not be attributed to other anxiety disorder (OCD, post-traumatic stress disorder) that also may occur among patients with GTS. Although HD and GTS are inheritable conditions which may show similar types of both hyperkinetic movements (tics and chorea) and associated psychiatric disorders (OCD spectrum disorders, depression, mania, psychosis and personality changes),28,48,49 anxiety is not commonly described in psychiatric reports of patients with HD.48 By contrast, the presence of severe non-OCD anxiety in the present study complements previous data reporting a high prevalence of anxiety across the entire lifespan in GTS.50–53 a finding that raises the possibility of increased susceptibility to anxiety in GTS patients54 or instead, that anxiety and other psychiatric disorders are variant expressions of GTS.55

Even though some patients with GTS received psychotropic medication (SSRI, benzodiacepines, neuroleptics) that can cause sedation to control hyperkinetic movements and associated conditions, this group exhibited significantly more agitation, irritability, anxiety, and euphoria than the group of patients with hypokinetic dis-
orders (PSP). While it could be argued that euphoria may be the logical consequence of SSRI action, it should be noted that in six of the 12 medicated patients, cyclic euphoria was present before starting the treatment. Taken together, these findings suggest that hyperkinetic behaviors in the GTS group are integral components of the disease rather than the effect of psychotropic medication.

Anxiety occurs in response to various stressors that can be environmental, physiological, or both. Patients with GTS do show higher than expected rates of anxiety symptoms, in part due to their heightened vulnerability to chronic intermittent stressful events.56 The negative impact of having GTS (i.e., punishment for saying obscene words, unemployment due to tics, interpersonal conflicts) is the most common psychosocial stressor. In addition, many GTS patients have enhanced stress reponsitivity induced by abnormal internal somatic states or provocative perceptions (i.e., uncomfortable premonitory urges, sensory tics, somatic discomfort related to anxiety)57–59 or by anticipated threatening sensory stimuli (i.e., images, sounds) coming from the peripersonal environment.60–62 These stressors result from altered brain mechanisms and are an integral component of GTS. Anxiety in GTS may be attributed to abnormal activity in some components of frontal-limbic-subcortical circuits (orbitofrontal cortex, amygdala, and ventral tegmental area) that are integral to the clinical expression of GTS (including stress sensitivity)58,63,64 and, less frequently, of HD.65

In summary, based on this study and those in the literature, we suggest that hyperactive behaviors in GTS are comparable to those observed in HD, and are secondary to an excitatory subcortical output through the medial and orbitofrontal cortical circuits, while in PSP, the hypoactive behaviors are secondary to hypostimulation of these circuits.

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