Determinants of Quality of Life in Children with Gilles de la Tourette Syndrome

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Abstract: **The objective of this study is to assess the association between tic severity, attention deficit disorder, obsessive-compulsive behavior, and quality of life (QOL) in children with Gilles de la Tourette syndrome (GTS). GTS is a multidimensional disorder with disturbances in motor function and behavior. However, little is known about what variables are associated with QOL in these patients. We evaluated 56 outpatients with a diagnosis of GTS. The mean age was 10 (range 5–17 years). Tics were assessed with the Yale Global Tic Severity Scale (YGTSS). Behavioral scales included the Leyton Obsessional Inventory—Child Version, Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), and Attention-Deficit/Hyperactivity Disorder (ADHD) rating scale. The patient's parent also completed the TNO-AZL Children's Quality of Life scale (TACQOL). YGTSS scores ranged from 4 to 30, indicating mild to moderate tic severity. Motor and phonic tic ratings were not correlated with QOL. However, both ADHD and OCD were significantly related to QOL. Subanalysis of ADHD subtypes demonstrated that inattentiveness but not hyperactivity predicted lower QOL. When ADHD, Leyton OCD, and tic severity were considered simultaneously, tic severity remained non-significant, while both ADHD and OCD remained significant contributors to QOL. In summary, in patients with mild to moderate GTS, QOL relates primarily to co-morbidities of ADHD and obsessive-compulsive behavior. ADHD with predominantly inattentive symptoms, rather than hyperactivity symptoms, was associated with lower QOL. To improve QOL, clinicians must consider treatments of co-morbidities among tic patients.**

Key words: movement disorders; pediatric disorders; neuropsychology/behavior

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INTRODUCTION

Gilles de la Tourette syndrome (GTS) is a chronic childhood neurobehavioral condition with an estimated prevalence of 10 cases per 10,000 children in the United States.[1] GTS can provoke a gamut of neurologic, behavioral, academic, and social problems for patients and families. In addition to motor and phonic tics, over half of these children have clinically significant problems with attention, hyperactivity, or obsessive-compulsive behaviors that can further compromise academic and social functioning.[2] Little is known about the variables most associated with quality of life (QOL) in these patients. One study addressing this issue in adults with GTS suggested an association between severe tics and significant obsessive-compulsive behavior with worse QOL, although attention-deficit/hyperactivity disorder (ADHD) was not specifically addressed.[3] The current study assessed the relationship between tic severity, ADHD, and obsessive-compulsive disorder (OCD) with QOL in a consecutive outpatient group of children with GTS.

METHODS

Sequential subjects from a university neurological practice who met DSM-IV[4] criteria for GTS were invited to participate in the study. Subjects received a neurological evaluation to assess tic severity using the Yale Global Tic Severity Scale (YGTSS),[5] and children and parents were interviewed with a number of behavioral scales: Leyton Obsessional Inventory—Child Version,[6] Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS),[7] and ADHD Rating Scale.[8] The parents also completed the TNO-AZL Children's Quality of Life scale (TACQOL).[9] The TACQOL subscales include Physical Complaints, Motor Functioning, Autonomy, Cognitive Functioning, Social Functioning, Positive Emotions, and Negative Emotions. This scale was selected because it is not disease specific, as are many of the child QOL scales. Forms were available for two age groups: age 1 to 5 and age 6 to 15. The senior author trained one of the coauthors to be an interviewer. We assessed the correlation between tic ratings, obsessive-compulsive behavior, ADHD, and parental perception of child QOL using Spearman's rho correlation.

The total score on the quality of life scale (TACQOL) was regressed univariately on tic severity (total of combined motor and phonic scores), obsessive-compulsive behavior (Leyton), total score on the attention deficit disorder scale (ADHD), as well as the

TABLE 1. *Mean age, disease duration, tic severity, obsessive-compulsive behavior, attention deficit disorder, and quality of life for patients with GTS*

Variable	Mean	SD	Range	Median
Age	10.46	2.90	5–17	10.0
Disease duration (years)	4.79	3.25	0–13	4.5
Tics-motor	9.45	4.47	4–20	8.0
Tics-phonic	5.75	3.55	0–14	6.0
Leyton	6.61	5.17	0–22	6.0
CY-BOCS	8.61	10.17	0–41	4.5
ADHD-inattention	11.36	7.71	0–27	10.0
ADHD-hyperactivity	8.5	7.00	0–26	7.5
TACQOL	156.80	14.81	107–179	158.5

TABLE 2. *Spearman correlation of age, disease duration, ADHD, OCD, and tic severity with quality of life for patients with GTS*

	Correlation coefficient	*P*
Age	0.01	0.964
Disease duration (years)	−0.02	0.904
ADHD-inattentive	−0.57	<0.001
ADHD-hyperactivity	−0.47	<0.001
ADHD (total)	−0.57	<0.001
Leyton	−0.37	0.006
CY-BOCS	−0.46	0.001
Tics-motor	−0.19	0.171
Tics-phonic	−0.19	0.175

inattentive and hyperactivity subscales. Multiple regression of ADHD, Leyton and tic severity was employed to test whether these variables were independently predictive of TACQOL. Exploratory regressions in which the two ADHD subscales were considered were also performed. Statistical significance was set at $\alpha = 0.05$.

RESULTS

Study Sample

There were 52 boys and four girls who participated in the study. The mean age was 10 ± 3 (range 5–17 years), and all subjects were attending school. All lived full time with the parent who completed the QOL scales. The mean YGTSS motor rating was 9.45 (±4.5) and the mean phonic rating was 5.75 (±3.6) (see Table 1). An additional 42 patients were approached to participate in the study and declined. Because of privacy restrictions on research, we could not access their demographic information to compare potential variables that may have been different from the study sample.

Twenty-two subjects (39%) were receiving medication for tics at the time of the study. Tics were generally assessed to be under good control (87.5% were judged to have good control of motor tics, and 89.3% were judged to have good control of phonic tics). Further, the majority were considered to be stable in terms of tic intensity (64.3% were judged by the neurologist to have stable motor tics, and 60.7% were judged to have stable phonic tics).

Of the subjects in the study, 36 met criteria for ADHD, and five subjects met criteria for OCD. Nonetheless, for the entire sample, mean obsessive symptoms reported on the Leyton Obsessional Inventory—Child Version were in the normal range (6.6 ± 5.2) for the age group assessed.[6] The mean obsessive and compulsive ratings reported on the CY-BOCS Total Scale was 8.6 (±10.2). The ADHD rating scale mean score was 19.6 ± 13.4. The mean TACQOL total score of 156.8 ± 14.8 was within the range of scores reported for a sample in which the majority of children were in good health or had temporary illness.[10]

Features Affecting QOL

Spearman correlation coefficients were calculated between ADHD, OCD, tic severity, and QOL (see Table 2). ADHD (total score, as well as the inattention and hyperactivity subscales), and the Leyton and Children's Yale-Brown Obsessive Compulsive scales were significantly related to QOL. However, neither the motor nor phonic tic severity scales were related to QOL. Likewise, neither age nor disease duration were related to QOL.

When entered separately in a multiple regression model, the TACQOL was significantly related to the ADHD total score ($F = 19.83$, df = 1,52, $P < 0.001$) and to the Leyton OCD scale ($F = 8.03$, df = 1,52, $P = 0.007$), but not to tic severity (total of motor and phonic scales; $F = 1.86$, df = 1,51, $P = 0.178$) or to age ($F = 0.09$, df = 1,52, $P = 0.767$). The TACQOL was also related to each ADHD subscale; inattention: $F = 18.87$, df = 1,52, $P < 0.001$; hyperactivity: $F = 11.60$, df = 1,52, $P = 0.001$). When ADHD total score, Leyton OCD scale, and tic severity were considered simultaneously, the tic severity score remained nonsignificant ($t = 0.039$, df = 3,49, $P = 0.969$) and both the Leyton ($t = -3.259$, df = 3,49, $P = 0.002$) and ADHD total score ($t = -4.491$, df = 3,49, $P < 0.001$) were statistically significant, indicating that both OCD and ADHD were significant contributors to TACQOL. In all models, the regression coefficients of

ADHD and OCD were negative, such that increased ADHD and OCD symptoms were associated with lower QOL.

When ADHD was separated into inattention and hyperactivity, the ADHD inattention score was a significant predictor of TACQOL independently of the Leyton score and ADHD hyperactivity ($t = -3.11$, df = 3,50, $P = 0.003$), but the ADHD hyperactivity score did not make a significant contribution to the prediction of TACQOL independent of the Leyton and ADHD inattention ($t = -0.288$, df = 3,50, $P = 0.775$).

DISCUSSION

In this sample of patients with GTS with mild to moderate tics, QOL related more to co-morbidities than to tic severity. Tic severity did not predict QOL, while both ADHD and OCD were strong predictors. These findings are similar to a study assessing psychosocial stress in patients with Tourette's syndrome and OCD, which found ratings of tic severity and OCD correlated with a self-report measure of stress, but not with clinician ratings of stress.[11] Based on the data from the current study, to improve QOL, neurological management of GTS must incorporate and prioritize treatment strategies to abate co-morbidities. Whether treatment of these co-morbidities actually improves QOL is a current research question that we are assessing.

A limitation of the study was that the measure of QOL we used relied on the parent's perception of the subject's QOL, rather than self-report from the child. We chose our measure in order to have a single tool applicable across all child ages. Prior studies have validated our selected measure and methods for young children as well as adolescents.[9] We are currently addressing the issue of whether the patterns we observed in children also occur among adults with GTS. In this context, a potential useful measure for outcome studies in GTS has recently been proposed, the Gilles de la Tourette Syndrome—Quality of Life Scale (GTS-QOL), a self-report scale for adults which takes into account some of the co-morbidities of GTS.[12] This new rating measure, however, has not been tested in children.

The study sample was a consecutive one from a tertiary care university center. The severity of tics was overall mild to moderate, and tics were generally stable and under good control. As such, we consider these cases quite typical, making our observations directly pertinent to most neurologists. It is possible that our subjects had more frequent co-morbidities, specifically ADHD, than the general tic population because we are a referral center that traditionally attracts cases with complex disorders. Although OCD and ADHD symptoms were frequent, severities were overall mild. We acknowledge that a small population of tic patients has severe tics and we do not presume that our findings extend to this small group of more unusual disability. The fact that typical tics have little impact on QOL and yet are the neurological manifestation most likely to be the focus of a neurologist's care underscores the need for treating physicians to broaden their treatment attention. Whether treated by the neurologist or a referral consultant, obsessive-compulsive symptoms and attentional/hyperactivity problems deserve focused expertise because these impairments clearly influence children's QOL.

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Telemedicine for the Care of Nursing Home Residents with Parkinson's Disease

Video

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Abstract: **Individuals with Parkinson's disease (PD) often require nursing home care, where access to neurologists is limited. Telemedicine uses information and communication technologies to provide health care to individuals who are geographically separate from providers. We present a video report of a nursing home resident with PD who received telemedicine visits over 8 months from a movement disorders specialist. The visits resulted in improvements in motor and cognitive symptoms and suggest that telemedicine may be useful for delivering care to this population.** © 2009 Movement Disorder Society

Key words: Parkinson's disease; telemedicine; nursing home

Up to 40%[1–3] of individuals with Parkinson's disease (PD) require nursing home care, and 5.1 to 6.8% of all individuals in nursing homes have PD.[4–6] These individuals, whose care and management is complex,[2,7] frequently have limited access to neurologists. When

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

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evaluated by neurologists, less than half are receiving optimal treatment.[4]

Telemedicine is the use of information and communication technology to provide health care to people who are located some distance from the provider.[8] Telemedicine can take many forms, including vital sign monitoring, store-and-forward static images, and live videoconferencing, but neurologic telemedicine has typically used live videoconferencing. Telemedicine has improved access and outcomes in neurologic conditions, such as stroke[9] and epilepsy,[10] but the published use of telemedicine for PD is limited.[11,12]

We report our initial experience in conducting telemedicine visits for an individual with PD who lives in a nursing home, 130 miles from our institution.

CLINICAL CASE

The patient is a 77-year-old retired male surveyor who has lived in a nursing home since June 2006. His symptoms began in the mid-1980s when he noted difficulty with skiing, followed by posturing and cramping of the right hand. He was diagnosed with PD in 1986 and was otherwise healthy except for anxiety. Initially, he had an excellent response to levodopa therapy. Several years later, he developed dyskinesias, freezing, and worsened rigidity. After his wife's death in 2006, he elected to enter a nursing home due to increasing difficulty with performing household tasks. At his final neurology outpatient visit in June 2006, he had moderate dyskinesias, freezing, and moderate rigidity. Rapid alternating movements were severely impaired, and he fell backwards on pull testing. His score on the Mini-Mental State Examination was 21 of 30.

Between June 2006 and October 2007, the nursing home staff noted increasingly impulsive behaviors, including climbing out of a window and trying to scale the fence to leave the facility. They also noted worsening short-term memory and anxiety. In October 2007, he elected to participate in telemedicine visits to manage his PD.

Telemedicine visits using live videoconferencing technology were first conducted with Collabworx Secure Real-Time Platform freeware run on Dell Notebook Computers. We subsequently switched to VSee Videoconferencing freeware in January 2008. For all visits, we used an encrypted high-speed internet connection and a Logitech Digicam (camera and microphone combined). A nursing home staff member and technical support staff were available at each visit to provide assistance.

Six visits took place between October 2007 and June 2008. Visits occurred monthly for 4 months; the fifth and sixth visits occurred three months apart. At one visit, technical difficulties limited visualization of the physical exam. For the other five visits, video quality was sufficient. Audio quality was sufficient for all visits. Recommendations were communicated to both the patient and staff at each visit. The initial visit lasted 60 minutes; subsequent visits were 30 to 45 minutes.

The patient was satisfied with the care he received. Initially, his exam was notable for moderate hypophonia and dysarthria, poor attention, marked generalized dyskinesias, and mild symmetric bradykinesia. He was able to rise from a chair using his hands. His initial medication regimen included total daily doses of 1,000 mg of levodopa and 250 mg of carbidopa, 600 mg of entacapone, 3 mg of trihexyphenidyl, 3 mg of alprazolam, 0.5 mg of pramipexole, 10 mg of donepezil, and 150 mg of fluvoxamine. Subsequently, trihexyphenidyl and donepezil were discontinued and the dosing and timing of the remaining medications were adjusted. After 8 months of telemedicine care, the patient reported fewer dyskinesias, which increased on time from 20 to 40% of the waking day. His Mini-Mental State Examination improved from 21 of 30 to 30 of 30 at the fourth visit. The illusions and behavioral concerns resolved, and he was better able to feed himself. There was mild hypophonia and dysarthria. Moderate dyskinesias were present during the first 15 minutes of the interview. Finger and heel taps were mildly slowed and reduced in amplitude. He continued to note frequent motor fluctuations and difficulty performing activities of daily living.

DISCUSSION

We used telemedicine to provide subspecialty care to an individual with PD residing in a remote nursing home. This effort builds on earlier telemedicine work in PD,[11,12] in which telemedicine was considered acceptable to patients and resulted in reduced travel costs.[12]

Telemedicine has the potential to improve access to and quality of care. Cheng et al. demonstrated that care by movement disorders specialists is associated with improved adherence to quality of care indicators.[13] Improved management can simplify medication regimens,[14] decreasing the use of potentially harmful or expensive medications.[15,16] This is especially relevant for PD, as individuals frequently have hallucinations and dementia that can be treated with non-pharmacological measures[17] or by reducing exacerbating medications. In our case, the elimination of trihexyphenidyl ($11.50 per month[18]) resulted in resolution of cognitive impairment and eliminated the need for donepezil ($170 per month[18]). Telemedicine can also

reduce the need for laborious and expensive transportation for nursing home residents. Finally, live videoconferencing provides direct communication between the consulting physician and nursing home providers and staff, which can improve the quality of information available about the patient, and minimize confusion or delays in implementing recommendations.

To realize telemedicine's potential, certain obstacles must be addressed. First, the centers delivering and receiving telemedicine visits need to create effective and sustainable partnerships. Second, telemedicine requires initial investments in equipment and infrastructure; fortunately, costs are declining rapidly. In the early 1990's, telemedicine startup costs totaled more than $100,000;[11] today, videoconferencing kits can cost between $5,000 and 10,000. Our initial equipment included an existing laptop computer, a free internet-based software program, and a combined camera and microphone (less than $100). More expensive equipment can further improve image quality and allow for additional opportunities such as recording video files and controlling camera movements remotely, but is not necessary. Third, patient concerns about confidentiality and embarrassment during the visit must be addressed[19] through patient and provider education.

Finally, reimbursement systems must be modified to permit continued growth of telemedicine services. Currently, to qualify for Medicare reimbursement, sites receiving telemedicine services must be located outside of a metropolitan area. Unfortunately, only about one-third of all US nursing homes currently meet this criterion.[20] An additional criterion is that these sites must be located within certain facilities: the office of a physician or practitioner, a hospital, a rural health clinic, or a federally qualified health center.[21] This currently excludes nursing homes, but recently passed legislation will permit Medicare reimbursement in this setting.[22]

Further research is required to establish the feasibility and potential benefits of telemedicine for nursing home residents with PD. One key consideration is whether dementia and psychosis associated with PD can be adequately managed via telemedicine, as suggested by work in telepsychiatry.[23] Also, data on the ability to accurately perform key PD assessments (such as the UPDRS) are currently mixed.[11,12] Finally, the ability to remotely manage patients with advanced PD may increase the pool of clinical research participants for trials, addressing the complications of advanced PD.[24]

The rise in the number of people affected by Parkinson's disease[25] and the rapid growth in assisted living facilities[26] suggest that the demand for improved care for this population will only increase. Further work to improve telemedicine and remove unnecessary hurdles could lead to significant benefits for patients, physicians, nursing homes, and payors.

VIDEO LEGEND

The video demonstrates selected motor segments of the neurologic examination for this patient over time. Segment 1 occurred January 2008, Segment 2 in April 2008, and Segment 3 in June 2008. In Segments 1 and 2, our patient reported being "off". In Segment 3, he reported being "on" with dyskinesias.

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Subthalamic Nucleus Deep Brain Stimulation for Camptocormia Associated with Parkinson's disease

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Abstract: **Camptocormia becomes increasingly recognized as a disabling symptom associated with Parkinson's disease (PD). We here report six patients with advanced PD in whom continuous bilateral stimulation of the subthalamic nucleus produced substantial (mean 78% ± 9.1% of the thoracolumbar angle) improvement of camptocormia along with other motor symptoms.** © 2009 Movement Disorder Society

Key words: camptocormia; Parkinson's disease; subthalamic nucleus; deep brain stimulation

Camptocormia, also known as "bent spine syndrome," is characterized by an abnormal posture of the trunk with marked forward flexion of the thoracolumbar spine, which increases during standing and walking and abates in the recumbent position.[1] Among a broad spectrum of neurologic etiologies involved in the genesis of camptocormia, Parkinson's disease (PD) is the most frequent.[1,2] Although camptocormia is increasingly recognized as a progressively disabling symptom in the course of PD, the optimal therapy for PD-associ-

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TABLE 1. *Clinical characteristics of patients with PD-associated camptocormia who underwent STN-DBS*

	Patient					
	1	2	3	4	5	6
Age at onset (yr)/sex	60/F	54/M	47/F	48/F	54/M	44/F
Duration of disease (yr)	11	10	8	5	11	9
Follow-up after surgery (months)	46	15	18	5	8	9
UPDRS III off medication						
Preoperatively	47	56	67	33	25	62
Postoperatively	20	15	32	5	7	11
Percent improvement (%)	57	73	52	85	72	84
UPDRS III on medication						
Preoperatively	38	56	32	33	25	62
Postoperatively	20	15	32	5	7	11
Percent improvement (%)	47	73	0	85	72	84
Thoraco-lumbar angle (°)						
Preoperatively	90	90	90	50	60	60
Postoperatively	30	30	10	10	10	10
Percent improvement (%)	67	67	89	80	83	83

The evaluation scores for motor symptoms were assessed using Unified Parkinson's Disease Rating Scale (UPDRS). For each patient, the preoperative baseline values and the scores at the last follow up after the inception of continuous stimulation are shown.

PD, Parkinson's disease; STN-DBS, subthalamic nucleus deep brain stimulation; F, female; M, male.

ated camptocormia remains to be established.[2–5] Individual case reports have shown that deep brain stimulation (DBS) of the subthalamic nucleus (STN)[6,7] and globus pallidus internus (GPi)[8] is effective in treating camptocormia, however, the overall efficacy of DBS in relieving PD-associated camptocormia has not been determined.[2,3] We here report the largest series to date of six patients with PD whose disabling camptocormia was substantially alleviated by bilateral STN-DBS.

PATIENTS AND METHODS

The clinical characteristics of the six patients with PD-associated camptocormia who underwent bilateral STN-DBS are summarized in Table 1. All the patients had been satisfactorily controlled by dopaminergic medication during the earlier stage of disease progression. Preoperative MRI study revealed no apparent brain lesion in all patients. At surgery, their mean age was 60 years (range 53–71 years); the mean disease duration was nine years (range, 5–11 years). All six showed marked flexion (over 45°) of their thoracolumbar spine that worsened during walking or prolonged standing and disappeared in the recumbent position.[1] Their mean duration of having camptocormia was 25 months (range, 12–60 months). Using video image analysis, we measured the thoracolumbar angles of the bent spine preoperatively (baseline) and at the latest follow-up. The patients were also assessed using the Unified Parkinson's Disease Rating Scale (UPDRS).

Levodopa equivalent daily dose (LEDD) was calculated before surgery and at the latest follow-up on the basis of the following formula[9]; 1 mg of pergolide = 1 mg of lisuride = 4 mg of cabergoline = 1 mg of pramipexole = 5 mg of ropinirole = 10 mg of bromocriptine = 20 mg of dihydroergocriptine = 100 mg of levodopa. Statistical analysis was carried out using a Student two-tailed t test. A P of <0.05 was considered as significant.

Stereotactic implantation of quadripolar DBS electrodes (Model 3389, Medtronic, Minneapolis, MN) into the STN were carried out as described elsewhere.[10] Briefly, the tentative target site determined by setting the coordinates was 2 mm posterior to the midpoint of a line drawn between the anterior- and posterior commissures (AC-PC line) and 12 mm lateral, and 4 mm ventral to the AC-PC line. Semi-microelectrode recordings were obtained at all 1.0-mm points along the trajectory toward the STN target site to determine the relative physiologic position of the probe. The trajectory that included more than four positive recording sites was chosen for placement of the DBS lead. The programmable pulse generators (Soletra, Model 7426, Medtronic) were placed in the subclavicular regions. All the patients were routinely evaluated and programmed for pulse every 2 to 3 months as follow-up after surgery.

RESULTS

The optimal stimulating parameters were determined to be a frequency of 130 Hz, a pulse width of 60 micro-

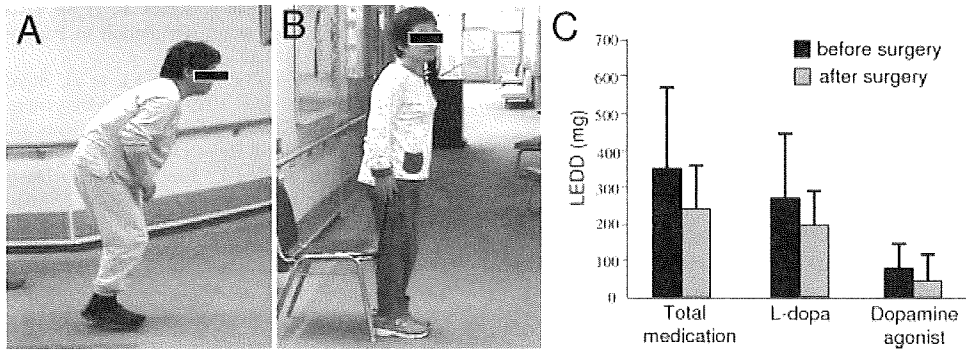

FIG. 1. Surgical results (**A** and **B**). Photograph of a patient with PD-associated camptocormia who underwent bilateral subthalamic stimulation. Preoperatively (A) she manifested a severe forward flexion of the thoraco-lumbar spine. At the latest follow-up after electrode implantation with continuous subthalamic stimulation (B), the camptocormia was markedly alleviated. (C) Mean levodopa equivalent daily dose (LEDD) before and after surgery.

seconds, and mean amplitude of 2.6 volts (range, 2.0–3.5 volts). Monopolar stimulation with single or double cathode contacts was used in all patients. As shown in Table 1, the mean UPDRS III (motor) score in the "off" phase decreased from 48 ± 16.6 (baseline) to 15 ± 9.9 (postoperative) ($P = 0.002$); in the "on" phase it decreased from 41 ± 14.7 to 15 ± 9.9 ($P = 0.005$). In all six patients camptocormia responded well to STN-DBS (for an example, see Fig. 1A,B); the mean thoracolumbar angle decreased from 73 ± 18.6 (preoperative baseline) to 17 ± 10.3 (postoperative follow-up); the mean improvement was 78% ± 9.1% (range, 67–89%; $P = 0.0001$). Pre- and postoperative mean LEDDs of dopaminergic medications are shown in Fig. 1C. Postoperative reduction of LEDD was trend, but no significant differences were found in daily doses of levodopa and dopamine agonists ($P < 0.5$).

DISCUSSION

It is a major preoperative issue to determine what motor features associated with PD reliably respond to the DBS surgeries.[11] Present study disclosed that in our six patients with advanced PD, continuous bilateral STN-DBS produced substantial improvement of their camptocormia and other motor symptoms. Its therapeutic efficacy on camptocormia varied in individual patients, with an improvement (mean 78% ± 9.1%) in the assessment of the thoracolumbar angle. Preoperatively, the motor symptoms of Cases 1 and 3 responded to levodopa; camptocormia of Patient 3, but not of Patient 1, also responded to dopaminergic therapy as have been reported.[5] In the other four (Cases 2, 4, 5, 6), the preoperative response of their motor symptoms to medication could not be determined because they were intolerant of dopaminergic therapy due to drug side-effects such as psychosis. Therefore, as has been reported for other patients,[11–13] their preoperative UPDRS motor scores in the "on" phase may not reflect the best obtainable scores in that phase. Our study showed that in all patients except for Case 3, there was no clear correlation between camptocormia improvement and levodopa therapy. PD-associated camptocormia itself is generally thought to be levodopa-unresponsive; in most patients, extreme anterior bending is not or only poorly improved, or even exacerbated by levodopa, and the severity of the bent spine is often unchanged during medication "on" and "off" phases.[2,5] Based on these considerations, we suggest that in individual patients, the preoperative levodopa-responsiveness of their motor symptoms may not be a predictor of the response to STN-DBS of their PD-associated camptocormia.

It has been proposed that camptocormia is an extreme form of the characteristic stooped posture of PD patients.[1–3] As the central mechanisms that control posture remain poorly-understood, the pathogenesis of camptocormia continues to be unknown.[1,2] However, the first report on camptocormia in PD patients suggested that "bent spine" might represent an action dystonia resulting from dysfunction of the striatum.[14] Another study on camptocormia associated with lenticular lesions also reported the critical role of the striatum and pallidum in the maintenance of axial posture.[15] Thus, it is possible that PD-associated camptocormia is a result of basal ganglia dysfunction that may result in (segmental) axial dystonia.[1–3,14,15] Based on this hypothesis, stereotactic intervention targeting the GPi may be a rational option to treat camptocormia since there is a growing body of evidences that show a dramatic effect of pallidal surgery on various forms of dystonia.[16–19] Indeed pallidotomy[20] and GPi-DBS[8] pro-

duced a marked improvement of severe thoracolumbar spine flexion in patients with PD. In non-PD patients, camptocormia has been shown to respond well to GPi-DBS.[21] However, there is a general concept that STN-DBS may be preferable to GPi-DBS for improving the cardinal motor symptoms[22] and for reducing the dosage of dopaminergic medications in PD patients.[22–24] With the recent reports showing beneficial effects of STN-DBS in the treatment of primary and secondary dystonias,[25–28] our present findings suggest axial posturing may be controlled by the STN as a function of the basal ganglia, and that bilateral STN-DBS can be as a potential surgical means to address camptocormia in PD patients. Further studies need to be performed to confirm this conclusion and to select PD patients with medically refractory camptocormia who are optimal candidates for STN- or GPi-DBS.

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Motor Complications in Patients Form the German Competence Network on Parkinson's Disease and the *DRD3 Ser9Gly* Polymorphism

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Abstract: **In addition to levodopa treatment and disease duration, genetic predisposition might contribute to the development of medication-related complications in Parkinson's disease (PD). As recent observations indicate the dopamine D_3 receptor (DRD3) to modulate both therapeutic action of levodopa and dyskinesia, we reappraised the impact of the *DRD3 Ser9Gly* polymorphism on development of motor complications in a large scale association study based on the gene bank of the German Competence Network on Parkinson's disease. Stepwise regression analysis revealed no effect of *DRD3 Ser9Gly* on chorea, dystonia, or motor fluctuations in PD, despite incorporating established clinical risk factors to avoid overlooking an effect of genotype. Duration of PD was confirmed as the most important clinical risk factor, followed by age of disease onset and female sex. Additional studies incorporating grading of motor complications, and combinations of risk genotypes, are warranted.** © 2009 Movement Disorder Society

Key words: Parkinson's disease; levodopa; motor complications; dyskinesia; DRD3 Ser9Gly

Motor complications, particularly dyskinesia and motor fluctuations, are side effects of long-term levodopa treatment in Parkinson's disease (PD), limiting the usefulness of this most effective symptomatic therapy.[1] Young age of PD onset, disease duration, period and dosage of levodopa treatment, and female sex were identified as risk factors.[2–6] However, these variables explain the appearance of motor complications only partially, as there is considerable interindividual heterogeneity of the response to levodopa, and some patients never develop dyskinesia.[4] These observations support the hypothesis that certain individuals are predisposed to develop motor complications in PD, prompting studies on genetic susceptibility.[4,7] So far, unconfirmed studies have reported an association of levodopa-induced dyskinesia or motor fluctuations with two polymorphisms in the gene of the dopamine D_2 receptor (DRD2),[8,9] and one in the gene of the dopamine transporter (DAT).[10]

Experimental evidence links levodopa-induced dyskinesia to DRD3 function: Striatal induction of DRD3, highly dependent on afferent dopamine innervation, parallels the development of levodopa-induced behavioral sensitization in hemiparkinsonian rats,[11] in whom reduction of striatal DRD3 binding was shown to block effects of prolonged levodopa treatment.[12] In MPTP-treated monkeys, dyskinesia was associated with overexpression of DRD3, attenuated by administration of a DRD3 selective antagonist.[13] In mental illness, the DRD3 gene has been extensively studied in tardive dyskinesia, and the *gly* allele carrier status of the *DRD3 Ser9Gly* polymorphism was established as an important risk factor.[14,15] *Ser9Gly* is the only known *DRD3* polymorphism affecting protein structure.[16] Also, cells expressing the *DRD3 gly* allele showed a higher binding affinity for dopamine, compared to heterozygotes or wild type.[17]

Only two studies tested the *DRD3 Ser9Gly* polymorphism for an association with dyskinesia[10] or wearing off[9] in PD. Both employed small patient samples, and found no significant effect of *Ser9Gly*. We reappraised the impact of *DRD3 Ser9Gly* on motor complications in PD in a large-scale association study based on the gene bank of the German Competence Network on Parkinson's disease (CNP), incorporating established clinical risk factors to avoid masking the effect of a genetic variable. Also, we were able to include various subtypes of PD motor complications in our analysis.

PATIENTS AND METHODS

The CNP is a national network composed of 35 university hospitals and specialized movement disorder clinics across Germany (www.kompetenznetz-parkinson.de). It collects information on PD patients in a database, including medical history, diagnostic procedures, suspected diagnosis, and drug treatment. Patient

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evaluations and data input are conducted by movement disorders specialists. The CNP gene bank (GEPARD) collects corresponding DNA samples.[18]

For the present study, only unrelated patients who met the UK Brain Bank criteria for PD with available DNA samples were included (n = 690). Information on gender, age, disease onset, disease duration, Hoehn & Yahr stage (H&Y), and present drug treatment was considered. Each patient's total dopaminergic load (in milligrams levodopa equivalent) was calculated as established previously.[19] For analysis of motor complications, we considered the following three types and 10 subtypes recorded in the database: dyskinesia: chorea (subtypes peak-dose, plateau, biphasic); dyskinesia: dystonia (subtypes off, on, biphasic); and fluctuation (subtypes wearing off = end of dose akinesia, random on/off, freezing during on, freezing during off). The *DRD3 Ser9Gly* genotype was determined as described previously.[10]

SAS 9.1 was used to perform the Wilcoxon rank-sum and chi-square tests for analyses of the patient sample, and comparisons of subgroups defined by motor complications and genotype. Significance was considered at $P < 0.05$. For each type and subtype of motor complications as dependent variable, we conducted a forward stepwise logistic regression analysis to select the best set of independent predictors from the pool of variables consisting of gender, age of disease onset, disease duration, H&Y, dopaminergic load and genotype. Only variables reaching $P < 0.05$ were included in the model.

The study protocol was approved by the appropriate local ethics committees, and all patients gave written informed consent.

RESULTS

Genotyping of *DRD3 Ser9Gly* was successful in 591 patients (ser/ser: 254 patients [43.0%]; ser/gly: 262 patients [44.3%]; gly/gly: 75 patients [12.7%]). Average age was 64.7 ± 10.1 years (for further patient sample characteristics, see Table 2). Fluctuations were the most frequent type of motor complications (40%), and wearing off (end of dose akinesia; 32%), freezing during off (23%), and peak-dose dyskinesia (16%) were the most common subtypes (Table 1). Patient groups defined by occurrence of at least one subtype of chorea, dystonia, or fluctuation (i. e., comparing all patients with at least one type of chorea and patients without chorea) differed significantly for all variables tested, most obvious for disease duration (Table 2). Similar results were obtained in subgroup analyses of all 10 subtypes of motor complications, again yielding most significant findings for disease duration in all calculations (not shown). However, female sex was significantly more frequent only in chorea plateau ($P = 0.01$), off dystonia ($P = 0.0005$), and wearing off ($P = 0.009$), with a trend for peak-dose chorea ($P = 0.05$). There were no significant differences in gender distribution, age, or age of PD onset in patient subgroups defined by *DRD3 Ser9Gly* genotype (not shown).

Stepwise regression analyses identified longer disease duration, earlier age of PD onset, female sex, and higher H&Y scores as the best set of predictors for occurrence of motor complications in general (Table 3). Also, higher total dopaminergic load remained in the models generated for chorea and fluctuations, but lost its effect in dystonia (including subtypes). Likewise, of all motor complications, disease duration had the weakest effect in dystonia (including subtypes). The number of *Ser9Gly* alleles was not significant after inclusion in the regression models for any type of motor complication. Again, widely concordant results were obtained when analyzing motor complication subtypes, without incorporation of the number of *gly* alleles in any of the models generated (not shown).

DISCUSSION

DRD3 Ser9Gly genotype frequencies (and allele frequencies; not shown) observed in our large German CNP gene bank sample were concordant with previous studies in PD patients, severe mental illness, and controls,[9,14–16] supporting a similar degree of genetic variability of *DRD3* in different populations and neuropsychiatric disorders.

Our analysis failed to confirm *DRD3 Ser9Gly* as a relevant disease modifying gene in PD with regard to motor complications. We included known clinical and demographic criteria in our analyses, since independent risk factors might very well conceal any contribution of a genetic variable. Nevertheless, no effect of *DRD3 Ser9Gly* on PD motor complications became obvious, confirming studies in smaller patient samples of Chinese and German origin.[9,10] Also, as these studies used broader or limited classifications of symptoms (any dyskinesia; wearing off), we looked at the various subtypes of dyskinesia and motor fluctuations, again without evidence for an impact of *Ser9Gly*.

This lack of association might be explained by phenotype classification. Severity of motor complications is variable, and several studies reported only 12% of dyskinesias to be clinically significant.[20,21] Likewise, in mental illness, *DRD3 Ser9Gly* was most strongly

TABLE 1. *Frequency of motor complications in 591 PD patients*

	Chorea				Dystonia				Fluctuation					
	Peak-dose	Plateau	Biphasic	Any chorea	Off	On	Biphasic	Any dystonia	Wearing off	Random on/off	Freezing off	Freezing on	Any fluctuation	Any complication
n	95	50	26	117	76	42	9	92	187	66	138	43	239	268
%	16	8.5	4	20	13	7	1.5	16	32	11	23	7	40	45

PD, Parkinson's disease.

TABLE 2. *Clinical characteristics of motor complications in PD*

		Chorea*			Dystonia*			Fluctuation*		
	All patients n = 591	Yes n = 117	No n = 474	*P* value	Yes n = 92	No n = 499	*P* value	Yes n = 239	No n = 352	*P* value
Male/female (%)	61.6/38.4	50.4/49.6	64.3/35.7	5.5×10^{-5}	42.4/57.6	65.1/34.9	3.7×10^{-5}	56.1/43.9	65.3/34.7	2.2×10^{-2}
Age of PD onset (y)	57.7 ± 11.3	50.8 ± 10.4	58.7 ± 11.1	2.3×10^{-12}	50.4 ± 10.9	58.4 ± 11.0	2.3×10^{-9}	58.2 ± 10.5	59.8 ± 11.2	3.7×10^{-13}
PD duration (y)	7.6 ± 5.9	12.7 ± 5.9	6.3 ± 5.1	9.0×10^{-26}	11.3 ± 5.8	6.9 ± 5.6	1.6×10^{-12}	11.0 ± 6.2	5.2 ± 4.3	3.1×10^{-33}
Hoehn & Yahr stage[a]	2.6 ± 1.0	3.1 ± 1.0	2.5 ± 1.0	3.1×10^{-9}	3.2 ± 1.1	2.5 ± 1.0	2.0×10^{-8}	3.1 ± 1.0	2.2 ± 0.9	4.6×10^{-22}
Dop. load[b] (mg)	551 ± 361	779 ± 339	496 ± 344	1.2×10^{-14}	701 ± 336	524 ± 358	4.1×10^{-6}	736 ± 346	427 ± 315	2.7×10^{-26}

Values are expressed as mean ± standard deviation unless otherwise specified.
*At least any one subtype (for analysis of the separate motor complication subtypes, see text).
[a]Information on Hoehn & Yahr stage was available in 589 patients.
[b]Information on dopaminergic medication was available in 584 patients.
PD, Parkinson's disease; y, years; dop. load, dopaminergic load; mg, milligrams.

TABLE 3. *Stepwise regression analysis of clinical risk factors, DRD3 Ser9Gly and motor complications*

	Chorea*		Dystonia*		Fluctuation*	
	Regression estimate	*P* value	Regression estimate	*P* value	Regression estimate	*P* value
Female sex	0.791	0.001	1.078	<0.0001	0.594	0.006
Earlier age of PD onset	−0.036	0.003	−0.052	<0.0001	−0.037	0.0005
Longer PD duration	0.113	<0.0001	0.047	0.03	0.11	<0.0001
Higher Hoehn & Yahr stage	0.289	0.02	0.638	<0.0001	0.682	<0.0001
Higher dopaminergic load	0.001	0.001	#		0.001	<0.0001
Higher number of *gly* alleles[a]	#		#		#	

*At least any one subtype (for analysis of the separate motor complication subtypes, see text).
[a]Of *DRD3 Ser9Gly*.
PD, Parkinson's disease; #, not included in the model generated by stepwise regression analysis.

associated to severe forms of tardive dyskinesia.[15] Assessment of motor complications in PD is difficult due to marked clinical variability between and within patients,[1,4] potentially impairing phenotype demarcation. Future pharmacogenetic studies should focus on more easily discernable variables, for example, severe forms of dyskinesias or fluctuations, or the time of their first presentation. Nevertheless, we believe that the large patient sample examined suffices to screen for a relevant effect of *DRD3 Ser9Gly* on susceptibility for PD motor complications.

Drug response and susceptibility to adverse effects are complex phenotypes, and other genes beside *Ser9Gly* might be involved, each contributing a small risk increment. In tardive dyskinesia, for example, an effect of a polymorphism in the *cytochrome P450 17 alpha-hydroxylase* gene on severity of dyskinesia was demonstrated only in patients homozygous for the *gly* allele of *DRD3 Ser9Gly*.[22] For motor complications in PD, variants that were shown to be associated with peak-dose dyskinesia (*STR* of *DRD2*),[8] any type of dyskinesia (*40-bp VNTR* of *DAT*),[10] and motor fluctuations (*TaqIA* of *DRD2*)[9] are probably the most promising candidates for a combined analysis of risk genotypes, including *DRD3 Ser9Gly*.

Prevalences and risk assessments of nongenetic predictors of motor complications in our sample are in line with most earlier evaluations.[2,3,8–10,21] Overall, disease duration had the most relevant impact on chorea and motor fluctuations. Interestingly, for dystonia, actual dopaminergic load did not reach significance in regression analysis, suggesting that intrinsic mechanisms outweigh contribution of pharmacological issues in development of dystonia in PD. Likewise, dystonia is assumed to be a hallmark of younger onset PD, in which genetic factors contribute considerably to etiology.[23]

Contribution of gender on PD motor complications is controversial: Several studies in larger patient samples (n = 215; 630) observed a higher risk in females,[5,6] which has not been confirmed in smaller examinations (n = 124; 126; 140; 183).[2,9,10,20] Some studies reported female sex to predispose for tardive dyskinesia in mental illness.[15] While mechanisms underlying gender susceptibility for drug-induced movement disorders are unknown, there is evidence suggesting that estrogens modify individual sensitivity to develop dyskinesia.[24] Our results support the notion that female sex predisposes for motor complications in general (and, especially, peak-dose and plateau chorea, dystonia during off, and end of dose akinesia), which calls for a more restricted use of levodopa in young female patients.

In conclusion, *DRD3 Ser9Gly* alone does not confer an increased susceptibility to develop any kind of levodopa-induced motor complications in PD. Duration of PD was confirmed as most important risk factor, followed by age of disease onset and female sex.

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Pathological Gambling Amongst Parkinson's Disease and ALS Patients in an Online Community (PatientsLikeMe.com)

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Abstract: **Pathological gambling (PG) has been identified in Parkinson's disease (PD), but such gambling behaviors may also occur in amyotrophic lateral sclerosis (ALS). We sought to estimate the prevalence of PG amongst members of a web-based community, PatientsLikeMe.com. A survey was constructed, consisting of demographic information, the South Oaks Gambling Screen (SOGS), the K-6 measure of distress, and items related to motivation for gambling. Data were obtained from 236 ALS patients and 208 PD patients. Of the PD patients, 13% were classified as problem gamblers compared with 3% of ALS patients (χ^2 = 14.005, $P \leq 0.001$). PD patients reported thoughts about gambling to be more distressing, harder to resist and more outside their control than ALS patients. Thus, the higher prevalence of compulsive behavior in PD may relate to damaged reward pathways or medication rather than to the effects of living with a chronic progressive neurological disorder per se.** © 2009 Movement Disorder Society

Key words: ALS; pathological gambling; neuropsychiatry; neuropsychology; depression

Pathological gambling (PG) was first described in Parkinson's disease (PD) in 2000[1] and has been estimated to affect between 3 and 7% of patients.[2] Current opinion suggests that such gambling behaviors may be triggered by dopaminergic medication (usually dopamine agonist drugs[3]), although younger age, increased impulsivity, and higher novelty-seeking traits appear pertinent risk factors in this population.[4] Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder traditionally held to affect only motor functions; however, it is now clear that a small proportion of ALS (~5–10%) patients experience florid personality changes consistent with frontotemporal dementia (FTD), whereas a larger proportion (33–50%) experience milder cognitive change of a predominantly executive nature.[5] Although there have been no reports in the literature of pathological gambling among ALS patients, it has been noted anecdotally in clinical experience. Patients with ALS-FTD have been described as engaging in repetitive and compulsive behaviors, including compulsive eating and other perseverative behavior,[6] and FTD in isolation has been reported as presenting with PG.[7] Previous reports have described PD patients as being particularly likely to use slot machines,[2] although other reports have mentioned internet gambling as being problematic for some.[8,9]

Many patients with ALS or PD use the internet for several hours a day to communicate, to participate in online communities, or for entertainment. We set out to estimate levels of PG and other compulsive behaviors among users of an online community for people with life-changing illnesses, PatientsLikeMe.com, reporting a diagnosis of PD or ALS. Approximately 80% of users are based in the United States, with smaller proportions in other parts of the English-speaking world. Given that the internet also offers increasing numbers of opportunities to gamble via online casinos, sports betting, and lotteries, we predicted that we would find higher estimates of PG in our PD sample than reported previously because of increased opportunities to gamble. We postulated that the prevalence of PG in ALS would be lower than that found in PD because of the absence of dopaminergic medication but that it would be higher than is found in the general population as patients may have had to give up work and spend many hours a day using the internet.

PATIENTS AND METHODS

Survey Construction

A survey was constructed consisting of demographic information (age, gender, disease duration, Hoehn and Yahr stage for PD) and the South Oaks Gambling Scale (SOGS, with a conservative cutoff of 5+), the K-6 measure of distress (using a cutoff of 13+[10]), and items related to motivation for gambling.

Participants

Participants reporting that they had been diagnosed with either ALS or PD were contacted via the online community, PatientsLikeMe.com. Although patients were not physically examined, all patients were asked

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Potential conflict of interest: Paul Wicks is a paid consultant for PatientsLikeMe and owns stock options in the company.

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TABLE 1. *Participant characteristics*

Mean (SD)	PD	ALS/MND	Significance
N	236	208	
Age (Years)	57.7 (10.4)	54.7 (10.4)	$t(442) = 3.097, P = 0.002$
Sex	43% Male	63% Male	$\chi^2 = 15.85, P \leq 0.001$
Disease duration in years	7.5 (6.7)	5.1 (4.7)	$t(438) = 4.400, P \leq 0.001$
K-6 Distress mean	6.6 (4.9)	5.0 (4.2)	$t(442) = 3.693, P \leq 0.001$
% depressed	15%	6%	
Positive family history	27%	6%	$\chi^2 = 36.7, P \leq 0.001$
Bet on horses/dogs	2%	3%	$\chi^2 = 0.135, P = 0.483$
Bet on sports	2%	5%	$\chi^2 = 1.871, P = 0.132$
Bet on dice games	2%	0%	$\chi^2 = 3.001, P = 0.102$
Went to a casino	14%	9%	$\chi^2 = 6.919, P = 0.007$
Played the lottery	21%	18%	$\chi^2 = 3.128, P = 0.050$
Played bingo	4%	0%	$\chi^2 = 7.263, P = 0.008$
Stock/commodities market	9%	12%	$\chi^2 = 0.243, P = 0.368$
Slot machines/gambling machines	12%	6%	$\chi^2 = 6.323, P = 0.010$
Played sport/skill for money	2%	2%	$\chi^2 = 0.221, P = 0.448$
Gambled on the internet	2%	3%	$\chi^2 = 0.000, P = 0.616$

to complete a diagnosis history upon registration with the website. Most patients were diagnosed by a specialist (ALS 78%, PD 64%) and sought a second opinion (ALS 64%, PD 53%). Patients provided the names of their diagnosing doctor, many of whom were well-known figures in the ALS and PD fields. Data were obtained from 236 of 1,607 ALS patients (15%) and 208 of 1,156 PD patients (18%). Ninety-six ALS patients (6%) and 75 PD patients (6%) declined to participate in the study. The remainders were classified as nonrespondents.

RESULTS

Because basic demographic data is collected on registration, we are able to establish that there were no significant differences between responders and opt-outs on any demographic or clinical variables. Therefore, we believe our sample is representative of the patients registered on PatientsLikeMe.

Table 1 shows a number of significant demographic differences among patient groups, all in keeping with the different natures of each disease. Table 1 also shows the distribution of gambling behavior between ALS and PD patients at the time of survey. PD patients were, at the time, more likely than ALS patients to go to a casino, play the lottery, play bingo, or use gambling/slot machines. Both groups had similarly low rates of internet gambling.

There was a trend approaching significance for PD patients to have spent more on gambling than ALS patients over the 12 months preceding the study (PD median: \$10 [\$0–\$12,000] vs. ALS Median \$0 [\$0–\$15,000]; $U = 1354.0$; $P = 0.065$). Only three patients in each group had spent more than \$3,000 in the preceding 12 months.

According to the SOGS cutoff of 5 and above, 13% of PD patients were classified as problem gamblers compared with 3% of ALS patients ($\chi^2 = 14.005$, $P = <0.001$). On average, PD patients had higher total SOGS scores than ALS patients (PD mean = 1.62 [SD 3.1], ALS mean = 0.75 [1.5]; U = 21303.0; $P = 0.006$). Problem gamblers in both groups spent similar amounts of money in the 12 months preceding the study (PD mean = \$2,812, SD = \$3,897 vs. ALS mean = \$2,171, SD = \$3,617; U = 75.0; $P = 0.811$) and in their lifetime (PD mean = \$24,076, SD = \$60,953 vs. ALS mean = \$20,471, SD = \$35,302; U = 69.0; $P = 0.420$). There were no differences in the types of gambling behavior engaged in between problem gamblers with either disease.

Data on dopaminergic drugs were available for 165 (79%) PD patients. Pathological gamblers were no more likely than nongamblers to be taking a particular drug or class of drug. For example, 67% of PD patients with PG were taking dopamine agonists as compared to 59% of PD patients without PG ($\chi^2(1) = 0.431$; $P = 0.342$). Two ALS patients were taking pramipexole experimentally; neither reported unusual behavior.

Participants were asked several questions about the motivation for their gambling behavior on a 4-point scale (strongly disagree, disagree, agree, strongly agree). Table 2 shows the collated responses from problem gamblers in each disease, identified by a SOGS score of 5 or more. PD patients found thoughts

TABLE 2. *Motivation/attribution of gambling behaviour by problem gamblers*

Mean (S.D)	PD problem gamblers (n = 26)	ALS problem gamblers (n = 7)	Significance
Gambling or thoughts about gambling cause me distress	2.5 (1.0)	1.3 (0.8)	$T(31) = 2.911$, $P = 0.007$
I have to strongly resist gambling or thoughts about gambling	2.6 (0.9)	1.3 (0.8)	$T(30) = 3.513$, $P = 0.001$
I have little control over my gambling or my thoughts about gambling	2.3 (1.0)	1.1 (0.4)	$T(26) = 4.476$, $P \leq 0.001$
I gamble or think about gambling because it brings me pleasure	2.8 (0.9)	2.4 (1.4)	$T(8) = 0.809$, $P = 0.537$
I gamble or think about gambling because it helps me feel in control or independent	2.4 (0.9)	1.3 (0.5)	$T(13) = 3.769$, $P = 0.002$
I gamble or think about gambling because of drugs that I'm taking	2.6 (1.0)	1.0 (0)	$T(23) = 7.264$, $P \leq 0.001$
I have always gambled, regardless of my current illness	2 (1.0)	2 (1.0)	$T(27) = 0.000$, $P = 1.000$

Lower numbers reflect disagreement, higher numbers agreement (1-Strongly disagree, 2-disagree, 3-agree, 4-strongly agree). Degrees of freedom vary due to unequal variance assumptions, missing data from 1 ALS PG and 1 PD PG.

about gambling more distressing, harder to resist, and more outside their control than ALS patients. PD patients were more likely to feel that gambling makes them feel independent or in control and more likely to think that the drugs they are taking are a cause of their gambling. According to the K-6 measure of distress, 27% of problem gamblers were classified as depressed overall as opposed to only 6% of nongamblers ($\chi^2 = 17.519$; $P < 0.001$). There was no difference in the proportion of depressed patients between ALS and PD problem gamblers ($\chi^2 = 0.199$; $P = 0.508$).

DISCUSSION

Using a widely used validated measure of PG behavior, the SOGS, we detected PG in 13% of patients with PD and 3% of patients with ALS. As predicted, the PG rate is higher in ALS than one might expect in the general population, where comparable studies have suggested a lifetime prevalence of between 0.25 and 1.7%.[11] By far the most prevalent forms of gambling behaviors among either PG patient group was visiting casinos, playing slot machines, playing bingo, or playing the lottery, all behaviors that have been identified previously. Internet gambling did not appear particularly common in either sample: current use of the internet for gambling was reported by only 2 of 27 PD patients with PG and none of the 8 ALS patients with PG.

Our findings suggest an ~50% higher rate of pathological gambling in PD patients than has been found in previous studies.[3] There are a number of possible explanations for this, such as the selection bias of respondents, the use of a self-report tool rather than a clinical interview, or perhaps something unique to the types of PD patients who are registered on the site. One plausible explanation is that because PG is socially stigmatized, it may go under-reported through traditional research methods, and the quasi-anonymous nature of the internet permits patients to be more candid.

ALS patients with PG seemed to find their gambling ego-syntonic; they were not distressed by their gambling, seemed to be in control, and did not attribute it to any drugs they were taking. By contrast, PD patients appeared to find their gambling ego-dystonic; they found it distressing and out of their control, had to resist urges to gamble, and attributed much of the blame to medication they were taking. Within both groups, about a third of problem gamblers were classified as having a clinically significant level of distress by the K-6. Aside from the dopaminergic hypothesis, one possibility for higher rates of gambling in PD might simply be higher rates of depression; however, we found only weak correlations between distress and gambling behavior, and the majority of patients with PG (two thirds) were not depressed. Further research is needed to fully elucidate this line of enquiry.

The current study should be interpreted in the context of its limitations. First of all, it is likely that users of an internet site are better educated and wealthier than the general patient population; however, this is also likely to be true of patients attending a specialist neurology centre. Secondly, it is likely that as the title of the survey invitation focused on gambling, we may have created some selection bias, and our prevalence numbers may be an overestimate. However, both of these biases should have occurred equally in the ALS and PD groups. Third, as we conducted the survey online, the patients were not physically examined to confirm their diagnoses; however, given the time

involved in participating in the site and the lack of reward for taking part, it seems unlikely that anyone would participate who was not a patient. Finally, we used self-report questionnaires rather than a clinical diagnostic interview against criteria for PG from the fourth edition of the diagnostic and statistical manual of mental disorders (DSM-IV).

PG is likely to represent a severe form of behavioral addiction[3] and may cause significant psychosocial problems for patients with PD and their families. Despite the financial consequences, patients are often meticulous and secretive and do not declare their behavior to spouses, other family members, or physicians unless specifically asked.[12] By the time the problem is discovered, a significant sum may be lost, causing irreparable financial damage and damaging trust or, in some cases, breaking up families.

PG in the general population is often associated with aversive stimuli such as anxiety, loneliness, or mood disturbance, which may be prevalent in sufferers of a chronic debilitating illness such as PD or ALS. However, the increased prevalence of PG and other repetitive and compulsive behaviors in PD as compared to ALS patients in this survey does not support the view that PG simply represents a nonspecific behavioral response to a chronic progressive neurological disorder.

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Very low-frequency rTMS modulates SEPs over the contralateral hemisphere.

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Abstract

In order to investigate the transcallosal effects of repetitive transcranial magnetic stimulation (rTMS), we studied median somatosensory evoked potentials (SEPs) before and after applying monophasic very low-frequency (0.2 Hz) subthreshold rTMS over the right motor cortex. For SEPs, median nerve was stimulated on each side. Sham rTMS served as the control. Twelve healthy subjects participated in this study. After rTMS over the right hemisphere, the amplitude of N34 component in right median SEPs recorded from the left parietal scalp (C3') increased significantly. Other components of right or left median SEPs or those after sham stimulation showed no changes. Monophasic 0.2 Hz subthreshold rTMS over the motor cortex predominantly affected the contralateral SEPs, probably through the transcallosal pathway.

Key words

Somatosensory evoked potential; Repetitive transcranial magnetic stimulation; Primary motor cortex; Contralateral sensory cortex

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) over the motor cortex modifies cortical excitability that outlasts the period of stimulation (1, 2, 3, 4, 5). The effect of rTMS has been explored by examining the changes of motor evoked potentials (MEPs), which reflect activities of the corticospinal tract. However, only a few studies of somatosensory evoked potentials (SEPs) have been reported on the effects caused by rTMS. The right median SEP components N20-P25 and P25-N33 generated in the left hemisphere significantly decreased in amplitude after low-frequency rTMS (1 Hz, biphasic, 200 times) applied over the ipsilateral left motor cortex (6). Their study suggested sensory inhibition occurred by direct cortico-cortical connection between motor and sensory areas because the N20 component reflects an activation of the sensory cortex by thalamocortival fibers. However, our previous study (7) found no changes of these SEP components after very low-frequency rTMS (0.2 Hz, monophasic, 250 times) over the left motor cortex. The discrepancy between these studies may be due to the different stimulation parameters; frequency (1 Hz *vs.* 0.2 Hz) or phase (biphasic *vs.* monophasic) of rTMS.

Seyal et al. (2005) reported significant reduction at base-to-peak amplitude of N20 and peak-to-peak amplitude of N20-P25 after very low-frequency rTMS (0.3 Hz, monophasic, 20 min.) applied over the contralateral hemisphere, but they did not examine ipsilateral effects (8). The present study aimed at examining not only ipsilateral but also contralateral SEP changes after very low-frequency monophasic rTMS given over the right motor cortex. In search for stimulus parameters suitable for this use, we used monophasic very low-frequency (0.2 Hz)