Psychogenic Palatal Tremor May Be Underrecognized: Reappraisal of a Large Series of Cases

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ABSTRACT

Background: Palatal tremor is characterized by rhythmic movements of the soft palate and can be essential or symptomatic. Some patients can have palatal movements as a special skill or due to palatal tics. Psychogenic palatal tremor is recognized but rarely reported in the literature.

Methods: We retrospectively evaluated all patients with palatal tremor seen in our center over a period of 10 years.

Results: Of 17 patients with palatal tremor, we identified 10 patients with isolated palatal tremor. In 70% of those the diagnosis of psychogenic palatal tremor could be made. Of the remainder, 2 had palatal tics and 1 essential palatal tremor.

Conclusions: We suggest that psychogenic palatal tremor may be underrecognized and propose that targeted clinical examination of positive signs for psychogenic movement disorders in these patients is essential. The correct identification of such patients has important clinical and scientific implications.

Key Words: essential palatal tremor; palatal myoclonus; psychogenic; tic; symptomatic

Palatal tremor (PT) (or palatal myoclonus) is a movement disorder characterized by rhythmic movements of the soft palate at 0.5 to 3 Hz.[1] PT is classically classified as essential (EPT)[1] when PT (with or without ear clicks) is the only feature and all imaging and laboratory investigations are normal, and as symptomatic (SPT) when PT is due to a structural or degenerative cause[1,2]; eg, lesion in Guillain-Mollaret triangle, glial fibrillary acidic protein (GFAP)[3,4] or polymerase-γ (POLG) mutations,[5] neuroferritinopathy,[6] or as part of progressive ataxia and PT (PAPT).[7] The tensor veli palatini innervated by the trigeminal nerve is mostly involved in EPT, whereas in SPT it is the levator veli palatini innervated mainly by the vagus nerve.[2,8–11]

Recently, a new classification has been proposed[12] in which EPT should be redesignated as "isolated," indicating the lack of any further signs, and include primary isolated PT (the classical EPT) and secondary isolated PT (PT as a special skill, palatal tic, and psychogenic PT). This report and our observation that some of our longstanding patients who initially presented with apparent isolated PT were in fact psychogenic, prompted us, in this study, to retrospectively revisit all PT patients seen in our center between 2001 and 2011.

Patients and Methods

We searched our database with the term "palatal," "palatal myoclonus," and "palatal tremor" for a period of 10 years (2001–2011). Twenty patients with PT were identified, of whom 3 were excluded because of insufficient clinical data. Of the excluded patients 1 had SPT and 2 isolated PT. We collected details on age, disease onset and duration, precipitating factors, treatment, evolution, concomitant conditions, clinical examination, psychiatric assessment, and further investigations. All patients were examined and followed by the same examiner (K.P.B.), and had at least 6 months of follow-up (range, 0.5–27 years).We specifically noted signs consistent with psychogenic movement disorders (PMDs)[13] and applied the criteria for PMDs to define the degree of diagnostic certainty.[14,15] Statistics were performed using PASW Statistics, version 19.

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

Dr. Stamelou and Dr. Saifee contributed equally to this work.

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Data are shown as mean ± standard deviation. Nonparametric variables were compared with the 2-sided Wilcoxon-Mann-Whitney test and $P < .05$ was considered significant.

Results

Of the 17 patients included, 7 had additional signs at first presentation and were therefore classified as SPT, and 10 had no additional signs at first presentation and were classified as having isolated PT. The mean age at onset for SPT was significantly older than for isolated PT (53.6 ± 5.2 vs 37.2 ± 7.4 years, respectively) ($P = .003$), in line with published data.[1,12] Of the 7 SPT patients, 5 were diagnosed as PAPT (2 negative for GFAP mutations), 1 developed PT subacutely after a left hemispheric stroke, and 1 had diaphragmatic myoclonus with coherent movements of the palate. Three had normal and 4 had abnormal brain MRI (1 olivary hypertrophy, 1 left hemispheric stroke, 1 cerebellar atrophy, and 1 olivary hypertrophy and cerebellar atrophy), whereas all EPT patients had extensive investigations that were normal (see Supporting Information).

From the 10 cases with isolated EPT at their first visit, 6 were diagnosed as primary EPT, 2 as palatal tics, and 2 as psychogenic PT. The patients were followed and the diagnosis was revised in 5 of 6 primary EPT cases to psychogenic PT. The duration from first visit to revision of diagnosis ranged from 2 to 18 years (Table 1). All patients with isolated EPT were examined for positive signs of PMDs according to published criteria (Table 1).[13,14] Of the 10 EPT cases, 7 (70%) had documented positive signs of PMD (Table 1), 6 of those 7 were female. The mean age at onset in those was 35.4 ± 6.4 years and the mean disease duration was 13.6 ± 11.2 years (range, 2–29 years). In all patients with psychogenic PT, there was a physical precipitant (Table 1). The latency from trigger to PT onset is shown in Table 1. All patients reported ear clicking, mostly bilaterally, and in 3 cases this resolved later.

On examination of the 7 psychogenic PT cases, there was PT that was documented to be incongruous, variable, entrainable, and distractible (Table 1). In 3 of 7 there was an electromyography (EMG) confirmation of the variability and the irregularity of the rhythm, and in 1 additional patient of distractibility while recording. In 2 of 7 patients there were further neighboring muscles involved on follow-up, but this was variable and inconsistent in further follow-ups. In 6 of 7 patients there were multiple somatizations recorded, in 4 of 7 there was a psychiatric evaluation suggesting an underlying psychiatric condition, and in 1 case each, psychotherapy and antidepressants improved the symptoms (Table 1). Based on these data, 3 patients would be classified as clinically definite, 3 as clinically established. and 1 as probable psychogenic PT, according to published criteria.[13] Further supportive signs of PMDs[14] were abrupt onset and static course of the symptoms (n = 7), multiple somatizations (n = 6), spontaneous remissions (n = 1), self-inflicted injury (n = 1), and other movements consistent with PMDs[15,16] (n = 3) (Table 1). Of 7 psychogenic PT patients, 2 improved with botulinum neurotoxin (BoNT) injections (duration of treatment: 5 years and 10 years, respectively) (Table 1). Of 7 patients, 1 improved after the first time injected, but subsequent injections did not help. She was then started on amitriptyline 10 mg with benefit (Video Segment 2). One (case 3) has never received any treatment and is stable, with a moderate aggravation of her symptoms in the form of facial spasms. Of 7 patients, 3 (cases 2, 4, and 6) have not received BoNT but tried oral medications without success (Table 1). Interestingly, over the years, these 3 patients developed multiple complex PMDs or/and further psychogenic neurological symptoms (Table 1).

The 2 patients with palatal tics had other motor tics and a tic-disorder in the family history, excellent response to BoNT injections, and did not demonstrate signs of a PMD (Table 1). Of 10 EPT patients, 1 (case 8) was diagnosed as primary EPT, in whom all signs suggestive of PMDs were tested and found to be consistently negative. Illustrative cases may be found in the online Supporting Information.

Discussion

We report here that 70% of the patients with isolated PT seen in our center over a period of 10 years, were likely to be of psychogenic etiology based on published criteria for diagnosis of PMDs.[13] This is the largest series of patients with psychogenic PT reported in the literature. In line with published literature on PMDs the majority of the patients were female[16,17]; there was a precipitating factor (predominantly a minor viral respiratory infection)[12,18]; PT was often accompanied by bilateral ear clicking[12]; and there was either an additional PMD or other somatizations.[13] Consistent with other PMD, BoNT helped even at long-term follow-up.[19] Some of our patients showed involvement of further neighboring muscles in a variable and inconsistent way over the years, which could also be a sign of incongruity for EPT.[1,12]

Patients with psychogenic PT are rarely documented in the literature and therefore psychogenic PT is thought to be uncommon.[12,20–24] However, signs of psychogenicity according to published criteria[13] are not frequently tested in these patients: in an extensive review of 103 cases with EPT, signs of PMDs such as distractibility and entrainment were commented on in only 11 patients.[12] Supportive of our data, 5 out of those 11 had positive signs for PMDs. Thus, we propose here that psychogenic PT may be underrecognized

Table 1. Clinical characteristics of patients with isolated PT

PN	G	Age at onset (yr)	Duration (yr)	Follow-up (yr)	Time from first visit to diagnosis (yr)	Precipitant (latency)	Other somatizations and evolution	Psychiatric history and evaluation	Incogruity/ variability/ entrainment/ distractibility	Diagnostic classification[a]	Treatment
Psychogenic PT											
1	F	30	2	0.5	0	Viral labyrinthitis (3 weeks)	PT stable, pressure on left side of head	History of sexual and physical abuse; positive psychiatric family history	+/+/+/+	Clinically definite	Symptoms better after psychotherapy-BoNT: improvement after 3 days; further BoNT treatments no clear benefit; 2 weeks treatment with 10 mg amitryptiline, clear improvement of PT
2	F	34	12	9	6	Tinnitus (same time)	PT stable, over the years other muscles involved, eg, larynx; 10-yr history dysphagia, 1-yr history sleep disturbance	Anorexia in her teens, later diagnosed with depression	+/+/+/+	Clinically established	Pregabalin, levetiracetam, clonazepam: no benefit; diazepam: better; BoNT refused
3	F	33	29	27	18	Flu-like illness (2 days)	PT stable, over the years other muscles involved but variability of those in each follow-up, new onset facial spasms	No obvious psychiatric disorder	+/+/+/+	Clinically established	BoNT not tried
4	F	40	9	7	3	Sore throat, right-sided otitis (same time)	3 yr after onset psychogenic head and neck jerks, rocking movements of the trunk, head bobbing	Dissociative motor disorder; mother depression; history of sexual abuse	+/+/+/+	Clinically established	Clonazepam, no benefit, BoNT refused; cognitive behavioral therapy declined
5	F	47	15	4	2	Flu (1 week)	Stable, no additional symptoms	No obvious psychiatric disorder	+/+/+/+	Probable	BoNT improvement
6	F	28	5	4	0	Endoscopy for nausea (2 weeks)	Nausea, tachycardia, fatigue,pain, headaches; 3 yr later generalized weakness; wheelchair; visual disturbance	Self-injury in the past; paternal aunt had depression and comitted suicide	+/+/+/+	Clinically definite	BoNT refused
7	M	36	28	23	14	Vomiting, vertex headache (same time)	PT stable; feeling of lump on scalp which he rubs causing hair loss; long periods of symptom remission with relapse	Depression diagnosed 10 yr after onset	+/+/+/+	Clinically definite	Benzehxol, baclofen, diltiazem, levodopa, clonazepam: no benefit; fluoxetine, paroxetine, BoNT: improvement

Table 1 (*Continued*)

PN	G	Age at onset (yr)	Duration (yr)	Follow-up (yr)	Time from first visit to diagnosis (yr)	Precipitant (latency)	Other somatizations and evolution	Psychiatric history and evaluation	Incogruity/ variability/ entrainment/ distractibility	Diagnostic classification[a]	Treatment
Primary EPT											
8	F	33	2,5	1	NA	Mild throat infection 2.5 months before	Generalized weakness-breathing problems, abdominal pain with no organic cause; uses wheelchair outside	No obvious psychiatric disorder	–/–/–/–	NA	BoNT: improvement
Palatal tics											
9	M	40	2	2	0	No	Motor tics	No obvious psychiatric disorder	–/–/–/–	NA	BoNT: improvement
10	F	40	7	4	0	No	Motor tics	No obvious psychiatric disorder	–/–/–/–	NA	BoNT: improvement

[a]According to criteria for psychogenic movement disorders.[14,15]EPT, essential palatal tremor; PT, palatal tremor; PN, patient number; G, gender; F, female, M, male; BoNT, botulinum toxin; NA, not applicable.

and misdiagnosed as primary EPT when targeted examination for signs of psychogenicity according to published criteria is not done. In our case series this is illustrated by the fact that the majority of these patients were diagnosed by us as primary EPT for many years, before direct examination for these signs led to revision of the diagnosis.

Misdiagnosis of these patients has implications for their management and their long-term outcome. Delay in correct diagnosis and failure to provide suitable treatments are predictors of poor prognosis in PMDs.[25–28] This is perhaps reflected in our series by the fact that 3 cases deteriorated significantly over the years, presenting with more complex PMDs that rendered them severely disabled. Accurate identification of these patients would also enable their exclusion from studies on the largely unknown pathophysiology and evolution of primary EPT, and inclusion in future studies of treatment for PMDs.

Limitations of this study are that there is no biomarker available for the diagnosis of PMDs, and we acknowledge the difficulties in clinically diagnosing psychogenic PT, particularly via application of clinical diagnostic criteria for PMDs. However, 8 in 10 of the patients in the isolated EPT group are under active follow-up, and therefore were accessible for current assessment. The high percentage of psychogenic PT found in our population may not be representative for the prevalence of psychogenic PT in the community, given the method of patient ascertainment.

Finally, we would like to suggest that although the proposed new classification for PT[12] has some merit, there are some important caveats. Classification of psychogenic PT as a form of "secondary PT" is confusing. Secondary movement disorders are typically those in which an identifiable secondary event occurs on the background of previously normal brain function. Other PMDs such as psychogenic dystonia are not classified within the "secondary" category. Therefore, we suggest that psychogenic PT should not be classified under secondary EPT and that PT should instead be divided into 3 categories: EPT ("primary"), SPT, and psychogenic PT.

Legends to the Video

Video 1. Segment 1. Case 1, with irregular, variable, and entrainable palatal tremor (as indicated by the overtitles during the video) about 1 month after BoNT treatment. **Segment 2**. Case 1, at 2 weeks after starting treatment with amitriptyline 10 mg and no further BoNT injections for the last 5 months. There is no palatal tremor at rest. There is entrainment with the tapping task and distractibility with the ballistic task (when the voice says "now" in the video). The patient has no palatal tremor at rest with head straight but this starts when head is held back. **Segment 3**. Case 3, with distractible palatal tremor that ceases during tapping and starts again when stopping tapping, and facial spasms that cease during tapping (see overtitles). ■

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Impairment of Brain Vessels May Contribute to Mortality in Patients With Parkinson's Disease

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ABSTRACT

Background: The effect of brain-vessel pathology on mortality in 57 consecutive PD patients was studied. **Methods:** Baseline clinical, neuropsychological, ultrasonographic (US), and MR data obtained from patients who died (n = 18) during a 4-year follow-up period were compared with the data of patients who survived. **Results:** US/MRI data displayed a more-severe vascular impairment in deceased patients. Differences were significant between both groups with respect to age, clinical and cognitive status, intima-media thickness, and resistance index (indicators of large and small vessel impairment). The sum score of white-matter hyperintensities was significantly higher among decedents. A cluster analysis displayed two clusters that differed in the two parameters (i.e. in age and in sum score). **Conclusions:** This study provides evidence that comorbid atherosclerosis and otherwise subclinical impairment of brain vessels may contribute to mortality in PD. The vascular pathology may act in association with other comorbidities on the terrain of progressive neurodegenerative pathology. © 2012 *Movement* Disorder Society

Key Words: cerebrovascular disease; Parkinson's disease; MRI; ultrasound

Reports about the impact of cerebrovascular disease (CVD) on clinical status in Parkinson's disease (PD)

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Table 1. Characteristics of investigated patients, principal clinical results, and results of US/MRI investigations in groups 1 and 2

	Group 1					Group 2					
	Valid N	Median	Lower Quartile	Upper Quartile	Range	Valid N	Median	Lower Quartile	Upper Quartile	Range	*P* Value
Characteristics of investigated patients and principal clinical and MRI results											
Actual age, years	18	74	72	75	28	39	64	62	71	29	< 0.001
Diagnosis, years	18	9	6	16	22	39	8	5	10	18	0.178
UPDRS III	18	22.5	18	36	56	39	17	13	25	50	0.011
H & Y	18	3	2	3	3	39	2	2	3	4	0.577
NPI	18	6	0	13	41	34	0	0	3	32	0.049
IADL	18	50	25	80	75	39	75	60	80	50	0.051
Barthel's index	18	90	60	100	55	39	100	95	100	35	0.003
Clock test	17	8	4	9	10	38	9	7	10	5	0.004
MMSE	18	26.5	25	28	11	39	28	27	29	13	0.006
Benton	17	0	0	4	23	38	0	0	0	10	0.109
VFT	17	17	14	19	16	39	20	14	24	24	0.077
MADRS	17	16	11	19	18	38	12.5	6	19	71	0.135
WMS-III-I-1.r	17	9	4	11	14	37	8	7	11	13	0.723
WMS-III-I-cs	17	6	5	10	12	37	9	6	10	14	0.412
WMS-III-II-r	17	11	10	13	14	37	12	11	13	7	0.154
WMS-III-II-recog	17	11	10	11	10	37	11	11	14	10	0.115
WMH score	16	8.5	5.5	10.5	15	19	3	1	5	9	< 0.001
Results of US investigation											
IMT	18	0.90	0.85	1.15	0.75	39	0.8	0.7	0.85	0.6	< 0.001
PI	15	0.93	0.85	1.2	1.01	33	0.91	0.81	0.98	0.85	0.114
RI	15	0.62	0.56	0.68	0.32	33	0.55	0.525	0.59	0.55	0.034
AS plaque*	11 Yes			7 No		15 Yes			24 No		0.154

Significant differences are shown in bold. P values according to Mann-Whitney's nonparametric U test for independent components.
*Fisher's exact p, paired.
Abbreviations: IADL, Instrumental Activities of Daily Living scale; Barthel index, activities of daily living; MMSE, Mini–Mental State Examination (raw scores); MMSE plus clock test, Mini–Mental State Examination plus clock drawing test (raw scores); Benton, Benton Temporal Orientation Test (raw scores); VFT, Verbal Fluency Test—Semantic Association Category (percentile scores); MADRS, Montgomery Asberg Depression Scale (raw scores); WMS-III (I) 1.r, Wechsler Memory Scale III, subtest Word Lists I–First Recall (weighted scores); WMS-III (I) ts, Wechsler Memory Scale III, subtest Word Lists I–Immediate Recall–total sum (weighted scores); WMS-III (II) r, Wechsler Memory Scale III, subtest Word Lists II–Delayed Recall (weighted scores); WMS-III (II) recog, Wechsler Memory Scale III, subtest Word Lists II –Recognition (weighted scores); WMH score, white-matter hyperintensities score (Scheltens' scale).

are rather controversial.[1–12] CVD is diagnosed in autopsy as the etiological factor of parkinsonism in only 1% to 3.2% of cases.[13–15] We recently reported that the pathology of vessels supplying the brain contributes to disease severity in PD patients, even without clinically manifest CVD.[16] We hypothesized that the baseline pathology of vessels supplying the brain contributes to fatal outcomes in PD patients over the 4-year follow-up period.

Patients and Methods

We examined 57 consecutive PD patients [16]. None of the patients had vascular parkinsonism[17,18] or was severely impaired by any other comorbidity. The local ethics committee approved the study, and informed consent was obtained from each patient.

A follow-up evaluation 4 years after the baseline visit was based on patient examination (in 26 patients), medical records (in 13 patients), and death register, respectively (in 18 patients).

Baseline clinical and neuropsychological data, MRI findings, and results of ultrasound (US) brain-vessel investigations of deceased patients (group 1; n = 18) were compared with data of the surviving patients (group 2; n = 39). Specialists in movement disorders, stroke, and MRI as well as neuropsychologists performed a blinded evaluation. An independent statistician evaluated all data.

MRI was performed using a 1.5-T Siemens Magnetom Symphony scanner (T1, T2, and FLAIR; Siemens Medical Solutions, Malvern, PA). FLAIR images accompanied by T2 images (5-mm, 30% interslice gap) were crucial for white-matter hyperintensity (WMH) scoring. A semiquantative Scheltens rating scale of WMH was used,[19,20] in which deep white matter, periventricular, basal ganglia, and infratentorial signal hyperintensities were rated separately. Valid MRI data were obtained from 54 patients.

US examinations of extracranial vessels to measure intima-media thickness (IMT) and the presence of atherosclerotic (AS) plaques were performed with a Toshiba Nemio (Toshiba Medical Systems Corp., Tokyo, Japan), equipped with a linear transducer (7.5 MHz) in duplex mode.[16] US examination of intracranial vessels was performed with the use of a 2-MHz annular array US imaging system; the resistance index (RI) and the pulsatility index (PI) on the medial cerebral artery were

assessed.[16] Both indices may show increased peripheral resistance in the cerebral circulation, which suggests microangiopathic changes of cerebral vessels.[21]

For comparing clinical parameters of both groups of patients, Mann-Whitney's nonparametric U test was used for independent variables, because the values used did not usually have a normal distribution (i.e., discrete values of a specific range, and so on). For two-state variables (e.g., AS plaque), Fisher's exact test was used. Characteristics of observed quantities are shown in Table 1.

Acquired data were tested by a general regression method (GRM) model to analyze the independence of age and US data. Normality of the logarithmized US data was controlled by Shapiro-Wilk's W test.

For a more-detailed analysis of the WMH scores of survivors and deceased, we checked whether the observed values had normal distribution (Shapiro-Wilk's W test). We also performed a cluster analysis by the k-means method for analysis of differences between groups 1 and 2 at baseline and after the 4-year follow-up. For confirmation of the hypothesis of the independence of age and of WMH score, the acquired data were tested by a GRM mode. WMH-score values were used as the dependent variable, age as a continuous independent variable, and the parameter "group 1 and group 2" as a categorized variable.

Results

The characteristics of the investigated patients and principal results are shown in Table 1.

AS plaque was detected in 27 patients; a lumen reduction of between 50% and 70% was present in only 3 patients.

In IMT, for the whole test, the multiple regression coefficient was R = 0.628 ($P < 0.0002$). Analysis of variance (ANOVA) showed that IMT value does not depend on age ($P = 0.440174$; but on the group 1/group 2 parameter: $P = 0.000362$). In PI, for the whole test, the multiple regression coefficient was R = 0.339 ($P = 0.159$). ANOVA displayed insignificant results (age: $P = 0.851695$; group 1/group 2 parameter: $P = 0.122003$). In RI, for the whole test, the multiple regression coefficient was R = 0.427 ($P = 0.048$). ANOVA showed that RI value does not depend on age ($P = 0.372494$; but on group 1/group 2 parameter: $P = 0.022353$).

The occurrence of hallucinations was more frequent ($P = 0.0018$) in group 1 (n = 9) than in group 2 (n = 4). Stroke/transient ischemic attack was reported in 4 subjects; 3 of them were in group 1. MRI revealed a territorial stroke in only 1 patient.

Volume of WMH was small in general. The 16 deceased and 19 surviving subjects with WMH measures differed significantly in age (mean: 72.75 ± 4.2 versus 63.8 ± 4.3) and in rating of WMH (sum score: 8.50 ± 4.06 versus 2.78 ± 2.34).

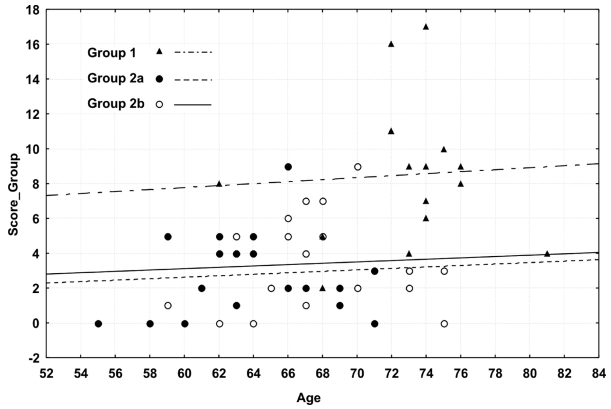

FIG. 1. Age: actual age at the time of MR investigation. Score: sum score of white-matter signal hyperintensities scaling (Scheltens' scale). Group 1: deceased; group 2a: survivors at baseline; and group 2b: survivors, the follow-up data (year 4 after the baseline). Lines represent the regression dependency of groups 1, 2a, and 2b.

A *t* test for independent values showed some statistically significant differences, both in age of groups ($P = 0.000001$) and in WMH-score values ($P = 0.000011$). Correlation analysis did not show any dependence of WMH score values on age in group 1 ($r = 0.058$; $P = 0.83$) or in group 2 ($r = 0.07$; $P = 0.75$) (i.e., the two variables were independent). The sum score of the semiquantative rating scale of WMH differed significantly between the two groups ($P < 0.0001$).

The distribution of WMH score and age values in the groups of patients is illustrated in Figure 1.

Cluster analysis displayed three clusters. The two basic groups of values showed cluster 1 (10 deceased of 11 total values) and cluster 2 (27 survivors of 29 total values). The ANOVA test confirmed that these three clusters differed in both parameters (age and score; $P < 0.00001$). According the GRM model, the multiple regression coefficient was R = 0.642 ($P < 0.0001$).

ANOVA showed that score does not depend on age ($P = 0.511785$; but on group 1/group 2 parameter: $P = 0.000039$).

Discussion

Of 57 patients with PD, 18 died within the 4-year follow-up period. Only 1 death, caused by an acute stroke, was reported. Nonacute CVD may be a factor influencing mortality, but the results of previous studies have been inconsistent.[4,22,23]

We were able demonstrate a possible effect of subclinical vascular impairment on PD mortality. Significant differences between survivors and deceased patients in our cohort were displayed when the results of the US/MRI investigation were compared. The IMT was significantly larger in decedents than in survivors.

The IMT is considered to be a valid index of the involvement of arterial beds with AS.[24] This suggests a possible link between AS involvement and the more-malignant clinical course of PD with a shorter survival. Statistical analysis showed that age, IMT, and RI are independent contributors to mortality.

MRI investigation of small vessels also displayed a relationship between IMT and a less-favorable course of PD.

A higher degree of white-matter lesions also occurred more frequently in decedents. The sum score of WMH was significantly higher among decedents than survivors. WMH scores are associated with cognitive and motor impairment in PD and with age.[20,25] In our cohort, cluster analysis revealed that both WMH and age have an effect on PD mortality. Statistical analysis showed that age and WMH score are independent contributors to mortality. Our findings support the hypothesis that the pathological processes underlying white-matter lesions may contribute to the death rate in PD patients.

Decedents were older, with more-severe clinical and cognitive impairment than the rest of the cohort. Other studies have reported that older age, longer disease duration, cognitive impairment, and hallucination were strongly associated with greater mortality risk.[2,3] In our cohort, despite similar disease durations, deceased patients had a more-advanced stage of parkinsonism at the baseline visit, suggesting that these patients may have had a more-rapidly progressing disease. Disease-related degenerative brain changes and coincident diseases are primary causes of death in PD. A comorbid hypoperfusion may contribute to mortality in PD. One possible mechanism is the deleterious effect of otherwise subclinical hypoperfusion on regions made vulnerable by the degenerative process.[26]

The cohort of examined patients was limited. Despite statistical significance, it did not enable a firm conclusion. There was an inherent bias in comparing patients who died to those who did not—the former group would almost certainly have more comorbidities. None of the PD patients was severely impaired as a result of comorbidities at the baseline assessment, but we lack accurate data concerning comorbidities at the period preceding death in those who were deceased. Larger studies are needed to precisely establish the role of vascular factors in PD. Another limitation of our study is the lack of clinicopathological correlation. Halliday et al.[27] demonstrated that older PD patients with a more-aggressive clinical course and shorter survival had more heterogenous brain pathology on the whole, including CVD brain pathology.

Conclusions

In summary, this study provides evidence that concomitant vascular pathology may contribute to a less-favorable course and increased mortality in PD patients, even when it is not itself clinically expressed. The vascular pathology may act in association with other comorbidites on the terrain of progressive neurodegenerative pathology. ■

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Addenbrooke's Cognitive Examination-Revised for Mild Cognitive Impairment in Parkinson's Disease

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ABSTRACT

Introduction: Cognitive impairment is common in Parkinson's disease (PD), even in the early stages, and appropriate screening tools are needed.

Methods: We investigated the utility of the Addenbrooke's Cognitive Examination-Revised for detecting mild cognitive impairment (MCI) in PD in an incident population-representative cohort (n = 132) and investigated the relationship between performance on this instrument and behavior and quality of life (n = 219).

Results: Twenty-two percent met criteria for MCI. Receiver operating curve analysis revealed an area under the curve of 0.81. A cutoff <89 gave a sensitivity of 69% and specificity of 84%. Scores on this instrument were highly correlated with the Parkinson's Disease Cognitive Rating Scale, and there were significant correlations with the Cambridge Behavioral Inventory-Revised and Parkinson's Disease Questionnaire 39.

Conclusion: This instrument is a useful screening tool for PD-MCI, and poor performance is significantly related to impaired behavior and quality of life. © 2012 *Movement* Disorder Society

Key Words: Parkinson's disease; dementia; mild cognitive impairment; Addenbrooke's Cognitive Examination; sensitivity; specificity

Cognitive deficits are common in Parkinson's disease (PD). Dementia may ultimately affect up to 80%[1] of patients, but more subtle cognitive impairments, recently termed mild cognitive impairment of PD (PD-MCI),[2] are estimated to affect approximately 25% of nondemented patients.[3] These early cognitive deficits may be prognostically important if PD-MCI defines a patient group at increased risk of later dementia, although it seems likely that particular subtypes of PD-MCI may differ in this respect,[4] with more posterior cortically based deficits being particularly associated with later occurring dementia.[5] For the concept of PD-MCI to be useful in clinical practice, appropriate tools must be available to detect it.

The Addenbrooke's Cognitive Examination-Revised (ACE-R) is a brief cognitive screening battery assessing five neuropsychological domains (orientation and attention, memory, verbal fluency, language, and visuospatial function). It incorporates the widely used Mini–Mental State Examination (MMSE), but provides a more thorough assessment of cognitive function. As a screening tool for dementia, it has high reliability and validity, and its utility in a number of neurological conditions has been demonstrated.[6] A small study (n = 44) has explored its usefulness in PD as a tool for diagnosing dementia and reported high sensitivity (92%) and specificity (91%) at a cut-off value of 83 of 100.[7]

In this study, we explored the utility of the ACE-R as a tool for evaluating PD-MCI in a newly diagnosed, community-based PD cohort. We performed receiver operating characteristic (ROC) analysis and validated the ACE-R against a recently developed disease-specific cognitive screening instrument: the Parkinson's Disease Cognitive Rating Scale (PD-CRS).[8] In a larger

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

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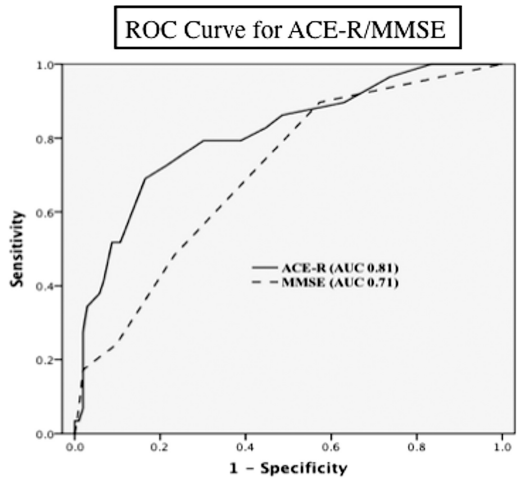
cohort (incident and prevalent), we investigated the effect of ACE-R score on behavior and quality of life using both the carer-completed Cambridge Behavioral Inventory-Revised (CBI-R)[9] and the patient-completed Parkinson's Disease Questionnaire 39 (PDQ-39).[10]

Patients and Methods

The PD cohort comprised (1) patients with incident PD recruited from the community as part of an ongoing epidemiological study and (2) consecutive prevalent patients attending the PD Research Clinic at the Cambridge Center for Brain Repair (Cambridge, UK). PD was defined using the UK Parkinson's Disease Society Brain Bank criteria. Dementia was excluded using *Movement* Disorder Society (MDS) dementia criteria.[11] The study was approved by the local research ethics committee.

Incident patients were assessed within 1 year of diagnosis. All patients completed the ACE-R (including MMSE), UPDRS/MDS-UPDRS,[12] CBI-R,[9] PDQ-39,[10] and Beck Depression Inventory (BDI).[13] Medication doses were converted to equivalent levodopa doses using a previously published formula.[14] Incident patients completed a detailed neuropsychological assessment, including CANTAB One-touch Tower of London, Spatial Recognition Memory, Pattern Recognition Memory, and Paired Associates Learning (www.cantab.com) semantic (animal) and phonemic (letter "p") fluency in the 90s, the Design Organization Test,[15] and, in a subset, the PD-CRS,[8] which has been previously independently validated.[16]

PD-MCI was defined as cognitive decline reported by the patient, carer, or clinician with performance 1 standard deviation (SD) below the mean for an age-matched control population on two or more tests from the neuropsychological battery as well as the lack of a confounding cause for poor test performance (e.g., depression). This is in accord with level 1 MDS criteria for PD-MCI.[2] Cut-off values <1 SD were in line with our previous studies.[14] ROC analysis was performed for ACE-R and MMSE using SPSS software (version 19; SPSS, Inc., Chicago, IL). Specificity, sensitivity, and positive likelihood ratios (LR+) were calculated. Positive predictive value (PPV) and negative predictive value (NPV) were calculated using the prevalence of MCI in our cohort. ACE-R total/domain scores were compared with appropriate domains of the PD-CRS using a correlation matrix with bivariate Spearman's rank correlation coefficients. The relationship between ACE-R score and quality of life, as measured by the CBI-R and PDQ-39, was assessed using ranked fourth-order Pearson's partial correlation analysis (for nonparametric data) with age, disease duration, UPDRS motor score, and BDI as covariates. All ACE-R analyses were done by an independent rater not involved in the collection of neuropsychological data and application of diagnostic criteria.



ACE-R Cut off <	Sensitivity %	Specificity %	LR+	PPV	NPV
87	0.52	0.91	5.94	0.62	0.87
88	0.52	0.89	4.83	0.57	0.87
89	0.69	0.84	4.18	0.53	0.91
90	0.72	0.79	3.38	0.48	0.91
91	0.79	0.70	2.63	0.42	0.92
92	0.79	0.61	2.04	0.36	0.91
93	0.83	0.55	1.85	0.34	0.92
94	0.86	0.52	1.78	0.33	0.93
95	0.90	0.37	1.42	0.28	0.93
96	0.97	0.26	1.31	0.26	0.96

FIG. 1. ROC curve for ACE-R and MMSE in PD-MCI. Diagnostic parameters for different ACE-R cut-off values are presented.

Results

One hundred and thirty-two incident patients completed the neuropsychological battery and were included in the ROC analysis. Forty-five incident patients completed the PD-CRS. Two hundred and nineteen patients (129 incident and 91 prevalent) completed the CBI-R and PDQ-39 forms.

Twenty-two percent of incident patients undergoing full neuropsychological evaluation met criteria for PD-MCI. They were significantly older and less educated, but did not differ in terms of motor impairment, disease duration, or depression scores. There was a significant between-group difference for ACE-R total and all subdomains (see Supporting Table 1).

ROC analysis (n = 132) of ACE-R revealed an area under the curve (AUC) of 0.81 (95% confidence interval [CI]: 0.72–0.90), indicating that ACE-R is an accurate tool for diagnosing PD-MCI. An ACE-R cut-off value of less than 89 of 100 gave the optimum results from the parameters calculated (sensitivity, 69%; specificity, 84%; LR+, 4.18; PPV, 0.54; NPV, 0.91), whereas an improved sensitivity was associated with a cut-off value of <91 (79% sensitivity), but at the expense of specificity (70%) (Fig. 1). Test accuracy was highest for those in the highest quartile of

Table 1. Relationship between ACE-R, CBI-R, and PDQ-39 in nondemented PD patients (n = 219)

	ACE-R Total	Attention/Orientation	Memory	Fluency	Language	Visuospatial
CBI-R total	−0.144[a]	−0.060	−0.180[b]	−0.054	−0.113[a]	−0.056
Memory	−0.098	−0.016	−0.075	−0.072	−0.114[a]	−0.056
Every day skills	−0.057	−0.031	−0.051	−0.004	−0.056	−0.107
Self-care	−0.147[a]	0.006	−0.130[a]	−0.070	−0.045	−0.109
Abnormal behavior	0.007	0.014	−0.029	0.059	−0.087	−0.092
Mood	−0.020	−0.035	−0.049	0.027	−0.049	−0.036
Beliefs	−0.132[a]	0.030	−0.103	−0.048	−0.223[b]	−0.079
Eating habits	−0.067	−0.020	−0.048	−0.027	−0.131[a]	−0.129[a]
Sleep	−0.036	0.020	−0.038	−0.036	−0.059	−0.033
Stereotypical behavior	−0.038	0.042	−0.009	0.028	−0.139[a]	−0.157[a]
Motivation	−0.076	−0.015	−0.136[a]	−0.008	0.024	−0.004
PDQ-39 total	−0.169[a]	−0.075	−0.142[a]	−0.140[a]	−0.106	−0.122[a]
Mobility	−0.130[a]	−0.106	−0.083	−0.116[a]	−0.075	−0.080
Activities of daily living	−0.187[b]	−0.054	−0.123[a]	−0.203[b]	−0.110	−0.139[a]
Emotional well-being	−0.111	−0.032	−0.096	−0.043	−0.100	−0.141[a]
Stigma	−0.104	0.027	−0.143[a]	−0.062	−0.008	−0.050
Support	−0.057	0.082	−0.106	0.002	−0.021	−0.098
Cognitive	−0.160[a]	−0.007	−0.107	−0.156[a]	−0.128[a]	−0.101
Body discomfort	−0.054	−0.084	−0.089	−0.011	0.003	−0.009

Ranked fourth-order Pearson's partial correlation coefficients, with age, disease duration, BDI, and UPDRS motor score as covariates. Significant correlations are shown in bold.
[a]$P < 0.05$.
[b]$P < 0.005$.

education (age range at leaving education: 15–22 years) (AUC, 0.94; 95% CI: 0.84–1.0) versus (AUC, 0.73; 95% CI: 0.55–0.91) those in the lowest quartile (age range at leaving education: 9–11 years).

The MMSE suffered from ceiling effects, with an ROC curve analysis showing an AUC of 0.71 (95% CI: 0.60–0.81). The optimum cut-off value was an MMSE <29, which gave a sensitivity of only 48% and a specificity of 77%, LR+ of 2.07, PPV of 0.37, and NPV of 0.84.

Total ACE-R scores correlated highly with total PD-CRS (n = 45; r = 0.8; $P < 0.0001$). All ACE-R domains correlated significantly with their relevant PD-CRS domains (Supporting Table 2). There were significant correlations between total ACE-R and behavior and quality of life, as measured on both the CBI-R and PDQ-39 (n = 219) (Table 1).

Discussion

The prevalence of PD-MCI of 22% in our incident community-based cohort is comparable to that reported in a recent large meta-analysis.[3] ROC analysis suggests that ACE-R is a good screening test in this population, with an AUC of 0.81 indicating high accuracy. It is superior to the MMSE, which has clear ceiling effects in this population. Furthermore, ACE-R correlates well with the PD-CRS, a validated disease-specific instrument, and it has ecological validity, affecting behavior and quality of life. A previous study reported a much lower AUC of 0.658 and only moderate sensitivity (61%) and specificity (64%) at an optimal cut-off value of ≤93.[17] However, there were important methodological differences, compared to our study, including their use of a prevalent clinic-based cohort with later stage PD (mean disease duration: 5.9 ± 5.2 years), with a definition of PD-MCI as performance <1.5 SD below the normative mean on any single test in the neuropsychological battery, possibly explaining the unusually high prevalence of PD-MCI (at 63%). Furthermore, in contrast to their finding of reduced utility of the ACE-R for PD-MCI at higher levels of education,[17] our data suggest the opposite, with the test being most accurate in more-educated patients. A post-hoc subgroup analysis for quartiles of educational level is presented in Supporting Table 3. This suggests that optimal cut-off values may be lower in those with a lower educational level.

Selection of the most appropriate ACE-R cut-off value for the diagnosis of PD-MCI depends on the requirements of the clinician or researcher. Our analysis suggests an optimal cut-off value of <89, which is associated with 84% specificity, 69% sensitivity, PPV of 0.54, NPV of 0.91, and LR+ of 4.18. The high LR+ shows that a patient with ACE-R <89 is over four times more likely than a patient with ACE-R ≥89 to have PD-MCI. Although such a cut-off value may be useful for trial purposes where a higher specificity and PPV are desirable, a cut-off value with higher sensitivity, though lower specificity, may be more appropriate for clinical purposes, where the aim is to identify individuals at risk of developing PD dementia (e.g., a cut-off value of <91 has a sensitivity of 79%, but specificity of 70%). NPV is high across a range of cut-off values (Fig. 1), suggesting that ACE-R is reliable in excluding PD-MCI.

Although a number of other instruments may be used to screen for cognitive impairment in PD, the ACE-R has several advantages. It is relatively brief, taking 8 to 10 minutes to complete in patients with normal cognition/MCI (compared to 17–26 minutes for the PD-CRS), yet it provides comprehensive coverage of neuropsychological function, including instrumental cortical functions, such as language and orientation, as well as fluency, visuospatial function, and memory. It can be used in a range of neurological conditions; hence, it is useful in settings where the diagnosis may be unclear and is freely available online. It has also been validated in many different languages.[18–20]

Some of these advantages also apply to the 30-item Montreal Cognitive Assessment (MoCA). In addition, it has recently been demonstrated to be an accurate test for detecting PD-MCI, with a sensitivity of 90%, specificity of 75%, and NPV of 95%.[21] However, direct comparison between this study and ours cannot be made because of methodological differences, including their use of a cross-sectional sample with a mean disease duration of 7.2 years versus our incident cohort (mean disease duration: 1.1 years), and differences in diagnostic criteria for PD-MCI, with the new MDS criteria being adopted in our study. Furthermore, another study examining the MoCA in PD suggested that its properties were much less favorable.[22]

A useful test should also identify cognitive changes relevant to day-to-day function, and indeed the ACE-R exhibits significant association with quality of life, as assessed by both the carer (CBI-R) and patient (PDQ-39), even after adjustment for age, depression, and motor disability. Visuospatial, memory, and verbal fluency deficits had the greatest effect on activities of daily living, possibly indicating that these deficits represent the earliest stages of the dementing process. Indeed, poor semantic fluency and impaired pentagon copying were the most significant predictors of later occurring dementia in our previously published longitudinal study of a different incident PD cohort.[14] There are relatively little previous data on the functional effect of early cognitive problems in PD.[23–26]

This study has certain limitations. In particular, the ROC analysis depends critically on the "gold standard" used to classify patients as PD-MCI. We have used recently published MDS PD-MCI criteria to define PD-MCI, but these criteria have yet to be validated.[2] The choice of neuropsychological tests adopted also influences the diagnostic process, and our battery did not provide complete coverage of language and attention, with its length being limited by the tolerability of extensive neuropsychological assessment in an elderly population. For this reason, we adopted level 1 MDS PD-MCI criteria, rather than the more stringent level 2 criteria.[2] It should also be noted that this study was not designed specifically for validating ACE-R, but was part of a large, community-based epidemiological study.

Conclusion

In conclusion, the ACE-R is a useful instrument in evaluating PD-MCI. Importantly, ACE-R deficits are significant in terms of their effect on patients' behavior and quality of life. Future longitudinal studies using ACE-R to monitor disease progression in PD are needed. ■

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Subthalamic Activity During Diphasic Dyskinesias in Parkinson's Disease

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ABSTRACT

Background: Diphasic dyskinesias are a subtype of levodopa-induced dyskinesias that appear typically at the onset and end of levodopa antiparkinsonian action. The pathophysiology of diphasic dyskinesias is not well understood.

Methods: We analyzed local field potentials recorded from the subthalamic nucleus in 7 Parkinson's disease (PD) patients who showed typical diphasic dyskinesias during postoperative recordings through a deep brain stimulation electrode. The evolution of the different oscillatory activities related to the onset and end of diphasic dyskinesias was studied by windowed fast Fourier transforms.

Results: Typical "off"-state beta activity disappeared with the onset of diphasic dyskinesias, whereas gamma activity was absent or minimal until their end. Theta activity during diphasic dyskinesias was similar to that observed during peak-dose dyskinesias.

Conclusions: From a neurophysiological viewpoint, patients exhibited oscillatory activity typical of the "on" medication state during diphasic dyskinesias. The minimal presence of gamma activity during diphasic dyskinesias, however, suggests that this "on" state might be incomplete or limited to dopaminergic mechanisms affecting the lower limbs.

Key Words: diphasic dyskinesias; subthalamic nucleus; local field potentials

Diphasic dyskinesias, initially termed "dyskinesia-improvement-dykinesia"[1] or "beginning-/end-of-dose dyskinesias,"[2] are a subtype of levodopa-induced dyskinesias that appear typically at the onset and end of levodopa antiparkinsonian action, coinciding with ascending and descending levodopa levels in the plasma. The prevalence of diphasic dyskinesias in different studies varies between 3% and 20% of patients showing motor fluctuations.[3–6] Diphasic dyskinesias have a net preponderance for the lower limbs and often consist of repetitive alternating movements in a stereotyped manner,[7] although the movements may

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Table 1. Clinical characteristics of the patients

Patient	Age	Sex	Evolution (y)	UPDRS-III off	UPDRS-III on	L-dopa daily dose equivalents
1	69	F	21	32	17	1500
2	61	M	25	43	8	2200
3	70	F	20	39	28	1077
4	54	M	13	52	11	1651, 38
5	55	F	11	60	13	1000
6	45	M	11	39	9	1059, 28
7	47	M	7	45	21	750

Age, age at the time of surgery; evolution (y), years since diagnosis at the time of surger; UPDRS-III off, preoperative UPDRS-III subscale score off medication; UPDRS-III on, preoperative UPDRS-III subscale score on medication; L-dopa daily dose equivalents, L-dopa equivalent daily dose, calculated as the L-dopa dose + L-dopa dose × 1/3 if on entacapone + bromocriptine (mg) × 10 + cabergoline or pramipexole (mg) × 67 + ropinirole (mg) × 20 + pergolide (mg) × 100.

acquire a ballistic and/or dystonic (even painful) nature,[3,6,8] making them particularly disabling for patients. Typically, while the legs are moving involuntarily, the upper half of the body still exhibits parkinsonian signs.[3] All these features have complicated our understanding of the pathophysiology of diphasic dyskinesias.[9,10] However, the major confounding factor is that drug-induced phenomena such as levodopa-induced dyskinesias are dose related, and their peak effects coincide with maximal action of the drug.[9] This is indeed the case for ''peak-dose'' or ''on'' dyskinesias in PD.[4] However, diphasic dyskinesias cease (or at least are reduced) at peak plasma levodopa levels, corresponding to the maximum antiparkinsonian effect of this drug.[11]

The use of deep brain stimulation (DBS) of different structures of the basal ganglia to treat Parkinson's disease (PD) has permitted the activity of these structures (mainly the subthalamic nucleus [STN] and globus pallidus pars interna) to be characterized in both the ''off'' and ''on'' medication states. In the ''off'' state, the STN shows a peak of abnormal activity in the low beta range (between 10 and 20 Hz), which disappears in the ''on'' medication state.[12,13] The disappearance of the low beta peak is accompanied in around 30% of patients by an increase in gamma activity (60–80 Hz).[14,15] Recent studies have also evidenced changes in higher frequencies (200–400 Hz) between both states, linked to complex interactions with the beta activities.[15,16] In the ''on'' state, an additional peak in the theta range has been associated with the presence of levodopa-induced dyskinesia or impulse control disorders.[14,17] Indeed, we previously reported preliminary evidence[14] suggesting that theta activity during diphasic dyskinesias was very similar to the activity observed during peak-dose dyskinesia.

The aim of the present study was to examine in detail the pattern of activity in the STN during diphasic dyskinesias in a larger series of implanted PD patients. Accordingly, we have addressed 2 specific questions. First, is the pattern of activity during diphasic dyskinesias consistent with the one encountered in the ''off'' or ''on'' motor state? And, second, if the latter is the case, is there a theta peak in subthalamic activity during diphasic dyskinesias that is comparable to the peak observed during peak-dose dyskinesia?

Patients and Methods

Patients

Seven of a cohort of 70 PD patients studied neurophysiologically after electrode implantation for DBS were noted to have a diphasic dyskinesia pattern during routine recording of local field potentials from the STN 3 days after surgery.[14,15,17,18] Of these 7 patients, diphasic dyskinesias were evoked by the subcutaneous administration of apomorphine (4 mg) in 1 patient and by the usual morning dose of levodopa (100–250 mg) plus a dopa decarboxylase inhibitor in the remaining 6 patients. The pattern and severity of these dyskinesias were similar to the ones present before surgery. The ''on'' and ''off'' motor states and the presence of diphasic dyskinesias were defined by clinical observation and examination. Clinical details of the patients are summarized in Table 1.

Recordings and Signal Analysis

The surgical procedure carried out was similar for all patients and has been described in more detail in previous publications by our group.[14,15,17] Postoperative MRI showed correct placement of the electrode in all patients. The recordings were carried out 3 days after the surgery by connecting the externalized connectors of the DBS electrode to the recording system using custom-made cables. A sequential bipolar montage was used with a total of 3 channels (0–1, 1–2, and 2–3 from ventral to dorsal) per side. Five of the recordings were sampled at 200 Hz with filters set at 0.3 and 100 Hz. The other 2 recordings were sampled at 2000 Hz with filters set at 0.3 and 1000 Hz.

A windowed Fourier transform was used to display the temporal evolution of the power changes in the STN over time in a color plot in all the channels. In 1

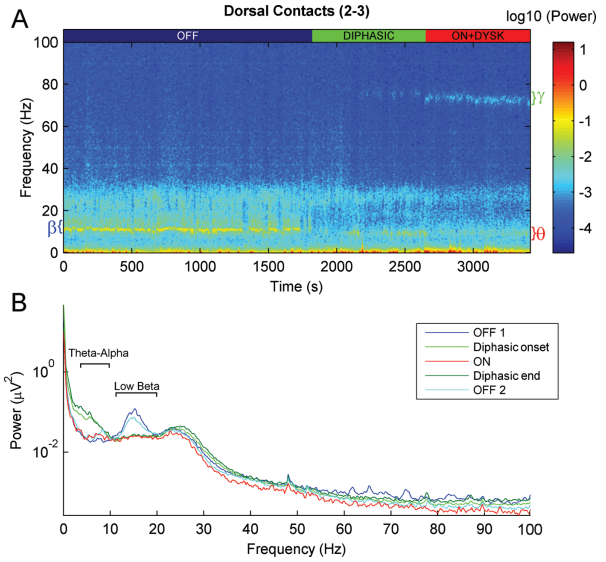

FIG. 1. *Top*: Subthalamic activity during the "off"–"on" transition, including a period with diphasic dyskinesias (patient 1). The disappearance of the "off"-state low beta peak (β) coincides with the onset of diphasic dyskinesias. Some gamma activity (γ) can be observed during the diphasic dyskinesias period but with lower power and higher frequency than during the actual "on" state. Theta activity (θ) can be observed both during diphasic dyskinesias and during the "on" state (when peak-dose dyskinesias were present). *Bottom*: Power spectra during different motor states in the patient in whom the complete off–on–off cycle was recorded (patient 4). The power spectra during the first "off" (OFF 1, before apomorphine, dark blue line) and the last "off" (OFF 2, after the medication effect disappears, light blue line) are nearly identical. The power spectra from the two periods with diphasic dyskinesias (diphasic onset [in the "off"–"on" transition, light green line] and diphasic end [in the "on"–"off" transition, dark green line]) are also very similar. A low beta peak ("low beta") is only present in the two "off"-period spectra, whereas a theta peak ("theta-alpha") is only present during the two periods of diphasic dyskinesias. This patient did not show peak-dose dyskinesia.

patient (after apomorphine), a complete off–on–off cycle was recorded, and 2 valid 1000-second segments around each motor state transition were analyzed. In 2 patients, continuous recording of an off–on cycle was undertaken, and a 2000-second segment around the onset of diphasic dyskinesias was selected. In the remaining 4 patients, 300-second segments were selected during 3 periods: (1) "off" state after overnight medication withdrawal, (2) during the presence of diphasic dyskinesias, and (3) in the "on" state after disappearance of the diphasic dyskinesias.

Results

Oscillatory Activity in the STN During Diphasic Dyskinesias

All patients exhibited a typical low-beta band peak in the "off" state in at least 1 electrode pair per side (Table, Supplementary Material). The pattern of activity observed during diphasic dyskinesias was consistent in the 7 patients. The low beta activity typical of the "off" state was absent in all cases while diphasic dyskinesias were occurring. Five nuclei (from 4 patients) exhibited gamma activity during the "on" state. A small peak of gamma activity was present in 2 nuclei from 2 of these patients during the diphasic dyskinesias, but with a smaller power than observed during the "on" state (see Fig. 1, top). Five of the 7 patients (9 of 14 nuclei) displayed a peak of theta activity during diphasic dyskinesias. The frequency of this peak (mean, 7.38 Hz) was similar to that described for peak-dose dyskinesia.[17] A comparison of the theta activity in 4 patients who had both diphasic dyskinesias and peak-dose dyskinesia showed no differences in frequency between either subtype (t_{13} = 0.83, P = .42). In those patients, the power of the theta oscillations during diphasic dyskinesias and peak-dose dyskinesias was similar in 2 patients, larger during diphasic dyskinesias in 1 (shown in Fig. 1, top), and larger during peak-dose dyskinesia in the fourth patient.

Motor State Transitions and Diphasic Dyskinesias: Temporal Correlations

Examination of the "off–on" transitions in patients 1 and 2 showed that the appearance of the diphasic dyskinesias coincided temporally with the suppression of the low beta peak, whereas the increase in gamma activity occurred subsequently (Fig. 1, top). The changes in oscillatory activity in the transitions were abrupt in all instances, independently of whether the administered drug was apomorphine or L-dopa. In the only "on–off" transition recorded (patient 4), the disappearance of diphasic dyskinesias coincided with the return of low beta (~16 Hz) activity. This patient did not show any gamma activity during the typical "on" state (Fig. 1, bottom).

Discussion

We have identified that the onset of diphasic dyskinesias in PD patients coincides with a net reduction in beta activity and the appearance of theta band activity in the STN. Both neurophysiological features are typically encountered in the STN during the "on" motor state. On the other hand, the expected increase in gamma band activity coinciding with the "on" state was not very pronounced.

Low beta activity in the STN, most evident in the dorsal (ie, motor STN region) electrode contacts, is the most accepted neurophysiological indicator of the "off" state.[12,14,15,19,20] The presence of beta activity in the STN has been correlated with rigidity and bradykinesia[21] and its suppression with the relief of parkinsonian motor symptoms.[22]

The similarity of the theta peak present in our patients during diphasic dyskinesias with the peak previously described during peak-dose dyskinesias[14,17]

(and also present in some of our patients) strongly suggests that diphasic dyskinesias and peak-dose dyskinesias are highly related neurophysiological phenomena. This similarity does not rule out that some distinct pathophysiological mechanisms may underlie either type and account for some of the clinical features. We observed only modest changes in gamma power during diphasic dyskinesias. It is well known that peaks in gamma activity only appear in about 30% of patients who are clinically in the ''on'' state, with no clear correlation with the motor state.[14,15] Furthermore, administration of a dopamine agonist in the intact rat is associated with increased gamma power in the STN, suggesting a direct relationship with the degree of dopaminergic stimulation.[23]

Our findings may be considered the first physiological evidence supporting the notion that diphasic dyskinesias are the beginning of ''on'' or ''peak-dose'' dyskinesias restricted to mechanisms controlling the lower limbs, thus representing the initial manifestation of levodopa-induced dyskinesias.[6,24] Any functional change observed while dyskinesias are present could also be a consequence rather than the cause of the movements. However, the theta band power was very constant throughout the recording, which goes somewhat against a movement-evoked activity.

Why the legs are preferentially involved in diphasic dyskinesias remains a mystery. We could not determine any putative topographical differences in the theta activity observed during diphasic dyskinesias and peak-dose dyskinesias because of the limited spatial resolution provided by the recording electrode, which was mainly limited to the dorsoventral axis.[25] A more discriminative analysis of STN activity could possibly reveal different functional states for distinct body parts.[2,6] The dopaminergic projection to the posterior and dorsal putamen is most vulnerable to the neurodegenerative process in PD and also in animal models of the disease (ie, 6-OHDA, MPTP). This region corresponds to the lower limb cortical projection, which could explain the preferential involvement of the lower limbs in diphasic dyskinesias. Admittedly, this does not readily explain why only a portion of patients develop DD or why increasing levodopa dose (or plasma levels) reduces the movements.

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