Benign Tremulous Parkinsonism

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Background: Benign tremulous parkinsonism has never been precisely defined nor has the long-term course been studied.

Objective: To report the clinical features and longitudinal course of patients with benign tremulous parkinsonism encountered in our movement disorders practice.

Design: Computer search of medical records database.

Setting: Mayo Clinic, Rochester, Minn.

Patients: Of 116 patients identified, 16 (10 male and 6 female) had at least an 8-year history of this disease, had been examined by a senior movement disorders specialist, and had ultimately been diagnosed as having benign tremulous parkinsonism after an initial diagnosis of Parkinson disease (PD).

Interventions: None.

Main Outcome Measures: Age at onset of disease, response to levodopa therapy, tremor characteristics, and family history.

Results: Mean disease duration was 11 years (range, 8-25 years) at last follow-up. Mean age at onset, 58.5 years, was younger than in most PD series, and most patients had a poor levodopa response (although levodopa trials were inadequate in some). A moderate to marked postural tremor was noted in 13 of the 16 patients, including 6 with a kinetic tremor. A family history of PD and/or tremor was reported in 10 (63%) of our patients. Three patients required thalamic deep brain surgery to treat their tremor.

Conclusions: Benign tremulous parkinsonism may be a distinct clinical entity characterized by tremor predominance plus minimal progression of other aspects of parkinsonism. The tremor is often not very responsive to levodopa therapy. In this series, most patients had immediate family members with a diagnosis of tremor or PD.

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In our routine movement disorders clinical practice, we have occasionally encountered patients with features similar to classic idiopathic Parkinson disease (PD) yet with a unique clinical course. These patients fulfill minimum criteria for PD with resting tremor plus other parkinsonian signs, without evidence of ataxia, corticospinal signs, apraxia, cognitive impairment, or prominent early dysautonomia. What has distinguished them has been a consistent constellation of clinical features: (1) prominent resting tremor that is the first or among the first signs and that persistently overshadows other aspects of parkinsonism throughout the course; (2) nontremor components of parkinsonism that remain mild; (3) absence of gait disorder apart from reduced arm swing or mild stooping; (4) no more than mild progression, except for tremor, despite at least 8 years of parkinsonism; and (5) absence of disability apart from tremor. We have also noted that the tremor is typically refractory to medications, including maximally tolerated levodopa. Furthermore, most cases also display a prominent action tremor that impairs eating and writing. Limited reports have alluded to such cases as “benign tremulous PD” or “benign tremulous parkinsonism.”1,2 However, previous series have not precisely defined the clinical criteria nor has there been follow-up beyond a few years of parkinsonism, except in rare cases.

We report on a series of patients with benign tremulous parkinsonism to better define the characteristics and describe the long-term outcomes.

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Methods

We identified 116 cases from a retrospective computer search of the medical records database of the Mayo Clinic, Rochester, Minn, spanning a single decade (January 1, 1994, through December 31, 2004), using the text word search terms benign tremulous parkinsonism, benign tremulous Parkinson’s disease, tremor predominant parkinsonism, or tremor predominant Parkinson’s disease. The medical records of all 116 cases were reviewed to exclude any case that, by the time of last evaluation, had not had at least an 8-year history of parkinsonism. Only cases evaluated and diagnosed by a senior movement disorders specialist (J.E.A. or J.Y.M.) were included.
The demographic characteristics of the 16 patients are given in Table 1. Six patients were female, and the mean age at onset of symptoms was 58.5 years (range, 42-71 years). Clinical features are given in Table 2, and Table 3 shows the tremor characteristics of each patient at last examination. More than half of the patients underwent magnetic resonance imaging of the head; all of the images either were normal or showed limited numbers of subcortical T2 hyperintensities, in keeping with age.

**INITIAL SYMPTOMS AND PRESENTATION**

In all but 1 patient the initial symptom was a resting hand tremor; this was unilateral in 13 (confined to the thumb in 1) and bilateral in 2. One patient initially noted a resting foot tremor. At the time of first evaluation, only 2 patients were receiving levodopa treatment, while 10 patients were not using any medication for tremor or PD. The initial examination showed a resting hand tremor in all patients, which was moderate or severe in 12, including the 2 patients taking levodopa. All but 1 patient had rigidity, bradykinetic alternating motor rates, or both at this first examination. All had a normal gait with the exception of reduced arm swing in 14 patients, which was unilateral in 5, and a stooped posture in 3 patients. Patient 16 also had a hypokinetic dysarthria. A postural tremor was present in 13 patients, which persisted yet was attenuated with visually guided movements toward a target in 7. None reported tremor response to alcohol.

**CLINICAL FINDINGS PRESENT AT LAST FOLLOW-UP**

The mean follow-up from onset of parkinsonism to time of the last movement disorder evaluation was 11.1 years (range, 8-25 years). Four patients had had more than 12 years of symptoms. In all patients, the symptoms remained relatively unchanged compared with the initial examination with the exception of the resting tremor, which worsened in 6 patients. In patient 3 the bradykinesia and rigidity were mildly improved, which may have resulted from levodopa treatment, as this patient was taking the highest levodopa dose in this group (1200 mg). The gait and balance remained unimpaired. Severity of the postural tremor almost mirrored severity of the rest component (Table 3). With visually guided movement toward a target, a kinetic tremor was also present in 7 patients. A resting chin tremor was noted in 7 patients. Additional symptoms and signs of PD, identified in 8 patients, were mild and included stooped posture, seborrhea, difficulty with fine motor tasks, difficulty turning in bed, sialorrhea, and decreased facial expression.

**RESPONSE TO TREATMENT**

Levodopa therapy was not consistently effective in treating the resting tremor or improving other aspects of parkinsonism. Levodopa therapy provided no benefit in 9 of the cases, although only 3 were treated with doses of at least 600 mg daily during the disease course. It provided partial benefit in 3 patients and moderate benefit in 1 (patient 3). The remaining 3 patients received only a single dose of levodopa. Only 2 patients developed levodopa dyskinesias, slight in both; these included facial dyskinesias in one and arm posturing in the other. At the time of last examination, 6 patients were receiving levodopa therapy.

The tremor was severe enough that 3 patients underwent thalamic deep brain surgery. All 3 patients were tremor free 1 month after surgery; however, the tremor returned in 1 patient after 1 month. One patient was lost to follow-up 1 month after surgery. The third patient (patient 13) had significant improvement of the action tremor.
up to 3 years after surgery with continued reprogramming of the stimulator, yet he had persistence and progression of the resting tremor, which became bilateral.

**FAMILY HISTORIES**

The family histories were remarkable, with 10 of the 16 patients reporting tremor or PD in at least 1 immediate family member. This included PD in the immediate family in 4 patients, tremor in 5, and both PD and tremor in 1. More than 1 immediate family member was affected in 6 cases (2 cases with PD in both 1 sibling and 1 parent; 4 cases with tremor in 2-4 immediate relatives). None of the family members was examined to confirm these observations.

**OTHER FINDINGS**

Dysautonomia, by report, was minimal to absent, with constipation recorded in 3 patients, erectile dysfunction in 2, and bladder dysfunction in 1. No patients developed cognitive impairment.

**COMMENT**

Following the lead of other authors, we have been recognizing patients with benign tremulous parkinsonism during the past 12 years. Although this syndrome does not appear to be rare, we are aware of no reports that have defined the clinical criteria or the long-term course for this diagnosis. We therefore report on our 16 patients with this diagnosis, who had symptoms for at least 8 years, to help better define consistent features and outcomes. We discourage the reader from trying to infer any prevalence data from this article.

When patients were initially examined early in the course of the disease, the clinical picture was consistent with PD, and that was typically the initial diagnosis. Subtle clues suggesting benign tremulous parkinsonism were a predominance of resting tremor and prominent postural-action tremor (in almost all cases), with other signs of PD being present but very mild. Benign tremulous parkinsonism became more apparent, however, after several years when the tremor remained the primary problem, with minimal progression of other aspects of parkinsonism. Also suggesting this condition was the ab-
sence of a satisfactory response to levodopa therapy in most patients in whom it was administered. This condition was clearly recognizable after many years (we arbitrarily selected >8 years), by which time patients with typical PD are experiencing myriad problems, including gait difficulties, which our patients were spared. Moreover, substantial levodopa complications were not part of the clinical picture. A significant number of the patients also reported a family history of tremor and/or PD, which may be a clue to the diagnosis of benign tremulous parkinsonism if confirmed in other series.

Neurodegenerative diseases are heterogeneous and display a variety of rates of progression. Could this simply represent one end of the bell-shaped curve of typical PD? Although we have no current means to be certain, as we did not have data from pathological studies, the near absence of progression apart from tremor and inconsistent response to levodopa therapy suggest that benign tremulous parkinsonism may represent a unique disorder.

The benign tremulous parkinsonism syndrome must be differentiated from other somewhat similar yet distinct tremor syndromes. The monosymptomatic resting tremor is defined by a pure or predominant resting tremor without signs of bradykinesia, rigidity, or problems with stance stability sufficient to be diagnosed as PD. The combined resting-postural tremor syndrome described by Koller and Rubino and essential tremor with isolated resting tremor are also different, as these syndromes are not associated with PD signs apart from resting tremor. Isolated tremor with very mild parkinsonian signs related to aging is a somewhat nonspecific rest tremor. Isolated tremor without signs of bradykinesia, rigidity, or problems with stance stability sufficient to be diagnosed as PD is unlikely because of the lack of progression of predate resting tremor. Combined essential tremor with frequent development of signs and symptoms consistent with a postural tremor or head tremor, with the subsequent development of signs and symptoms consistent with PD. In none of our patients did postural tremor predate resting tremor. Combined essential tremor with PD is unlikely because of the lack of progression of parkinsonism. “Tremor-predominant PD” is a very broad category that, as originally defined, required only tremor greater than gait-posture deficits. Thus, in the article by Jankovic et al, more than half of the DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) cohort of 800 patients fit the criteria for tremor-predominant PD.

A striking finding in our cases was the family history. An immediate family member with either tremor or PD was reported by 10 (63%) of our 16 patients, including 5 (31%) with PD. This contrasts with recent epidemiologic studies in which approximately 10% to 16% of patients with classic PD reported a history of PD in an immediate family member. Similarly, a family history of essential tremor has been reported to occur in 3% to 17% of patients with PD, contrasting with 38% in our cohort. This raises speculation that this disorder might have more substantial genetic underpinnings than typical PD.

The neuropathology of benign tremulous parkinsonism, and specifically whether it is similar to classic PD, is unknown. Previous striatal dopaminergic imaging studies, however, have identified reduced uptake, typical of PD in patients with this phenotype. Despite this similarity, identification of these patients in clinical neuroprotective therapy trials may be important, since disproportionate distribution of these patients in treatment groups will distort the outcomes.

The term benign tremulous parkinsonism, as originally used, highlights the course of the syndrome and is not necessarily inappropriate. However, the tremor can be very disabling, such that 3 of our patients opted for surgical intervention for their tremor.

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REFERENCES