

Benign tremulous Parkinson's disease

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Abstract

Objective : To analyze the long-term outcomes of patients presenting with pure parkinsonian tremor and to determine whether or not such patients develop the other features of Parkinson's disease (PD) eventually.

Methods and materials : Two hundred fifty-one patients with PD followed at our referral center, were examined regularly. In this study, we evaluated the long-term follow up of the the patients with parkinsonian tremor without bradykinesia or rigidity.

Results : The mean disease duration was 5 years (range : 2-10 yrs.) at the last follow-up visit. This final group included 7 female and 16 male patients with a mean age of 66.6 ± 10.8 years. Four groups of patients were identified. First group consisted of 15 patients presenting with rest tremor, most prominently in one upper limb and/or contra-lateral upper limb. In the second group, there were 3 patients who had parkinsonian tremor with greatest severity in one lower limb and ipsilateral upper limb. Group 3 comprised 2 patients who had parkinsonian tremor in only one lower limb. The fourth group comprised 3 patients with isolated jaw tremor.

Conclusions : Some patients with pure parkinsonian tremor may remain without bradykinesia or rigidity for a long time, which may be considered a benign form of Parkinson's disease.

Key words : Parkinson's disease ; tremor ; pure parkinsonian tremor ; rest tremor ; benign tremulous parkinsonism.

Introduction

PD is a slowly progressive condition that affects a group of cells in the substantia nigra (SN). These cells produce dopamine, which, along with acetylcholine, control and regulate normal muscle movements and coordination. As PD progresses and dopamine levels decrease, symptoms develop. The first to describe the disease was the British physician James Parkinson, who in 1817 wrote a famous essay on "The Shaking Palsy". In his original *Essay on the Shaking Palsy*, he emphasized rest tremor as the characteristic finding of PD (Parkinson, 1817). The clinical diagnosis of PD is based on the presence of at least two of the following : tremor, rigidity, and bradykinesia.

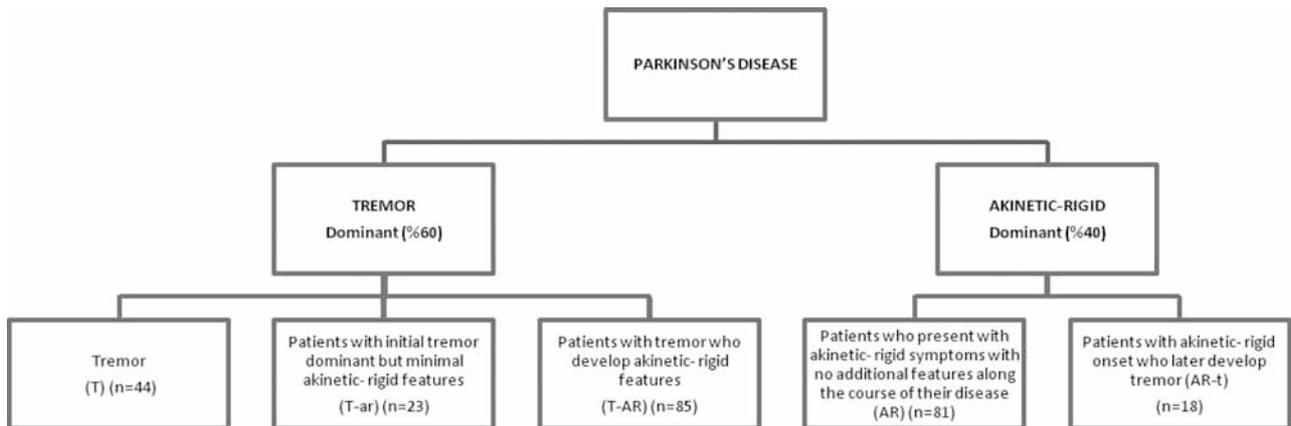
Tremor is one of the most common involuntary movement disorders seen in clinical practice. Even though different forms of tremor may be seen in Parkinson's disease, resting tremor is generally regarded as characteristic of PD. Tremor is defined as an involuntary, rhythmic, and sinusoidal movement of one or more body parts. It diminishes with sleep, improves with activity, and can be stopped for a while if the patient concentrates on a subjects or task in the early stages. The etiology of isolated resting tremor is still obscure. Some patients initially have a parkinsonian resting tremor without overt signs of rigidity or bradykinesia (Marshall, Grosset, 2003 ; Chang, Chang, 1995). This so-called "mono-symptomatic resting tremor" (mRT) was defined by the Consensus Statement of the Movement Disorder Society on Tremor (Deuschl, Bain, 1998) with the following criteria : (i) pure or predominant resting tremor ; (ii) no signs of bradykinesia, rigidity, or problems with stance-stability sufficient to diagnose PD ; and (iii) tremor duration of minimum 2 years (Ghaemi, Raethjen, 2002).

In this paper, we report a clinical follow up study of 23 patients who typically have had asymmetric resting tremor for an average of 5.5 years in the absence of other features of PD.

Methods and materials

Two hundred fifty-one patients that were clinically diagnosed as idiopathic PD between years 1993-2004 were examined regularly during this period. All the past records were analyzed retrospectively in terms of patients' complaints, physical and neurological examination findings, past history, and familial history. The diagnosis of PD was made when two of -three symptoms, i.e. bradykinesia, rigidity, and/or tremor were evident. Hoehn-Yahr staging was done in all patients in order to determine the disease stage (Goetz, Poewe, 2004). The Hoehn-Yahr disability scale and the Unified Parkinson's Disease Rating Scale (UPDRS) were used for each patient (Fahn S, Marsden CD, 1987). The severity of rest tremor was classified based on visual inspection and graded into mild, moderate, or

Table 1
Subtypes of Parkinson's disease according to the primary symptoms



severe. The patients with PD were divided in two groups as “tremor dominant” and “akinetic-rigid” according to their primary symptoms. The tremor dominant group was further divided into 3 subgroups (Table 1). Forty-four of 251 patients with PD, who were followed up for 2 years, had tremor as the sole manifestation of their disease. In this group, we found 23 patients who typically had pure parkinsonian tremor for more than 2 years in the absence of the other features of PD. Patients with tremor, past history of encephalitis, cerebrovascular disease, and intoxication and those with a history of acute onset disease were excluded from the study. Patients with a past history of drug intake with parkinsonian side effects were likewise not included.

The demographic variables included history of tremor or rigidity, age at onset of symptoms, duration of disease.

Results

This study included 7 female and 16 male patients with a mean age of 66.6 years (median : 65 yrs ; range : 50-89 yrs). The mean tremor duration was 4.8 ± 2.3 years (median : 4 yrs, range : 2-10 yrs). The patients responded to dopaminergic treatment with levodopa and/or levodopa and dopamine agonist (n = 18, 500-750 mg/day), dopamine agonist (n = 10) and biperiden (n = 5). More than half of the patients underwent cranial magnetic resonance imaging ; all of the images were normal or showed limited numbers of subcortical T2 hyperintensities. Computed tomography brain scans were normal in the other patients. Four groups of patients were identified.

GROUP 1

Fifteen patients (5.9% of all the PD cases reviewed) had rest tremor most prominently in one upper limb and/or contralateral upper limb. A

family history of a movement disorder was positive in 2 patients. There were 11 men and 4 women in this group (mean age at onset, 64.6 years ; mean follow-up period, 5.5 years). The side of the tremor was on the right in 40%, left in 53.3%, and bilateral in 6.7%.

GROUP 2

Three patients (1.1% of all the PD cases reviewed) had resting tremor that was most pronounced in one upper limb with ipsilateral lower limb. There were 3 males in this group (mean age of disease : 65.3 years ; mean follow-up period : 3 years). A family history of essential tremor was positive in 2 patients.

GROUP 3

There were only 2 patients (1 male, 1 female ; 0, 7% of all the PD cases reviewed) (mean age ; 58 years) followed for 2.5 years who had parkinsonian tremor in only one lower limb. There was no family history of movement disorders in this group.

GROUP 4

Three patients (1 male, 2 female ; 1.1% of all the PD cases reviewed) had only jaw tremor. Other features of parkinsonism did not show side dominance, including bradykinesia and rigidity. For this group, the mean age of PD was 83.6 years and the mean follow-up period was 5 years. There was no family history of movement disorders in this group.

The mean age of the patients with only lower limb tremor was significantly younger than that of the patients with jaw tremor.

Discussion

Rest tremor, one of the cardinal features of PD, is present sometime during the course of the disease

Table 2

Clinical details of the patients in four groups

	Group I	Group II	Group III	Group IV
Tremor distribution	one upper limb and/or contralateral upper limb	one upper limb with ipsilateral lower limb	only one lower limb	only jaw tremor
Gender				
Female	4	–	1	2
Male	11	3	1	1
Age (mean yr)	64.6	65.3	58	83.6
Duration (yr)	5.5	3	2.5	5
Family history	2	2	–	–

in 68%-100% of pathologically proved cases of the disease (Jankovic, 1999). This type of tremor is typical of PD and may be easily seen by the inspection of the patient. Onset of tremor is usually unilateral in the distal limb, mostly in the arm, very rarely in the lower extremity, and chin. In the legs, it is typically seen when the patient is seated with the knees relaxed and feet resting on the ground. The etiology of pure parkinsonian tremor and its underlying pathophysiology remains unknown. Some patients have rest tremor for many years without any definite signs of bradykinesia or rigidity, and it may be difficult to decide whether they really have PD. Consequently, the clinical findings may not be sufficient to diagnose PD. Such clinical conditions are confusing for medical practitioners and young neurologists.

Group 1 patients demonstrated persistence of rest tremor in one limb and/or the other upper limb. The most common mode of PD onset is asymmetrical tremor (Rajput, Pahwa, 1993 ; Hughes, Ben-Shlomo, 2001). It typically occurs initially in the distal upper extremity, and over time, moves proximally and then to the other upper extremity, again in a distal to proximal pattern. On average, the tremor spreads bilaterally six years after the onset of symptoms (Scott RM, Brody, 1970), and the side initially affected continues to have more tremor than the contralateral side. Pure parkinsonian tremor is infrequent in PD ; the combination of rest and postural kinetic tremors is common. Isolated postural and kinetic tremor rarely occurs in PD. Postural tremor without parkinsonian features and without any other known etiology is often diagnosed as essential tremor, but isolated postural tremor may be the initial presentation of Parkinson's disease, and it may be found with higher than expected frequency in relatives of patients with Parkinson's disease (Jankovic, Beach, 1995).

Group 2 patients had initially unilateral tremor of the ipsilateral leg and arm. The typical tremor of PD starts unilaterally in the hand, followed in time by the involvement ipsilateral leg or the contralateral arm (Hughes, Daniel, 1993).

Group 3 patients had tremor only in one lower limb. Unilateral leg tremor is unusual. In PD, tremor in the lower limbs is uncommon. In 1998, Keller *et al.* (Keller, Tcheng, 1998) presented a case of tremor isolated in the lower extremity that was treated with stereotactically guided thalamotomy in a patient with PD.

Group 4 patients demonstrated jaw tremor, which can be considered as a constituent of various neurological disorders such as Parkinson's disease, dystonia, essential tremor. The correct nature of this tremor is unknown. There is an underlying physiological tremor associated with the resting tone in the jaw, but its frequency is 6 Hz (Jaberzadeh, Brodin, 2003).

We have recognized patients with pure parkinsonian tremor during the past 5 years. Josephs and colleagues reported 16 patients with isolated resting tremor of 12 years. In this series, most patients had immediate family members with a diagnosis of tremor or PD (Josephs, Matsumoto, 2006)

Eighteen patients were on combined L-dopa treatment. During L-Dopa treatment, 7 (39%) patients showed improvement, but 11 (61%) patients showed less marked improvement, which suggests that resting tremor is often not very responsive to levodopa treatment.

The pathologic characteristic of PD is the degeneration of dopaminergic cells within the substantia nigra compacta and the following in time dopamine depletion of the striatum. The medial SN, especially the retrorubral area, is more severely affected by dopaminergic cell degeneration in the tremor dominant form (Deuschl, Fietzek, 2003). Thus, parkinsonian tremor is likely to be associated with cell loss of the retrorubral SN (Brooks, 1995). Brooks and colleagues studied 11 patients with rest tremor who underwent 18 F-dopa PET scan studies, and showed reduced putaminal uptake, an abnormal characteristic of PD (Brooks, Playford, 1992). This finding has been replicated on 5 patients using MRI scanning by Chang and colleagues ; MRI has shown a reduction of the distance between the SN and the red nucleus in mRT compared with normal

controls, which may indicate abnormal iron depletion in the pars compacta of the SN (Chang, Chang, 1995). Brooks and associates have stated that a parkinsonian rest tremor requires dysfunction of both cerebellar and dopaminergic connections, the latter being interrupted either structurally or by the way of dopamine receptor blockade. They reported reduced striatal F-dopa uptake in 11 patients with isolated resting tremor. In their study, the putaminal F-dopa binding contralateral to the more affected limbs ranged from 50 to 80% of the normal controls (Brooks, 1999). Similarly, Ghaemi and associates reported reduced striatal F-dopa uptake in 8 patients with isolated resting tremor. They found identical putaminal and caudate F-dopa K_i values in the mRT and the PD subgroups with similar disease duration. In addition, they assessed the RACLO-binding indices in the same study and found a similar putaminal upregulation of the dopamine D2 receptor binding in mRT as well as in early PD (Ghaemi, Raethjen, 2002). Deiber and colleagues, using deep-brain stimulation of the ventral intermediate nucleus, demonstrated a significant decrease of the activity in the paramedial rostral and medial cerebellum with no significant lateralization during effective stimulation in tremulous PD (Deiber, Pollak, 1993). These findings showed that resting tremor originates from the cerebellum rather than the basal ganglia (Stein, Aziz, 1999). Furthermore, some co-twins of PD patients with an isolated postural tremor on examination showed reduced levels of putamen ^{18}F -dopa uptake (Piccini, Morrish, 1997; Burn, Mark, 1992). Therefore, mRT can be classified as a clinical variant of PD, but why patients with mRT do not develop bradykinesia and rigidity remains without an answer at this point (Ghaemi, Raethjen, 2002).

We suggest that some patients with pure parkinsonian tremor may remain without any signs of bradykinesia or rigidity for many years, which we considered a phenotype and benign form of PD. Finally, in spite of sophisticated technological developments in the field of neurology, we feel that clinical research is still valuable especially in the movement disorders.

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