

Clinical and Imaging Study of Isolated and Mixed Rest and Action Tremor-Essential Tremor versus Parkinson's Disease

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Abstract

Background: Some patients present an unusual association of both action tremor (AT) and rest tremor (RT) making the differential diagnosis between essential tremor (ET) and Parkinson's disease (PD) difficult. **Aim:** To investigate this particular clinical picture trying to focus on possible peculiar clinical inferences. **Patients and Methods:** Twenty-three patients with atypical tremor syndrome were selected for the study. They underwent neurological examination, neuroimaging study, and brain DaTSCAN single-photon emission computed tomography. **Results:** Twenty-three patients were evaluated; 17 presented mixed-tremor syndrome, while six patients showed only isolated AT or RT. DaTSCAN was pathological in 19 patients and normal in 3 patients. The emerging statistical data highlighted a positive correlation between disease duration and DaTSCAN abnormalities; Fisher's exact test showed a marked difference in evolution toward a dysfunction of dopaminergic pathways in patients with both AT and RT phenotype. **Conclusion:** The possible correlation between PD and ET has often been discussed without any clear findings. Are these patients suffering from ET prone to develop PD? Or are they the expression of a specific clinical phenotype? Our clinical survey has not led to absolute considerations; however, it seeks to highlight the clinical markers that might arouse the suspicion of extrapyramidal disease in patients with atypical tremor syndrome.

Keywords: Action tremor, essential tremor, Parkinson's disease, resting tremor

INTRODUCTION

Tremor is the main symptom of Parkinson's disease (PD) and essential tremor (ET), and usually, it shows distinct semeiological characteristics within these two conditions.

Nevertheless, some patients could present a peculiar clinical picture typified by both action tremor (AT) and rest tremor (RT) or isolated RT without other extrapyramidal features. In these conditions, the differential diagnosis between ET and PD may be difficult. RT is likely to occur in 20% of ET patients,^[1] particularly in the elderly, while postural tremor may sometimes be a presenting symptom of PD.^[2] Several clinical series about the greater risk of developing PD of ET patients have been recorded in literature. This topic has been debated for a long time: some authors maintain that there is a link between these two diseases,^[3-10] whereas others deny it.^[11] Moreover, the possible presence of a monosymptomatic Parkinsonian syndrome exclusively characterized by RT should be considered.^[12-13]

Therefore, we selected a group of patients with isolated tremor symptomatology – typical of neither PD nor ET – who underwent DaTSCAN single-photon emission computed tomography (SPECT) imaging to identify the clinical parameters suggestive for nigrostriatal dysfunction.

PATIENTS AND METHODS

Twenty-three patients (13 males, 10 females) with at least a 6-month history of atypical tremor were selected from our clinical consecutive series of 392 patients followed by the Movement Disorder Outpatient Clinic of the Neurological Departments of Trieste and Belluno. We ruled out other possible causes of tremor and pseudodementia dosing thyroid

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hormone levels, Vitamin B12 and folate, and testing liver and kidney functions. Other exclusion criteria included the presence of neuropsychiatric disorders (depression, anxiety disorder, dementia, restless leg syndrome, sleep disorders, etc.); the chronic use of neurological or psychiatric medications (excluding medication for tremor) that could cause tremor (anti-asthma drugs such as theophylline and salbutamol, stimulants such as amphetamines, heart medicines such as amiodarone, procainamide, thyroid medication such as levothyroxine, cancer medicines such as thalidomide and cytarabine, anti-epileptic drugs such as valproic acid) or could affect cognitive functions (e.g., antiepileptic agents, antidepressants, etc.); the presence of disorders of prostate, diabetes mellitus, any kind of cancer; declining to participate; and other reasons of intellectual disability.

ET was categorized based on the criteria set in Table 1, and PD was diagnosed in accordance with the UK Brain Bank criteria.

Those patients whose clinical phenotype consisted of an association by both AT and RT, or isolated postural tremor or monosymptomatic RT without any other extrapyramidal signs, were evaluated by a movement disorder specialist. They had a mean 5-year period of follow-up. Complete neurological and general examinations were assessed. We evaluated tremor according to the Consensus Statement of the Movement Disorder Society on Tremor.^[4] All patients underwent brain DaTSCAN SPECT and neuropsychological tests so as to ensure comparability in terms of cognitive

functions (short-term memory, attention, and working memory). Tests consisted of mini-mental state examination, Rey auditory-verbal learning test (Rey-Rey-I and D), Digit Span, Symbol Digit Modalities Test, Raven Progressive Matrices (Raven), activities of daily living (ADL) and instrumental ADL. Neuropsychological tests, brain TC, or magnetic resonance imaging to exclude cognitive impairment and other symptomatic causes of tremor were performed. All patients were treated with L-Dopa, b-blockers, or primidone. We also evaluated the possible benefit after a small amount of alcohol.

The study protocol was conducted in accordance with the ethical principles stated in the “Declaration of Helsinki.” The study was approved by the local ethics board.

Statistical analysis

SPSS 21.0 was used for statistical analysis SPSS 21.0 (SPSS, Chicago, IL, USA). The definitive statistics from the study were summarized by the arithmetic mean, mean \pm standard deviation, etc. Numbers and percentages were used in the representation of categorical variables. Kruskal–Wallis test was used for representation of numerical data regarding the comparison of control and patient groups, under the assumption that the data were not distributed normally. The comparisons for categorical variables were represented and analyzed by cross-tabulation (Chi-square test). Fisher’s exact test was used to compare the frequency of DaTSCAN SPECT abnormality imaging between the PD and ET groups.

Table 1: Demographic, clinical, and instrumental data

Patient	Age	Sex	Family history	Tremor onset (years)	Disease duration (years)	Debut	Symmetry	Actually	DaTSCAN-SPECT
1	79	Female	No	50	29	ET	Asym	RT + AT	Abn
2	64	Male	Yes	46	18	ET	Asym	RT	Abn
3	86	Female	No	76	7	RT + AT	Asym	RT + AT	Abn
4	69	Male	Yes	54	15	ET	Asym	RT + AT	Abn
5	74	Male	No	69	5	ET	Asym	AT	Abn
6	76	Male	Yes	71	5	ET	Asym	RT + AT	Abn
7	80	Male	Yes	64	16	RT + AT	Sym	RT + AT	Abn
8	86	Male	No	40	46	RT + AT	Sym	RT + AT	Abn
9	78	Male	Yes	30	48	RT	Asym	RT + AT	Abn
10	68	Female	Yes	59	9	AT	Sym	RT + AT	Abn
11	81	Female	No	20	60	AT	Asym	RT + AT	Abn
12	83	Male	No	80	3	ET	Asym	RT + AT	Abn
13	77	Female	Yes	50	27	ET	Asym	RT + AT	Norm
14	61	Male	Yes	56	5	RT + AT	Asym	RT + AT	Abn
15	85	Female	Yes	77	8	ET	Asym	RT + AT	Abn
16	88	Male	Yes	45	45	ET	Sym	AT	Norm
17	72	Male	No	62	9	ET	Asym	RT + AT	Abn
18	70	Female	yes	40	30	ET	Asym	AT	Norm
19	89	Female	No	79	20	RT + AT	Asym	RT + AT	Abn
20	79	Female	Yes	68	11	RT	Asym	RT	Abn
21	77	Female	No	70	4	RT + AT	Asym	RT + AT	Norm
22	56	Male	No	56	15	AT	Asym	RT + AT	Abn
23	73	Male	No	40	33	AT	Asym	ET	Abn

AT = Action tremor, RT = Rest tremor, Asym = Asymmetric symptoms (unilateral tremor), Sym = Symmetrical symptoms (bilateral tremor), Abn = Abnormal uptake, Norm = Normal uptake, ET = Essential tremor, SPECT = Single-photon emission computed tomography

A statistical significance limit of $P < 0.05$ was used. As for correlations, we carried out Pearson's correlation analysis.

RESULTS

Twenty-three patients were evaluated, 13 males and 10 females [Table 2]. Seventeen patients presented a tremor syndrome constituted by the association of rest with AT, while 6 showed either isolated AT or RT. Within the overall sample, the mean age was 76.27 ± 8.84 years, the onset of tremor symptoms was at 57.36 ± 16.22 years, and the mean duration of tremor was 19.27 ± 16.67 years. Both groups shared similar sociodemographic features (age, gender, education level, and employment).

The DaTSCAN was abnormal in 20 patients and normal in three patients.

Group of patients with associated rest and action tremor

In group of patients with both AT and RT, family history was frequent (12/17 patients) and tremor was mainly asymmetric [Table 2]. Their action component had been evident since the clinical onset. This cohort showed longer disease duration. The long follow-up highlighted mild late extrapyramidal features, such as the reduction of pendular movements, micrography, and slight muscle rigidity.

Group with isolated tremor symptomatology

In this group, patients had exclusively AT or RT. DaTSCAN showed pathologic findings only in those individuals whose resting tremor was clearly identified.

The emerging statistical data are (1) positive correlation between disease duration and DaTSCAN abnormalities: longer disease was correlated with the onset of possible Parkinsonian syndrome; (2) Fisher's exact test showed a marked difference in the evolution toward a dysfunction of dopaminergic pathways in patients with phenotype RT + AT, compared with patients in whom the initial phase RT or AT dominated singularly [Table 1].

DISCUSSION

Tremor is the most common movement disorder and it is one of the main clinical manifestations of PD and ET, though with different semeiological aspects. However, the presence of clinical cases characterized by the simultaneous presence of RT and AT, or monosymptomatic RT, may support the hypothesis

that ET can predispose patients to PD; otherwise, a novel exclusively tremor disease phenotype could be suspected. ET and PD are different diseases; however, they might share some common features regarding the role of the thalamus in the oscillator circuit. The literature confirms a possible clinical epidemiological correlation between ET and PD.^[3-5] Currently there is no evidence of a precise-related neuropathology in ET, even though the presence of the Lewy bodies reported in ET strengthened a possible link between these two conditions.^[14] Indeed, the nonmotor signs in ET suggest the involvement of other circuits in the oscillatory cerebellar-thalamic-cortical one.

Our clinical study mainly included patients with a complex tremor syndrome, having characteristics of both AT and RT. In addition, we distinguished a minority group with rather isolated unspecific tremor, AT or RT. The presence of impaired putaminal uptake in these individuals can be the link between the functional impairment and the anatomical basis. Are these patients suffering from ET prone to develop PD? Or are they the expression of a specific clinical phenotype? The neurological literature has often debated whether there is a connection between PD and ET; however, the analyses of various systematic works – including neuropathological data – have provided no clear evidence for this topic. Specifically, a neuropathological correlation between the two diseases still has not been established. These patients could suffer from a clinical phenotype characterized only by mild evolution tremor symptomatology, mainly with asymmetrical AT. Dopaminergic treatment brought only partial or no benefits. Undoubtedly, our sample was limited and further studies are needed to clarify this point. Nevertheless, there is a possibility that these patients might represent a rare clinical phenotype, often underestimated and with mainly exclusively tremor features, based on the association of AT and RT.

CONCLUSION

In clinical practice, atypical tremor syndromes are rare but not so uncommon. This implies a careful analysis of the patient, since certain conditions of action tremor, may be secondary to a dysfunction of the basal ganglia, although not configuring a classic picture of Parkinson's Disease.

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Conflicts of interest

There are no conflicts of interest.

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	ET patients (n)	ET + RT patients (n)	DaTSCAN (n)	P
Debut	13	6	Abnormal (20) Normal (3)	0.5
Actually	4	17	Abnormal (20) Normal (3)	0.05*

Results of Fisher's exact test are indicated (* $P < 0.05$).
ET = Essential tremor, RT = Rest tremor

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