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ORIGINAL COMMUNICATION

Associated co-morbidities in a retrospective cohort of orthostatic tremor

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Abstract

Background Orthostatic tremor (OT) is characterized by tremor in orthostatism. Primary OT is characterized by a high-frequency tremor at surface EMG recording and assumed to be idiopathic, whereas slow-frequency OT is classically associated with neurological pathologies. We report here a retrospective monocentric cohort study of primary (fast OT) and pseudo-OT (slow OT) patients to describe associated neurological and non-neurological co-morbidities.

Methods Between November 2014 and October 2019, 27 patients with OT were selected from the EMG database of the Department of Clinical Physiology in Lariboisière' s hospital. Patients were classified in primary OT if tremor frequency was ≥ 13 Hz and in pseudo-OT if tremor frequency was < 13 Hz.

Results Leg tremor on standing represented 10.2% of all tremor recordings. Ten patients were included in the primary and 17 in the pseudo-OT group. Females were predominant (62.9%) ($p = 0.04$). Mean age at diagnosis was 64.8 ± 1.1 years. At the first visit, a movement disorder was associated with 30% of primary OT, among them one CADASIL patient, whereas extrapyramidal or cerebellar disorders were reported in 100% of pseudo-OT, among them three Wilson's disease patients. These pathologies all preceded primary OT and occurred concomitantly with pseudo-OT. Frequency remained unchanged during evolution, except pseudo-OT in two patients that completely resolved following the introduction of antiParkinsonian drugs. Treatment of primary OT was partially effective in 28% and in 50% of pseudo-OT patients.

Conclusion In this monocentric study, movement disorders were present in 30% of primary OT patients. This result questions the term "idiopathic" or "primary" OT, but the small number of patients does not allow answering this issue.

Keywords Orthostatic tremor plus · Primary orthostatic tremor · Pseudo-orthostatic tremor · EMG polygraphic recording · Electrophysiology

Introduction

Tremor is an involuntary rhythmic activity, which causes a regular oscillation of a part of the body around a point of equilibrium. Orthostatic tremor (OT) is a rare tremor disorder that appears while standing in orthostatism. Primary OT was first described in 1984 by Heilman [1]. Immediately or within minutes after upstanding, the patient most often complains of unsteadiness that stops when the patient walks, sits, or lies down. "Vibrations" can be perceived on muscle palpation or auscultation. Neurological examination is reported to be normal most of the time [2]. OT is considered as a rare pathology [2], but misdiagnosis is probably frequent, given the low specificity of the symptoms. This may account for the long diagnosis delay with a median of 6 years [3] and scarcity of cohort studies. Surface EMG

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polygraphic recordings confirm the diagnosis showing a pathognomonic high-frequency tremor between 13 and 18 Hz [4], also defined as "fast" OT only present at orthostatism [4]. A lower frequency has, however, been reported and referred to as "slow" OT [4]. By contrast to primary OT, slow OT is more often associated with other neurological pathologies [4] including extrapyramidal [5] or cerebellar [6] disorders. This dichotomy has been recently questioned, since a retrospective study of 184 primary OT patients, collected over 37 years, showed that 40% of them presented a neurological comorbidity, such as Parkinsonism or Parkinson's disease [2]. In a 5-year follow-up multicenter study of 68 patients with primary OT, additional neurological symptoms were evidenced in 13.2% patients at the first visit and 26% at the end of the follow-up [7]. To better account for all the clinical situations depicting tremor occurring during standing, and to avoid confusion between the two types of tremor with or without associated neurological symptoms, consensus criteria were recently suggested: fast orthostatic tremor, characterized by a frequency of 13–18 Hz is better labeled primary OT or primary OT-plus if associated with neurological disorders, and slow orthostatic tremor with a frequency less than 13 Hz, pseudo-OT [8, 9].

The aims of our study were to depict clinical and neurophysiological characteristics of patients diagnosed with fast compared to slow-frequency tremor at orthostatism, recorded between 2014 and 2019 in the Clinical Physiology Department of Lariboisière's hospital and related neurological and non-neurological co-morbidities. As a rare disease, it seemed to us interesting to report the incidence and disease's characteristics of primary OT patients from our center. Moreover, we describe here, for the first time, pseudo-orthostatic tremor in Wilson's disease patients.

Methods

Patients

Medical records and EMG surface recordings of all patients with a final diagnosis of tremor at orthostatism and performed at the Clinical Physiology Department of Lariboisière's hospital (Paris, France) were analyzed between November 2014 and November 2019 (RGPD # 20181009115547). According to French data-protection authorities, no informed consent is required, but patients are given the opportunity to decline the use of their data. Fast OT was defined by a frequency tremor ≥ 13 Hz and slow OT by a frequency tremor < 13 Hz, coherent between homologous muscles of right and left legs and only present at orthostatism, according to the Consensus Statement on the Classification of Tremors [8].

Patients underwent a standardized neurological examination by one of the authors. Demographic data (age at first symptoms, sex), diagnosis delay (between first symptoms onset and first electrophysiological recordings), and personal neurological and general medical history were collected. Characteristics of complaints, follow-up when available, response to treatment, and evolution of surface EMG characteristics were analyzed. Biological, cerebral MRI, or dopamine transporter (DAT) single-photon emission computerized tomography imaging technique (DaTSCAN) data were also collected when available.

Patients with fast OT were then further referred to primary OT and primary OT-plus when associated with additional neurological features, and slow OT to pseudo-OT [8, 9].

EMG surface recordings

Surface multichannel recordings were performed with an NATUS device (Natus France, Paris—put into operation on the 03/11/2014) using bipolar silver/silver chloride electrodes 2 cm apart over the muscle bellies. Impedances were set below 5 kOhm. EMG signals were band pass-filtered at 20 Hz to 10 kHz. For all patients, recordings were systematically performed on both anterior tibialis and gastrocnemius muscles and occasionally rectus femoris muscles. Moreover, depending on the clinical examination, extensor common digitorum and flexor carpi ulnaris muscles were additionally recorded. EMG bursts were recorded at rest (patient sitting at the edge of the bed), voluntary contraction, at orthostatism (patient standing still, arms along the body), and walking in place (alternative left and right monopodal support).

Statistical analyses

Data are expressed as mean ± SD. Categorical data are expressed as percentages (%). The Shapiro–Wilk normality test was used to test whether data might conform to a Gaussian distribution. Comparisons of quantitative data between slow and fast OT patients were made using the unpaired Student's *t* test when following a Gaussian distribution, the Mann–Whitney test if not. Comparisons of categorical data were made using Fisher's exact test. Statistical significance was set at $p < 0.05$.

Results

Demographics

Demographic and clinical characteristics are reported in Table 1; 263 patients (317 EMG polygraphic recordings) were identified in our database with the search term

Table 1 Demographic, clinical characteristics, and tremor complaints of fast OT and slow OT patients

Patients (*n*)	Primary OT (10)	Pseudo-OT (17)	All OT (27)	*p* value
Female, *n* (%)	9 (90)	8 (47)	17 (63)	0.04
Age at diagnosis (years), mean ± SD	63.3 ± 12	65.8 ± 17.2	64.8 ± 1.1	0.4
Diagnosis delay (years), mean ± SD	8.4 ± 11.1	2.5 ± 2.9	4.7 ± 0.6	0.5
Neurological co-morbidities at first recording, *n* (%)[a]	4 (40)	13 (76)	17 (63)	0.1
Complaints				
Lower limb tremor, *n* (%)	3 (30)	12 (71)	15 (55)	0.06
Unsteadiness, *n* (%)	7 (70)	3 (17)	10 (37)	0.01
Lower limb weakness, *n* (%)	1 (10)	1 (6)	2 (7)	1
Falls, *n* (%)	2 (20)	2 (12)	4 (15)	0.6
Pain, *n* (%)	1 (10)	0 (0)	1 (4)	–

OT orthostatic tremor

[a]Details on Table 2

"tremor", between November 2014 (date of commissioning of the machine) and November 2019. Among them, 27 patients had a final diagnosis of OT: 10 patients with primary OT (corresponding to 17 records) and 17 patients with pseudo-OT (corresponding to 26 records). Diagnosis of primary OT was made after EMG polygraphic recording, at this first examination, for all the patients. For pseudo-OT, tremor diagnosis had already been performed in 67% of patients, but tremor etiology prior to EMG polygraphy was only known in 59% of them (Table 2).

The majority of patients were females (63%) who were significantly more represented in the primary OT group ($p < 0.05$). The mean age was 64.8 ± 1.1 years [25.4–83.4], with no significant differences between groups. Mean delay from symptom onset to diagnosis was not significantly different between the primary OT group (8.4 ± 4.8 years [0.5–16.3]) compared to the pseudo-OT OT group (2.5 ± 2.9 years [0.2–10.3]).

Clinical

Unsteadiness was the main symptom reported by primary OT patients (70%) and significantly more frequently than in pseudo-OT patients ($p = 0.01$). By contrast, tremor was the main symptom reported by pseudo-OT patients (73%), although there were no significant differences with primary OT patients. Weakness, pain, or falls were more rarely reported (26% overall). One patient in the primary OT and three in the pseudo-OT reported concomitant additional upper limb tremor (Table 1).

In the primary OT group, neurologic co-morbidities were reported in 4 out of 10 patients: cervical dystonia, CADASIL, essential tremor, and restless leg syndrome. In 2 of them, depression was also reported. One depression, 3 hypothyroidism, and 1 hyperthyroidism were reported in 5 other patients. These associated pathologies all preceded primary OT, delay being specified in Table 2.

Table 2 Medical history of fast and slow OT patients

Medical history, *n* (delay before OT in years)	Primary OT (*n* = 10)	Pseudo-OT (*n* = 17)
Cervical dystonia	1 (2)	
CADASIL	1 (18)	
Restless leg syndrome	1 (2)	
Upper limb essential tremor	1 (46)	
Hypothyroidism	3 (NA)	
Hyperthyroidism	1 (NA)	
Depression	3 (NA)	
Idiopathic Parkinson's disease		9
Parkinson plus syndrome		2
Ataxic paraneoplastic neuropathy		1
Wilson's disease		3
Cerebellar syndrome in a diffuse neurodegenerative process		1
Sudden Holmes tremor caused by stroke		1
None	1	–

The delay between associated disease and OT onset is only mentioned for the primary OT group, since all diseases or symptoms in the pseudo-OT group started with the orthostatic tremor. In primary OT, patients could cumulate several diseases, which was not the case in pseudo-OT patients

OT orthostatic tremor, *NA* not available

In the pseudo-OT group, associated neurological symptoms were concomitant with the tremor onset in all patients. Idiopathic Parkinson's disease (PD) was the main cause (53%). After the EMG polygraphic recordings, two patients were newly diagnosed with idiopathic Parkinson's disease (Table 2).

Electrophysiology

Repetitive bursts of short duration and side-to-side synchrony were observed in primary OT with a mean 16.15 ± 0.6 Hz frequency (Fig. 1). In pseudo-OT, repetitive bursts were of longer duration with a 4.8 ± 2.6 Hz frequency (Table 3) (Fig. 1). When vastus lateralis ($n = 8$) muscles were additionally recorded, frequency remained the same, whatever the type of OT.

In the primary OT group, 4 patients were recorded more than once, with a mean delay of 1.3 ± 1.5 years between two recordings: 4 patients 2 times, 2 patients 3 times, and 1 patient 4 times. The frequency did not change significantly over time in patients recorded twice or more and the delta between two recordings remained below 1 Hz. In the pseudo-OT group, eight patients were recorded more than once, with a mean delay of 0.6 ± 0.54 years: eight patients 2 times, 2 patients 3 times, and 1 patient 4 times. The frequency did not change significantly in the patients recorded twice or more, except in 2 patients. In those 2 patients, idiopathic Parkinson's disease diagnosis was made at this first recording. They were treated with L-DOPA and EMG recordings completely normalized at the second recording. Interestingly, one of these two patients had no resting upper limb tremor.

In the primary OT group, 3/17 upper limb recordings were performed additionally. For 2 patients, the same tremor characteristics were evidenced in the upper limbs as in lower limbs. For the third patient, a bilateral symmetrical postural tremor of the upper limb extremities at 8 Hz was found. This postural tremor preexisted the feeling of unsteadiness for years and had been interpreted as an essential tremor. This lower frequency activity was found to be a subharmonic of the 16 Hz tremor found in her lower limbs at orthostatism, as already reported [10].

In the pseudo-OT group, 22 upper limb recordings were performed and showed the same characteristics as in lower limbs.

Treatment response (Table 4)

In the primary OT group, 7 patients received a treatment for the OT and data were missing in 3. Two out of seven improved. Three patients received Gabapentin at first that was not effective in one and not tolerated for the other two. Gabapentine was then switched for Clonazepam without

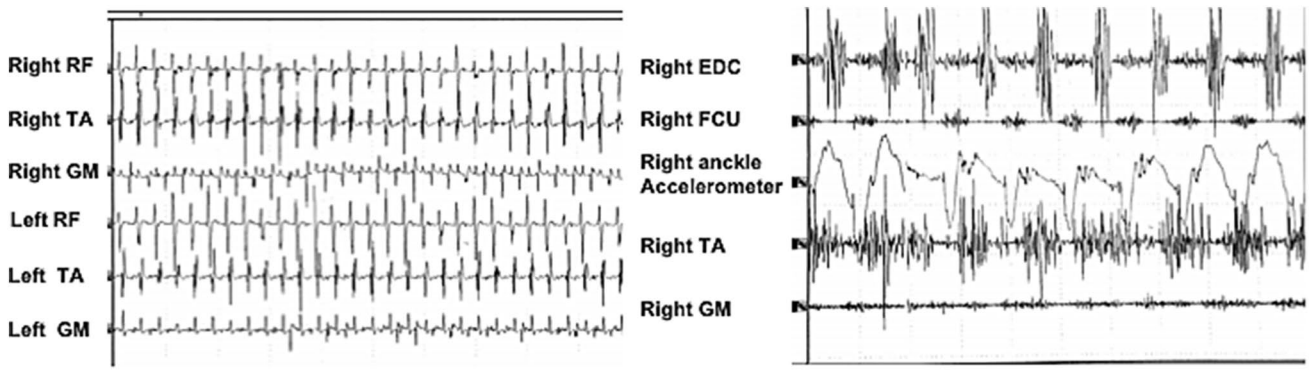

Fig. 1 Surface EMG recording from bilateral rectus femoris (RF), tibialis anterior (TA), and gastrocnemius (GM), while the patient was standing and walked in place revealed a 14.2 Hz Tremor (200 ms/division) (fast or primary orthostatic tremor) (left panel), in a patient with primary orthostatic tremor. Surface EMG recording from extensor digitorum communis (EDC), flexor carpi ulnaris (FCU), tibialis anterior (TA), and gastrocnemius (GM), while the patient was standing still, arms at rest, revealed a 4.6 Hz tremor (200 ms/division) (pseudo-orthostatic tremor associated with rest tremor in the upper limbs) (right panel), in a patient with vascular parkinsonism

Table 3 Electrophysiological characteristics of the orthostatic tremors

	Primary OT (10)	Pseudo-OT (17)
Mean initial frequency (Hz) ± SD	16.2 ± 0.6	4.8 ± 2.6
Evolution of the tremor frequency between first and second recording in 4 primary OT patients and 8 pseudo-OT patients (mean Hz ± SD)	16.2 ± 1.3 → 16.3 ± 0.7	5.1 ± 0.9 → 4.7 ± 3.2
Delay between first and second recording in 4 primary OT patients and 8 pseudo-OT patients (mean years ± SD)	1.4 ± 1.5	0.6 ± 0.5

OT orthostatic tremor

Table 4 Clinical responses to specific treatment in slow and fast OT groups

	Pseudo-OT						Primary OT
	PD	Parkinson plus syndrome	Wilson	Holmes (stroke)	Cerebellar (ND)	APN	
No treatment			1		1		
Partial	2						1
Total	2			1			1
None	1		2				5
Missing Data	4	2				1	3

Despite clinical benefit, electrophysiological control was unchanged in the two fast OT patients

OT orthostatic tremor, *PD* idiopathic Parkinson's disease, *ND* neurodegenerative, *APN* ataxic paraneoplastic neuropathy

any additional benefit for 1 and mild benefit in 1. Four patients received at first Clonazepam: efficacy was good in one patient (4 drops a day) and absent in 3 (9 to 12 drops a day). Gabapentin was not tried in those patients.

In the pseudo-OT group, 8 patients received a treatment for OT; 2 were not treated and data were missing in 7. Among Wilson's disease patients, D-Penicillamine was tried in two patients out of three, but did not improve the OT. Patient with Holmes's tremor significantly improved with Levodopa (125 mg, 3 times a day). Among the 5 treated patients with Parkinson's disease with available follow-up, tremor completely disappeared in two patients, efficiency was partial in two, and tremor did not respond to treatment for the last one.

Discussion

In this retrospective monocentric cohort of patients with a feeling of unsteadiness or leg tremor occurring at standing, and sent to the Physiology Department for EMG surface polygraphic recordings, we found that leg tremor on standing represented about 10.2% of all recordings, primary OT being twice less frequent than pseudo-OT (3.8% versus 6.4%), as already reported by others (4%) [11]. Female prevalence was observed in primary OT (90%) and mean age at diagnosis was around 65 years, as already described [2, 7, 12]. Symptoms reported by patients may be misleading [2]. In pseudo-OT, 12 out of 17 patients reported lower limb tremor, whereas only 3 out of the 10 primary OT patients, who rather reported "unsteadiness".

The true incidence of primary OT is difficult to determine. It is considered a rare disease, but might as well be underdiagnosed. Unsteadiness, and not tremor, is the main specific complaint in patients with primary OT. However, establishing the diagnosis is much easier once the patient confirms that symptoms disappear at walking. Systematic history taking should include these questions.

We decided to classify patients between primary OT and pseudo-OT, with a cut-off frequency at 13 Hz [1, 4, 8]. In contrast to other series [4, 5, 13], none of the patients of our cohort had an intermediate frequency between 10 and 13 Hz. The initial cut-off value at 13 Hz has been considered in the literature to discriminate OT with no associated neurological pathologies, i.e., idiopathic or primary orthostatic tremor, from OT more often associated with a neurological disease [2, 4, 8]. In our cohort, 8 out of the 10 primary OT patients had co-morbidities: 4/10 had associated neurological diseases (cervical dystonia, CADASIL, postural upper limbs tremor, restless leg syndrome) that all preexisted to the occurrence of OT, and 4/10 presented dysthyroidism. One patient presented a frequency tremor of 18–18.5 Hz under antithyroid drug therapy. A slower orthostatic tremor (8–9 Hz) has also been reported in one case report as the first symptom of Grave's disease [14] that dramatically improved under specific therapy. The association with hypothyroidism in 3 out of 10 patients (30%), as was depression, might also be fortuitous, due to the high frequency of these pathologies. One patient in our cohort had a CADASIL disease with cerebellar stroke and vascular leucopathy at cerebral imaging and known familial history. Primary OT started at the age of 43 years. Besides OT, neurological examination was normal and the patient only suffered from migraine with aura since the age of 26. This patient recovered partially when a new stroke occurred in the posterior limb of the internal capsule territory. As already reported with a similar incidence (25–42%) [3, 15], we also found associated movement disorders in our cohort: one had restless leg syndrome, one cervical dystonia, and the last one upper limb postural tremor. In Gerschlager's retrospective study of 41 primary OT patients [3], 25% of the patients had Parkinson's disease (4/41), drug-induced Parkinsonism (1/41), restless leg syndrome (3/41), and orofacial dyskinesias (2/41). In Mestre's study [15], neurodegenerative diseases were additionally depicted (progressive supranuclear palsy and dementia with Lewy bodies). Primary OT is considered to

be caused by as a central generator that could be located in the posterior fossa [16, 17], whereas primary OT-plus, associating neurological features, could be linked to basal ganglia or brainstem dysfunction [3], but this is still a matter of debate, since spinal cord and basal ganglia have been implicated in isolated forms of OT too [18]. During the follow-up of our patients with primary OT, one control EMG polygraphic recording evidenced a new tremor, only at rest, with a slower frequency in the upper and lower limbs. This motivated further exploration by a Dat SCAN© which was normal. The delay between the two EMG polygraphic recordings was 2.5 years, but the onset of primary OT reported by the patient was 20 years before. Thus, the possibility that primary OT might also be the first symptom of a neurodegenerative disease cannot be ruled out [7]. In a prospective multicenter cohort, only 15% of patients had associated pathologies and 7 developed new neurological symptoms during the 6-year follow-up (rising to 26%) [7]. The association of primary OT with these pathologies, however, questions the term "primary", as already been discussed in the literature.

By contrast, pseudo-OT was consistently associated with a concurrent onset of another neurologic condition. Eleven extrapyramidal pathologies were recorded (9 patients with idiopathic Parkinson's disease and 2 with Parkinson plus syndrome), 3 with Wilson's disease, 1 patient with a cerebellar tremor integrated in a more diffuse familial degenerative disease, 1 patient with Holmes tremor secondary to bicerebellar infarcts, and 1 patient with an ataxic paraneoplastic neuropathy. Extrapyramidal pathologies represented the majority of these patients, with an over-representation of Wilson's disease, because of a reference center in the same hospital. We report here for the first time that OT may be part of Wilson's disease. For these three patients, the tremor was recorded at a slow frequency between 3.4 and 7.7 Hz (mean: 5.3 ± 2.2 Hz). Cerebral MRI showed hypointensity of the basal ganglia in T2*-weighted (T2W) images in two and additional hyperintensity in corpus callosum, midbrain, and supratentorial regions in fluid-attenuated inversion recovery (FLAIR) images in one. Cerebral MRI was normal in the last patient but PET using [18F]-FDG showed pons and midbrain hypometabolism.

The maximal duration of follow-up in the primary OT group was 3.1 years (range 0.8–3.1 years). Additional resting tremor in upper and lower limbs occurred in one patient during follow-up. No new neurological co-morbidities were observed during the follow-up of pseudo-OT patients (mean: 0.6 ± 0.5 years [0.2–7.2 years]).

The frequency of the tremor in the primary OT group did not change significantly during the follow-up (delta 1 Hz) (mean 1.4 years, between 4 months and 3.1 years), as already found in another study that followed patients up to 6 years) [7]. However, patients consistently reported worsening of symptoms and enhanced disabling, suggesting that primary OT is an evolutionary pathology, despite unchanged EMG polygraphy.

The frequency of the tremor in the pseudo-OT group did not change between the first and second EMG polygraphic recording (delta 1.2 Hz, mean 7 months, between 3 months and 7.2 years). For 2 out of 17 patients, recordings completely normalized under treatment. In the literature, the role of the dopaminergic system remains debated in pseudo-OT and only 14.3% of patients reported benefit from levodopa in a recent review of combined large series [18].

A few treatments have been effective on primary OT, corresponding to what has been previously described [19]. In our cohort, only 2 treated patients over 7 improved.

Conclusion

Although retrospective, our cohort highlights that primary OT is probably misdiagnosed and remains badly known. It evidenced that 40% of the patients corresponding to the classical terminology of "primary" orthostatic tremor had neurological co-morbidities that questions the term "primary", but might be just as well coincidental given the very small number of these patents in our cohort. Although characteristics of primary tremor did not change on follow-up, enhanced disabling overtime was reported by patients with a little effect of usual medications, which shows that it is a non-benign disease. For patients with pseudo-OT, levodopa should be tried even in the absence of the other symptoms of idiopathic Parkinson's disease, as these symptoms are disabling and often do not respond to any other treatment. A prospective study including functional cerebral imaging could help to better understand this pathology.

Compliance with ethical standards

Conflicts of interests The authors report no conflict of interest for this work and no disclosure. Dr. Poujois has received fees for travel expenses and congress registration from Merz Pharma, and fees for serving as advisory member and consultancy activities from Alexion, Univar, GMP-O, and Vivet therapeutics.

Ethical standards This research was conducted according to the ethical standards issued by the Declaration of Helsinki.

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