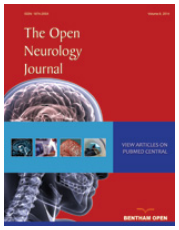

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RESEARCH ARTICLE

Parkinson's Disease in Patients with Essential Tremor: A Prospective Clinical and Functional Neuroimaging Assessment

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Abstract:

Introduction:

Patients with essential tremor (ET) have 3.5 times greater risk of developing Parkinson's disease (PD) throughout their lives, also known as PD with antecedent ET (ET-PD). Single photon emission computed tomography with radiotracer imaging of dopamine transporters (TRODAT-SPECT) can help differentiate these two diseases.

Method:

Relate the results of TRODAT-SPECT imaging in patients with ET to potential progress to ET-PD. Thirty-six patients with ET were evaluated by neurological examination, the Archimedes spiral, and the MDS-UPDRS III scale on two occasions, after a mean interval of three years. SPECT was performed on all patients after the first visit.

Results:

Overall, six patients (16.6%) progressed clinically to ET-PD. Patients with ET-PD were older, and the age of tremor onset was later. The ET-PD group scored higher on the MDS-UPDRS III scale, especially for the presence of bradykinesia. SPECT imaging was altered in 83.3% of the ET-PD patients compared to 33% of the ET patients (p=0.034). Changes on the SPECT with asymmetrical hypouptake suggested progress to ET-PD (p=0.025).

Conclusion:

Advanced age at the onset of tremor, the presence of bradykinesia, and asymmetrical alterations in SPECT may be related to progression to PD in patients with ET. Changes in neuroimaging suggest that SPECT-TRODAT can be used to predict progression to PD in selected patients.

Keywords: Essential tremor, Parkinson's disease, SPECT, TRODAT, Neuroimaging assessment, Patient.

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1. INTRODUCTION

The main differential diagnosis for essential tremor (ET) is Parkinson's disease (PD) [1], and although these diseases have distinct pathophysiology and clinical criteria, diagnosis may be difficult or require several years of follow-up [1, 2]. In a minority of cases, the two diseases share clinical signs, however, their association is a matter of debate [1, 2]. These two disorder trajectories, in fact, intersect in different ways; for example, up to 20% of ET cases may present associated resting tremor with characteristics of PD throughout life [2], while

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mild bradykinesia without decrement has been reported in ET in some studies [1 - 3]. Moreover, up to 48% of PD patients may present action tremor in the same proportion as resting tremor, with postural and intentional tremor predominating [1] and in cases of initial PD, action tremor may indeed be the predominantly clinical sign for several years [1].

In 1907, Gowers was the first to report that some cases of ET and PD could present similar clinical signs, making its distinction difficult [4]. The term ET-PD has been used by some authors to label patients who initially fulfill the criteria for ET but later also develop parkinsonism, fitting concomitant clinical criteria for PD, PD with antecedent ET [2]. Epidemiological data on this association is controversial and prone to bias, reaching 20% in some studies [5, 6] but failing to be observed in others [7].

Functional neuroimaging using radiotracers, such as dopamine transporter single photon emission computed tomography (DaT-SPECT scanning), can be helpful in differential diagnosis, especially in cases where clinical signs of both diseases are present [8]. DaT-SPECT using the ^{99m}Tc-TRODAT-1 tracer (TRODAT-SPECT) has 96.4% sensitivity and 91.7% specificity in differentiating ET from PD [9], and its use has already been approved by the American Food and Drug Administration to differentiate these diseases [10]. DaT-SPECT has led to changes in medical conduct in approximately 1/3 of cases with dubious diagnosis between ET and IPD, and this number is even higher when this technique is used for hard-to-diagnose cases [11].

This study aims to correlate TRODAT-SPECT findings with clinical outcomes of patients with an initial diagnosis of ET, considering their demographic and semiological profile as potential predictive markers.

2. MATERIALS AND METHODS

2.1. Patient Selection

Patients diagnosed with ET according to the Movement Disorders Society criteria [12] were evaluated by the same movement disorders specialist (GF) in a private clinic and at the Hospital Angelina Caron from 2015 to 2017. After enrollment and initial clinical assessment, patients underwent functional neuroimaging using 99mTc TRODAT-SPECT, all performed at the CMN Unit of the CETAC Group. The second assessment was performed at least three years after the first (GSF). For this second step, were not included those who withdrew consent or not wish to participate in this phase of the study patients who developed severe psychiatric disease, alcohol or illegal drugs, patients exposed to neurotoxic agents, with malignant neoplasias, or central nervous system (CNS) comorbidities that could cause tremor.

2.2. Ethical Aspects

This study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Hospital Angelina Caron Ethics Review Board (09454119.2.0000.5226). All patients in the study signed an informed consent form.

2.3. Clinical Evaluation

The patient evaluation protocol was the same for the first and second evaluation. The researchers (GSF and GF) were trained to perform the clinical examination and apply the scales in a standardized manner. Dubious or inconsistent information arising during the evaluations was revised by two other researchers who specialized in movement disorders (CHC and HT).

Demographic data, clinical history, disease progression, medication regimen, paraclinical test results, and family history were collected using a standardized questionnaire.

A neurological examination focusing on motor disorders was performed, and the motor symptoms section of the Movement Disorders Society's Unified Parkinson's Disease Rating Scale Part III (MDS-UPDDRS-III) was used [13]. This part of the scale contains 18 items that assess speech, facial expression, rigidity, bradykinesia, gait, postural stability, posture, and tremor. Each item is scored from 0 to 4, with a minimum score of zero and a maximum of 132. We defined hypokinesia as slowness of movement without reducing amplitude (decrement), and it was associated with a total score for bradykinesia in the UPDRS equal or below 6 points.

The Archimedes spiral (AS) test was applied to assess the severity of the action tremor; the patient drew a spiral on a paper with the same pen and A4 paper used by all patients. The spiral is graded from 0 to 10 according to the visual scale created by Peter Bain *et al*. (1993) [14].

2.4. TRODAT-SPECT Imaging

2.4.1. Patient Preparation

All patients were asked to suspend medications that could interfere with the examination. Patients remained immobile throughout the entire duration of the examination within the camera range of two Millenium ME detectors (GE, Milwaukee, USA).

2.4.2. Preparing the Radiotracer

The radiopharmaceutical 99mTc TRODAT-1 (*Institute of Nuclear Energy Research*, *Atomic Energy Council, Executive* Yuan, Taoyuan, Taiwan; imported/distributed in Brazil by Produtos Farmacêuticos e de Radioproteção Ltd., Porto Alegre) was prepared for intravenous administration. The recommended dose for scintigraphy in evaluating adult patients weighing 70 kg is 814–1036 MBq (22–28 mCi); the dose was adjusted for patients weighing less than 70 kg. The TRODAT-1 kit was labeled with technetium-99m, and each case was labeled with a maximum activity of 44 mCi derived from the newly generated eluate. The maximum volume removed from the generator was less than 5 mL, the material was added to the remaining 0.9% saline solution in a sterile flask, homogenized until fully diluted, and incubated for 30 minutes at 100°C in a water bath. After incubation, the material was left to cool to room temperature in appropriate packaging for 5 minutes. Before administration, the mixture was checked to confirm visual appearance, radiochemical purity, and pH. The active dose was administered to patients from 814 to 1030 MBq

(22–28 mCi) in a volume of approximately 2 mL through peripheral venous access.

2.4.3. Image Acquisition and Analysis

The images were acquired and reconstructed in the transverse, coronal, and sagittal planes 4 hours after intravenous injection of 99mTC-TRODAT. Circular step-by-step orbits and a 140+/-15 key energy and a 128x128 window were used, with 360 diameters and degrees of rotation. The acquisition time per projection was 30 seconds, and the zoom was set at 1.0.

A filtered back-projection reconstruction algorithm with Butterworth filter was used. The images were obtained after processing to 3.39 mm thickness. Visual quantification considered the intensity of radiopharmaceutical uptake in relation to background radiation and the occipital cortex. The uptake results were divided into mild, moderate, severe, or accentuated and absolutely without the radiopharmaceutical [15].

Visual and qualitative evaluation was used to interpret the images by a single experienced nuclear radiologist, based on the principles described by Catafau *et al*. [15]. The results are divided between normal and abnormal, symmetrical, and asymmetrical, with mild, moderate, accentuated, and severe degrees of impairment.

2.5. Statistical Analysis

The results were presented as means, medians, minimum and maximum values, and standard deviations (quantitative variables) or as frequencies and percentages (categorical variables). Student's t-test or the Wilcoxon-Mann-Whitney nonparametric test were used to compare the two groups in terms of quantitative variables. Normality of the variables was assessed using the Kolmogorov-Smirnov test. The chi-square test or Fisher's exact test was used to compare the groups in terms of categorical variables. To evaluate the association between two quantitative variables, Pearson or Spearman's correlation coefficient was used, depending on the normality of the variables. P values below 0.05 indicated statistical significance. The data were analyzed using SPSS Statistics software version 20.0 (IBM Corp., Armonk, NY, USA).

3. RESULTS

A total of 66 cases were initially enrolled, 30 of which were subsequently excluded: 16 decided not to participate in the study, nine were lost to follow-up, two died, two developed severe structural injury according to the cranial MRI, and one developed severe psychiatric disease at the time of the second assessment. In all, 36 patients of the initial ET cases completed the study, 21 (58%) were women, the mean age at onset of symptoms was 41±19 years (range), and the duration of tremor from symptom onset until the time of the second evaluation was 20.7±13 years (range) (Table **1**).

Between the two evaluations, 30 patients continued to be classified as ET, and 6 patients (16.6%) were clinically reclassified as ET-PD. The mean age of the ET group was 58.7±18 years, significantly lower than the ET-PD group (76.8± 9 years; p=0.021). Age at onset of the tremor was also lower in the ET group than in the ET-PD group (p=0.033) (Table **1**).

Clinically, in the first assessment, the ET-PD group tended to have worse scores for the Archimedes spiral than the ET group (p=0.071). All patients in the ET-PD group exhibited hypokinesia, 4 patients demonstrated rigidity, and only 2 patients presented with associated resting tremor (Table **1**).

The mean age at the time of the first assessment and when SPECT was performed was 61.7±18 years, and there was no statistical difference in the time between symptom onset and this examination among the two groups (Table **2**). Of the 30 patients with ET, 10 (33.3%) had altered SPECT results, and of the 6 patients with ET-PD, 5 had altered findings (83.3%) (p=0.034).

Table 1. Clinical and epidemiological indicators.

Variable	All Patients (n=36)	Patients with ET (n=30)	Patients who Progressed to PD (n=6)	p value
Sex - Men (%)	15 (41.6%)	13 (43.3%)	2 (33.3%)	-
Age (years)	61.7±18	58.7±18	76.8±9	**0.021****
Age at onset of tremor (years)	41±18.6	38.1±18.2	55.6±14.3	**0.033****
ET duration (years)	20.7±13.1	20.6±13.6	21.2±11.4	0.922**
Time between evaluations (years)	4.4±1.1	4.4±1	4.7±1.6	0.508**
Family history of tremor	26 (72.2%)	21 (70%)	5 (83.3%)	0.562*
Archimedes spiral (first evaluation)	2.6±1.8	2.5±1.9	3.3±1.3	0.256**
Archimedes spiral (last evaluation)	2.7±2.3	2.4±2.3	4.3±1.9	0.071**
Archimedes spiral (change from first to last evaluation)	0.08±1.5	-0.1±1.5	1±0.89	0.110**
UPDRS (first visit)	11.1±5.7	9.9±4.9	17.1±6.0	**0.003****
UPDRS (last visit)	10.9±7.2	8.9±5.3	20.8±7.6	**<0.001****
Bradykinesia	2 (0–22)	2 (0–12)	11 (6–22)	**0.0004*****
Rigidity	1 (0–6)	0.5 (0–6)	1 (0–4)	0.555***
Resting tremor	0 (0–3)	0 (0–3)	0 (0–3)	0.727***
UPDRS (change from first to last evaluation)	-0.19±6.3	-0.96±5.8	+3.6±8.1	0.229**

*Fisher's exact test, **Student's t test, ***Mann-Whitney test.

Table 2. SPECT results.

Variable	All patients (n=36)	Patients with ET (n=30)	Patients who progressed to PD (n=6)	p value
Time of tremor until SPECT (years)	12.8 (3–55.6)	12.8 (3–55.6)	13.7 (9.6–40.3)	0.864*
Presence of hypokinesia (1st eval.)	21 (58.3%)	15 (50%)	6 (100%)	**0.027****
Change in slowness of movement (median points in bradykinesia - MDS-UPDRS)	1 (-3–15)	0 (-3–5)	7.5 (1–15)	**0.001***
Alterations in exams	15 (41.6%)	10 (33.3%)	5 (83.3%)	**0.034****
Assymetrical Hypouptake (%)	11 (30.5%)	7 (23.3%)	4 (66.6%)	**0.025****
Assymetrical Hypouptake contralateral to the hypo/bradykinesia (%)	5 (13.8%)	2 (6%)	3 (50%)	**0.024****

*Mann-Whitney test, **Fisher's exact test

Changes in the SPECT with asymmetrical hypouptake were suggestive of progression to ET-PD (OR=10, 95% CI, 1.025–97.504, p=0.047). Development of ET-PD was more evident when related to the presence of contralateral bradykinesia on the hypocaptant side in SPECT (p=0.024) (Table **2**). The presence of hypokinesia in the first evaluation, although mild in both groups, was more significant in the ET-PD group (p=0.027). This symptom only became more severe, being reclassified as bradykinesia per se in the ET-PD group (Table **2**).

A total of 10 patients with ET, but without signs of parkinsonism, had altered SPECT findings (Table **2**). These patients tended to present less resting tremor, but the difference was not significant (p=0.064). There was also no significant difference in clinical aspects between patients with ET and normal SPECT findings and those with abnormal results (p=0.91 for action tremor and p=0.35 for tremor duration).

Of the 10 patients with ET and abnormal SPECT findings, four cases exhibited accentuated hypouptake in the examination, while two had SPECT with moderate uptake abnormalities. Of the patients with ET-PD, two had marked and two had moderate uptake abnormalities. There was no correlation between the severity of the tremor evaluated by the AS and SPECT results (rho= -0.116, p=0.53).

4. DISCUSSION

Only a limited number of studies utilized SPECT as a mean to differentiate ET and PD [7, 9, 16 - 18]; in our search, only five such studies were found, using various methodologies but dedicated to the analysis of the progression of patients with tremor to PD using SPECT [16, 17, 19 - 21], similar to the present study. We demonstrated a 16.6% conversion rate from ET to PD, a significant proportion, which can be in part explained by the assumption that the typical ET patient tends to seek specialized medical attention only when symptoms are more advanced and that our sample had a higher mean age (when parkinsonian signs are more prone to occur). In the literature, this conversion rate is very varied, reaching 19 and 20.2% in two clinical studies with a larger number of participants in the 80's [5, 6]. However, a similar study at that time did not find any association between the two diseases [7]. More recent studies found figures that range between 3–7.8% [22, 23]. All these studies have an important caveat: none used functional imaging.

We found that the mean age of patients with ET that progressed to PD was higher (76 years), with tremor labeled as ET beginning later in this group (around age 55) than in those who did not progress to PD. Similar results have been found in other studies, while the mean age at which tremor began was even higher, at 55–65 years [5, 7]. We also observed a higher number of patients with a family history of tremor among those who progressed to PD (83% vs 70%), although there was no statistical significance, a finding similar to that of Lou *et al*. [6].

The ET-PD group tended to have slightly lower scores for the AS compared to the ET group, in spite of similar disease duration. Some studies have demonstrated greater severity as measured by AS in patients with ET or in patients with ET-PD [24, 25]. The presence of hypokinesia was higher in the ET-PD group (100% versus 50% in the ET group). Although debatable, subtle bradykinesia or hypokinesia may be present in some patients with ET, typically without a decrement in amplitude, which is usually found in PD [3]. Until the term bradykinesia is better addressed in clinical and neurophysiological studies, in ET, it should be referred to as slowness of movement (hypokinesia) only [26].

Of the total of 36 patients in our sample, 15 (41%) had abnormal SPECT findings. According to Sixel-Döring *et al*. [21], only 10% of patients with isolated tremor (not specified ET) presented altered SPECT, and after 6 months of follow-up they continued to have clinical ET [26]. Another study that evaluated a population with isolated tremor without bradykinesia or rigidity found that SPECT results for 68% of this group exhibited hypouptake in the striated body, with only 32% normal results, concluding that isolated action tremor does not necessarily mean, but may be the initial symptom in cases of PD [27]. This is in line with the low specificity regarding action tremor [1]. As in our study, these patients were selected from a movement disorder outpatient clinic, where ET patients rarely seek care in early stages. Of our 15 patients with altered SPECT results, 5 presented clinically with ET-PD. Approximately 83% of the ET-PD patients had abnormal SPECT results compared to only 33.3% of the ET patients, previous corroborating studies suggesting that SPECT

imaging in ET-PD patients resembles that of PD patients [25, 28]. According to Algarni *et al*. [1], this is in agreement that action tremor may be an early manifestation in PD or represent another neurodegenerative condition rather than ET.

Asymmetrical hypouptake in SPECT suggested progression to ET-PD. There was a relationship between the presence of contralateral hypokinesia on the altered side of TRODAT and progress to ET-PD. According to Coria *et al*. [27], 68% of the sample of action tremor patients had abnormal SPECT findings, mostly asymmetrical striatal hypouptake. The greatest predictors of striatal hypouptake were onset of action tremor after age 50 and asymmetry. In our study, we found the same tendency for striatal hypouptake in ET patients, but not statistically significant (p=0.35 and p=0.15, respectively, for the age of tremor onset and for clinically asymmetrical tremor). Waln *et al*. [25] also found that ET patients may have alterations in TRODAT, mainly when there are signs of Parkinsonism. According to De Verdal *et al*. [29], 75% of patients with mixed tremor (action and resting) have abnormal SPECT findings, and in most patients the alteration was bilateral hypouptake, in contrast to 30% with asymmetrical hypouptake.

Only one patient with clinical ET-PD had normal TRODAT, exhibiting mild, asymmetrical bradykinesia (worse on the right side) with mild rigidity in the right arm and evident postural instability. These authors questioned whether this might be a case of SWEDD (scan without evidence of dopaminergic deficit), which is uncommon but may occur in up to 11-15% of patients with clinical PD [21]. This diagnosis may be controversial since some cases were reviewed later and reclassified as dystonic tremor, underlying and functional orthopedic diseases, with only 4% of the patients remaining SWEDD [23]. Our patient used low-dose medications for depression (duloxetine 30 mg and clonidine 0.5 mg), but did not present psychomotor slowness at the time of evaluation.

Of the patients who continued to have ET alone, 10 (33%) had abnormal SPECT-TRODAT results, 7 (23%) with asymmetrical uptake. These patients may or may not develop signs of PD in the future. Patients with ET do not necessarily have to present normal SPECT, and there may be mild hypouptake in the caudate nucleus in semiquantitative SPECT analysis [17, 19]. Our follow-up was relatively short; following these patients clinically for a longer period and conducting a levodopa test may help diagnose Parkinsonism, since these patients may have initial PD with only action tremor as a symptom. Furthermore, repeating SPECT in patients with Parkinsonism but with normal initial SPECT findings may help clarify inconclusive cases [20, 30]. According to Gerasimou *et al*. [17], in a group of 20 patients with ET and normal SPECT findings who were followed over several months, only one had symptoms of PD, and repeated SPECT showed a result similar to PD. And according to Tolosa *et al*. [31], even with the use of SPECT, after two years of follow-up, approximately 10% of the patients with a doubtful diagnosis still continued to have a clinical diagnosis, which did not agree with the SPECT results. Repeating the SPECT, however, helped establish the diagnosis in 87% of these inconclusive cases [31]. Other studies have confirmed the accuracy of SPECT in the following cases of doubtful Parkinsonism [10, 31].

Our results can also be important for therapeutic conduct. Recommending the SPECT scan in patients with ET and signs of Parkinsonism may change medical conduct in 44% of cases [11]. According to Mirpour *et al*. [11], when SPECT results showed alterations, dopaminergic replacement was performed in 89.5% of the cases. However, when SPECT results were normal, drug treatment was changed in only 32% of the patients. This can generate savings in the public health system and increase adequate treatment time for patients [30].

This study has a number of limitations. The main one was the difficulty evaluating patients during the COVID-19 pandemic; because of this situation, fewer patients wanted to participate in the second evaluation, which may have compromised the statistical significance of the study. SPECT was performed only once and could not be repeated after the second evaluation. These examinations were only evaluated visually, which may have resulted in normal reports for exams with subtle alterations. We did not use a tremor scale besides AS, since our main objective was to identify parkinsonism in ET patients. Nevertheless, we attempted to reduce this absence with a detailed neurologic examination that was performed and revised in all patients by movement disorders experts. Moreover, postural tremor can be graduated by the UPDRS-III scale.

CONCLUSION

In conclusion, our study suggests that SPECT can help in the early identification of patients who progress from ET to Parkinsonian symptoms, especially when there is an asymmetrical hypouptake and tremor starts at a later age. Patients with ET and alterations in SPECT need to be carefully followed in the clinical setting. Future longitudinal studies with longer follow-up and serial SPECT may yield additional evidence on the relationship between ET and PD.

LIST OF ABBREVIATIONS

ET	=	Essential Tremor
CNS	=	Central Nervous System

DISCLOSURE

The authors report no disclosures relevant to this manuscript.

AUTHORS' CONTRIBUTIONS

The authors contributed equally to the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Hospital Angelina Caron Ethics Review Board (09454119.2.0000.5226).

HUMAN AND ANIMAL RIGHTS

No animals were used for studies that are the basis of this research. All the humans included in the study were in

accordance with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was obtained from the participants involved.

STANDARDS OF REPORTING

Strobe guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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CONFLICT OF INTEREST

Carlos Henrique Camargo is the Editorial Advisory Board of The Open Neurology Journal.

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