

# Significance of Parkinsonian Manifestations in Essential Tremor

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**ABSTRACT:** Parkinsonian features, notably resting tremor may be seen in some essential tremor patients but the significance of those is unknown. The reported risk of parkinsonism in essential tremor patients varies from being unchanged to 35 times higher than expected. We studied 9 patients with essential tremor who had autopsies. In 6 of the 9 (66%) resting tremor was noted and in 3 (33%) cases fully developed parkinsonism was noted. The parkinsonism was consequent to neuroleptic usage in 2 and to basal ganglia status lacunaris and cribrosus in one case but no consistent abnormalities were noted in 3 essential tremor only and 3 essential tremor plus resting tremor cases. We conclude that resting tremor is an age-related natural evolution in some essential tremor patients. We recommend that the additional diagnosis of parkinsonism in the essential tremor be made only when resting tremor, bradykinesia and rigidity are all evident. The risk of idiopathic Parkinson's disease in essential tremor cases is similar to the general population.

**RÉSUMÉ:** Signification des manifestations parkinsoniennes dans les cas de tremblement essentiel. Des manifestations parkinsoniennes (PS), particulièrement le tremblement de repos (TR), peuvent être observées chez certains patients souffrant de tremblement essentiel (TE), mais leur signification est inconnue. Selon la littérature, le risque de parkinsonisme (PS) chez les patients souffrant de TE varie de identique à 35 fois celui de la population en général. Nous avons procédé à l'autopsie de 9 patients souffrant de TE. Chez 6 des 9 patients (66%), un TR avait été noté et chez 3 (33%), un PS évident avait été noté. Le PS était consécutif à l'utilisation de neuroleptiques chez 2 et à l'état lacunaire et criblé des noyaux gris centraux chez un cas. Cependant, aucune anomalie constante n'a été notée chez 3 patients atteints de TE seulement et chez 3 patients avec TE et TR. Nous concluons que le TR est une évolution naturelle, en relation avec l'âge, chez certains patients atteints de TE. Nous recommandons que le diagnostic additionnel de PS chez le patient atteint de TE ne soit posé que lorsque le tremblement de repos, la bradycinésie et la rigidité sont tous évidents. Le risque de maladie de Parkinson idiopathique chez les cas de TE est le même que celui de la population en général.

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Essential tremor (ET) is the most common pathological tremor in man<sup>1</sup> and Parkinson syndrome (PS) is a common neurological disorder in the elderly population.<sup>2-6</sup> Therefore these two conditions may coexist in some individuals. Essential tremor may first manifest in childhood, young adult or old age but PS is concentrated in the later age. When an individual suffers from both ET and PS the usual sequence is an earlier onset of ET and subsequent emergence of PS. Considering that pattern of evolution there is now an active debate on the risk of parkinsonism in the ET patients.<sup>7-12</sup>

The presence of parkinsonian features in the ET cases may indicate: (1) a natural evolution of ET; (2) an incidental coexistence of PS (or IPD); (3) an exaggerated risk of PS (or IPD); or (4) some ET patients may in fact suffer from an unusual tremor-dominant slowly progressive form of IPD.

The literature dealing with this subject is based exclusively on epidemiological and clinical observations and the conclusions have been contradictory.<sup>7-13</sup> Parkinson syndrome diagnosis

is based on the presence of two of the three – bradykinesia, rigidity and resting tremor. The main reasons for the reported difference for the risk of PS in the ET cases between various studies are: (1) resting tremor (RT) may be seen in some ET cases;<sup>14-15</sup> (2) cogwheeling phenomena consequent to the coarse tremor in the ET may simulate cogwheel rigidity of PS;<sup>14-15</sup> and (3) the terms PS and IPD have been used interchangeably.

Parkinson syndrome includes a heterogenous group of disorders, the most common being the idiopathic Parkinson's disease (IPD) which is characterized by marked substantia nigra (SN) neuronal loss and Lewy body (LB) inclusions.<sup>16</sup> Even if the clinical diagnosis of PS were made correctly in the ET cases, the underlying pathology cannot be predicted accurately in a large proportion of these cases.<sup>17-19</sup> The pathological findings in the IPD are highly characteristic but there is no known brain pathology in the ET. A carefully conducted clinical study which is followed by pathological verification would therefore help verify the co-existence of IPD in the ET cases.

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The objective of this study was to determine: (a) the frequency of parkinsonian features in ET patients, and (b) the significance of those clinical features.

### MATERIALS AND METHODS

All patients were seen at the Movement Disorder Clinic (MDC), Royal University Hospital, Saskatoon by one of us (AHR) between 1968 and 1991. The clinical diagnosis of ET was based on a prolonged history of postural or kinetic upper limb or head tremor which could not be attributed to any other neurological or systemic disorder. A positive family history of similar tremor was not essential for the diagnosis.

The additional diagnosis of PS in the ET cases was made only when there was a history of change in the tremor characteristic, and an unequivocal clinical evidence of RT, bradykinesia and rigidity. The tremor amplitude was assessed by visual inspection and was classified as small (fine), medium (moderate), or large (coarse).<sup>20-22</sup> All pathological studies were conducted by a qualified neuropathologist (BR or LA) and six of these cases were reported previously.<sup>21</sup> Several areas of the neocortex, hippocampus, basal ganglia, brainstem, including SN, superior cerebellar peduncles, locus ceruleus, inferior olivary nuclei, cerebellum and the deep cerebellar nuclei were examined routinely in every case.<sup>21</sup> Special stains, e.g., Bielschowsky and Luxol Fast Blue preparations, were performed when neces-

sary for making the proper histological diagnosis. Formal cell count was not conducted at any of the sites.

### RESULTS

Table 1 is a summary of our 9 ET cases. Resting tremor was observed in six (#1, 2, 3, 7, 8, 9) patients. In three (patients #1, 2 and 7) all parkinsonian features – RT, bradykinesia and rigidity were noted and therefore an additional diagnosis of PS was made. Of these three, two (patients #2 and 7) had a history of prolonged neuroleptic usage, and another had brain abnormality which could account for the PS. The final diagnosis in these two cases was drug induced parkinsonism (DIP). The third PS patient (patient #1) had status lacunaris and cribrosus in the basal ganglia and the striatal dopamine (DA) levels were reduced up to 50% in some areas.<sup>23</sup> However, the regional distribution of the DA loss was different from that seen in the IPD.<sup>24</sup> The PS in this patient was attributed to the basal ganglia pathology.<sup>25,26</sup> Basal ganglia lacunar state was also noted in patient #5 who at last clinical evaluation two years before death had no clinical features of PS.

The SN neuronal population was estimated as normal for age in all nine cases and none had LB inclusions at any of the sites examined. There was no consistent gross or histological abnormality in the brain which could be considered as characteristic of ET.

**Table 1: Summary of Case Histories**

Case #, Sex & Age at Death	Age at ET Onset, Site & Peak Tremor Severity Noted	Family History of ET	PS - Onset or Age at Diagnosis and Manifestations	Other Significant Clinical Features, Illnesses and Treatment	Pathological Findings
(1) AR-78 yrs. F	Onset in childhood UL, coarse post. & kine. vert. head tremor - medium amplitude	+ve-son, daughter, granddaughter (all examined)	Onset at 60 yrs. (R) metacarpophalangeal joints, (R) ankles, reduced facial expression. Rig. more (R) than (L), post. instab.; Brady. more (R) than (L)	ET improved with alcohol & propranolol each. No PS improvement on levodopa or anticholinergics. Had MI at 60 & (L) cerebral stroke at age 77 yrs.	Died of acute MI. Grossly moderate cerebral atherosclerosis, (L) insular old infarct. Micro: infarct (L) cerebral insular cort. adjacent white matter. Status lacunaris in (L) GP & Put. Normal SN for age. No LB.
(2) DR-58 yrs. F	Onset in childhood UL - medium amplitude; Head - small amplitude	-ve	Diagnosed at age 54 yrs. Bil. UL resting tremor rig. & brady. and post. instab.	Had severe depression & anxiety, needed ECT & longterm neuroleptics. Attempted suicide x 3. Could not hold job due to tremor and anxiety. Did not tolerate levodopa. Had MI at 55 yrs.	Died following coronary artery bypass surgery. Brain - normal gross & histological. Normal SN cells. No LB.
(3) ET-69 yrs. F	Onset at age 51 yrs. UL post. & kinet. tremor. Vertical head tremor. Intermittent resting tremor (R) finger of small amplitude	+ve mother	No PS diagnosis	Leukemia	Died of complication of leukemia. Normal gross & histological exam of brain. No LB.
(4) GB-51 yrs. M	Onset in childhood UL, post. & kine. - small amplitude	+ve father, brother & cousin	No PS diagnosis	Hypertension, alcohol excess - drank to relieve tremor	Died of presumed cardiac dysrhythmia. Normal gross & histological exam of brain. No LB.
(5) MW-83 yrs. F	Onset at 25 yrs. Head tremor - coarse UL post. & kine. tremor - fine	-ve	No PS diagnosis	Abdominal aortic aneurysm. Was well adjusted & lived in her home independently until death. Last evaluation 2 years prior to death	Died of ruptured abdominal aortic aneurysm. Brain - grossly normal. Bilateral basal ganglia status lacunaris. No LB.

(Continued)

**Table 1: Summary of Case Histories (Continued)**

Case #, Sex & Age at Death	Age at ET Onset, Site & Peak Tremor Severity Noted	Family History of ET	PS - Onset or Age at Diagnosis and Manifestations	Other Significant Clinical Features, Illnesses and Treatment	Pathological Findings
(6) FB-86 yrs. M	Onset at 68 yrs., UL post. fine tremor & kine. coarse tremor. Head - coarse tremor	+ve brother	No PS diagnosis	Dysphagia at 69 yrs. Pharyngeal myotomy with good result. Tremor became progressively coarse & disabling. Responded to primidone but had side effects. Leukemia	Died of complication related to leukemia. Normal gross & histological exam of brain except for senile changes. No LB.
(7) LH-67 yrs. M	Onset at 61 yrs. UL post. & kine. - moderate amplitude	+ve father	Diagnosed at age 65 yrs - resting tremor, (R) UL more than (L). Bil. rigidity & brady.	Propranolol 20 x 2 helped tremor. Angina pectoris treated with nitroglycerine. Long history of affective disorder, paranoia - was on neuroleptics & received ECT	Died of M.I. Grossly & microscopically normal brain. No LB.
(8) KS-81 yrs. M	Onset a age 30 yrs. UL post. & kine. - medium amplitude. (R) finger resting tremor - small amplitude	+ve father, sister	No PS diagnosis	Tendency to depression & anxiety. (L) frozen shoulder. No improvement on amantadine	Died of cardio-respiratory arrest. Grossly & microscopically normal brain for age. No LB.
(9) KM-62 yrs. F	Onset at age 36 yrs. UL post. & kine. - coarse tremor. (L) & (R) thumb resting tremor - small amplitude	-ve	No persistent PS manifestations	Depression towards the end. MRI - Brain normal	Died of neuroleptic malignant syndrome. Hemorrhagic lesions consistent with neuroleptic malignant syndrome. Foci of perivascular calcification in basal ganglia. Normal SN. No LB.

LL = Lower Limb  
UL = Upper Limb  
Bil = Bilateral  
-ve = Negative  
+ve = Positive  
Kine = Kinetic Tremor  
Post = Postural Tremor  
Rig = Rigidity  
Brady = Bradykinesia  
PS = Parkinson Syndrome

LB = Lewy Body Inclusions  
ET = Essential Tremor  
SN = Substantia Nigra  
GB = Globus Pallidus  
Put = Putamen  
MI = Myocardial Infarct  
(L) = Left  
(R) = Right  
Cort = Cortex  
Vert = Vertical

ECT = Electroconvulsive Therapy  
MRI = Magnetic Resonance Imaging  
Post. Instab. = Postural Instability

## DISCUSSION

Resting tremor which is one of three major clinical manifestations in PS was noted in 66% of our ET patients. In three of those (#1, #2 and #7) there was an additional clinical evidence of PS – bradykinesia and rigidity. In the other three cases (#3, #8 and #9) RT was the only manifestation suggestive of PS diagnosis.

The subgroup with RT without bradykinesia and rigidity, we believe represents a natural late stage evolution in some ET patients.<sup>14,15</sup> The reasons for the emergence of RT in the ET cases are unknown. Our patients had no pathology in the nigro-striatal system or at any other site which may produce RT. All three ET plus RT cases who had no other PS features, had history of ET of more than 10 years duration and each was older than 60 years when the RT emerged. It is possible that some age related changes resulted in this clinical evolution. Striatal DA loss, a characteristic finding in the IPD (which often manifests as RT<sup>20</sup>) is also seen in normal aging,<sup>27</sup> and may have contributed to the development of RT. Age-related striatal DA loss alone however does not produce RT in the normal elderly. It is conceivable that the ET diathesis primes these individuals to developing RT when the age-related striatal DA decline reaches a critical level.

In three (33%) of our patients, there was an unequivocal evidence of PS, though none had pathological features typical of IPD.<sup>16</sup> Two cases (#2 and #7) had DIP and no pathological findings in the brain. In the third patient (#1) with the diagnoses of ET and PS, basal ganglia status lacunaris and cribrus were detected. Such abnormalities have been reported to produce PS in some individuals.<sup>25,26</sup> One additional patient (#5) had similar pathology, but there was no clinically documented PS. The last assessment in this patient was done two years prior to death. It is possible that the basal ganglia pathology in this patient evolved subsequent to the last neurological assessment. We do not believe that the ET predisposed to DIP in our two (#2 and #7) patients. Because of the age-related striatal DA decline the elderly are more susceptible to neuroleptic stress and consequently the DIP. The pathological findings of basal ganglia status cribrus and lacunaris which we believe was the basis of PS in patient #1 was unrelated to ET. Thus in none of the three ET patients who had PS did the pre-existing ET enhance the susceptibility to PS and none had IPD pathology.<sup>16</sup> We conclude that the PS in these ET cases was incidental.

Our report of 9 ET cases by most standards of clinico-pathological studies in common neurological disorders is small. However it is the largest of its kind in the ET patients in the

literature so far. These patients were studied for a long time – seven of the nine cases were followed for more than 10 years before coming to autopsy and 5 had suffered from ET for more than 30 years at the time of death. Thus, in spite of the limitations consequent to the size of the study, because of the careful clinical and pathological observations, questions pertaining to the risk of IPD can be addressed satisfactorily.

Definite clinico-pathological correlation between SN neuronal loss and LB inclusions in the IPD was first made in 1919.<sup>28,29</sup> Incidental LB inclusions are reported in non-parkinsonian general population between 6th and 9th decade in 3.8% to 12.8% of the autopsied subjects.<sup>30,31</sup> Individuals with incidental LB findings are regarded by some observers as suffering from pre-clinical IPD.<sup>30</sup> Pathological evidence of definite<sup>16</sup> and pre-clinical IPD<sup>30</sup> may therefore be used to assess the risk of IPD in the autopsied ET patients. None of our nine patients or the six ET autopsies reported by others<sup>1,32-36</sup> since 1919 had pathological findings indicative of definite or preclinical IPD.

If the risk of IPD in the ET patients were merely twice that in the general population, rather than the 24 to 35 fold increase suggested in some studies,<sup>8,9</sup> we would expect to find LB inclusions in 7% (3.8% x 2) to 25% (12.8% x 2) of the autopsied ET patients. However none of the 15 patients reported so far had LB inclusions. Thus the autopsy literature on ET indicates that ET does not increase the risk of IPD.<sup>7,10,11</sup> Our observations also mitigate against the possibility that some ET patients may suffer from an unusual form of IPD. Considering that RT may represent a natural evolution in some cases we propose that the additional diagnosis of PS be made only when all three cardinal features – RT, rigidity and bradykinesia are identifiable in an ET patient.

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