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Brief Communication

Essential Tremor and Dementia: Incidental Co-Occurrence or Real Association in Aging?

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ABSTRACT

Essential tremor (ET) was considered to be mono-symptomatic. However, it has been reported recently that motor and non-motor findings other than kinetic tremor may accompany the disease.

The records of the cases evaluated in the dementia policlinics were retrospectively analyzed. The demographic and clinical characteristics of cases with dementia and isolated kinetic tremors were noted.

There were 8 patients diagnosed with dementia in the follow-up after the presentation with ET. The mean onset age of the kinetic tremor was 65.75 years. Parkinsonian findings were observed in the follow-up of 6 patients. The neurocognitive evaluation revealed depression, dysfunction in attention, and visuospatial skills in half of the patients. The clinical picture is compatible with dementia with Lewy bodies in half of our ET cases with dementia.

ET is now recognized as a neurodegenerative disease accompanied by neurological symptoms other than kinetic tremor. This report supported that other neurodegenerative diseases may accompany ET.

1. INTRODUCTION

Essential tremor (ET) is one of the most common movement disorders whose main feature is 8–12 Hz kinetic tremor. The prevalence of ET increased markedly with age. The mean age at tremor onset has been reported as 45.3 years in ET. Earlier onset of the tremor was observed in the patients who have a positive family history of tremors. Both genetic and environmental factors are implicated in the etiology. The main reason for the kinetic tremor in ET is the problem in the cerebellar outflow pathways.[1,2] Reported postmortem changes are segmental loss of Purkinje cells, presence of torpedoes, and Bergmann gliosis in the cerebellar cortex in 3/4 of ET patients. The remaining 1/4 is characterized by Lewy bodies mainly in the locus ceruleus (LC). Therefore, ET is pathologically classified into two groups: "cerebellar ET" and "Lewy body variant of ET (LBVET)".[3]

Until recent years ET has been accepted as a mono-symptomatic disease characterized by the kinetic tremor. But within these two decades, reports increasingly come about additional motor and non-motor features in ET. Ataxic gait, postural instability, and resting tremor have been reported on the motor side, and cognitive deficits and psychiatric features in the non-motor side of ET.[1–3]

Reports on cognitive deficits have recently begun to appear in the literature.[3,4] Mild cognitive deficits, mainly in frontal-executive function and memory, have been reported in patients with ET. Population-based studies have demonstrated also an association

between ET and mainly Alzheimer's disease (AD) related dementia.[1,2,5]

Here we aim to review the features of 8 cases who present as ET and then clinically develop dementia.

2. METHODS

In this single-center, observational study 10 years of records of the dementia cases evaluated in the dementia clinic were evaluated retrospectively. The demographic and clinical characteristics of dementia cases who presented with isolated kinetic tremors consistent with ET were recorded and analyzed. Tremor diagnosis was made clinically and tremor severity at admission was determined with The Essential Tremor Rating Assessment Scale (TETRAS).

3. RESULTS

269 patient records of the dementia clinic were evaluated retrospectively. There were 8 patients diagnosed with dementia in the follow-up after the diagnosis with ET. Seven of 8 patients were male. The mean of onset age of the kinetic tremor was 65.75 years (±7.5)(52–81 years). The interval from the onset of tremor to the other motor and non-motor findings was in the range of 1–20 years. The mean of the interval was calculated at 8.86 (±6.58) years. The tremor severity determined by the TETRAS score was in the range of 6–22. The mean score for the patients' tremor severity was 11 (±5.39). Parkinsonian findings were observed in the follow-up of 6 patients. REM sleep behavior disorder was found in 2 patients and the history of fluctuant confusion and visual hallucinations was detected in 4 patients. Four patients had a family history of tremor, and 2 patients had a family history of both dementia and tremor. Five patients had received treatment for their essential tremor and their response to first-line therapy varied from medium to high. In detailed neurocognitive evaluation, depression was found in half of the patients. Also, in half of the patients, the dysfunction in attention, executive functions, and visuospatial skills were prominent without any memory problem. Cranial magnetic resonance imaging (MRI) tests showed mild to severe global atrophy in all patients. The demographic and clinical features of the patients are shown in Table 1.

4. DISCUSSION

The concept of ET as a benign single-symptom disease has changed in recent years, with the identification of additional motor and non-motor symptoms and new pathological features. Today, the accepted view with much evidence is that ET is a progressive neurodegenerative disease. Firstly, the pathological changes of ET seem to be degenerative. Besides the pathological findings, increasing the disease prevalence by age, progressive clinical nature, concomitant motor, non-motor features, and neurodegenerative disorders prove to us that ET may be the result of at least two different neurodegenerative processes.[1,2,5,6]

We described 8 cases who initially have isolated kinetic tremors and later developed dementia in this report. The average time to the development of additional symptoms to kinetic tremor is almost 9 years. This long period also the absence of the Parkinsonian features at onset and the cases with extensive family history for ET provides evidence that the onset is associated with ET in our cases. In addition, 5 patients used primidone, which was accepted as one of the first-line treatments for ET. Their responses to this treatment were in the direction of benefiting in tremor severity, ranging from medium to high. This supports that the isolated kinetic tremors of the cases are associated with mechanisms compatible with ET.

The pathological process may have also spread into motor systems outside the cerebellar outflow connections and caused other defined motor features in this progressive disorder.[1] Especially Parkinsonian features have commonly been discussed among these other motor symptoms. Actually, the presence of parkinsonian features in ET patients is an important dilemma. But it is undoubtedly known that the frequency of Parkinson's disease (PD) in ET is more than would be reported in the general population.[1,5,7] Similarly, Parkinsonian findings were observed in the follow-up of 3/4 of our ET patients who developed dementia. Numerous reports in the literature report the presence of cognitive deficits and dementia as a nonmotor feature in ET.[3,4] Presence of dementia appeared to be greater than that expected for age in ET patients. More recently, population-based studies have demonstrated an association between ET and mainly AD related dementia.[2,5] Mild cognitive deficits, mainly in frontal-executive function and memory, have been reported in patients with ET. Cognitive deficits may result from the main pathology; cerebellar dysfunction and alternately, they may be a feature of concomitant neurodegenerative diseases.[1] Additionally, in the light of the post-mortem studies it has been speculated that ET cases with dementia may be related to cortical Lewy body pathology.[2]

The researchers accept that the brain stem Lewy pathology is different from normal aging and also they speculate that it is possible that the patients with LBVET are at increased risk of developing more complete Lewy body syndrome.[5,6]

Lewy body pathology causes a spectrum of diseases including PD, dementia with Lewy bodies (DLB), AD with Lewy bodies, and LBVET. DLB and AD with Lewy bodies are directly associated with dementia. Dementia

can also be observed in later stages of PD.[7] There are no significant reports in the literature regarding the association of ET with DLB. On the other hand, it is mentioned in the literature that neurodegeneration of the LC is an important pathological finding in different types of dementia, including DLB.[8]

Here we defined 8 patients with dementia and ET with the retrospective evaluation of dementia clinic reports. All of these patients or their families reported cognitive impairment themselves. The clinical profile of dementia of 4 patients (Case1–4) was consistent with probable DLB depending on the recent criteria.[9] In the detailed neurocognitive assessment in this group, dysfunction in attention, expressive behavior, and visuospatial skills together with normal memory fit the profile of DLB. It is classically known that typical antipsychotic hypersensitivity can be observed in DLB.[9] In our cases, there are also cases with fluctuant confusion and visual hallucination episodes triggered by pribedil and quetiapine. There wasn't observed any acute impact of pribedil on cognitive performance between the confusion attacks. In addition to typical antipsychotics, one should be aware of profound confusion attacks that may develop during the use of atypical ones and pribedil, which also has strong anticholinergic effects with dopamine agonism.

Table 1. Demographic and clinical characteristics of the patients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age-gender	80-male	83-male	70-male	80-female	75-male	78-male	89-male	83-male
Follow up period	6 years	10 years	3 years	4 years	5 years	6 years	8 years	1 year
Neurologic examination at presentation	Isolated kinetic tremor	Isolated kinetic tremor	Isolated kinetic tremor	Isolated kinetic tremor	Isolated kinetic tremor	Isolated kinetic tremor	Isolated kinetic tremor	Isolated kinetic tremor
Tremor presentation age	69	64	67	66	65	52	81	62
TETRAS score	7	14	9	22	7	16	7	6
Response to the first-line ET treatment	Not used	Primidone-moderate response	Primidone-moderate response	Primidone-moderate response	Not used	Primidone-high response	Not used	Primidone-high response
Parkinsonian features in follow up	Left side dominant bilateral resting tremor	Bilateral resting tremor, hypophonia, tachyphemia, micrographia, shuffling gait	Mayerson, bradimimia, bilateral resting tremor, right-sided cogwheel rigidity	Not observed	Bilateral resting tremor	Not observed	Mayerson, right side dominant bilateral resting tremor and cogwheel rigidity, postural instability, anteflexion posture	Left side dominant bilateral slight resting tremor, chin tremor
Duration from kinetic tremor to secondary neurologic symptoms related to other neurodegenerative disorders	5 years	10 years	1 year	10 years	1 year	20 years	1 year	15 years
Fluctuant confusion history and visual hallucinations	Yes Uremia and piribedil induced	Yes Spontaneous and quetiapine induced	Yes Spontaneous and uremia induced	Yes Spontaneous and typical antipsychotic-induced	No	No	No	No
REM sleep behavior disorder	Yes	No	Yes	No	No	No	No	No
Cranial MRI	Mild global atrophy	Moderate global atrophy	Mild global atrophy	Mild global atrophy	Mild global atrophy	Mild global atrophy	Severe global atrophy	Severe global atrophy
Family history	No	No	Yes 66-year-old sister have severe ET for 30 years without any parkinsonian features and dementia. Dad, aunt, two uncles, and grandfather have dementia, confusion, and tremor history.	Yes ET in one sister	Yes A late-onset tremor in one sister	No	Yes Dementia and tremor in two brothers, two aunts, and an aunt's son who is 68 years old	Yes Dementia in grandmother and her sister
Self-reported cognitive impairment	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Neuropsychiatric evaluation	Depression, normal memory, mild dysfunction in attention and executive functions	Depression, normal memory, mild dysfunction in attention and visuospatial skills	Normal memory, mild dysfunction in attention and visuospatial skills	Depression, moderate impairment in memory and attention	Normal memory, severe impairment in attention and visuospatial skills	Depression, mild dysfunction in memory and visuospatial skills, moderate impairment in attention and executive functions	Severe impairment in all modalities	Moderate impairment in memory and severe impairment in attention, executive functions and visuospatial skills

TETRAS: The Essential Tremor Rating Assessment Scale; ET: essential tremor; REM: rapid eye movement; MRI: magnetic resonance imaging

The fact that it is an observational study and the small number of observed cases are important limitations in making a definite conclusion. Large prospective studies of ET patients will provide more evidence-based information regarding the pathogenesis, course of ET, and its association with dementia. Since aging is the major risk factor for both ET and DLB, our observations of their co-occurrence may be coincidental. However, it is important to share these observations with detailed neurocognitive evaluation results and contribute to the discussions on this subject in the literature.

In this observational study, we found that the distribution of dementia types in the dementia archive of 269 patients is consistent with the universally expected frequency distribution. The dementia type of 73% of the patients is compatible with AD followed by Frontotemporal dementia in 7.7% of the patients. However, dementia is associated with DLB in half of our population. Besides, half of the remaining also have Parkinsonian symptoms with dementia. Again, in the cognitive profile of 75% of this half, there were moderate to severe memory problems in addition to attention, executive dysfunction, and visuospatial impairment. Rapid eye movement (REM) sleep behavior disorder and fluctuant confusion were not observed in any of the patients in this group. A progressive clinic has been described, which is similar to the AD process. However, Parkinsonian findings in their neurological examinations are confusing. These patients seem to be able to form a new group on the spectrum of this disease.

Additionally, we may discuss the onset age of kinetic tremor and its severity as a predictor for identifying the cases who have a risk for progression to dementia. The mean onset age of kinetic tremors in our study group was higher than expected.[10] Moreover, the mean score of all patients for tremor severity is lower than expected for this age.

5. CONCLUSION

With the all literature knowledge and our observations, we can say that at least some types of ET, PD, and DLB are possibly on the clinical spectrum of the same pathology.[1,3,5] There may be transitions within this spectrum with time. The patients who have isolated kinetic tremors must follow periodically for the motor and nonmotor symptoms related to Lewy body spectrum disorders. Also, it is important to add cognitive system questioning in the follow-up of ET patients to identify common cognitive impairments. Moreover, patients with ET should be questioned about the history of REM sleep behavior disease, fluctuant confusion and visual hallucinations, which may be a predictor of DLB. Particular attention should also be paid to parkinsonian features in their examinations.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

ETHICS

The study followed the Declaration of Helsinki Ethical Principles for Medical Research.

DISCLOSURE

The authors hereby certify that the work shown here is genuine, original and not submitted anywhere, either in part or full.

This study was presented in 56th National Neurology Congress and 7th Congress of the European Academy of Neurology.

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