

Cognitive Assessment in Patients with Essential Tremor: A Prospective Study

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Abstract

Introduction: Tremor is a rhythmic, oscillatory movement produced by alternating or synchronous contractions of antagonist muscles. Essential tremor (ET) is neurodegenerative disease it is clinically progressive disorder because of frontal and temporal lobe involvement of brain. ET is commonly associated with cognition impairment.

Aim: This is the study to analyze the cognition impairment in ET patients.

Methods: ET patients were analyzed by tremor rating scale and their cognitive assessment was done by neuropsychological test, mini-mental state examination, Addenbrooke's cognitive scale, Alzheimer's disease assessment scale-cog scale, and frontal assessment battery test.

Results: A total of patients included in this study were 50. Out of these, 31 were male and 19 were female. There was a significant family history in 21 patients (42%). Tremor frequency was 5-10 Hz in 80% of patients. Nearly 20% of patient had frequency more than 10 Hz.

Conclusion: Finding that the subclinical cognitive deficits characterized by attention and verbal memory impairments and executive dysfunction is a clinical feature of ETs.

Key words: Age, Cognition, Education, Essential tremor

INTRODUCTION

Tremor is a rhythmic, oscillatory movement produced by alternating or synchronous contractions of antagonist muscles.¹ Tremors are classified by means of phenomenology, frequency, etiology, and distribution.¹ By phenomenology, it is divided into action and rest tremors. By frequency, it is divided into slow (3-5 Hz), medium (6-10 Hz), and fast (11-20 Hz). In anatomical distribution, it is divided into tongue, head, limb, trunk, and voice.¹ The tremor of essential tremor (ET) is kinetic or postural, with frequency of 4-10 Hz.¹ ET prevalence is 0.5-5% in

community-based studies and also in more than 65 years aged people, prevalence was 14%.^{2,3} Originally in essential tremor, essential is synonymous with "idiopathic." There is growing evidence that ET is a multiple-system disorder and it has additional motor features (e.g., intention tremor and ataxia) and non-motor features such as mild cognitive deficits and personality changes (mood disorders), and possible sensory manifestations include mild olfactory dysfunction and hearing impairment.¹⁻⁵ Cognitive deficits such as attention, executive functions, and memory are reported.⁶ ET is neurodegenerative disease and clinically progressive disorder.⁷ Recent work has shown widespread white matter pathology in ET, primarily involving the frontal area and with some temporoparietal area involvement. Other studies have shown that the cerebellum is functionally connected to the cerebral cortex through feed forward and feedback pathways.⁸ In addition, there are evidence that the circuit involved includes the frontosubcortical pathways, which play a role in cognitive and affective processes in

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patients with ET. Conversely, these neuropsychological findings in ET are similar to those observed in some cerebellar disorders. Aging is one of the important risk factors commonly related to the increased incidence and prevalence of ET.⁵ The median age of onset is 15 years, and it has bimodal age distribution. All patients are symptomatic by the age of 65 years.² There are studies in ET that point toward environmental factors in the form of lead and β -carboline alkaloids.¹⁻⁵ β -carboline alkaloids (e.g. harmaline) are potent tremor-producing chemicals those are present in the human diet mainly in animal proteins (meats) that are cooked at very high temperatures for prolonged periods. The harmaline blood concentration has been reported to be higher in patients with ET than in normal control. A metabolic defect has been hypothesized to underlie the increased blood harmaline concentration in patients with ET. Recently, it has been demonstrated that blood lead levels are very high in ET patients than the control individuals.^{9,10} This study shows that lead is a neurotoxicant and also produces cerebellar damage which will produce tremor.

Aim

This is the study to analyze the cognition impairment in ET patients.

MATERIALS AND METHODS

This prospective study was conducted in Madras Institute of Neurology Movement Disorder Clinic. The patients, diagnosed as ET on regular follow-up in Movement Disorder Clinic, were taken for this study. The Institutional Ethics Committee approval and informed consent were obtained. In this study, 50 patients who were diagnosed as ET according to the criteria by consensus statement of the Movement Disorder Society on tremor were analyzed. ET patients were analyzed clinically and tremor severity was analyzed by tremor rating scale (TRS). The cognitive assessment was done by neuropsychological test, mini-mental state examination (MMSE), Addenbrooke’s cognitive scale, Alzheimer’s disease assessment scale (ADAS)-cog scale, and frontal assessment battery (FAB) test.

RESULTS

A total of patients included in this study were 50, out of which 31 (62%) were male and 19 (38%) were female.

A total of patients studied were 50, out of which 10 patients (20%) were illiterate or studied up to 5th standard. 20 patients (40%) were completed secondary schooling. 20 patients (40%) were degree holders.

Out of 50 patients, 30 patients (60%) had disease duration in between 5 and 10 years and 20 patients (40%) had disease duration more than 10 years.

In this study, a total of cases studied were 50, out of which 12% were having hearing loss. Number of patients with hearing loss were 6. 5 patients were done audiometry showing sensorineural deafness. In this study, 8% of patients were having psychiatric illness. Number of patients with psychiatric illness were 4. 2 patients were having anxiety disorder and 2 had depression

There was a significant family history in 21 patients (42%). There was no positive family history for 29 patients (58%).

Tremor frequency was 5-10 Hz in 80% of patients. Nearly 20% of patient had frequency more than 10 Hz. Increased frequency was seen more in younger patient <25 years (Table 1).

Out of 50 patients, 60% had duration of disease illness from 5 to 10 years and they all had TRS score <16. Nearly 40% of patients had duration of disease illness more than 10 years and they all had TRS score of more than 16. This reflects the increased severity of disease as duration of illness increases.

MMSE in ET

MMSE was less than 23 in 32% of studied population. MMSE was more than 23 in 68% of studied population. The mean MMSE score was 26 in studied population. On comparison of MMSE with TRS scoring, TRS score more than 16, 8 patients had MMSE <8 (Table 2).

Addenbrooke’s Cognitive Examination

In Addenbrooke’s cognitive examination, total score was 100. 20 patients were scored more than 80 points (40%). 10 (20%) patients were scored 60-80 points. 20 patients were

Table 1: Comparison of tremor frequency with age of the patient

Age of the patients (years)	Tremor frequency 5-10 Hz	Tremor frequency >10 Hz
<25	10 patients	10 patients
25-50	20 patients	0
>50	10	0

Table 2: Comparison of MMSE with TRS score

	TRS score <16	TRS score >16	Total
MMSE<23	8	8	16
MMSE>23	22	12	34
Total	30	20	50

MMSE: Mini-mental state examination, TRS: Tremor rating scale

scored <60 points (40%). In Addenbrooke's cognition test, total score for attention and orientation was 18. All of them had more than 12. The average score was 15.40, and there was no gross impairment in attention and orientation. In Addenbrooke's cognition test, total score for memory was 26. 20 patients (40%) were score <18. Remaining 30 patients (60%) were scored more than 18. In Addenbrooke's cognition test, total scoring for verbal fluency was 14. Average scoring is 7 (50%). 24 patients (48%) had verbal fluency <8. 26 patients (52%) had verbal fluency more than 8. On comparing TRS with verbal fluency, verbal fluency was less than in 14 of the patient with TRS scores more than 16. The maximum number of score for language testing in Addenbrooke's scale was 26. 25 patients scored language score <18. 25 patients scored language score more than 18. On comparing of TRS with language testing score: 20 patients with TRS more than 16, 14 patients had language score of less than 18. It denotes that the increased tremor frequency is associated with severe language impairment. In Addenbrooke's cognition scale, visuospatial total score was 16. The mean value is 15. There was no impairment noted in visuospatial function (Table 3).

ADAS-Cog Scoring

In ADAS-cog, word recall task contains 10 words. Here, the subject score is the average number of words not recalled on three trials and maximum point is 10, i.e., if point is increased means, they are making more mistakes. Out of 50 patients, 33 patients had world recall score <3 and 17 patients had world recall score 3-7. On comparing with TRS scale with ADAS-cog word recall task, it shows that TRS score >16, 13 patients were scored in between 3 to 7. In TRS score <16, only 4 patients scored in between 3 and 7. This implies increased severity of tremor will cause more word recall impairment. In ADAS-cog, word recognition task was to discriminate the new words from the already presented ones (0-12 points). Maximum score is 5. In this study, average word recognition task was 1. Only 20% of patients had word recognition task >3 (Table 4).

FAB Test

In FAB test, total score was 18. Average score of studied population was 16, which signify no gross abnormality noted in this test. In Luria's triangle test, total score is 3. In studied population, 30 patients scored 3 and 20 patients scored 2. In go-no-go test, total score is 3; 36 out of 50 study population scored 3. 14 out of 50 study population scored 2. On comparing TRS score with go-no-go test, TRS >16, 13 patients scored go-no-go test 3 (Table 5).

DISCUSSION

Tremors are the most common movement disorder in clinical practice. In this study, ET patients were analyzed

and their cognitive assessment was done by battery of neuropsychological test. In this study, a total of patients studied were 50. Majority of the patients were male (62%). The reasons for male preponderance were several. Usually in India, females ignore because they do not disturb the daily activities. The mean age of study population was 42.2%. This correlates with study Dogu *et al.* (2003), Turkey, which demonstrated that the prevalence of ET was between 40 and 50 years of age.¹¹ Thanvi *et al.* suggested that the prevalence of ET above 65 years was 4%.¹²

Duration of the illness varies from 5 to 13 years. Mean duration for illness in this study was 7.8 years. In Addenbrooke's scoring, the patients who were having duration of illness from 5 to 10 years of the study population, 33% of patients showed memory disturbances. In the patients who were having the illness more than 10 years, the memory disturbance was 50%. This shows that there was impairment of memory and it was more if duration of illness is more than 10 years. It was not statistically significant.

In this study, a total of cases studied were 50, out of which 12% were having hearing loss. A total of patients with hearing loss were 6. 5 patients were done audiometry showing sensorineural deafness. Benito-León and Louis in their study analyzed hearing impairment in ET and controls. He concluded that hearing impairment in ET was 30% more than the controls (Table 6).³

Table 3: Comparison of Addenbrooke's language score with TRS score

	TRS score <16	TRS score >16	Total
Language score <18	11	14	25
Language score >18	19	6	25
Total	30	20	50

TRS: Tremor rating scale

Table 4: Comparison of ADAS-cog word recall task with TRS score

	TRS score <16 (%)	TRS score >16 (%)	Total
Word recall <3	26 (78.8)	7 (21.2)	33
Word recall 3-7	4 (23.5)	13 (76.5)	17
Total	30	20	50

ADAS: Alzheimer's disease assessment scale, TRS: Tremor rating scale

Table 5: Comparison of FAB go-no-go test score with TRS score

	TRS score <16 (%)	TRS score >16 (%)	Total
Go-no-go test score 3	23 (63.9)	13 (36.1)	36
Go-no-go test score 2	7 (50)	7 (50)	14

FAB: Frontal assessment battery, TRS: Tremor rating scale

Table 6: Comparison of duration of tremor with Addenbrooke's score for memory

Duration of illness	Addenbrooke's score for memory <18	Addenbrooke's score for memory >18	Total
5-10 years	20	10	30
More than 10 years	10	10	20
Total	30	20	50

Chi-square value: 1.389; $P=0.239$

In this study, 8% of patients were having psychiatric illness. Number of patients with psychiatric illness were 4. 2 patients were having anxiety disorders and 2 were having depression. Thanvi *et al.* suggested that ET patients were commonly associated with anxiety and depression. They also suggested that there was no correlation of psychiatric disorders with severity of tremor.¹²

There was a significant family history in 21 patients (42%) out of 50. There was no positive family history in 29 patients (58%). A previous study in Madras Institute of Neurology (Chennai) showed that 46.5% had positive family history. They also suggested that there was a predominant autosomal dominant transmission.

Tremor frequency was 5 to 10 Hz in 80% of patients. 20% of patient had frequency more than 10 Hz. Increased frequency was seen more on younger patient (<25 years). Thanvi *et al.* suggested that the frequency of tremor in the hand in ET was 5-12 Hz.¹² In this study, also the frequency was ranged from 5 to 13 Hz. The mean tremor frequency in this study was 7.2 Hz.

Out of 50 patients, 30 had TRS score <16 and 20 patients had TRS score more than 16. The patients with TRS score <16 (60%) had duration of disease illness from 5 to 10 years and the patient with TRS score more than 16 (40%) had duration of disease illness more than 10 years. The mean TRS score in this study was 11.85. This reflects there is a linear relationship between severity of tremor and duration of the illness. Felix Bermejo-Pareja suggested that the severity of this disorder increases and it can affect more body parts as year's progress.⁷

MMSE is <23 in 32% of the studied population. MMSE was more than 23 in 68% of the studied population. The mean MMSE score was 26. Kim *et al.*'s study revealed that there was small impairment in MMSE in ET patients but which was statistically significant when compared with controls.⁴

In Addenbrooke's cognitive examination, total score was 100. In this study, 20 patients scored more than 80 (40%), 30 (60%) patients scored 60-80, and 10 patients scored <60 (20%). The average score was 83.20.

In Addenbrooke's cognition test, total score for attention and orientation is 18. All of our patients scored more than 12. The average score was 15.40, and there was no gross impairment in attention and orientation. Gasparini *et al.*, Lombardi *et al.*, and Felix Bermego *et al.* in their study indicated that there was disturbance in attention and orientation.^{7,13,14} Duane and Vermilion, and Sahin *et al.* in their study, they stated that there was no disturbance in attention and concentration.^{15,16}

In Addenbrooke's cognition test, total score for memory is 26. 20 patients (40%) scored <18. Remaining 30 patients (60%) scored more than 18. This study showed that there was impairment in memory in ET patients. Gasparini *et al.*, Lombardi *et al.*, Duane and Vermilion, Sahin *et al.*, and Troster *et al.*, all concluded that there was significant impairment in memory which correlates with this study.^{8,13-16}

In Addenbrooke's cognition, total scoring for verbal fluency is 14. Average scoring of this study was 7. 24 patients (48%) had verbal fluency <8. 26 patients (52%) had verbal fluency more than 8. Gasparini *et al.*, Lombardi *et al.*, Duane and Vermilion, Sahin *et al.*, and Troster *et al.*, all concluded that there was significant impairment in verbal fluency.^{8,13-16} This study also shows impairment in verbal fluency which correlates with the above-mentioned studies.

In comparing TRS with language testing score, TRS <16, out of 30 patients, 44% of patients had language score <18. In TRS more than 16, 14 of patients had language score of <18. If there is increased TRS score which statistically increase language impairment. . This was statistically significant.

On comparing with TRS scale with ADAS-cog word recall task, it shows that TRS score >16, 13 patients were scored 3-7. Word recall task impairment was well correlated with Benito-Leo'n *et al.*'s study.⁵

In TRS score <16, only 4 patients scored in between 3 and 7. This implies increased severity of tremor will cause more word recall impairment and was also statistically significant. In FAB test, total score is 18. Average score of studied population is 16, which signify no gross abnormality noted in cognition. In this study, there is no significant impairment in frontal executive function. Passmonti *et al.* detected a significant impairment in frontal deficits in FAB.¹⁷ As the severity of tremor increases (assessed by TRS), the deficits in various cognitive domains such as language, verbal fluency, and word recall task increase, which was also statistically significant (Table 7).

Table 7: Summary of cognitive assessment in essential tremor on comparison with TRS scale

	TRS score <16 n=30 (%)	TRS score >16 n=20 (%)	Total	P value
MMSE				
MMSE<23	8 (50)	8 (50)	16	0.327
MMSE>23	22 (64.7)	12 (35.3)	34	
Verbal fluency - (Addenbrooke's cognitive testing)				
Verbal fluency<8	10 (41.7)	14 (58.3)	24	0.011 (<0.05) significant
Verbal fluency>8	20 (76.9)	6 (23.1)	26	
Language score (Addenbrooke's cognitive scoring)				
Language score<18	11 (44)	14 (56)	25	0.021 (<0.05) significant
Language score>18	19 (76)	6 (24)	25	
Word recall (ADAS-cog)				
Word recall<3	26 (78.8)	7 (21.2)	33	0.000 (<0.05) significant
Word recall 3-7	4 (23.5)	13 (76.5)	17	

ADAS: Alzheimer's disease assessment scale, TRS: Tremor rating scale, MMSE: Mini-mental state examination

CONCLUSION

This study shows that there is male preponderance in the prevalence of ET. There was a significant impairment in cognition in various domains such as memory, language, verbal fluency, global cognitive function - MMSE, and mood disturbances. This study did not show impairment in sustained attention, visuospatial abilities, and calculation in ET patients. As severity of tremor (assessed by TRS) increases, the cognitive dysfunction also increases. This study highlights that the ET is no more benign.

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