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Neuropsychological Profile, Quality of Life and Associated Psychiatric Symptoms in Patients with Essential Tremor

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Abstract

Essential tremor (ET), a common a movement disorder, associated with cognitive dysfunction.

Objective: To assess the cognitive function in non-western cohort of patients with ET and correlate with concomitant anxiety, depression and quality of life.

Method: The sample consisted of 30 patients with ET and 30 matched healthy controls. The tools used were socio - demographic data sheet, Edinburgh Handedness inventory, Hospital anxiety and depression rating scales, World Health Organization Quality of life - BREF (QOL) and the NIMHANS Neuropsychological Battery.

Results: The results shows patients with ET performed significantly worse than controls on tests of motor speed, sustained attention, executive functions, learning and memory. In addition, patients with ET had higher measures of anxiety and depression as well as lower measures of QOL.

Conclusion: The current study results support the finding that cognitive deficits along with emotional disturbances and impaired QOL are clinical features of ET.

Keywords: Essential Tremors (ET); Neuropsychological profile; Cognitive deficits; Depression; Anxiety; Quality of life

Introduction

Essential tremor (ET) is a common movement disorder, which most often presents, with involuntary tremor involving both upper limbs. Despite researchers have recognized ET for a long time; we are still in the process of developing a consensus regarding the pathophysiology and the clinical spectrum of this disease. Studies found that ET occurs due to dysfunction in the Dentate-rubro-olivary pathway [1,2] also known as the 'Guillain Mollaret Triangle'. This dysfunction results in abnormal oscillations within this pathway that act as central neuronal pacemaker for the tremor. A pathological study by Louis et al. [3] found abnormalities within the cerebellum in the form of torpedo formation of Purkinje cells. The relationship between these structural changes and abnormal functioning of the Dentate-rubro-olivary pathway requires further clarification. The evidence obtained from post-mortem studies and neuroimaging studies in ET found structural changes similar to neurodegenerative disorders. Hence, the emerging view of ET raises the possibility that ET is a neurodegenerative disease [4].

One of the clinical aspects, cognitive dysfunction in patients with ET, are detected among the western population [5-9]. These studies have recognized frontal dysfunction among patients with ET and the authors have postulated that frontal dysfunction results due to abnormal functioning of the Cerebello- thalamic-cortical pathways [5,6].

Considering the prevalence of non-motor symptoms in ET patients [10] studies highlight the potential value of conducting neurocognitive assessments. Finding the neuropsychological correlates of ET will have a tremendous impact on understanding of the human motor system and will facilitate treatments. The above literature reviews show the presence of segmental approach to neuropsychological evaluation of patients with essential tremors. There is a paucity of research in non-western population. Assessing the Quality of life will helps in identifying concomitant disabilities of these patients. Further, many aspects of these disorders are not noticed in clinical evaluations. This highlights the need for a comprehensive assessment of the neuropsychological functions, depression, anxiety and Quality of life in patients with ET.

The purpose of the present study was (1) to establish the presence of cognitive dysfunction in non-western cohort of patients with ET and (2) to examine neuropsychological deficits, QOL as well as affect or mood state in patients with ET.

Subjects and Methods

The study was conducted using a cross-sectional, case-control study design at the National Institute of Mental Health & Neurosciences (NIMHANS), Bangalore, India between September 2008 and February 2010. Thirty patients with ET (six female, twenty-four male) and thirty healthy controls matched for age, gender, education and socioeconomic status gave their written informed consent to participate in the study that was approved by the Institute's Ethics Committee. For each ET patient an age, education, gender matched healthy peer controls from neighborhood likely to have similar socioeconomic characteristics were recruited by purposive sampling method. We conducted a 1:1 matching for patients to controls. Neurologist from the department of

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Neurology working predominantly with movement disorders made the diagnosis of cases. This was based on the 'National Institute of Health Collaborative Genetic Criteria'. The inclusion criteria of both groups were age ranging from 16 to 65 years; right handed [11], normal or corrected vision and hearing (examined by the neurologist). Patients, as well as controls, were excluded from the study if they had neurological abnormalities other than ET based on neurology evaluation, presence of major psychiatric illness and mental retardation based on screening with International Classification of Disorders (ICD 10), diagnostic criteria F 20 – F 29 and F 70- F 79. The neuropsychologist carried out detailed clinical interviews with all participants and family members of the participants before initiating the neuropsychological assessment.

Assessment

The tools used for the assessment are as follows:

Edinburgh Handedness inventory [11] is an instrument to determine the handedness of an individual. This consists of ten items assessing the hand preference on various tasks. A laterality quotient, which is a measure of handedness, based on the responses constitutes the score. A laterality quotient ≥ +40 indicates right-handedness.

Hospital anxiety and depression rating scale (HADS), a validated instrument for assessing anxiety and depression in the outpatient setting [12]. It consists of questions which assess both anxiety (HADS-A) and depression (HADS-D). A score of ≥8 on either HADS-A or HADS-D indicates the presence of anxiety and/or depression.

World Health Organization Quality of life-BREF (WHO QOL-BREF) is an instrument, which was applicable cross-culturally [13]. The questionnaire assesses 4 domains of QOL which include physical health, psychological, social relationships and environmental. A single composite score (WHO) of QOL, were calculated using an average of the individual domain scores [14].

NIMHANS Neuropsychological battery

The battery consists of 21 sub tests assessing different domains of neuropsychological functioning originally developed by different authors. Rao et al. standardized these tests in the Indian population on an age range of 16-65, on samples of both males and females and education ranging from illiteracy to college education. The factor analysis was carried out on different neuropsychological domains (with a ratio of variables to the number of subjects at 1:5) and established the factorial validity of the tests for literate subjects. The data of literate and illiterate groups were subjected to principal component analysis. The profiles of patients with different clinical etiologies (e.g. patients with focal lesions, head injury, epilepsy and movement disorder) were compared and established the validity of the tests using measures of criterion validity.

The different areas of functions in the test battery selected for the present study are (Table 1).

Domain	Function	Test
Speed	Motor Speed	Finger Tapping Test
Attention	Focused Attention	Colour Trials
	Sustained Attention	Digit Vigilance Test
Executive Functions	Verbal Fluency	Controlled Oral Word Association Test
	Category Fluency	Animal Names Test
	Working memory	Verbal N Back Test
		Visual N Back Test
	Planning	Tower of London Test
	Set Shifting & Concept Formation	Wisconsin Card Sorting Test
	Response Inhibition	Stroop Test
Learning and Memory	Verbal	Auditory Verbal Learning Test

Table 1: Neuropsychological Tests measuring different domains of cognitive functions.

Speed

Motor speed- Finger tapping test [15]: The speed of the index finger of each hand tap is measured using an electronic counter.

Mental speed: Digit symbol substitution test [16]: Numbers one to nine, (in figures) arranged randomly in rows on a page. The subject substituted each number with a symbol using a number–symbol key. The time taken to complete the test is the score.

Attention

Digit vigilance test [17] - Numbers one to nine (in figures) arranged randomly in rows on a page. The subject had to identify target digits 6 and 9 amongst other distracter digits. The time taken and the number of errors were the scores.

Color trial test [18]- (I) Color trial 1: Numbers 1 to 25 arranged randomly on a page with odd numbers in pink circles and even numbers in yellow ones. The subject was asked to point to successive numbers in ascending order. (II) Color trial 2: Numbers 1 to 25 were printed twice, once on pink circles and also on yellow circles and arranged randomly on a page. The subject has to point to numbers in alternating colors with successive numbers being in an ascending order. The time taken to complete each of the color trials was the score.

Executive functions

Fluency test: (I) Category fluency test [19] - The subject was asked to generate the names of as many animals (excluding names of fish, birds and snakes) as possible in one minute. The total number of new animal names generated formed the score. (II) Phonemic fluency test [20] - The subject was asked to generate words (excluding proper nouns and names, avoiding repetition of the same word with a suffix) beginning with the letter F, followed by A and S each for one minute. Subject who did not know English were asked to generate words in their own mother tongue commencing with consonants 'Ka', 'Pa', 'Ma'. The average new words generated over three trials formed the score.

Working Memory: (I) Verbal working memory N Back test [21] - The N- Back task asses verbal working memory. The Verbal N- Back requires verbal storage and rehearsal while the two back versions requires in addition to the above, manipulation of information. The 1 Back version would involve the articulatory loop in the verbal modality and visuo-spatial sketchpad in the visual modality. The two back involve the central the central executive in both the modalities.

Thirty randomly ordered consonants common to multiple Indian languages were recited aloud by the examiner at the rate of one per second. Nine of the thirty consonants were randomly chosen to repeat. In the 1 Back test, the patient is asked to respond by tapping the table whenever a consonant was repeated consequently. In the 2 Back tests, the patient was asked to respond similarly whenever a consonant was repeated after an intervening consonant. (II) Visual working memory N Back Test [21]: Utilizes 36 cards each of which have one black dot placed randomly on an imaginary circle. Each card presented

individually to the subject. The subject is told to tap the table whenever the location of the dot repeated itself.

Hits and errors are the scores. Hits were the number of times the subject tapped correctly, and errors were the number of times the subject failed to tap or tapped incorrectly.

Planning: Tower of London test [22] -The test consists of two identical wooden boards with three beads each painted red, green and blue. Each board's fitted with three round pegs of different sizes. The subject was presented with a goal state of arrangement of the three beads on one of the boards, which had to be arrived at on the other board, based on set rules. A total of fourteen such problems were provided. Scoring is based on the average time taken to complete a problem, the average number of moves taken for problems with 2, 3, 4 and 5 moves and the total number of problems solved with the minimum number of moves.

Set shifting and concept formation: Wisconsin Card Sorting Test [23] – Utilizes a pack of 128 cards, each card has a color, shape and number. After placing four stimulus cards in front of the subject, they were asked to match each successive card from the pack to one of the four stimulus cards. The subject was only told whether each response was right or wrong, and was not told the sorting principle. The subject had to guess the concept based on the examiners feedback and have to continue with the test. After the patient placed 10 consecutive cards correctly, the examiner changes the principal without the patient's knowledge. The patient's capacity to perceive a change in the concept when the next sorting principle was introduced is a measure of set shifting ability. The test was terminated after the patient attains all 6 concepts or after all the 128 cards have been used. The first principle of matching was color, followed by form, and finally number. Then the same sequence was repeated again. The test scores are based on the total number of trials to attain 6 categories, perseverative responses, perseverative errors, conceptual level responses and failure to maintain set.

Response inhibition: Stroop test [24] - In this test the color names blue, green, red and yellow are printed in capital letters on a paper. The color of the print did not always correspond with the color designated by the word. The time taken for reading the color names (reading time) subtracted from the time taken for naming the color of printed words (naming time) is the Stroop effect score.

Verbal Learning and memory

Learning and memory: Reys Auditory Verbal Learning and Memory test [25]: Uses two different lists (A and B) consisting of 15 words each designating familiar objects. Words in List 'A' are presented at the rate of one word per second during 5 successive trials. Each trial followed by the recall of the same. After the completion of all the five trials of List A, words in List B are presented once and an immediate recall is taken for the same. This is followed by the immediate recall of words from List A. After a delay of 20 minutes, words from List 'A' are again recalled forming the delayed recall score.

Statistical methods

The data were analyzed using the Statistical Package for Social Sciences (SPSS; Version 15.0). Descriptive statistics such as mean and standard deviation were used for continuous variables. Frequency and percentages were used for categorical variables. Shapiro Wilk test were used to assess normality. Non-parametric Wilcoxon Signed Rank test based on positive and negative ranks were used for comparison of continuous variables. Categorical variables were compared using chi-square test. In view of the large number of tests of association, a domain-wise Bonferroni correction was employed with four domains of neuropsychological functions assessed (Speed, Attention, Executive Functions and Memory). P value of<0.01 was taken as significant for measures of anxiety, depression and QOL. Individual Cohen's effect size was calculated for each test (95% confidence intervals; CIs). An effect size between 0 and 0.3 are considered small; an effect size of above 0.3 to 0.7 is medium and an effect size of 0.8 and above is large.

Results

Demographic and clinical details

Thirty patients and thirty controls matched for age, gender, education and socioeconomic status were assessed. The mean age was 43.9 ± 15.2 Years, most (93.3%) were school and college educated. In patients as well in the controls, approximately 76.7% were from the middle socioeconomic strata (above the poverty level), and 23.3% in the low socioeconomic strata in both groups (Table 2). The mean duration of illness for the patient group was seven years three months. Twenty-six patients had a tremor of both upper limbs and two patients had a tremor of only one upper limb. Two patients had head tremor along with tremor of both upper limbs.

Anxiety and depression

Result shows a significant difference on the scores of anxiety and depression between patients with ET and controls (Table 3)

Quality of life

Result shows a significant difference between ET and controls on all the domains of WHO QOL-BREF (Table 3).

Neuropsychological profile

Compared to controls, ET patients show significant impairments in motor speed (finger tapping test), sustained attention (digit vigilance test); Executive functions such as fluency (category and phonemic fluency), working memory both verbal and visual, planning (Tower of London), set shifting and concept formation (Wisconsin card sorting test) and learning and memory (Rey's Auditory Verbal Learning test). However, there were no significant differences between patients with

Variables	ET patient's Mean ± SD (N=30)	Control Mean ± SD (N=30)	Degrees of Freedom	Exact significance P Value
Age	43.9 ± 15.2	43.9 ± 15.4	1	0.134
Gender	N (%)	N (%)		
Male	24 (80)	24 (80)	1	0.626
Female	6(20)	6(20)		
Education				
Illiterate	2 (6.7)	2 (6.7)	2	1.000
School	16(53.3)	16(53.3)		
College	12 (40)	12 (40)		
Socio-Economic Status				
LSES	7(23.3)	7(23.3)	1	0.619
MSES	23(76.7)	23(76.7)		

Table 2: Demographic details of the sample.

ET and controls in focused attention (color trial test) and response inhibition (Stroop test). The test of mental speed could not be carried out in patients with ET on account of tremor and hence not included in analysis (Table 4).

Results show that all mean ES's (95 % CIs) were positive indicating reliable performance differences between patients with ET and controls. Effect Size (ES) was calculated for all the variables with 95% confidence intervals (CIs). Larger effect sizes were found in anxiety, depression, QOL scores. On neuropsychological functions, a larger effect size was found on tests of motor speed (right and left), focused attention (DVT), working memory(verbal and visual), planning (TOL), set shifting and concept formation(WCST), learning and memory (AVLT) except sub score of long term percent retention (LTPR) of AVLT. Medium effect size was found on sustained attention (color trial), fluency (phonemic) and response inhibition (Stroop) tests. Small effect size was found on category fluency test (ES-0.1). Exceptionally, LTPR of AVLT shown a mean ES of 0.06 (CIs that included zero) indicating no mean difference between groups at $p<0.05$. Overall mean ES shows poorer performance in patients with ET when compared to controls (Table 2 and 3).

Discussion

ET is one of the most common neurological disorders with motor and non motor manifestation of symptoms. Studies show involvement of the prefrontal cortex and frontocerebellar network in patients with ET [5,7,8,26]. In accordance with these studies, we examined the neuropsychological profile, anxiety, depression and QOL in patients with ET using demographically matched healthy controls. The current study findings suggest significant deficits in motor speed, sustained attention, executive functions (fluency, working memory both verbal and visual, planning, set shifting and concept formation) and verbal learning and memory.

The impairment in motor speed may be attributable to motor disability. This is similar to the findings reported in western cohort of patient's with ET [5,7,8]. We also found higher scores of anxiety and depressive symptoms in ET compared to controls, which is consistent, with the findings of several other studies [9,26,27,28]. However, most of these studies highlighted the need for a demographically matched control and considered this as a major limitation of their studies [5,29]. To the author's knowledge current study is the first report of cognitive deficits in patients with ET on non-western population using a matched control design.

In the current study, patients with ET showed a significant difference with control in both left and right finger tapping test with high effect size suggestive of involvement of premotor cortex. Studies using transcranial magnetic stimulation [30] electroencephalography [31] and magneto encephalography [32] in patients with ET have demonstrated involvement of the cortex as part of the network in tremor generation. The present study shows deficits in executive functions, which is similar to the FMRI studies by Cerasea et al. [33] and Bagepally et al. [34]. Cerasea et al. [33] study on functional magnetic resonance imaging during Stroop task found that patient with ET showed increased activation in the dorsolateral prefrontal cortex and the inferior parietal cortex. Bagepally et al. [34] study shows that while performing working memory task patients with ET had increased activation of the posterior lobule of the cerebellum (PLC). Patients with lower scores on neuropsychological test had decreased connectivity with areas involved in focusing attention i.e. executive control circuit (dorsolateral prefrontal cortex, inferior parietal lobule, thalamus) and increased connectivity areas responsible for generating distracting self-related thoughts i.e. default mode network (pre cuneus, ventromedial prefrontal cortex and hippocampus). These studies provide insights into the neurobiological basis for the cognitive dysfunction and suggest that certain areas of the brain are overactive, and there may be altered functioning of neural networks in patients with ET. However, the underlying relationship between these changes and the cerebellar pathology requires further elucidation.

The limitations of the current study include relatively small sample size and so findings of this study alone cannot be generalized to the broader community of patients with ET. The present study was a cross-sectional study, which makes it difficult to make inferences about the factors that predict differences in QOL overtime. Further, we could not assess the tremor severity or its impact on cognitive deficits or QOL, which could provide a more valid index of tremor induced disability in ET. And finally, we couldn't quantify the tremor intensity, which could have possibly helped in verifying the correlation between tremor and the cognitive impairment.

To conclude, the present study results support the finding that cognitive deficits along with emotional disturbances and impaired QOL are clinical features of ET. However, further studies using longitudinal and large sample size with detailed evaluation of tremor severity is needed to identify the pathologic basis for cognitive deficits in patients with ET.

Tests	ET patients Mean ± SD (N=30)	Controls Mean ± SD (N=30)	Degrees of freedom (df)	Z	P Value	Effect Size Cohen's d
HADS-A	9.23 ± 3.81	3.97 ± 1.75	29	-4.450	p<0.001	1.91
HADS-D	8.30 ± 3.36	4.03 ± 1.56	29	-4.280	p<0.001	1.77
QOL Physical	11.93 ± 1.89	16.07 ± 1.25	29	-4.709	p<0.001	2.71
QOL Psychological	11.93 ± 2.93	16.23 ± 0.82	29	-4.571	p<0.001	2.34
QOL-Social	13.07 ± 3.37	19.17 ± 1.08	29	-4.683	p<0.001	2.83
QOL Environmental	12.83 ± 2.81	18.90 ± 1.06	29	-4.633	p<0.001	3.19
QOL-Total of all domains	49.33 ± 8.57	70.67 ± 3.43	29	-4.707	p<0.001	3.58

Wilcoxon Signed Rank test based on positive and negative ranks
HADS-A: Hospital anxiety and depression rating scale-Anxiety; HADS-D: Hospital anxiety and depression rating scale-Depression; QOL- Quality of life
P value of<0.01 was taken as significant

Table 3: Anxiety, depression and quality of life scores among patients with Essential Tremor and controls.

Tests	ET patients Mean ± SD	Controls Mean ± SD	Degrees of freedom (df)	Z	Bonferroni Adjusted P value	Effect Size Cohen's d
Motor Speed – *Finger Tapping Test* (ET Patients, N=30 Vs Control, N=30)						
Right side	38.35 ± 6.23	52.59 ± 7.11	29	-4.434	<0.004***	2.14
Left Side	37.77 ± 6.55	49.54 ± 6.88	29	-4.167	<0.004***	1.76
Test of attention						
Digit Vigilance test (ET Patients, N=28 Vs Control, N=28)						
Time taken (sec)	595.04 ± 179.4	471.07 ± 72.91	27	-2.642	<0.032**	0.98
Errors	7.25 ± 3.76	5.04 ± 1.13	27	-2.747	<0.024**	0.91
Color trials test ((ET Patients, N=28 Vs Control, N=28)						
Trial 1st (sec)	95.8 ± 38.22	88.93 ± 30.06	27	-1.002	1.264	0.21
Trial 2nd (sec)	225.7 ± 105	192.29 ± 80.49	27	-1.264	0.824	0.36
Executive Functions						
Fluency(ET Patients, N=30 Vs Control, N=30)						
Category	13.17 ± 3.31	15.17 ± 18.51	29	-1.215	<0.08*	0.18
Phonemic	7.37 ± 5.28	9.26 ± 2.24	29	-2.407	<0.064*	0.51
Planning-*Tower of London Test* (ET Patients, N=30 Vs Control, N=30)						
Total Number of Moves	9.87 ± 1.33	11.23 ± 1.61	29	-3.021	<0.012**	0.93
Set shifting and concept formation-*WCST*(ET Patients, N=30 Vs Control, N=30)						
% Perseverative responses	35.16 ± 14.93	20.37 ± 10.79	29	-3.644	<0.004***	1.15
% Conceptual responses	33.67 ± 16.4	48.94 ± 16.81	29	-3.045	<0.008***	0.91
Number of categories completed	3.20 ± 1.81	4.53 ± 1.33	29	-3.284	<0.004***	0.84
Response Inhibition(ET Patients, N=28 Vs Control, N =28)						
Stroop	149 ± 73.72	133 ± 41.51	27	-1.048	1.16	0.27
Working Memory- N Back Test (ET Patients, N=30 Vs Control, N=30)						
Verbal N Back- 1 Back hits	8.53 ± 0.68	8.8 ± 0.5	29	-1.795	<0.292*	0.45
1 Back errors	0.9 ± 1.24	0.2 ± 0.5	29	-2.976	<0.012**	0.81
2 Back hits	6.3 ± 1.57	7.7 ± 0.93	29	-3.304	<0.004***	1.12
2 Back errors	4.67 ± 2.3	1.8 ± 1.2	29	-4.146	<0.004***	1.64
Visual N Back Test (1 Back hits)	6.57 ± 1.507	7.83 ± 0.6	29	-3.378	<0.004***	1.19
1 Back errors	6.6 ± 3.1	2.27 ± 1.14	29	-4.575	<0.004***	2.04
2 Back hits	4.27 ± 1.94	6.33 ± 0.8	29	-3.962	<0.004***	1.51
2 Back errors	7.8 ± 2.4	3.97 ± 1.4	29	-4.353	<0.004***	2.02
Learning and memory – AVLT(ET Patients, N=30 Vs Control, N=30)						
Total trials(1 to5)	38.8 ± 8.79	52.87 ± 8	29	-4.521	<0.004***	1.67
Immediate Recall	8.87 ± 2.2	12.03 ± 2.15	29	-4.043	<0.004***	1.45
Delayed Recall	8.9 ± 2.5	11.73 ± 2.06	29	-4.243	<0.004***	1.24
Long Term Percent Retention	87.48 ± 23	88.44 ± 8.02	29	- .977	1.316	0.06

*P-value<0.05 (0.2 with Bonferroni correction)
**P-value<0.01 (0.04 with Bonferroni correction)
***P-value<0.001 (0.004 with Bonferroni correction)

Table 4: Comparison of Neuropsychological Raw score's between patients with ET and controls.

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