*Available online* www.ijpras.com

International Journal of Pharmaceutical Research & Allied Sciences, 2017, 6(1):227- 235


Research Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

# *Cognitive Functions in Essential Tremor*

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**ABSTRACT**

*Background: Essential tremor (ET) is no longer considered as tremor genic mono symptomatic movement disorder but it has several non-motor manifestations including cognitive dysfunctions. Objectives: to study the cognitive abnormalities in ET patients and their relation to the tremor severity. Methods: This study was performed on 30 ET patients and 15 healthy controls subjected to history taking, neurological examinations with tremor severity assessment using The Essential Tremor Rating Assessment Scale (TETRAS). They were also submitted to the Montreal Cognitive Assessment Scale (MoCA), Stroop Color Word Test, subtest of Wechsler Adult Intelligence Scale IV (WAIS-IV), Wisconsin Card Sorting Test (WCST), brain MRI volumetry and event related potential mismatch negativity (MMN). Results: the neuropsychological tests revealed significant impairment in the global cognitive evaluation, executive functions, attention and working memory of ET patients. Brain MRI volumetry showed significant reduction in cerebellar cortical and white matter volumes, thalamic volume and total white matter volume. Patients also had either absent or diminished amplitude and delayed MMN. Conclusion: Cognitive impairment is a common underdiagnosed ET manifestation affecting patients' socio–occupational career and should be respected in the management plan.*

**Key words:** *Essential tremors, cognition, brain MRI volumetry and mismatch negativity*

## INTRODUCTION

Essential tremor (ET) is the most common adult onset movements' disorders affecting 1% of general population and 4% of those above the age of 40 years [1]. The classic form of ET is characterized by bilateral largely symmetrical 6 – 12 Hz postural and kinetic tremors of the forearms and hands with or without involvement of other body parts in the absence of endogenous or exogenous triggers or other neurological signs [2]. Genetic predisposition seems to play a major role in the pathogenesis of ET and till 2015, more than 10 genes had linked to it. More than 50% of ET patients have positive family history with high concordance among monozygotic twins [3].

Essential tremor is no longer considered as the benign tremor genic mono symptomatic illness but a progressive neurodegenerative disorder with both motor and non-motor manifestations [4]. Patients with ET often experience varieties of cognitive deficits affecting memory, attention and executive functions markedly reducing their activities

of daily living [5]. Other non-tremor manifestations of ET include ataxia, personality changes, depressive symptoms, mild olfactory or hearing dysfunctions, upper airways dysfunction and sleep disorders [6].

## AIM OF THE WORK

To study the cognitive abnormalities in ET patients and their relation to the tremor severity.

## SUBJECTS AND METHODS

The study was conducted on 30 ET patients attending the movement disorder clinic, neuropsychiatry department, Tanta university hospitals in the period from 1st October 2016 to the end of March 2017. Fifteen healthy control subjects matching the patient's age, sex and educational level were also included.

Essential tremor was diagnosed according to the Movement Disorder Society on Tremor [7]. The study protocol was approved by the local ethics committee, participation was voluntary and informed consents were obtained from all participants before engagement in the study.

Exclusion criteria included ET patients had comorbid neurological or psychiatric disorders, endocrinal disorders, renal or hepatic diseases. Patients with hearing problems, middle ear dysfunction or MRI contraindications were also excluded.

All patients were subjected to history taking and neurological examination stressing on family history of ET, disease duration and response to propranolol with tremor severity assessment using The Essential Tremor Rating Assessment Scale (TETRAS) [8].

Patients and control were submitted to a battery of standardized neuropsychological tests covering different cognitive domains included the Montreal Cognitive Assessment Scale(MoCA) Arabic Version, subtest of Wechsler Adult Intelligence Scale IV(WAIS-IV), [9] Stroop Color Word Test [10] and Wisconsin Card Sorting Test [11] (WCST) (Computerized version) derived from the Psychology Experiment Building Language (PEBL).

Cortical reconstruction and automatic volumetric segmentation was performed according to Reuter and colleagues [12] with the Free surfer image analysis suite, used both intensity and continuity information from the entire 3-dimensional MR volumes in segmentation and deformation procedures to produce representations of cortical thickness.

Subjects were also submitted to basic audio logical evaluations and Mismatch Negativity (MMN) test in the oddball paradigm using tone and speech stimuli presented at 1/s repetition rate, 15% deviant probability and 50dB sound level. The standard / deviant stimuli were 1000 / 1050 Hz for tone and da / ga for speech MMN respectively (re pure tone audiometry "PTA" average at 500, 1000, 2000 and 4000 Hz) monaurally to each ear via an insert phone. MMN was calculated in the difference waveform according to manual specification of Smart-HIS.

Statistical analysis was conducted by SPSS prism using the mean ± standard deviation and student t- test. Correlation analysis was performed using Pearson’s correlation test. P value $< 0.05$ considered statistically significant.

## RESULTS

The study included 30ET patients aged 48.7±7.4 years, 13females (43.3%), 17males (56.7%) and 17 (56.7%) had positive family history of ET. All patients had bilateral nearly symmetrical hands tremors, 6 (20%) had head tremors, 3 (10%) had voice tremors and 4 (13.3%) had lower limbs tremors. Patients' tremor durations were 15.9±7.3 years and severities were 40.5±12.1 as measured by TETRAS. Eighteen (60%) of patients had good sustained propranolol response with improvement of TETRAS more than 50% and 12 (40%) had weak response mainly those with head, voice and lower limb tremors.

Neuro-psychological cognitive assessment showed mild but significant decrease of MoCA scale in ET patients than control (25.2±2.2and 27.9±1.1respectively with p<0.0001). MoCA was lower among non-propranolol responders, negatively correlated with tremor severity and duration but not correlated with patients' age (table 1, figure 1).

Stroop test showed significant prolongation in the sum time of the 3 tasks (dots, words and colors) in ET patients than control (210±99.4versus134.5±28.7 respectively with p=0.0064).

The WCST showed significant increases in each of preservative response, preservative errors, non-preservative errors and trials to complete the 1stcategory in ET patients than control (36.4±9.8, 15.7±7.3, 18.3±4.5, and 14.9±2.8 versus20.1±6.8, 9.1±2.7, 9.4±2.6 and 12.5±1.6 with p-values <0.0001, 0.0016, <0.0001 and 0.0035 respectively). At the same time, there were significant decreases in the conceptual level response and number of categories completed in ET patients than control (34.1±9.1 and2.3±0.5 versus 44.3±2.6 and 4.2±0.7 respectively with p<0.0001for both) (table 1).

Regarding WAIS, there were significant decreases in digit span forwards, digit span backward and arithmetic tests in ET patients than control (4.6±1.1, 3.8±0.6 and 8.4±2.3 versus 6.8±1.2, 5.3±1 and 10.9±2.1 with p-values <0.0001, <0.0001 and 0.0008 respectively). Language vocabulary component of the test showed non-significant difference with p=0.831 (table 1).

Table 1. Neuropsychological assessment in essential tremor and control subjects

| | Patients | Control | T-test | |
|---|---|---|---|---|
| | Mean ± SD | Mean ± SD | t-value | p-value |
| Montreal Cognitive Assessment Scale | 25.2 ± 2.2 | 27.9 ± 1.1 | 4.47 | <0.0001* |
| Stroop Color Word Test | 210±99.4 | 134.5±28.7 | 2.48 | 0.0064* |
| Wisconsin Card Sorting Test | | | | |
| Preservative response | 36.4±9.8 | 20.1±6.8 | 5.76 | <0.0001* |
| Preservative errors | 15.7±7.3 | 9.1±2.7 | 3.36 | 0.0016* |
| Non-preservative errors | 18.3±4.5 | 9.4±2.6 | 6.96 | <0.0001* |
| Trials to complete the 1st category | 14.9±2.8 | 12.5±1.6 | 3.089 | 0.0035* |
| Conceptual level response | 34.1±9.1 | 44.3±2.6 | 4.25 | <0.0001* |
| No. of categories completed | 2.3±0.5 | 4.2±0.7 | 9.97 | <0.0001* |
| Wechsler Adult Intelligence Scale IV subtest | | | | |
| Digit span forwards | 4.6±1.1 | 6.8±1.2 | 6.31 | <0.0001* |
| Digit span backward | 3.8±0.6 | 5.3±1 | 5.93 | <0.0001* |
| Arithmetic test | 8.4±2.3 | 10.9±2.1 | 5.59 | <0.0001* |
| Language vocabulary | 23.1±3.8 | 23.4±5.5 | 0.214 | 0.831 |

*: significant.

Brain volumetric MRI study revealed significant reduction in each of cerebellar cortical volume, cerebellar white matter volume, bilateral thalamic volume and total hemispheral white matter volume in ET patients than control (82447±1558, 22949±757.4, 14144±859.7 and 522579 ±17082 mm3 versus 92921±1287, 27152±851.9, 15778 ±595.2 and 510877±10921 mm3 with p-value < 0.0001 for the first 3 variables and 0.028 for the last one. The total cortical volume, the caudate volume, the putamen volume, the amygdala and hippocampal volumes showed non-significant differences between both groups. There was non-significant difference in the mean cortical thickness between both groups and there was no specific focal cortical thinning in any cerebral area (table 2, figure 2).

Thalamic, cerebellar cortical and white matter volumes were negatively correlated with the tremor severity (table 3, figure 1).

The study showed that, tone evoked MMN (t-MMN) was absent in 9 (30%) and 10 cases (33.3%) of right and left ears respectively. The rest of patients showed significant prolongation of the t-MMN latencies than control in both ears. None of the control group showed absent response. The amplitudes of evoked responses were significantly diminished in patients than control in both sides. Speech evoked MMN (s-MMN) was absent in 15 (50%) and 17 (56.7%) ET patients in right and left ears respectively. The rest of ET patients showed bilateral significantly delayed s-MMN latencies with diminished amplitudes than control (table 2). Absent responses and higher MMN abnormalities were present among those with older ages, longer disease duration and higher TETRAS.

Table 2. Brain volumetric MRI and mismatch negativity in essential tremor and control subjects

| | | | Patients | Control | T-test | |
|---|---|---|---|---|---|---|
| | | | Mean±SD | Mean±SD | t-value | p-value |
| Brain volumetric MRI | | | | | | |
| Total cerebral cortical volume | | | 519586 ±25646 | 518250 ±21819 | 0.172 | 0.863 |
| Totalcerebral white matter volume | | | 522579±17082 | 510877±10921 | 2.26 | 0.028* |
| Cerebellar cortical volume | | | 82447±1558 | 92921±1287 | 21.25 | <0.0001* |
| Cerebellar white matter volume | | | 22949±757.4 | 27152±851.9 | 16.83 | <0.0001* |
| Bilateral thalamic volumes | | | 14144±859.7 | 15778 ±595.2 | 6.59 | <0.0001* |
| Bilateral caudate volumes | | | 8074±365.7 | 8062±387.1 | 0.102 | 0.818 |
| Bilateral putamen volumes | | | 13007±288 | 13016±244.2 | 0.107 | 0.914 |
| Amygdala and hippocampal volumes | | | 12223±411.3 | 12043±280.6 | 1.521 | 0.135 |
| Mean cortical thickness | | | 2.4 ± 0.8 | 2.5 ± 0.7 | 0.411 | 0.682 |
| Mismatch negativity | | | | | | |
| Tone- MMN | Latency | Right | 253.7±51.98 | 186±23.82 | 4.67 | <0.0001* |
| | | Left | 353.8±51.86 | 186±25.69 | 4.65 | <0.0001* |
| | Amplitude | Right | 1.07±0.24 | 1.63±0.53 | 4.202 | 0.0002* |
| | | Left | 1.03±0.27 | 1.67±0.47 | 5.08 | <0.0001* |
| Speech-MMN | Latency | Right | 294.5±32.39 | 181.3±15.6 | 12.2 | <0.0001* |
| | | Left | 269±30.98 | 180.3±13.98 | 13.04 | <0.0001* |
| | Amplitude | Right | 0.91±0.21 | 1.5±0.4 | 4.99 | <0.0001* |
| | | Left | 0.94±0.2 | 1.5±0.42 | 4.505 | <0.0001* |

*: significant, MMN: mismatch negativity.

Table 3. Correlation of tremor severity with the cognitive scales and MRI volumetry

| Variables | Essential Tremor Scale |
|---|---|

| | r | p |
|---|---|---|
| MoCA | -0.89 | <0.0001* |
| Stroop | 0.801 | <0.0001* |
| Wisconsin Card Sorting Test | | |
| Preservative errors | 0.828 | <0.0001* |
| Non-preservative errors | 0.735 | <0.0001* |
| Trials to complete the 1st category | 0.661 | <0.0001* |
| Conceptual level response | -0.826 | <0.0001* |
| Wechsler Adult Intelligence Scale IV subtest | | |
| Digit Span Forwards | -0.658 | <0.0001* |
| Digit Span Backward | -0.506 | 0.0043* |
| Arithmetic | -0.549 | 0.0017* |
| Brain volumetric MRI | | |
| Total white matter volume | -0.277 | 0.137 |
| Total Cerebellar cortical volume | -0.912 | <0.0001* |
| Total Cerebellar white matter volume | -0.923 | <0.0001* |
| Bilateral Thalamic volumes | -0.933 | <0.0001* |

*: significant.

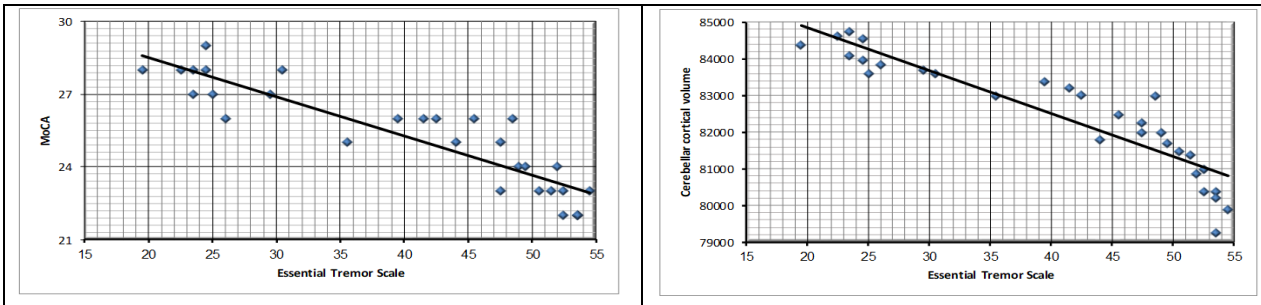


Figure 1. Negative correlation between essential tremor severity and each of the Montreal Cognitive Assessment Scale (left) and the total cerebellar cortical volume (right).

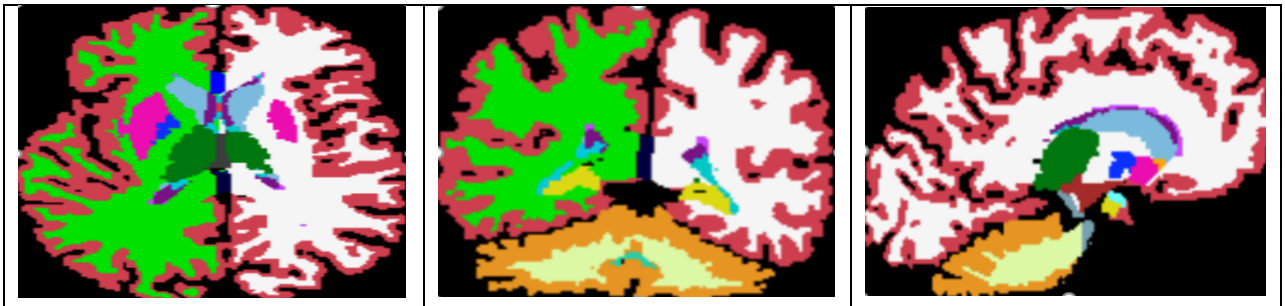

Figure 2.Brain volumetric MRI study in an essential tremor patient with diminished cerebellar cortical, cerebellar white matter, thalamic and total cerebral white matter volumes

## DISCUSSION

Essential tremor is a pathologically heterogenous progressive neurodegenerative disorder with both motor and non-motor manifestations [13]. Cognitive decline is a common under diagnosed ET manifestation and due to its slow progression, most ET patients are unaware of its existence resulting in progressive decline in their activity of daily living [14].

The study showed mild but significant decrease in the global cognitive functions in ET patients as measured by MoCA scale. This cognitive decline was higher in patients with longer tremor durations, non-propranolol responder and higher tremor severity but was not correlated with the patients' age. These results are passing with the work of Kim and colleagues [15]and Louis and colleagues [16] who found a great cognitive decline in ET patients and considered this as a risk for dementia. On the other hand, Medeiros and colleagues [17] found non-significant diminution of the global cognitive functions in ET patients possibly due to wide patients' age range, shorter tremor duration and selection of control from patients' 1st degree relatives. Janicki and colleagues [18] found significant correlation between cognitive decline and patients' age probably due to inclusion of late onset ET patients. Chung and colleagues [19] agreed with that cognitive decline is more common among non-propranolol responders.

The study showed that, the executive functions were at the heart of cognitive decline in ET patients. These functions were assessed mainly by the WCST which measures the cognitive flexibility, problem solving, abstraction, set shifting, use of feedback and the ability to modify incorrect strategies. The interference control component of inhibition as measured by the Stroop test was significantly affected in ET patients which is in accordance with the work of Mohan and colleague [20]. At the same time, Hunjhunwala and colleague [21] agreed with these results and concluded that, ET patients suffer from impairment in several domains of cognition mainly the executive functions.

The WAIS showed significant impairment in attention and working memory of ET patients as measured by arithmetic test, digit span forwards and backwards but language vocabulary was nearly normal. These results are in accordance with the work of Janicki and colleagues [18] who found significant reduction in attention of ET patients. On the other hand, Medeiros and colleagues [17] found non-significant difference between ET patients and control regarding digit span forwards and backwards which may be explained by the different selection pattern in the control group as mentioned before. At the same time, Lombardi and colleague [22] found significant verbal fluency deficits in ET patients possibly due to small sample size, different patients' age and use of other assessment scale.

Brain MRI volumetric study showed symmetrical reduction in total white matter, thalamic, cerebellar cortical and white matter volumes in ET patients with the cerebellum was the most affected. Each of cortical, caudate, putamen, amygdala and hippocampal volumes as well as cortical thickness were not affected. The degree of cognitive decline was proportional with the severity of thalamic, cerebellar cortex and white matter volumes reduction. Moore and colleague [22] and Bhalsing and colleagues [23] agreed with the cerebellar volume reduction but in the contrary, they found significant reduction in the medial frontal gyrus, insular and cingulate cortical volumes in ET patients. The latter difference may be due to their subgrouping of the patients to ET with and without cognitive impairment

and cortical changes were obvious in the 1st subgroup. Kim and colleagues [15], Louis and colleagues [24] and Koçer and colleagues [25] agreed with that cognitive decline in ET is mainly subcortical due to abnormal cerebello–thalamo–cortical connections rather than actual cortical loss and this cognitive decline is proportional with cerebellar volume reduction.

The present study showed a high incidence of absent tone and/or speech MMN in ET patients with more s-MMN absence. Patients with evoked responses showed prolonged latencies and reduced amplitudes than control without significant side to side difference. Pauletti and colleagues [26] studied t-MMN only in ET patients and they agreed with the present study results in that ET patients had delayed lowered amplitudes t-MMN evoked potential but they had little number of absent MMN evoked responses in their work probably due to their use of other protocol with higher standard / deviant difference paradigm (1000 / 1100 Hz at a sound level of 80 dB).The previous results reflected impaired cognitive functions evaluated by MMN including the working memory and automatic pre-attentive discrimination of acoustic changes which reflects attentional switch. The study also showed that MMN abnormalities were not significantly correlated with the tremor duration and/or severity which pointed to the heterogeneity of ET with different manifestations among patients.

Restuccia and colleagues [27] reported that, pre-attentive detection of somatosensory input is mediated by cerebellar processing of the incoming somato-sensory input and this cognitive function is impaired in patients with abnormal cerebello-cortical connections. So, the results of both MMN and brain MRI volumetry are in accordance with that cognitive dysfunction in ET patients is mainly subcortical and related to impaired cerebello-cortical connections and reduced cerebral white matter volume.

## DISCLOSURE OF INTEREST

No conflict of interest was reported.

## LIMITATIONS

The relatively small sample size in relation to the heterogeneous ET disease which need further subgrouping and exclusion of ET patients with psychiatric problems which may be an ET manifestation affecting cognition.

## ACKNOWLEDGEMENT

We would like to thank Dr. Michael S. Baghdadi and Dr. Mina F. Rizk Allah for their help in MRI brain volumetry interpretation.

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