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Essential tremor: what is beyond the oscillatory monosymptomatic illness?

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Abstract

Background: Essential tremor (ET) is now considered as a slowly progressive neurodegenerative disorder with a variety of motor and non-motor manifestations. The objectives of this work were to study the existence of cognitive, mood, olfactory, and balance dysfunctions in ET patients and their relation to tremor severity as well as patients' activity of daily livings.

Methods: This study was performed on 36 ET patients and 24 healthy controls subjects (HCS) submitted to The Essential Tremor Rating Assessment Scale (TETRAS), advanced activity of daily living scale (AADLs), Montreal cognitive assessment scale (MoCA), Montgomery–Åsberg Depression Rating Scale (MADRS), auditory mismatch negativity (MMN), Sniffin' Sticks test (SST), computerized dynamic posturography (CDP), and brain MRI diffusion tensor tractography (DTT).

Results: ET patients showed significant decrease in AADLs, MoCA, SST (threshold, identification, and discrimination subscales) as well as visual and vestibular ratios of CDP compared to HCS. Auditory MMN showed significant reduction in the amplitude and prolongation of latencies while corticospinal tracts, thalamo-cortical connectivity, and middle cerebellar peduncles DTT revealed reduced fractional anisotropy in ET patients with normal tracts densities.

Conclusion: ET patients exhibit a wide variety of non-motor manifestations including cognitive impairment, depressive symptoms, hyposmia, and increased risk of falls with consecutive reduced activity of daily living beyond the deleterious effects of the kinetic tremor.

Keywords: Essential tremors, Sniffin' sticks test, Posturography, Mismatch negativity, DTI

Introduction

Essential tremor (ET) is the most common adult onset movements' disorders affecting 1% of the general population and > 5% of those above the age of 65 years [1]. The traditional descriptions of ET as a benign monosymptomatic illness with postural and/or kinetic tremors had been given way while the disorder is now considered as a slowly progressive neurodegenerative movement disorder which is highly heterogenous in its hereditability, affected body parts, response to treatment, rate of progression, and possible existence of non-motor manifestations [2].

In 2018, The International Parkinson and Movement Disorder Society (MDS) had introduced the term ET–plus to describe patients with additional neurological signs of uncertain significance that are not enough for the assumption of comorbidity or additional diagnosis. However, the permissible spectrums and severities of these non-motor manifestations are poorly defined in

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objective assessments [3, 4]. These non-tremorgenic manifestations include subtle cerebellar dysfunctions, balance and gait impairments, oculomotor disturbances, cognitive decline, psychiatric abnormalities, hearing and olfactory problems, and upper airways dysfunctions and sleep disturbances [5].

Aim of the work

The aim of the work was to study the cognitive, mood, olfactory, and balance dysfunctions in ET patients and their relation to tremor severity as well as patients' activity of daily livings (ADLs).

Subjects and methods

The study was a cross-sectional case-control study conducted on 36 ET patients and 24 age, sex, and educational level matched healthy control subjects (HCS). Inclusion criteria consisted of consecutive ET patients aged 50–65 years (to avoid the aging effect on the studied parameters) and diagnosed according to The Consensus Statement on the Classification of Tremors of the MDS [6]. Patients were recruited from the movement disorder clinic, Center of Neurology and Psychiatry, Tanta University Hospitals, in the period from 1 October 2017 to the end of December 2019.

Exclusion criteria encompassed ET patients with comorbid endocrinal, renal, or hepatic diseases as well as middle ear dysfunctions or MRI contraindications. The study protocol was approved by the Research Ethics Committee and Quality Assurance Unit, Faculty of Medicine, Tanta University; the participation was voluntary and informed consents were obtained before engagement in the study.

Included patients were subjected to tremor severity assessment using The Essential Tremor Rating Assessment Scale (TETRAS) [7] as well as history taking stressing on family history of ET, disease duration and response to propranolol (ET was considered propranolol responsive if the TETRAS improved by ≥ 50% from the baseline). Included subjects were also submitted to the Montreal Cognitive Assessment Scale (MoCA) Arabic Version, the advanced activities of daily living scale (AADLs) [8], and Montgomery–Åsberg Depression Rating Scale (MADRS) [9].

Studied subjects were also submitted to auditory mismatch negativity (MMN) test which used the oddball paradigm for speech stimuli, da/ga sounds as standard/deviant stimuli, presented at 1/s repetition rate, 15% deviant probability, and 50 dB sound level. MMN was calculated in the difference waveform according to manual specification of Smart Evoke Potential, Home Intelligence Service (HIS), USA (Additional file 1).

Computerized dynamic posturography (CDP) and sensory organization test (SOT) were also performed to examine the somatosensory (SOM), visual (VIS), and vestibular (VEST) balance systems using the Balance Quest provided by Framiral, Cannes, France (Multitest Equilibre 6.1.37.0) with static/dynamic platform by Micromedical Technologies (http://perso.wanadoo.fr/framiral/multi_gb.htm) [10] (Additional file 1).

Olfactory performance was performed using the extended n-Butanol, Burghart Sniffin' Sticks Test (SST), LA-13-00134, Wedel, Germany, regarding Rumeau and colleagues, 2016 [11]. The test consists of three subtests: threshold (TSST), discrimination (DSST), and identification (ISST). The global TDI olfactory score (sum of threshold, discrimination, and identification) classify smell functions as follows: 31–48 normosmia, 16–30 hyposmia, and ≤ 15 functional anosmia [11] (Additional file 2).

Brain MRI images were acquired using 1.5–Tesla, General Electric Scanner with quadrature 8 channels head coil, GE Healthcare, Milwaukee, WI, USA. Diffusion tensor tractography (DTT) and 3D macroscopic orientation of the corticospinal tract (CST), middle cerebellar peduncle (MCP), and thalamo-cortical connectivity (TCC) were reconstructed through data acquired from diffusion tensor imaging (DTI). It was assessed by single-shot spin echo–planar imaging with TR 8830 ms, TE 80 ms, acquisition matrix 112 × 110 mm, acquisition voxel 2.00/2.03/2.00 mm, field of view: right–left 224 mm, anteroposterior 224 mm and feet–head 120 mm, voxel size: right–left 2 mm, anteroposterior 2 mm, and slice thickness 2 mm, reconstruction voxel size 1.75 mm, gradient direction 32, *b* value 1000 mm/s, and number of slices was 60 with total scan time 9:51 min [12].

Statistical analysis was conducted using SPSS Prism, version 20, 2013 created by IBM, Chicago, IL, USA. Statistical differences were tested using chi-square for categorical variables and Student's *t* test for numerical ones. For bilaterally assessed parameters, all included subjects were represented by the mean measure of both sides. Correlation analysis was performed using Pearson's correlation test. p value < 0.05 was considered statistically significant.

Results

The studied ET patients' age was 62.6 ± 4.6 years, 20 males (55.6%), 16 females (44.4%), and 22 (61.1%) had positive family history of ET. All patients had bilateral nearly symmetrical hands tremor, 6 (16.7%) had head tremor, 5 (13.9%) had voice tremor, and 4 (11.1%) had lower limbs tremor. The mean TETRAS was 37.7 ± 11.1, disease duration was 13.4 ± 4.4 years, 24 (66.7%) were propranolol responsive, and 12 (33.3%) had weak response mainly those with head, voice, and lower limb tremors.

The results of the present study showed highly significant decrease of MoCA scale in ET patients compared to that in HCS with p < 0.001. Regarding the speech

MMN, 10 (27.8%) of ET patients had absent evoked potential compared to none of the HCS. Patients with evoked responses showed highly significant prolongation of the latencies and reduction of the amplitude compared to HCS with p values < 0.001. Absent responses and higher MMN abnormalities were present among those with older ages, longer disease duration, and increased TETRAS (Table 1).

The results showed statistically significant increased depressive symptoms and decreased AADLs of ET patients compared to HCS with p value 0.004 and 0.003, respectively (Table 1). At the same time, analysis of patients' complaints showed that 24 (66.7%), 22 (61.1%), 5 (13.9%), and 2 (5.6%) suffered subjective cognitive decline, depressive symptoms (sense of sadness and hopelessness), balance problems, and smell dysfunctions respectively.

Regarding the results of CDP, there were significant decreases in VIS and VEST ratios of ET patients compared to HCS (p values < 0.001) while SOM ratio showed non-significant difference (p value = 0.149) (Table 1, Fig. 1).

The present study showed significant reduction in each of TSST, ISST, DSST, and TDI in ET patients compared to HCS with p values 0.001, 0.001, 0.004, and 0.001, respectively. Regarding the results of TDI sum score, 9 (25%) ET patients had normal smelling performance and 27 (75%) were hyposmic compared to 17 (70.8%) and 7 (29.2%) for HCS, respectively. None of the included subjects had functional anosmia with TDI ≤ 15 points (Table 1).

Regarding the DTT data, the results revealed highly significant reductions in mean FA for CST, TCC, and MCP of ET patients compared to HCS with p values < 0.001. On the other hand, the studied tract densities showed non-significant differences between ET patients and HCS with p values > 0.05 (Table 1, Fig. 2).

The VIS and VEST, CDP as well as examined tracts FA were lower in patients with positive family history of ET, propranolol response, and/or those with additional head, voice, or lower limb tremors. In contrast, MoCA scale, auditory MMN, and SST had no relations to such variables.

Correlation analysis data revealed that MoCA as well as VEST were negatively correlated with disease duration and TETRAS, but positively correlated with AADLs (Fig. 3). At the same time, MADRS as well as MMN latency showed positive correlation with disease

Table 1 Comparison between essential tremor patients (group I) and healthy control subjects (group II) regarding the non-tremorgenic manifestations

	Group I	Group II	*t* test	
			t value	*p* value
Age	**62.59 ± 4.62**	**62.02 ± 6.70**	**0.392**	**0.696**
MoCA	**25.33 ± 1.76**	**26.75 ± 1.57**	**3.192**	**0.002[a]**
AADLs	**25.50 ± 4.17**	**28.70 ± 3.35**	**9.382**	**0.003[a]**
MADRS	**16.31 ± 8.43**	**10.36 ± 5.11**	**9.135**	**0.004[a]**
Threshold	**7.92 ± 1.18**	**9.58 ± 1.67**	**4.539**	**0.001[a]**
Identification	**10.69 ± 1.24**	**12.17 ± 1.17**	**4.616**	**0.001[a]**
Discrimination	**10.75 ± 1.23**	**11.79 ± 1.44**	**3.001**	**0.004[a]**
TDI total score	**29.50 ± 3.11**	**33.50 ± 3.58**	**4.595**	**0.001[a]**
MMN (amplitude)	**0.93 ± 0.22**	**1.55 ± 0.38**	**7.041**	**< 0.0001[a]**
MMN (latency)	**272.27 ± 42.03**	**181.54 ± 14.19**	**10.052**	**< 0.0001[a]**
SOM ratio	**93.19 ± 15.24**	**97.87 ± 1.22**	**1.463**	**0.149**
VIS ratio	**79.17 ± 2.70**	**89.09 ± 2.45**	**14.266**	**< 0.0001[a]**
VEST ratio	**48.19 ± 4.42**	**67.39 ± 2.98**	**18.312**	**< 0.0001[a]**
CST (mean FA)	**0.59 ± 0.06**	**0.71 ± 0.07**	**7.170**	**< 0.0001[a]**
CST (density)	**370.03 ± 31.23**	**370.03 ± 31.23**	**1.503**	**0.138**
MCP (mean FA)	**0.56 ± 0.05**	**0.71 ± 0.07**	**8.716**	**< 0.0001[a]**
MCP (density)	**604.35 ± 38.88**	**591.22 ± 34.59**	**1.307**	**0.197**
TCT (mean FA)	**0.47 ± 0.06**	**0.69 ± 0.07**	**26.259**	**< 0.0001[a]**
TCC (density)	**680.29 ± 72.93**	**676.57 ± 75.20**	**0.035**	**0.852**

AADLs advanced activities of daily living scale, *CST* corticospinal tract, *FA* fractional anisotropy, *MADRS* Montgomery–Åsberg Depression Rating Scale, *MCP* middle cerebellar peduncle, *MMN* mismatch negativity, *MoCA* Montreal cognitive assessment scale, *SOM* somatosensory, *TCC* thalamo-cortical connectivity, *TDI* threshold, discrimination, identification, *VEST* vestibular, *VIS* visual

[a]Significant

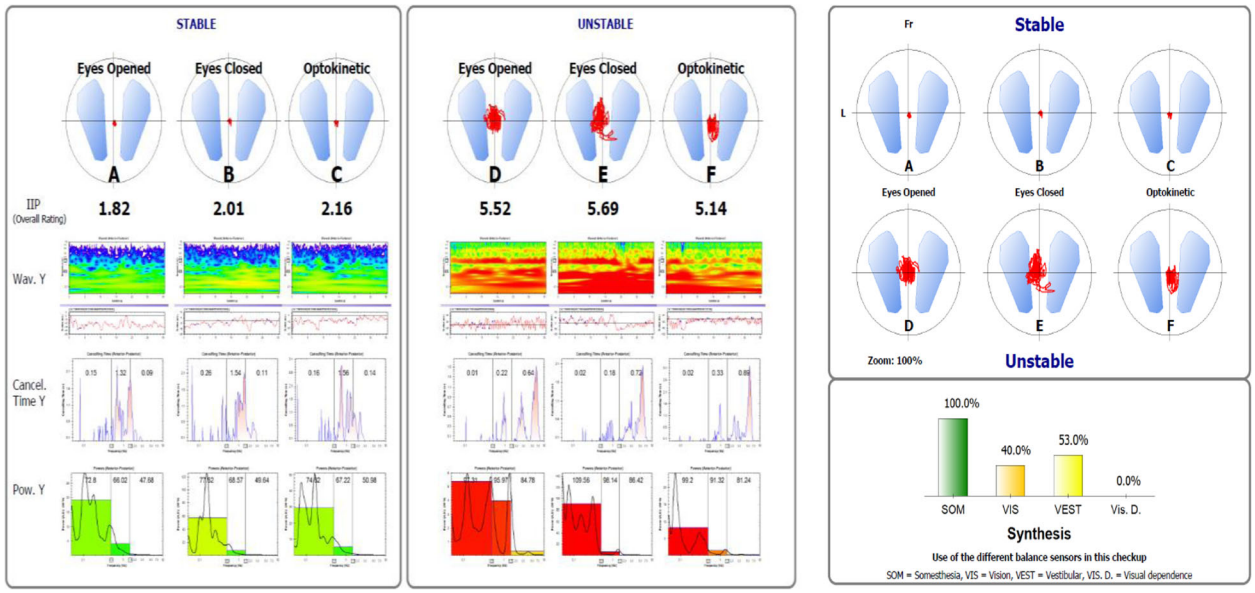
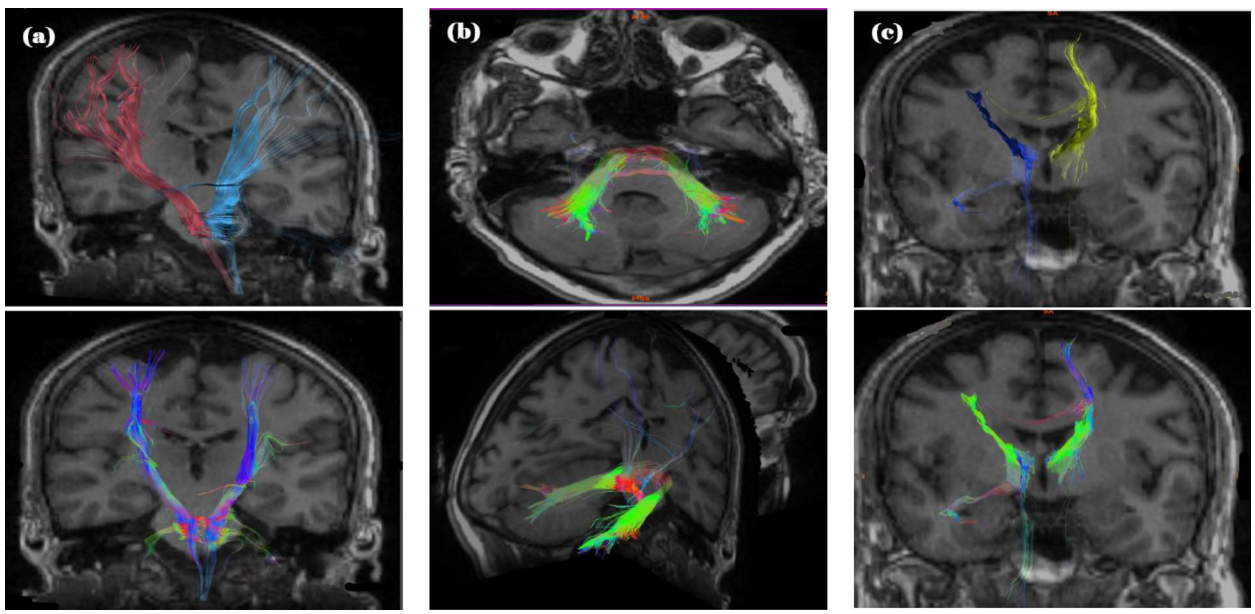


Fig. 1 Computerized dynamic posturography sensory analysis ratios of an essential tremor patient showing impaired visual and vestibular inputs with normal somatosensory balance systems



CST	Right	Left
Minimum FA	0.281	0.243
Maximum FA	0.912	0.934
Mean FA	0.469	0.462
Tract density	402	389

MCP	Right	Left
Minimum FA	0.341	0.264
Maximum FA	0.943	0.894
Mean FA	0.462	0.493
Tract density	534	468

TCC	Right	Left
Minimum FA	0.257	0.224
Maximum FA	0.897	0.824
Mean FA	0.334	0.348
Tract density	892	720

Fig. 2 Diffusion tensor tractography of an included essential tremor patient **a** corticospinal, **b** middle cerebellar peduncle, and **c** thalamo-cortical tractography. FA: fractional anisotropy

duration and TETRAS, but negative correlation with AADLs. On the other hand, TDI showed non-significant correlation with each of disease duration, TETRAS, and AADLs.

The correlation analysis of DTT results showed significant negative correlation between tremor severity (TETRAS) and each of MCP and TCC, FA with p values 0.001 and 0.004, respectively. On the other hand, TCC, FA showed no correlation with each of MADRS, TDI, and MMN (amplitude and latency as well as CDP (VIS and VEST) with p values > 0.05. The only NMM parameter, which was positively correlated with TCC, FA was the MoCA scale (p value 0.008) (Table 2).

Discussion

The present study showed that ET patients exhibit a variety of cognitive, mood, olfactory, and balance impairments exceeding their age- and sex-matched counterparts pointing to the multi-systemic neurological nature of the disorder which affects a wide range of brain areas. This result is passing with the works of Louis, 2019 [13] as well as Soto and Fasano, 2020 [14] who stated that ET is no longer considered as a benign monosymptomatic illness with isolated postural tremor but a slowly progressive neurodegenerative disorder with a variety of motor and non-motor manifestations due to enhanced brain biological aging.

The results revealed that the most common non-motor symptoms of ET patients were subjective cognitive decline and mild depressive symptoms while most patients were not aware of their olfactory or balance problems except after objective assessment. Lack of awareness to the existence of non-tremorgenic dysfunctions is most probably related to their very slow rate of progression as well as cultural believes that these manifestations were attributed to the effect of physiological brain aging. These results are in harmony with the study of Azar and colleagues, 2017 [15] who stated that, despite the great negative impacts of ET non-motor manifestations on the quality of life, many patients are unaware of their existence.

The study showed higher incidence of mild cognitive impairment among ET patients than their age- and sex-matched peers. At the same time, the abnormal auditory MMN-evoked response reflects impaired working memory, attentional switch as well as automatic pre-attentive discrimination of acoustic changes. These results are passing with the work of Meyers and colleagues, 2019 [16] as well as Novellino and colleagues, 2020 [17] who demonstrated greater cognitive decline not only among ET patients but also their 1st degree relatives. They also identified hippocampal microstructural damage correlated with the ET-associated cognitive impairment and make it as a risk for dementia. On the other hand, Medeiros and colleagues, 2016 [18] found non-significant diminution of the global cognitive functions in ET patients compared to healthy control possibly due to the wide age range of their included patients beside recruitment of young ET patients with short disease duration.

The present work revealed that a great proportion of ET patients experienced depressive symptoms with feeling of sadness, helplessness, and hopelessness. These mood disturbances had very mild positive correlation with the tremor severity but greatly impair patients' ADLs. These data are in accordance with the study of Cersonsky and colleagues, 2019 [19] who demonstrated high demoralization feelings and psychological distress in ET patients even in those with mild tremor disability scores.

Regarding olfactory performance, the results showed mild hyposmia in some ET patients greater than expected for age which was not correlated with the disease duration and/or severity. This finding is passing with the work of Giorelli and colleague, 2014 [20] who identified

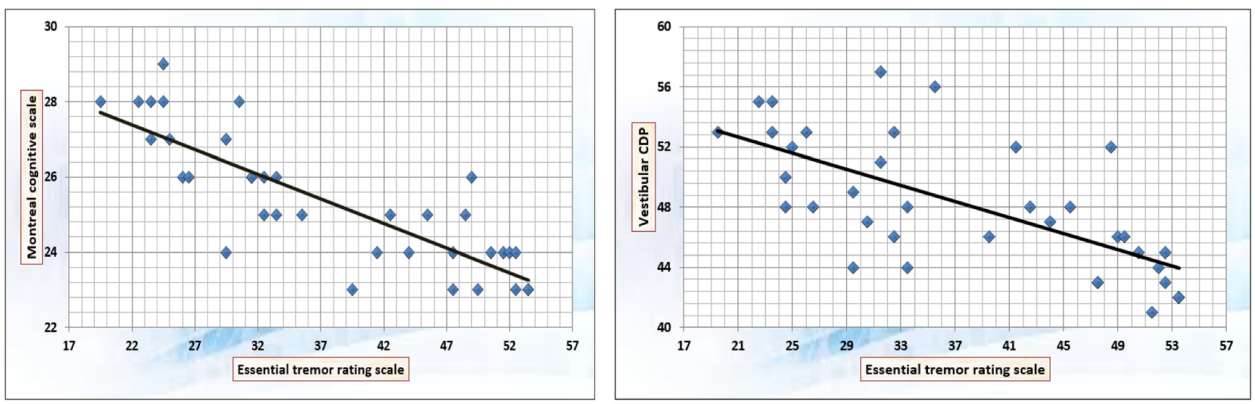


Fig. 3 Negative correlation between the essential tremor rating assessment scale and each of Montreal cognitive assessment scale (left) as well as vestibular computerized dynamic posturography ratio (right)

Table 2 Correlation of Modified Barthel Index score in included lacunar infarction patients 3 months after stroke onset with other studied baseline parameters

	Duration		TETRAS		AADLs		TCC, FA	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
MoCA	− 0.809	0.001[a]	− 0.831	0.001[a]	0.784	0.001[a]	0.446	0.008[a]
MADRS	0.474	0.003[a]	0.354	0.046[a]	− 0.392	0.026[a]	− 0.324	0.062
TDI	0.078	0.649	0.167	0.332	− 0.271	0.121	0.038	0.829
MMN, amp (μV)	− 0.225	0.268	− 0.450	0.021[a]	0.421	0.032[a]	0.442	− 0.298
MMN, latency (ms)	0.486	0.012[a]	0.709	0.001[a]	− 0.657	0.001[a]	0.352	0.058
VIS ratio	− 0.092	0.592	− 0.199	0.244	0.659	0.001[a]	0.111	0.532
VEST ratio	− 0.447	0.006[a]	− 0.641	0.001[a]	0.572	0.001[a]	0.334	0.054

AADLs advanced activities of daily living scale, *FA* fractional anisotropy, *MADRS* Montgomery–Åsberg Depression Rating Scale, *MMN* mismatch negativity, *MoCA* Montreal cognitive assessment scale, *TCC* thalamo-cortical connectivity, *TDI* threshold, discrimination identification Sniffin' Sticks Test sum score, *TETRAS* The Essential Tremor Rating Assessment Scale, *VEST* vestibular computerized dynamic posturography, *VIS* visual computerized dynamic posturography
[a]Significant

mild olfactory dysfunction in their included ET patients higher than control. On the other hand, Wu and colleague, 2016 [21] revealed non-significant difference regarding olfactory performance in ET patients compared to healthy control. This discrepancy is possibly related to their inclusion of older age group subjects, use different methods of olfactory assessment, and the racial difference in smelling performance.

The results of the present work showed impaired static and dynamic balance control in ET patients evidenced by decreased VIS and VEST, CDP ratio. On the other hand, the SOM ratio was not significantly impaired. Moreover, VEST ratio was negatively correlated with the disease duration and severity while VIS ratio had no such association. All these data point to the increased risk of falls in ET patients and the different pathogenic effect induced by ET on the three sensory components of balance. These results are in accordance with that of Prasad and colleagues, 2018 [22] who concluded that CDP reveals significant balance impairment in ET patients which adds to the growing body evidence of cerebellar involvement in ET.

The study revealed reduces FA in each of CST, MCP, and TCC, DTT of ET patients while tracts density was non-significantly affected pointing to the microstructural connectivity changes induced by ET. These changes include increased heterogenicity of axon FA (myelination) with preserved tract density (fiber number) which results in decreased synchrony of impulses transduction. These results are passing with that of Chung and colleagues, 2013 [23] who identified that ET induces heterogeneous cortical thinning and white matter alteration with a resultant alteration in the rate of disease progression as well as clinical response to propranolol.

The results also showed positive correlation between brain network changes (DTT, mean FA) and each of tremor severity (TETRAS) as well as cognitive impairment (MoCA) while such association was absent with other examined parameters including olfactory, mood, and balance dysfunctions. This information suggests that ET-associated kinetic tremor and cognitive decline may share the same neuroanatomical basis. At the same time, neuropeptides and neuro-circuits involved in olfactory, mood, and balance changes are different. The net result hypothesizes that ET is a multisystem, multipeptide, and multi-networks brain disorder with each manifestation; either motor or non-motor has its own route of progression. These data may open a small window in solving the mystery of ET heterogenicity which could improve the treatment results. These data are in harmony with that of Tian and colleagues, 2018 [24] as well as Akram colleagues, 2018 [25] who demonstrated an association between brain microstructural and cognitive impairment in ET. They also stated that good assessment of such matrices changes allows for better selective targeting of disrupted networks during deep brain stimulation as well as MRI-guided focused thalamotomy. On the other hand, Sengul and colleagues, 2019 [26] revealed significant correlation between depression severity and DTT parameters including FA. This discrepancy is possibly due to different patients' demography with enrollment of higher number of female genders, the use of a different depression scale, and DTT measurements in other regions of interest (ROI) including the prefrontal cortex, paralimbic, and limbic structures.

Conclusion

Essential tremor patients exhibit a wide variety of non-tremorgenic manifestations including mood disturbances, cognitive impairment, olfactory dysfunctions, and increased liability to fall which have great negative impacts on the patients' ADLs beyond that is caused by the postural tremor itself.

Recommendations

The managing physician of ET patients should be vigilant enough to avoid under-estimation of the ET non-motor manifestations and their negative impact on the patients ADLs. These non-motor dysfunctions need specific management protocol apart of tremor treatment for better patients' quality of lives.

Limitations

Lack of standardized normative data for CDP is considered abnormal when reduction was more than 1.5 times the standard deviation of HCS. Longitudinal follow-up of patients is further needed to determine the value of such non-motor manifestations as prognostic biomarkers for ET progression which will be the objectives of the 2nd phase of this work.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s41983-020-00200-4.

Additional file 1. Mismatch negativity

Additional file 2. Sniffin' Sticks test

Abbreviations

ADLs: Activity of daily livings; AADLs: Advanced activities of daily living scale; CDP: Computerized dynamic posturography; DTI: Diffusion tensor imaging; DTT: Diffusion tensor tractography; ET: Essential tremor; HCS: Healthy control subjects; MADRS: Montgomery–Åsberg Depression Rating Scale; MDS: Movement Disorder Society; MMN: Mismatch negativity; MoCA: Montreal Cognitive Assessment Scale; SOM: Somatosensory; SST: Sniffin' Sticks Test; TCC: Thalamo-cortical connectivity; TDI: Sum of threshold, discrimination and identification; TETRAS: The Essential Tremor Rating Assessment Scale; VEST: Vestibular; VIS: Visual

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Consent of publication

Not applicable.

Authors' contributions

MEME participated in the study's design, patients' selection, statistical analysis, data analysis, references collection, manuscript writing, and revision and final approval. KHR participated in the study's idea, design, patients' selection, neurological examination, posturography assessment, statistical analysis, data analysis, references collection, manuscript writing, revision, and final approval. WSB participated in the study's idea, design, patients' selection, neurological examination, posturography assessment, statistical analysis, data analysis, references collection, manuscript writing, revision, and final approval. YAE participated in study's idea and design, patients' assessment and inclusion, data analysis, statistical analysis, references collection, manuscript writing, revision, and final approval. EASE participated in the study's idea, design, patients' selection and evaluation, data analysis, references collection, manuscript revision, and final approval. MOT participated in study's idea and design, patients' assessment and inclusion, Sniffin' Sticks test performance, data analysis, references collection, manuscript writing, revision, and final approval. KMR participated in study's design, patients' assessment, DTT performance, manuscript revision, and final approval. MAK participated in study's idea and design, patients' assessment and inclusion, mismatch negativity and posturography interpretation, data analysis, statistical analysis, manuscript writing, revision, and final approval. RAA participated in study's design, patients' evaluation, inclusion and neuropsychological assessment, statistical analysis, revision, and final approval. SAE participated in the study's design, patients' selection, statistical analysis, data analysis, references collection, manuscript writing and revision, and final approval. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

-The manuscript was approved from The Research Ethics Committee and Quality Assurance Unit, Faculty of Medicine, Tanta University.
-The URL: http://tqac.tanta.edu.eg/new-tqac/QualityAssuranceUnit@hotmail.com
-Approval Code: 31129/09/16
-Name of the PI: Wafik Said Bahnasy
-Name of the department: Neuropsychiatry
-Type of the research: Promotion research
-Date of approval: September 2016
-The study's protocol had permitted by The Research Ethics Committee and Quality Assurance Unit, Faculty of Medicine, Tanta University.
-Participations were voluntary, informed consents were approved by all participants' guardian, and any possible risks were clarified.

Competing interests

All authors declare that they have no competing interests.

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