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Correlation of Quantitative EEG and Tumor Necrosis Factor Alpha Induced Protein-8 Like-2 in Cognitive Evaluation of Patients with Parkinson Disease

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Abstract

Background: Cognitive deterioration is common and devastating in patients with Parkinson disease (PD).

Aim of Study: To explore the correlation between quantitative spectral Electroencephalography (EEG) measures and serum levels of Tumor Necrosis Factor Alpha Induced Protein-8 Like-2 (TIPE2) in cognitive assessment of PD patients.

Patients and Methods: This case control study enrolled 80 participants (40 PD patients and 40 matched healthy controls). Patients were subjected to clinical and neuropsychological assessment using unified Parkinson's disease Rating Scale (UPDRS), Modified Hoehn and Yahr staging scale (HY), and Montreal Cognitive Assessment Scale (MOCA). Quantitative EEG (QEEG) assessment of all study participants included spectral relative power and peak frequency of delta, theta, alpha and beta bands over bilateral frontal, temporal and occipital regions TIPE2 serum level was measured in all participants.

Results: PD patients had statistically significant higher TIPE2 serum levels and relative power of all frequency bands especially over the right temporal region. TIPE2 levels correlated with UPDRS and HY clinical severity scales. Frontal and temporal alpha/beta relative powers correlated with total MoCA score and its individual cognitive domains while TIPE2 correlated with visuospatial/executive function. TIPE2 levels correlated with spectral peak frequency of delta, theta and alpha bands over frontal and temporal regions.

Conclusions: Serum TIPE2 levels and quantitative spectral EEG measures have a potential role supporting clinical and neuropsychological assessment of patients with PD.

Key Words: Parkinson's disease – Cognitive decline – QEEG – Spectral analysis – TIPE2.

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Introduction

NON-MOTOR symptoms of Parkinson disease especially cognitive deterioration were frequently reported and common to precede onset of motor presentation **[1,2].**

Biomarkers of Parkinson disease cognitive dysfunction included parameters derived from neuroimaging, genetics, blood, and CSF **[3-6].**

Different quantitative EEG (QEEG) parameters, especially relative power, were proven to be useful as an adjunct to neuropsychologicalassessment in evaluation of PD-related cognitive decline **[7].** EEG has the advantages of being simple, inexpensive, widely available, not affected by the candidate education and intelligence and non-invasively measures brainactivity directly with good temporal resolution **[8,9].**

It has been determined that Tumor Necrosis Factor Alpha Induced Protein-8 Like-2 (TIPE2) regulates both innate and adaptive immunity negatively. It expresses itself in lymphoid and neurological tissues, where it keeps immune hemostasis **[10].** TIPE2 functions by preserving the bactericidal activity of phagocytes and controlling the inflammatory cascade and apoptosis. Hematopoietic cells produce TIPE2, which inhibits T cell receptors and Toll-like receptors through nuclear factor-kappa-B and C signalling processes of Jun N-terminal kinase. This regulates inflammation **[11].**

The aim of this study is to explore the correlation between different parameters of QEEG assessment and TIPE2 in cognitive evaluation of patients with Parkinson disease.

Patients and Methods

Case-control research was carried out in the neurology department at Beni-Suef University hospitals between April 2019 and May 2021. From an ethical standpoint, it was authorised by the Beni-Suef University Research Ethics Committee, Faculty of Medicine (Approval number: FMB-SUREC/05032019).

All participants were informed about it and gave their consent.

There were 80 participants in all: 40 Egyptian patients who met the clinical diagnostic criteria of the UK Parkinson Disease Society Brain Bank for Parkinson's disease (PD) **[12]** and were receiving treatment for the condition, as well as 40 healthy volunteers who were matched for age and sex and lived in the same region as a controlgroup.Individuals with the following illnesses were excluded: serious physical, hearing, or visual impairment.

The following procedures were performed on the patients: A thorough clinical assessment that included a history and a general and neurological examination. The Modified Hoehn and Yahr staging scale **[13]** and the Unified Parkinson's Disease Rating Scale (UPDRS) **[14]** were used for Parkinson's disease assessment and staging. The Arabic version of the Montreal Cognitive Assessment (MoCA) with a cutoff value of less than 26 was used to conduct neuropsychological and cognitive testing. Visuospatial/executive functions, name, memory, attention, language, abstraction, and orientation are the seven cognitive domains that are assessed **[15,16].**

A quantitative electroencephalogram (QEEG) was used to evaluate each participant. The international 10/20 system of electrode placement was followed to insert 19 gold disc electrodes on the scalp using electrode paste in order to record the EEG. The Natus, Neurowork EEG system (Nicolet EEG V32 amplifier) was used to record raw EEG data at a sampling rate of 512 Hz and a frequency band of 1–70 Hz. In order to obtain 2-s epochs with a minimum total duration of one minute of EEG without any obvious artefacts, an EEG segmentation method was carried out using the NeuroGuide software programme (NeuroGuide, Deluxe 3.2.1, Applied Neuro Science).

Kaiser and Sternman's 25% sliding window approach for the Fast Fourier Transform (FFT) was used to perform power spectrum analysis on all of the chosen EEG segments **[17].**

This produces the average power spectral values at each of the 19 recording sites for the various frequency bands. The following frequency bands were used: Delta (1-4 Hz), Theta (4–8 Hz), Alpha (8–13 Hz) and Beta (14–30 Hz).

Six electrodes were used to calculate the relative band power independently: F3, F4, T3, T4, O1, and O2. For F3 and F4. 17 electrodes were used to average the global average relative power (FP1 and FP2 were left out). For every channel, the peak frequency inside each of the four frequency ranges was calculated. Six electrodes (F3, F4, T3, T4, O1, and O2) were used to analyse this independently, and 17 electrodes were used to average the global average peak frequency (FP1 and FP2 were removed).

Tumour necrosis factor-α-induced protein-8 like-2 (TIPE2) serum levels were measured in both the patient and control groups using enzyme-linked immune-sorbent assays (ELISA) with a commercially available ELISA kit (My Biosource, USA) in accordance with manufacturer's instructions and previous research **[18].** After the serum was extracted, the samples were frozen and kept at a temperature below 80°C until they were needed to measure TIPE2. Tumour necrosis factor-α-induced protein-8 like-2 (TIPE2) level in samples is measured using a double-antibody sandwich ELISA kit.

Human TIPE2 antibody has been pre-coated onto the plate. After being introduced, TIPE2 in the sample binds to the antibodies coated on the wells. Next, the addition of the biotinylated human TIPE2 antibody. After being introduced, the biotinylated TIPE2 antibody binds to the streptavidin-HRP. Wash away unbound streptavidin-HRP. When the substrate solution is introduced, the colour changes in direct proportion to the human TIPE2 concentration. The addition of an acidic stop solution ends the process, and the absorbance is measured at 450nm.

Version 25.0 of SPSS (the statistical tool for the social sciences) was used to analyse the data. When applicable, quantitative variables were presented as mean, standard deviation, and 95% confidence interval, or as median and interquartile range (IQR). The independent *t*-test or Mann-Whitney U-test were used to compare the data. The χ^2 test was used to compare qualitative variables that were reported as numbers and percentages. When comparing two continuous variables, Pearson correlation was employed; in other cases, Spearman correlation was utilised. *p*-values less than 0.05 were deemed significant in all tests.

Results

Parkinson's disease patient group comprised 18 males, their mean age was 62.9±8.7 years, and control group comprised 20 males, their mean age was 59.2±8.3 years. The age and sex distribution were matched between patients and controls (p=0.19 and 0.72, respectively). Additional clinical and cognitive traits of the patients are given in (Table 1). Twenty-two (67.5%) of the patients met the MoCA score limit, indicating cognitive impairment.

Regarding quantitative EEG spectral analysis in all frequency bands and studied regions, the PD patients generally exhibited increased relative power; however, this difference was statistically significant primarily over the right temporal region (Table 2).

Conversely, there was no statistically significant variation in peak frequency across all frequency bands and brain areas between the two study groups.

As regards TIPE2, PD patients had statistically significant higher serum levels compared to healthy controls (Table 2).

Table (1): Clinical and cognitive characteristics of PD patients.

	Mean	SD	Median	IQR	95% CI for mean
Disease duration (years)	3.2	2.5	3	2.9	2.3 / 4.1
UPDRS total score	63.4	27.5	67	34.5	53.7 / 73
Hoehn & Yahr score	2.5	1.3	2.5	1.5	2.1 / 3
MoCA total score	20.6	5.8	20	10.8	18.6 / 22.6

UPDRS : Unified Parkinson's Disease Rating Scale.
MoCA : Montreal Cognitive Assessment.
SD : Standard deviation.
IQR : Inter-quartile ratio.
CI : Confidence interval.

Table (2): Comparison between patients and controls of right temporal relative power and TIPE2.

	PD patients		Controls		*p*-value
	Median	IQR	Median	IQR	
Right temporal relative power of Delta	2.9	7.1	0.35	0.53	0.007
Right temporal relative power of Theta	3.8	13.8	0.37	1.34	0.008
Right temporal relative power of Alpha	7.6	22.7	0.6	2.5	0.031
Right temporal relative power of Beta	3.8	8.6	0.43	0.82	0.004
TIPE2	61.9	86.8	28.9	17.4	0.016

PD : Parkinson disease.
TIPE2: Tumour necrosis factor-α-induced protein-8 like-2.
IQR : Inter-quartile range.

Serum levels of TIPE2 correlated with severity of PD assessed by both UPDRS (p=0.012, r=0.425) and Modified Hoehn and Yahr staging scale (p= 0.003, r=0.488).

Regarding correlation with MoCA score of cognitive functioning, TIPE2 levels showed no significant correlation (p=0.279, r=–0.191) while right frontal alpha and beta relative powersshowed significant correlation with MoCA score (p=0.029, r= –0.375 and p=0.004, r=–0.476 respectively).

On the other aspect of individual cognitive functions, TIPE2 levels correlated with Visuospatial/executive (p=0.04, r=–0.347) and attention (p=0.05, r=–0.336) functions. Moreover, frontal and temporal alpha and beta relative powers significantly correlated with individual cognitive domains especially abstract, naming and memory functions. (Fig. 1).

Serum levels of TIPE2 showed no correlation with relative power of all frequency bands and over all scalp regions. On the contrary its levels showed significant correlation with spectral peak frequencies of delta, theta and alpha bands especially over the frontal and temporal regions. (Fig. 2).

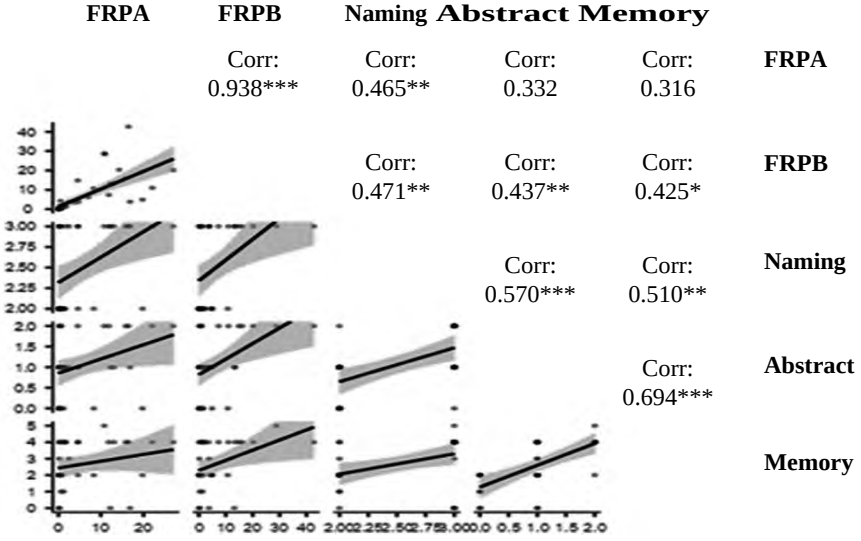

Fig. (1): Correlation of relative power of frontal alpha and beta bands with individual cognitive functions. FRPA, frontal relative power of alpha; FRPB, frontal relative power of beta.

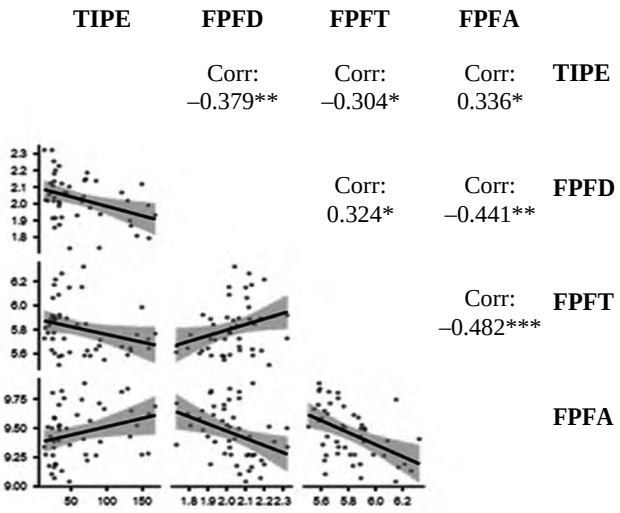

Fig. (2): Correlation of TIPE2 levels with peak frequency of delta, theta and alpha bands in frontal region. TIPE2, Tumour necrosis factor-α-induced protein-8 like-2; FPFD, frontal peak frequency of delta; FPFT, frontal peak frequency of theta; FPFA, frontal peak frequency of alpha.

Discussion

The resent study aimed to explore the values and correlation of quantitative EEG and TIPE2 in cognitive evaluation of PD patients.

PD patients had higher relative power of all spectral EEG frequencies over the right temporal region and higher serum levels of TIPE2 that correlated with disease severity which highlighted their potential role as diagnostic and severity biomarkers.

TIPE2 was found to exert its effects through maintaining immunological homeostasis, promoting angiogenesis, anti-inflammatory actions and reducing oxidative stress, apoptosis, and dopaminergic neuronal death **[18,19].**

Alpha and beta relative power over frontal and temporal regions significantly correlated with total MoCA score and its individual cognitive domains, compared to TIPE2 levels that only showed negative correlation with Visuospatial/executivecognitive function.

Some previous reports linked the cognitive-neurophysiological relationship to numerous pathological alterations of the subcortical–cortical ascending projection networks. The neurotransmitter systems of the dopaminergic, cholinergic, noradrenergic, serotoninergic, glutamatergic, and monoamine systems were also implicated in the pathophysiological causes of Parkinson's disease (PD) cognitive decline and neurophysiological alterations **[20-22].**

Furthermore, functional MRI revealed that PD patients' fronto-striatal brain networks were less active when they performed cognitive tasks **[23].**

The thalamocortical and local cortico-cortical networks produce the alpha rhythm, which is involved in attention and a wide range of cognitive processes. The primary source of beta activity is neocortical activity, which is implicated in both motor and cognitive functions **[24,25].**

In the current study, serum levels of TIPE2 showed statistically significant negative correlation with spectral peak frequency of delta and theta bands over the frontal and temporal regions and positive correlation with spectral peak frequency of alpha band over the same regions. To our knowledge this is a novel finding that may require further studies to explore its potential. However, higher TIPE2 levels and leftward shift of EEG power spectrum in PD patients accords with such finding.

In conclusion, our study showed significant correlation of frontal and temporal alpha/beta relative power with cognitive functioning, and significant correlation between serum TIPE2 levels and frontal/temporal spectral peak frequency. This indicates the potential role of these laboratory and neurophysiological biomarkers in cognitive evaluation of patients with PD.

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الارتباط بين التحليل الكمى لموجات المخ وعامل نخرالورم ألفا المستحث البروتين-8 (TIPE2) فى التقييم المعرفى لمرضى الشلل الرعاش

يعد التدهور المعرفى لمرضى الشلل الرعاش مشكلة صحية شائعة ووخيمة. تهدف الدراسة الحالية لاستكشاف الارتباط بين التحليل الطيفى لموجات رسم المخ الكهربائى ومعدل عامل نخر الورم ألفا المستحث البروتين-8 (TIPE2) فى الدم ودوره فى التقييم المعرفى لمرضى الشلل الرعاش.

شملت هذه الدراسة ٤٠ مريضاً يعانون منمرض الشلل الرعاش و٤٠ متطوعين أصحاء كمجموعة ضابطة.

تم تقييم جميع المشاركين من خلال التحليل الكمى الطيفى لموجات الرسم المخ الكهربائى (نسبة كل من ترددات المجال الطيفى والمعدل الشائع لترددات المخ) وقياس معدل عامل نخر الورم ألفا المستحث البروتين-8 (TIPE2) فى الدم، بالإضافة إلى تقييم المرضى باستخدام المقاييس الإكلينيكية (المقياس الموحد لدرجة مرض الرعاش و مقياس هوين و يهر) والمقاييس العصبية الإدراكية (مقياس مونتريال المعرفى).

استنتجت الدراسة أن مرضىالشلل الرعاش لديهم ارتفاع ذو دلالة إحصائية في معدل عامل نخر الورم ألفا المستحث البروتين-8 (TIPE2) فى الدم ، كذلك ارتفاع نسبة كل ترددات المجال الطيفى لموجات رسم المخ فى منطقة الفص الصدغى الأيمن من الدماغ. وكذلك أوضحت الدراسة أن معدل عامل نخر الورم ألفا المستحث البروتين-8 (TIPE2) فى الدم أظهر ارتباطاً ذى دلالة إحصائية مع المقاييس الإكلينيكية (المقياس الموحد لدرجة مرض الرعاش ومقياس هوين و يهر) والقدرات التنفيذية والبصرية المكانية فى مقياس مونتريال المعرفى. وكذلك ارتباط إحصائى بين القوة النسبية لموجات ألفا وبيتا فى المناطق الأمامية والصدغية من الدماغ مع مختلف الجوانب المعرفية لمقياس مونتريال المعرفى.

كما أوضحت الدراسة وجود ارتباط ذى دلالة إحصائية بين معدل عامل نخر الورم ألفا المستحث البروتين-8 (TIPE2) فى الدم ومعدل التردد الطيفى المخ لموجات دلتا وثيتا و ألفا فى المناطق الأمامية والصدغية من الدماغ.

خلصت الدراسة الحالية إلى أنه يمكن استخدام معدل عامل نخر الورم ألفا المستحث البروتين-8 (TIPE2) فى الدم وكذلك مقاييس التحليل الكمى لموجات المخ كعوامل مساعدة للمقاييس الإكلينيكية والعصبية الإدراكية فى تقييم التدهور المعرفى لمرضى الشلل الرعاش.