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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - ORIGINAL ARTICLE

Vestibular reflexes in essential tremor: abnormalities of ocular and cervical vestibular-evoked myogenic potentials are associated with the cerebellum and brainstem involvement

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Abstract
This study utilized cervical vestibular-evoked myogenic potentials tests (cVEMP) and ocular vestibular-evoked myogenic potentials tests (oVEMP) to investigate the vestibulocollic and vestibuloocular reflex arcs and to evaluate cerebellar and brainstem involvement) in essential tremor (ET). Eighteen cases with ET and 16 age- and gender-matched healthy control subjects (HCS) were included in the present study. Otoscopic and neurologic examinations were performed on all participants, and both cervical and ocular VEMP tests were performed. Pathological cVEMP results were increased in the ET group (64.7%) compared to the HCS (41,2%; $p > 0.05$). The latencies of P1 and N1 waves were shorter in the ET group than in HCS ($p = 0.01$ and $p = 0.001$). Pathological oVEMP responses were significantly higher in the ET group (72.2%) compared to the HCS (37.5%; $p = 0.01$). There was no statistically significant difference in oVEMP N1-P1 latencies between groups ($p > 0.05$). Because the ET group had high pathological responses to the oVEMP, but not the cVEMP, the upper brainstem pathways may be more affected by ET.

Keywords Vestibulocollic reflex · Vestibuloocular reflex · cVEMP · oVEMP · Essential tremor

Introduction

Essential tremor (ET) is among the most common neurological diseases and is among the most common movement disorders, with a prevalence of 1.33%, including all ages (Louis and McCreary 2021). ET is characterized by a 4–12 Hz kinetic tremor that primarily impacts function in the upper extremities. The prevalence of ET among individuals age 65 years and older is 5.79%, which is comparable to that of Alzheimer's disease. The past two decades have witnessed numerous clinical, neuroimaging and neuropathological studies. Growing evidence suggests that, in addition to kinetic tremors, a series of motor features (gait changes, ocular abnormalities, mild slowing of movements, etc.) and non-motor features (mild cognitive dysfunction, dementia, personality changes, depression, anxiety, sleep disturbances, fatigue, and sensory deficits including hearing impairment, etc.) may be present and are associated with ET (Louis 2018; Sengul 2020). Despite its high prevalence, the underlying pathomechanisms of ET have been obscure for many years. Recent studies place prime importance on the cerebellum (Benito-León and Labiano-Fontcuberta 2016; Filip et al. 2016; Marin-Lahoz and Gironell 2016). The neuropathology of ET primarily involves the cerebellar cortex, centered on Purkinje cells and surrounding neuronal populations. (Louis and Faust 2020; Louis et al. 2023).

Vestibular-evoked myogenic potential (VEMP) is an electrophysiological test procedure used for the objective assessment of otolith organs (utriculus and sacculus) and their associated pathways (Minor et al. 1998). VEMP uses surface electrodes to record muscle excitation and inhibition during reflexes that are induced by an intense auditory stimulus. Although abnormal VEMP results provide only limited

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information about the location of the nature of underlying pathology, it can be informative with respect to the reflex arc and/or its connections. Cervical VEMPs (cVEMPs) measure the vestibulocollic reflex (VCR) and include electromyography (EMG) measurement of tonically activated ipsilateral sternocleidomastoid (SCM) muscles' responses elicited by acoustic stimulation of the saccule (Colebatch et al. 1994). Ocular VEMPs (oVEMPs) measure the vestibulocular reflex (VOR) and include EMG measurement from contralateral extraocular muscles (especially the inferior oblique muscles) elicited by acoustic stimulation of the utricle (Todd et al. 2007). Vestibulocollic reflex arcs are elicited by the acoustic stimulus of the saccular maculae; inferior vestibular nerve; the medial vestibulospinal tract (VST) from the medial, inferior, and lateral vestibular nuclei; and lastly the accessory spinal nuclei's motor neurons associated with the neck muscle. In contrast, the utricle contributes to the VOR that is transmitted through the medial longitudinal fasciculus (MLF) and other tracts in the dorsomedial brainstem. In animal models, the principal cerebellar projection from the saccule is to the uvula and has a weaker projection to the nodulus. In contrast, a strong signal from the utricle to the cerebellum is projected to the nodulus and weak projections are projected to the flocculus, paraflocculus, and uvula (Newlands et al. 2003) (Fig. 1).VEMP responses in diseases of the brainstem have been investigated in literature many times (Heide et al. 2010). It has been reported that VEMP responses may be abnormal in many neurodegenerative diseases (e.g., spinocerebellar degeneration, Parkinson's disease (de Natale et al. 2015), and multiple sclerosis (Versino et al. 2002)) due to brainstem pathology. In our previous research, we presented abnormalities of auditory

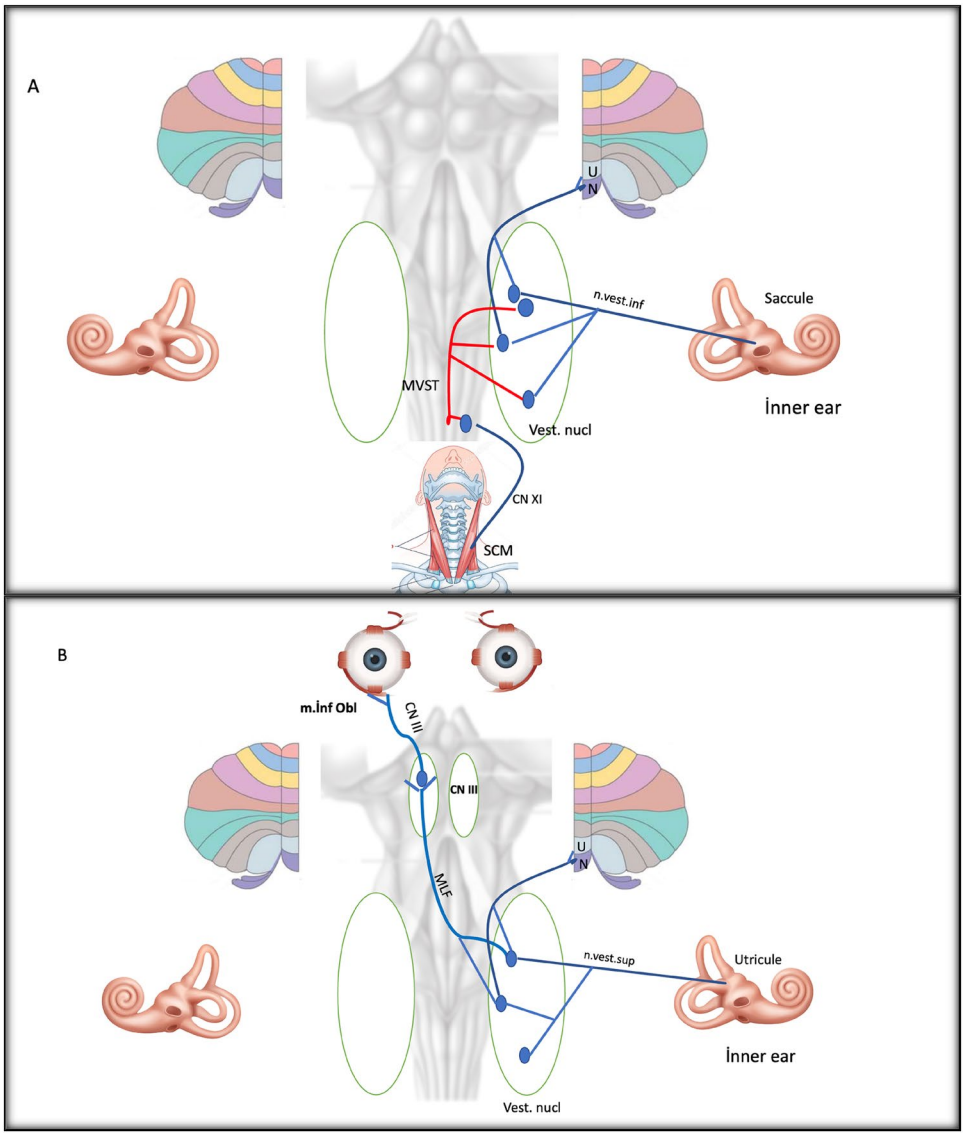

Fig. 1 Schematic illustration of the anatomic pathways involved in the generation of cVEMP (**A**) and oVEMP (**B**). The blue line represents inhibition, and the red line represents excitation. **A** The cVEMP projects the vestibulocollic reflex (VCR). Saccule, the nervous vestibularis inferior (n.vest.inf.), the vestibular nuclei: the medial, inferior, and lateral vestibular nucleus (Vest. nucl.) the medial vestibulospinal tract (MVST), the motor nucleus of accessory nerve, the accessory nerve (CN XI)SCM sternocleidomastoid muscle are main parts of this pathway. **B** The oVEMP projects the vestibuloocular reflex. Utricule, nervous vestibularis superior (n.Vest.Sup), the vestibular nuclei: the medial, inferior, and lateral vestibular nucleus (Vest. nucl.), the medial longitudinal fasciculus (MLF), the oculomotor nerve nucleus, the oculomotor nerve (CN III), inferior oblique muscle (m.Inf.Obl) main parts of this reflex arc

brainstem response and middle latency response as evidence of central involvement from the superior olivary complex to the cortex in ET (Sengul et al. 2020b). The present study is the first to report both cervical and ocular VEMPs together. We hypothesized the differences in the cVEMP and oVEMP tests' results which reflect VCR and VOR arcs arising from the vestibular nucleus will account for the deficiencies in the brainstem involvement in ET cases compared to HSC.

Method

Study population

This cross-sectional study was conducted at the Bezmialem Foundation University, Eyup additional building. A power analysis based on latencies of P1–N1 and N1–P1 at a statistical power of 80% at 5% significance indicated that the total sample size required for the study was 28.

We recruited 18 drug-naïve pure ET cases (18–80 years old) who were seen at the outpatient movement disorders clinic in our hospital. These cases were carefully examined by a movement disorder specialist (YŞ) according to International Parkinson and Movement Disorder Society criteria (Bhatia et al. 2018). Sixteen healthy control subjects (HCS) (18–80 years old) with no history of tremor were recruited from hospital staff, faculty, and students at our university. The HCS were also examined by a movement disorder specialist to confirm normal status (YŞ). Tremor severity was assessed using the Fahn Tolosa Marin tremor rating scale (FTM-TRS). There are five severity scores (0–4) for each category of movement. Increasing scores correspond to the increase in the severity of the disease. (Stacy et al. 2007).

Exclusion criteria for both groups included a history of vestibular diseases, a history of retrocochlear hearing loss (cerebellopontine angle tumors, acoustic neuroma, hearing loss due to tumors affecting the brainstem, etc.), history of middle ear surgery, middle ear disease, neurodegenerative disease, severe chronic systemic disease, brain surgery, head trauma, stroke history, use of antipsychotics or antiepileptics, and refusing to participate. Patients who had other neurological signs such as dystonia, ataxia, or parkinsonism were also excluded (ET plus cases, essential tremor–Parkinson disease cases). Eleven participants were excluded due to these criteria.

Procedure

Before the study procedure, an otoscopic examination was performed on all participants. All participants underwent a tympanometric evaluation to confirm normal middle ear status.

The VEMP responses were recorded using the GN Otometrics ICS Charter EP 200 (Denmark). We obtained informed consent from all cases and controls before starting the testing procedure.cVEMP: After skin preparation, four disk electrodes were placed in the following locations: the subject's scalp (referfence), the sternal ridge (non-inverting), the middle-third of SCM muscle (inverting), and the forehead (ground). After determining the average wave, the first positive P1 (P13) and negative N1 (N23) peaks were noted.oVEMP: During the test recordings, subjects were asked to look straight up at a small, fixed target above them. The inverting electrode was placed below the center of the lower eyelid, and the non-inverting electrode was put below the inverting electrode bilaterally. The ground electrode was placed in the center of the forehead. After determining the average wave, the first negative N1 and first positive P1 peaks were marked on the screen.

500 Hz tone burst stimuli were presented at 100 dB nHL with a bandpass filter of 1–1000 Hz and at a rate of 5.1/s using rarefaction polarity and Blackman window. The P1 and N1 latencies, N1–P1 latency, amplitude asymmetry ratio (AR), and amplitude values of the two groups were statistically analyzed as described below. AR was calculated as follows: (Larger response − smaller response)/(larger response − smaller response) · 100% (Welgampola and Colebatch 2001). When unilateral waves were absent, the AR was reported as 100%. When bilateral waves were absent, the AR was not included in the statistical analysis.

We used normative data to determine abnormal responses (Papathanasiou et al. 2014; Truong 2015) (Table 1).

Statistical analysis

Statistical analysis was performed with IBM SPSS 22.0 program. The distribution of the data was examined with the Shapiro–Wilk test. Between-group comparisons were performed using an independent sample *t* test for parametric variables and the Mann–Whitney *U* test for non-parametric variables. Correlations were found using Spearman's correlation coefficient. All statistics were analyzed and reported at $\alpha = 0.05$ significance level and 95% confidence level.

Table 1 Normative values of cVEMP and oVEMP response (Papathanasiou et al. 2014; Truong 2015)

Normative values	cVEMP	oVEMP
P1 latency, ms	19.2	18.8
N1 latency, ms	26.6	14.4
P1–N1 amplitude, mV	528.4	38.5
Asymmetry ratio, %	32.0	36.1

Table 2 Demographic features of participants

	HCS ($n=16$)	ET ($n=18$)
Age	54.1 ± 11.8	54.8 ± 16.2
Sex	13 F (%81,2) 3 M (%18,8)	15 F (%83.3)3 M (%16,7)
Tremor duration	N/A	9.83 ± 9.71 (min3, max 30)
FTM-TRS scores	N/A	18.17 ± 6.09 (min10, max27
Family history	N/A	15 (%83.3)
Age at tremor onset	N/A	45 ± 19.99 (min 20, max 71)

N/A not available

Results

Demographic features

The ET group consisted of 18 cases (83.3% female). The HCS consisted of 16 subjects (81.2% female). The mean age was 54.8 ± 16.2 years in the ET group and 54.1 ± 11.8 years in the HCS ($p=0.88$) Within the ET group, the mean tremor duration was 9.8 years, the mean FTM-TRS was 18.2, and 83.3% had a family history of ET. The demographic features of participants are shown in Table 2.

Comparison of VEMP procedures

a. cVEMP

In the cVEMP, right P1 and N1 latencies significantly differed between ET and HCS groups, but there was no significant difference between the left P1 and N1 latencies (Table 3).

When the P1 and N1 latencies of both groups were evaluated, we found that the ET group latencies were significantly shorter than those of the HCS group (Table 4). The median P1 latency was 15.75 ± 1.52 ms in the ET group and 17.03 ± 2.14 ms in HCS ($p=0.01$). The median N1 latency was 22.74 ± 1.89 ms in the ET group and 24.76 ± 2.39 ms in the HCS group ($p=0.001$).

The difference in cVEMP AR was not significant between the ET group (M = 37.11%, SD = 29.36%) and the HCS group (M = 22.88%, SD = 24.01%; $p=0.15$). Overall, 11 (64.7%) of the ET group had pathological cVEMP results, while 7 (41.2%) of the HCS had pathological cVEMP results (ns: $p>0.05$). In the ET group, cVEMP response was absent

Table 3 cVEMP results

	P1 latency	*p*	N1 latency	*p*	N1–P1 latency	*p*
Right and left ears						
HCS ($n=31$)	17.03 ± 2.14	**0.01**	24.76 ± 2.39	**0.001**	6.99 ± 1.60	0.10
ET ($n=28$)	15.75 ± 1.52		22.74 ± 1.89		7.68 ± 1.58	
Right ear						
HCS ($n=14$)	16.78 ± 2.07	**0.02**	24.26 ± 2.37	**0.02**	7.51 ± 1.52	0.23
ET ($n=14$)	15.43 ± 1.57		22.30 ± 1.74		6.87 ± 1.31	
Left ear						
HCS ($n=14$)	16.77 ± 1.95	0.07	24.75 ± 2.22	0.05	7.84 ± 1.66	0.27
ET ($n=14$)	16.07 ± 1.45		23.19 ± 2.00		7.11 ± 1.89	

*P1, N1–P1: Mann–Whitney *U* test **N1 independent sample *T* test

Bolded values are significant at $p \leq 0.05$

Table 4 oVEMP results

r	N1 latency	*P* value*	P1 latency	*P* value*	N1–P1 latency	*P* value*
Right and left ears						
HCS ($n=27$)	10.66 ± 0.91	0.46	16.06 ± 1.52	0.06	5.39 ± 1.03	**0.03***
ET (n = 13)	10.40 ± 0.60		15.51 ± 1.47		4.70 ± 1.05	
Right ear						
HCS ($n=13$)	10.75 ± 0.99	0.75	16.07 ± 1.43	0.28	5.31 ± 1.03	0.26
ET ($n=10$)	10.55 ± 0.75		15.34 ± 1.77		4.79 ± 1.15	
Left ear						
HCS ($n=14$)	10.57 ± 0.86	0.42	16.05 ± 1.65	0.09	5.47 ± 1.06	0.06
ET ($n=9$)	10.25 ± 0.34		14.85 ± 1.09		4.60 ± 1.00	

*Mann–Whitney *U* test

Bolded values are significant at $p \leq 0.05$

bilaterally in three subjects and unilaterally in two subjects, P1 and/or N1 latencies were abnormally long in two subjects, and AR was high in six subjects. In HCS, cVEMP response was absent unilaterally in one subject, P1 and/or N1 latencies were abnormally long in three subjects, and AR was high in two subjects (5). Additionally, significantly more ears showed abnormal responses in the ET group (67.6%) than the HCS (38.2%) ($p=0.02$).

There was no correlation between cVEMP response latency and FTM, or between cVEMP response latency and duration of tremor.b. oVEMP

There was no significant difference in the N1 and P1 latencies between the ET group and HSC. Median N1 latency was 10.40 ± 0.6 ms in the ET group and 10.66 ± 0.91 ms in HCS ($p > 0.05$). Median P1 latencies were 15.51 ± 1.47 ms in the ET group and 16.06 ± 1.52 ms in HCS ($p > 0.05$).

In the oVEMP study, bilateral N1 and P1 latencies were not significantly different ($p > 0.05$) (Table 4). However, the absolute latencies were shorter, but not significant and N1–P1 interpeak latencies were significantly shorter in the ET group. The oVEMP AR was $52.30 \pm 45.33\%$ in the ET group and $22.94 \pm 27.45\%$ in HCS. This difference was not statistically significant ($p=0.93$).

Overall, 13 subjects (72.2%) in the ET group had pathological oVEMP results, and 6 subjects (37.5%) of the HCS had pathological oVEMP results ($p=0.01$). In the ET group, oVEMP response was absent bilaterally in six subjects and unilaterally in five subjects, AR was abnormal in two subjects, and no subjects had latency elongation. In the HSC group, oVEMP response was absent in two subjects bilaterally and one subject unilaterally, AR was abnormal in two subjects, and one subject showed latency elongation (Table 5).

There was no correlation between oVEMP response latency and FTM, nor between oVEMP response latency and duration of tremor.

Discussion

The nature of ET is still not fully understood. Although central nervous system involvement in ET has been the subject of few studies (Louis and Faust 2020; Sengul et al. 2020a; Sharifi et al. 2014), more investigation is needed to understand ET pathology. The cVEMP has been used to evaluate ET cases in the literature, but there was no study in which ET patients were subjected to the oVEMP test. We are the first to report both oVEMP and cVEMP in ET cases (Bayramoglu et al. 2021; Uyaroglu et al. 2021). We aimed to evaluate the lower and upper brainstem in ET patients by both cVEMP and oVEMP via the vestibulocollic and vestibuloocular reflex tracts. We found that abnormal oVEMP test results primarily occurred in ET cases. oVEMP response could not be obtained bilaterally in five cases and unilaterally in four cases. Additionally,

Table 5 Abnormal VEMP results in ET

Subject	cVEMP			oVEMP		
	Right	Left	AR	Right	Left	AR
1		A*	High	Ø		High
2	Ø	Ø			Ø	High
3		A				
4	Ø	Ø		Ø	Ø	
5				Ø		High
6		Ø	High	Ø		High
7				Ø	Ø	
8		A	High			
9						
10	Ø	LP***	High			
11	A		High	Ø	Ø	
12						
13		A	High		A	High
14	Ø	Ø		Ø	Ø	
15					Ø	High
16		A	High	Ø	Ø	
17		LP		Ø	Ø	
18					A	High

*Amplitude decreased

**Øs: no response

****LP* latency elongation

latency asymmetry could not be determined because of absent response bilaterally. Although this result did not reach statistical significance, cVEMP pathological results were higher in the ET group than in the HCS. Our results suggest there may be pathological changes at and above the brainstem in ET.

The use of cVEMP in the evaluation of central nervous system pathologies, especially to show lower brainstem involvement, has increased in recent years (Oh et al. 2016; Su and Young 2011; Venhovens et al. 2016). In one study, all cases who had lower brainstem pathology showed abnormal cVEMPs, namely, absent wave formations and increased response latencies. In contrast, cVEMP results of cases with upper brainstem infarction were normal (Oh et al. 2016). In Uyaroglu's cVEMP study (2021), P1 latency was decreased, but not significantly different, in ET cases compared to healthy controls. In the same study, however, decreased N1 latencies in the ET group were found to be significant compared to healthy controls (Uyaroglu et al. 2021). In another study, N1 latency elongation was found in only the right ears in the ET group. Additionally, P1–N1 latencies were shortened on the right side of the ET group (Bayramoglu et al. 2021). In our study, however, P1 and N1 latency shortening was statistically significant in the ET group compared to HCS on the right side. Although, like previous studies, we found no significant difference in pathological cVEMP results between groups [23,24], significantly decreased latencies of ET cases may be an important finding to understand central nervous system involvement in ET. Similarly, a reduction of absolute latencies (N1, P1 waves) in oVEMP test results had been found, but they were not statically significant; only N1–P1 interpeak latencies shortened significantly. The cerebellum has an important role in compensation for vestibular loss. Changes in inhibitory control of brainstem vestibular networks by the cerebellum had been demonstrated previously (Duffin et al. 2010; Dutia 2010). In a study with Lurcher mouse mutants with progressive loss of Purkinje cells, researchers found that compensatory VOR gains stopped after a period of time in this group compared to controls (Duffin et al. 2010). An fMRI study demonstrated vestibular otolith activations in humans in the brainstem and cerebellum, showing dominance for the saccular input from the right ear (Schlindwein et al. 2008). In postmortem studies, degeneration of Purkinje cells and reorganization of Purkinje cells' connections were observed, although the physiological effects of this reorganization are not fully understood (Babij et al. 2013; Yu et al. 2012). Considering the literature outlined here, it can be speculated that latency reduction in both oVEMP and cVEMP may be due to the reorganization of the cerebellum or selected samples in the studies.oVEMP represents the VOR and is mediated by a crossed pathway linking vestibular and oculomotor nuclei via the MLF (Todd et al. 2007). oVEMP test abnormalities are usually found in cases with brainstem lesions (Oh et al. 2013; Su & Young 2011). Su et al. (2011) also suggest using oVEMP test results to differentiate cerebellar lesions and brainstem involvement (Su and Young 2011). In our study, oVEMP responses were absent in a substantial proportion of the ET patients (bilateral 33.3%, unilateral 27.8%) compared to HCS (bilateral 12.5%, unilateral 0.0%). Additionally, pathological oVEMP results such as absent response, high AR, or prolonged N1–P1 latencies were seen in the ET group at 72.2%, compared to 37.5% in HCS ($p=0.01$). Although these pathological findings are more common with increasing age, our results are still statistically significant (Papathanasiou et al. 2014; Truong 2015).

Our previous research found brainstem involvement in ET after lateral lemniscus via auditory brainstem response and auditory middle latency responses (Sengul et al. 2020b). Taken together with our previous findings, the current analysis supports upper brainstem involvement in ET.

Limitations

This study is the first to evaluate both the lower and upper brainstem pathways in ET cases, and we hope will motivate future studies to further define brainstem involvement in ET. Nevertheless, our study must be interpreted in the context of some limitations. Firstly, a history of retrocochlear hearing loss has been reported as an exclusion criterion. However, we did not perform any specific tests to assess possible subclinical deficits.

Secondly, we did not assess non-motor symptoms that may impact VEMP response such as excessive daytime sleepiness and sleep disturbances, among other non-motor symptoms. Correlations of these non-motor symptoms' severity and VEMP response may help explain the roots of these non-motor symptoms.

Conclusion

In conclusion, the current study confirms pathological changes in the brainstem and its cerebellar connections in ET. When evaluated together with our previous work, we conclude that ascending central vestibular pathways are more affected than descending pathways in ET cases. Further studies are warranted to reproduce the correlation of VEMP responses in ET.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by NB, YŞ, and MBB. The first draft of the manuscript was written by NB and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The data that support the findings of this study are available from the corresponding author, [Nilüfer Bal], upon reasonable request.

Declarations

Conflict of interest There is no conflict of interest of the authors.

Ethical approval The study protocol was conducted in accordance with the ethical principles stated in the 'Declaration of Helsinki' and approved by the Ethical Committee of Bezmialem Foundation University Hospital.

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