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Analysis of the tremor in juvenile myoclonic epilepsy

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ABSTRACT

Purpose: We aimed to investigate juvenile myoclonic epilepsy (JME) patients complaining of tremor unrelated to valproate (VPA) treatment and evaluate if there were differences between JME patients with and without tremor and essential tremor (ET) patients to exclude comorbidity.
Methods: Fifteen JME cases with the complaint of tremor, 14 JME patients without tremor, 14 patients with ET and 14 healthy subjects (HS) were included. Regularity, frequency and amplitude of the tremor and superimposed myoclonia were assessed by accelerometric analysis. Cortical SEPs evoked by the stimulation of the median nerve were recorded bilaterally. Clinical and neurophysiologic features were statistically compared between the groups.
Findings: Amplitude of postural tremor of the left hand was significantly increased in the ET group compared to JME patients with tremor, but there were no differences regarding to frequency. Strikingly, there were superimposed irregular, low-amplitude inconstant myoclonic jerks located to distal part of the fingers in JME group with tremor. Initial frequency of myoclonic seizures was also significantly higher in this group compared to JME patients without tremor but this difference disappeared after treatment. The group of JME with tremor had the highest N20-P25 and P25-N35 amplitudes, followed by JME without tremor, ET and HS, respectively.
Conclusion: Tremulous hand movements in JME resembled ET, but their amplitude was lower and characterized with accompanying irregular myoclonic jerks. The presence of tremor in JME patients should be taken into consideration to create more homogeneous groups in genetic and pathophysiological studies of JME.

1. Introduction

In clinical practice, tremor can be seen in patients diagnosed with juvenile myoclonic epilepsy (JME). This complaint is usually thought to associate with valproate (VPA) treatment and it is usually ignored. It was reported that VPA-induced tremor had the characteristics of intentional type and emerged or increased with position. Additionally, resting and postural components were prominent. Tremor may appear from the 2nd-3rd months of the start of the VPA treatment. This side effect was reported to emerge earlier and more prominent in patients who had tremor history before the treatment (Hyman et al., 1979).

On the other hand, tremor is a common movement disorder and develops mostly related to essential tremor (ET) (Britton, 1995). Clinical diagnostic criteria for ET have been determined (Deuschl et al., 1998); it is characterized with postural and kinetic tremors; and mostly seen in the upper extremity. Symptoms are usually progressive and can potentially affect the quality of life. It may lead to patients' decisions for job changing or early retirement (Sullivan et al., 2004).

There is no information in the literature so far, regarding the presence of tremor in some of the patients diagnosed with JME before VPA treatment, characteristics of this tremor and possi-

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ble similarities and differences with ET. The aim of this study is to demonstrate distinctive features of tremor with clinical and accelerometric analyses in JME patients with tremor complaints. It was aimed to investigate if JME group with tremor was actually a sub-group of JME or even a different syndrome by comparing clinical and EEG properties, and SEP findings. Furthermore by comparing the tremor characteristics of patients diagnosed with JME those with ET; the possibility of comorbidity was also addressed. Median nerve SEP evaluations of all patients were also planned to have an insight for the origin of tremor seen in JME group and those seen in ET patients.

2. Subjects and method

Four groups of patients, consisting of patients with regular follow-ups between the years of 2012 and 2014, who admitted to Istanbul Faculty of Medicine, Department of Neurology, Epilepsy and Movement Disorders Outpatient Clinics, were included in the study. The study groups were:

Group 1: 15 JME patients, who spontaneously complained about tremor without prior questions by a physician were selected out of 137 patients who were under follow-up at least for one year and were diagnosed with JME according to the criteria of International League Against Epilepsy (ILAE) (Berg et al., 2010) and have shown diagnostic generalized spike-waves (GSW) in their EEG.

Group 2: 14 patients diagnosed with JME according to the same criteria and had no trembling complaints in their hands in their history and during one year of follow-up.

Group 3: 14 patients who show similar age and gender distributions and met the ET criteria defined by "Movement Disorder Society's Ad Hoc Committee on Tremor" (Deuschl et al., 1998).

Group 4: 14 healthy controls (HC) with similar age and gender distribution and without chronic diseases and medication use.

All participants were right handed and evaluated clinically and neurophysiologically.

2.1. Clinical evaluations

The patients included in the study were questioned regarding tremor using standard forms and their detailed neurological examinations were performed. In the clinical evaluations of tremor, "Fahn-Tolosa-Marin Tremor Rating Scale" (FTM-TRS) was used.

JME patients were also evaluated in terms of the course of their epilepsy, the anti-epileptic drugs they use and their temporal relationships with the tremor.

2.2. Neurophysiologic evaluations

2.2.1. Electroencephalographic evaluation

EEGs were recorded using surface electrodes placed according to the International 10–20 system and in accordance with our laboratory standards on various activation methods reported previously (Baykan et al., 2005).

Two clinical neurophysiologists, reviewed the current and all available EEGs and video-EEGs in a standard procedure. Background activity, the effects of IPS, hyperventilation, eye closure, sleep (if any), the presence of focal abnormalities and asymmetric discharges, other pathological findings and the frequency of generalized epileptiform discharges.

2.2.2. Tremor analysis

A four channel electromyography/evoked potential (EMG/EP) device (Viasys Healthcare Neurocare, Nicolet Viking Select Neurodiagnostic System Version 11.1) and a 3-axis accelerometric sensor (Square Movement Sensor, 20 × 20 mm, TEMEC Instruments B.V. P.O. Box 3011 NL-6466LZ, Kerkrade, The Netherlands) was used.

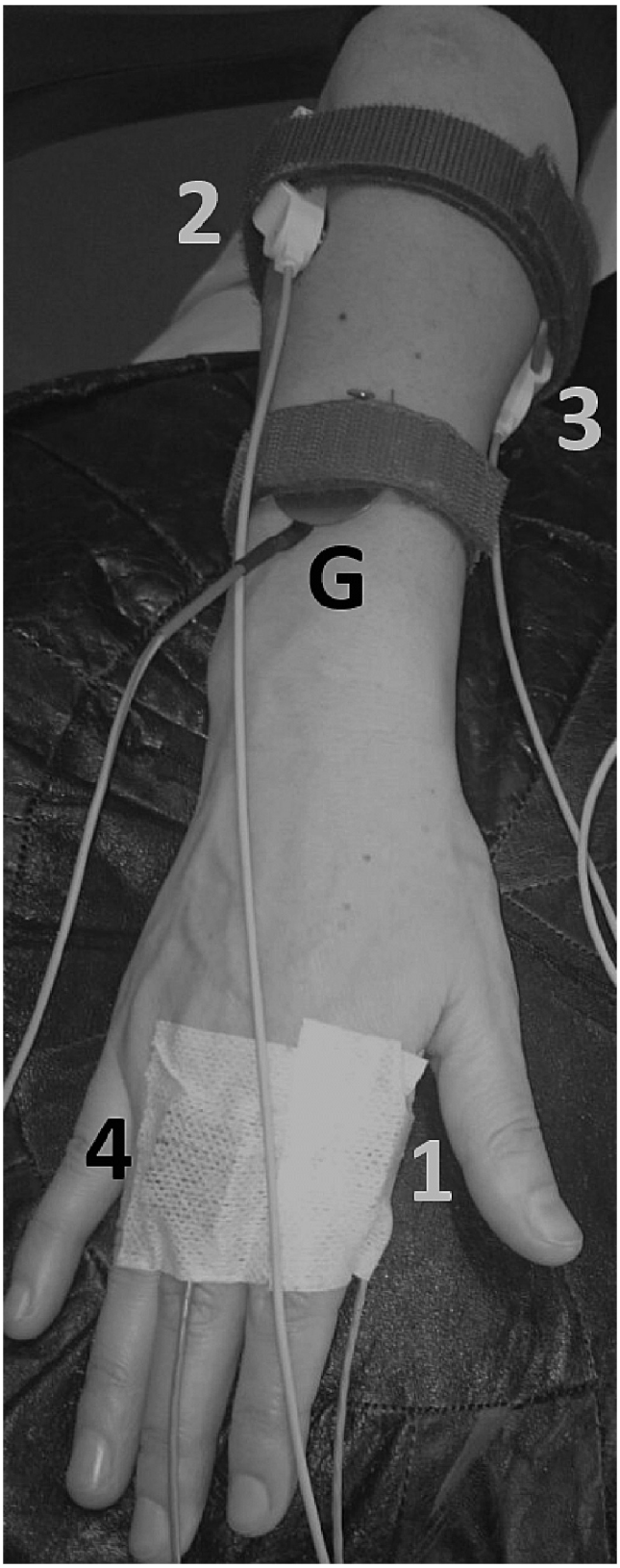

Fig. 1. Electrode/Sensor placement. Chanel 1: Accelerometer sensor attached on the extensor surface of the 3rd finger metacarpophalangeal joint, chanel 2: Surface EMG electrode pair placed on the forearm extensor muscles, chanel 3: Surface EMG electrode pair placed on the forearm flexor muscles, chanel 4: Accelerometer sensor attached on the lateral surface of the 2nd finger metacarpophalangeal joint, G: Ground.

Medications taken by the patients for their tremor were terminated 48 h prior to the tremor analysis. Recordings were made while the patient was sitting on a comfortable chair in a silent room, kept at a quite constant average temperature. Input channels were connected to the sensors or electrodes are shown in Fig. 1.

Filter settings were 2–500 Hz for the EMG channels and 1–30 Hz for the accelerometer channels. Maximum acceleration amplitude range is +5/−5 gravity (g; 1 g = 9.81 m/sec^2).

Forearm and hand of the subject were kept in a constant position during recordings. Measurements on each upper extremity were performed while (a) the arm and hand was in the resting position on a pillow placed on knees of the subject, (b) the arm and hand were extended straightly forwards making nearly an angle of 90° with the body (postural position) (c) the arm and hand were extended forwards and lifting 500 g of weight, (d) the arm and hand were extended forwards and lifting 1000 g of weight. Thirty seconds long recordings were taken for analysis. The recordings in each position were repeated at least three times and those containing inconsistent deflections (due to the inability of the patient to maintain the position, etc) were repeated after a period of rest.

Accelerometric data were analyzed with a software developed for the EMG device (Viking Select Master Software V8.1, Viasys Healthcare, CareFusion Switzerland 317 Sàrl A-One Business Centre Zone D'activités Vers-la-Pièce no 10 CH-1180 Rolle, Suisse). While consistent and reproducible results were obtained with automatic spectral analysis of the data recorded from ET patients, it was not possible in the JME group, mainly because of the large variability of the amplitude and frequency of the tremor and the superimposed distal myoclonic jerks. Hence, the polygraphic recordings were allocated into 16-s epochs, and the tremor frequency, amplitude and the number of superimposed myoclonia were analyzed on those epochs. Tremor frequency was accepted as the most common repetitive value (peak tremor frequency). Tremor amplitude was calculated as the acceleration amplitude from the first channel and the values were recorded as milligravity. Sampling frequency of the tremor sampling program was 1000, the number of data-points was 30000 and confidence interval was 90%. The results automatically generated by the software were "spectral analysis results and graphics" and "polygraphs" as shown in Fig. 2.

2.2.3. Median somatosensory evoked potentials (SEP) and C reflex

Five channel EMG/EP device (CareFusion, Synergy, Middletown, WI, 53562 USA) was used for the examination. Each median nerve was stimulated with submaximal electrical stimulation at the wrist level using surface electrodes. The recordings were made from the three-channels connected to the standard electrodes at C3-Fz, Cz-Fz, C4-Fz (according to the international 10–20 system) and from the surface electrodes placed on the thenar eminence.

The filters were set between 0.3 Hz and 1 kHz. The sensitivity was 5 μV for first three channels and 1 mV for the last one, sweep duration was 100 ms. At least two series of minimally 250 averaged responses were recorded The latencies of the N20, P25 and N35 waves (ms), and N20-P25 and P25-N35 amplitudes (μV) were measured. N20-P25 and P25-N35 peak to peak amplitudes higher than three standard deviations (SD) calculated from the data obtained from the healthy controls were regarded as "enhanced cortical SEPs".

2.3. Statistical analysis

SPSS 20.0 software was used for statistical analyses and $p < 0.05$ was accepted as the limit of significance. The distribution of the numerical parameters were evaluated by histograms and found to be abnormal, therefore, the comparison of the SEP results of the four groups was conducted non-parametrically by using Kruskal-Wallis test. When significant differences were detected, binary group comparisons were done (Mann-Whitney Test) with post-hoc correction (Bonferroni). Chi-square test was used for the inter-group ratio comparisons. Correlations between the group values were evaluated using Spearman Rho test.

3. Results

3.1. Clinical findings

All examination results and clinical information were merged and three patients from JME group with tremor complaints were excluded from further comparative analyses as two of them were accepted as ET (based on their family histories in addition to the frequency and accelerometric analysis results), while another one was accepted as VPA-related tremor (certain temporal relationship with VPA and discontinuation of tremor when VPA treatment was ended during the follow-up). VPA was the most the most commonly used AED in 66.7% in the group with tremor and 64.3% in the group without tremor. Clinical and EEG properties of the remaining 12 patients and JME group without tremor were shown in Table 1, comparatively. The median age of the group with JME with tremor was 29 years (ranges: 20–61 years), whereas that of the JME without tremor group was 27 (ranges: 20–61 years).

Seven patients were females in ET group and their median age was 34 (min: 22, max: 73) years. The age at onset of tremor was 27.8 ± 13.57 years (min: 15, max: 53). There were no Parkinsonism findings accompanying the tremor in any of the patients and the characteristics of their tremors were essentially postural and kinetic. For the tremor treatment, propranolol was prescribed for 35.7% of the patients while primidon treatment was administered to another 7%. There was family history of ET in 57% of the patients and all of them were first degree relatives. There was no history of antiepileptic drug use or epilepsy in the families of the patients.

Six of the 14 healthy controls were females. The median age in this group was 33 (min: 25, max: 72).

3.2. Fahn-Tolosa-Marin tremor rating scale (FTMTRS) results

The median tremor scores in the JME group with tremor by using FTMTRS was 11.8 ± 4.86 (min: 6, max: 20), whereas the median tremor scores in ET group was 24.0 ± 19.21 (min: 4, max: 68). In the comparison of all relevant items between JME group with tremor and ET group, there were no statistically significant differences although total FTMTRS tended to be higher in ET group ($p = 0.06$, Mann-Whitney U). JME patients performed significantly better only in "Drawing B" with non-dominant hand (left) ($p = 0.04$, Chi-square).

3.3. Accelerometric analysis results

Tremor frequencies in the right hands were 7.0 ± 1.14 Hz (min: 5, max: 10) in JME group and 6.5 ± 1.24 Hz (min: 4.6, max: 10.7) in ET group. For the left hand, tremor frequencies were 7.2 ± 1.46 Hz (min: 5, max: 10.8) in JME group, and 6.9 ± 1.29 Hz (min: 5.0, max: 12.1) in ET group. No significant differences were found between the groups. Additionally, there were no differences between the right and left sides within both groups.

Postural tremor amplitude in ET group was significantly higher than those in JME group with tremor ($p = 0.04$, Mann-Whitney U, Fig. 3). No other significant differences were found between the groups regarding the amplitude values. In both groups, amplitudes increased in the arm extended posture with increased weights (Fig. 3).

Tremor amplitude and frequency in the JME group showed significant changes during recordings related to the intervening myoclonia. Myoclonus frequency and amplitude during posture

Table 1
Comparison of the JME groups with and without tremor.

Clinical features		JME with tremor group (n = 12)	JME without tremor group (n = 14)	Statistical results
Age at onset of epilepsy in years mean ± SD (min–max)[a]		14,5 ± 2,57 (11–18)	15,92 ± 1891 (12–18)	n.s
Age at onset of MYC in years mean ± SD (min–max)[a]		14,6 ± 2,57 (11–18)	15,92 ± 1891 (12–18)	n.s
Age at onset of GTCS in years mean ± SD (min–max)[a]		19 ± 7,01 (11–34)	19,1 ± 7,08 (14–40)	n.s.
Duration of epilepsy in years mean ± SD (min–max)[a]		14,41 ± 11,63 (3–48)	15,84 ± 12,83 (3,5–42,3)	n.s.
Family history of epilepsy n(%)[b]		6 (50)	4 (28,6)	n.s
Family history of tremor n(/%)[b]		8 (66,7)	4 (28,6)	n.s.
Consanguinity of the parents n(%)[b]		2 (16,7)	3 (21,4)	n.s.
First seizure type, n (%)[b]	GTCS	2 (16,7)	1 (7,1)	n.s.
	MYC	10 (83,3)	13 (92,9)	
All seizure types, n (%)[c]	MYC	–	1 (7,1)	n.s.
	MYC + GTCS	8 (66,7)	12 (85,7)	
	MYC + ABS	1 (8,3)	1 (7,1)	
	MYC + GTCS + ABS	3 (25)	–	
Initial MYC frequency	≥30/a month	8 (66,7)	2 (14,3)	p:0,012
n(%)[c]	<30, ≥4/a month	4 (33,3)	8 (57,1)	
	<4/a month	–	4 (28,6)	
	Total MYC patients	12 (100)	14 (100)	
Last reported MYC	≥4/a month	2 (16,7)	–	n.s.
frequency n(%)[c]	≥1, <4/a month	4 (33,3)	2 (14,3)	
	<12/a year	1 (8,3)	1 (7,1)	
	none since 2 years	5 (41,7)	11 (78,6)	
Initial GTCS frequency n	≥12/a year	2 (18,2)	–	
(%)[c]	2–11/a year	7 (63,6)	7 (58,3)	
	<2/a year	1 (9,1)	2 (16,7)	n.s.
	Only once	1 (9,1)	3 (25)	
	Total GTC patients	11 (91,7)	12 (85,7)	
Last reported GTCS	2–11/a year	2 (18,2)	–	n.s.
frequency n (%)[c]	<2/a year	1 (9,1)	1 (8,3)	
	none since 2 years	8 (72,7)	11 (91,7)	
AED that used n (%)[c]	VPA	11 (91,7)	12 (85,7)	n.s.
	LEV	5 (41,7)	5 (35,7)	
	FNT	–	3 (21,4)	
	BBX	3 (25)	3 (21,4)	
	CBZ	2 (16,7)	2 (14,3)	
	LAM	3 (25)	—	
	ETX	1 (8,3)	–	
Current AED (n/%)[c]	VPA	8 (66,7)	9 (64,3)	
	LEV	3 (25)	4 (28,5)	n.s.
	VPA + LEV	1 (8,3)	1 (7,1)	
Seizure predisposing	Stress	8 (66,7)	10 (71,4)	n.s.
factors (n/%)[c]	Sleeplessness	11 (91,7)	12 (85,7)	
	Fatigue	9 (75)	9 (64,3)	
	Sadness	6 (50)	4 (28,6)	
	Waking up	5 (41,7)	3 (21,4)	
	Pregnancy	1 (8,3)	1 (7,1)	
	Alcohol intake	1 (8,3)	–	
	TV-light-computer	5 (41,7)	2 (14,2)	
	Menstruation	1 (8,3)	1 (7,1)	
Concomitant disorder[c]	Psychiatric Disorders	6 (50)	1 (7,1)	n.s.
	Migraine	5 (41,7)	2 (14,3)	
	Hypertension	1 (7,1)	–	
Interictal discharge[b]	Generalized 3–3,5 Hz SW or mSW	3 (25)	11 (78,6)	p: 0,016
	Generalized ≥4–5 Hz SW or mSW	9 (75)	3 (21,4)	
Photosensitivity[b]		8 (66,6)	3 (21,4)	p: 0,04
Sensitivity to hyperventilation[b]		6 (50)	4 (28,6)	n.s.

ABS: absence, AED: antiepileptic drug, ASE: absence status epilepticus, BBX: barbexaclone, CAE: childhood absence epilepsy, CBZ: Carbamazepine, ETX: etosuximide FNT: pnehytoin, GGE: genetic generalized epilepsy, Hz: hertz, JAE,: juvenile absence epilepsy, JME; juvenile myoclonic epilepsy, GTCS: generalised tonic-clonic seizure, LEV: levetiracetam, MYK: myoclonus, n.s.: non-significant, mSW: multiple spike-wave, SD: standard deviation, SW: spike-wave, VPA: Na-Valproat.

[a] Mann-Whitney *U* test.

[b] Fisher Exact Test.

[c] Pearson Ki-Kare.

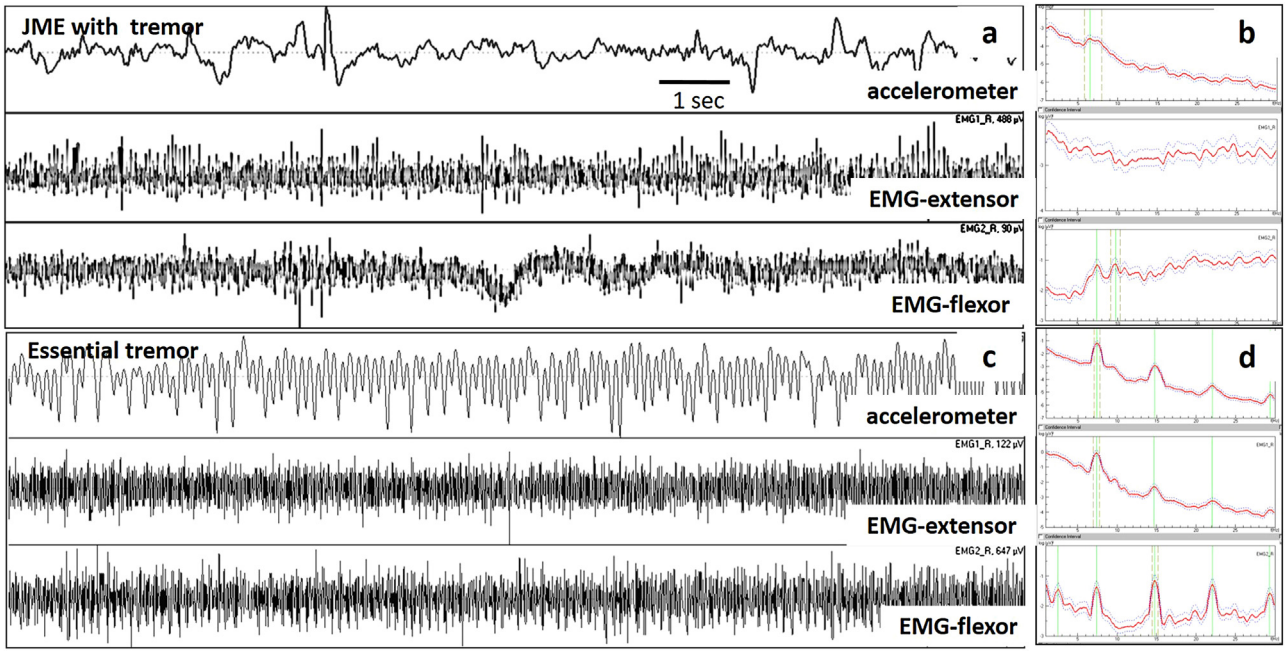

Fig. 2. Polygraphs and spectrograms belonged to a patient with juvenile myoclonic epilepsy with tremor (2a, 2b) and a patient with essential tremor (2c, 2d) during posture recording. Accelerometer recording showed quite regular oscillations in essential tremor whereas non-regular oscillations with variable amplitudes and frequency in JME with tremor. Spectrograms of essential tremor revealed peak frequencies matching with each other on both channels, but this was not the case for JME with tremor.

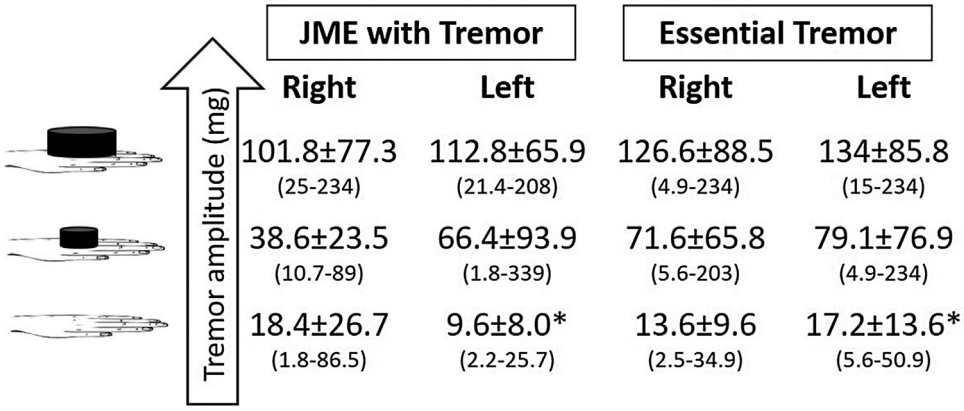

Fig. 3. Acceleration amplitudes in JME with tremor and ET groups at different positions. Significant difference was found only in the left hand at posture position (*p = 0.04, Mann-Whitney *U* test).

did not change with 500 mg and 1000 mg weight applications. The number of myoclonia observed in 30 s intervals varied between 2 and 9 (average:3.6) in JME patients with tremor.

3.4. SEP and C reflex findings

No significant differences were found between the four groups in terms of height and age. The mean age was partially higher in the ET group; however it was not significantly different from those of other groups.

In four different study groups (HC/JME with tremor/JME without tremor/ET), N20, P25 and N35 latencies, N20-P25 and P25-N35 amplitudes were evaluated separately in each hand. The findings were given in detail in Fig. 4. As a result of the comparison of amplitudes between the four groups; significant differences were found on both sides (for the N20-P25 amplitude, right p = 0.004 Fig. 4a, left p = 0.003, Fig. 4b and for the P25-N35 amplitude, right p = 0.002, Fig. 4c, left p = 0.001, Fig. 4d). Amplitudes were always the highest in JME group with tremor. Also the amplitudes in the JME group without tremor were higher as compared to those of ET and HC groups.

According to our definition in the Methods, 'enhanced cortical SEP' was accepted as >5.8 μV for N20-P25 amplitudes on the right and >5.4 μV on the left, and >4.7 μV for P25-N35 amplitudes on the right and >3.7 μV on the left sides. Accordingly, unilateral or bilateral enlargement of cortical SEP was detected in 6 patients (50%) in the JME group with tremor and 5 patients (35%) in JME group without tremor.

There were no statistically significant differences regarding the evaluated clinical properties and EEG findings between JME patients with 'enhanced cortical SEPs' and JME patients without 'enhanced cortical SEP'.

3.5. Correlation between the SEP findings and accelerometric analyses

In the JME group with tremor, right N20 latency revealed a negative correlation with tremor peak frequency of the left side (p = 0.04,

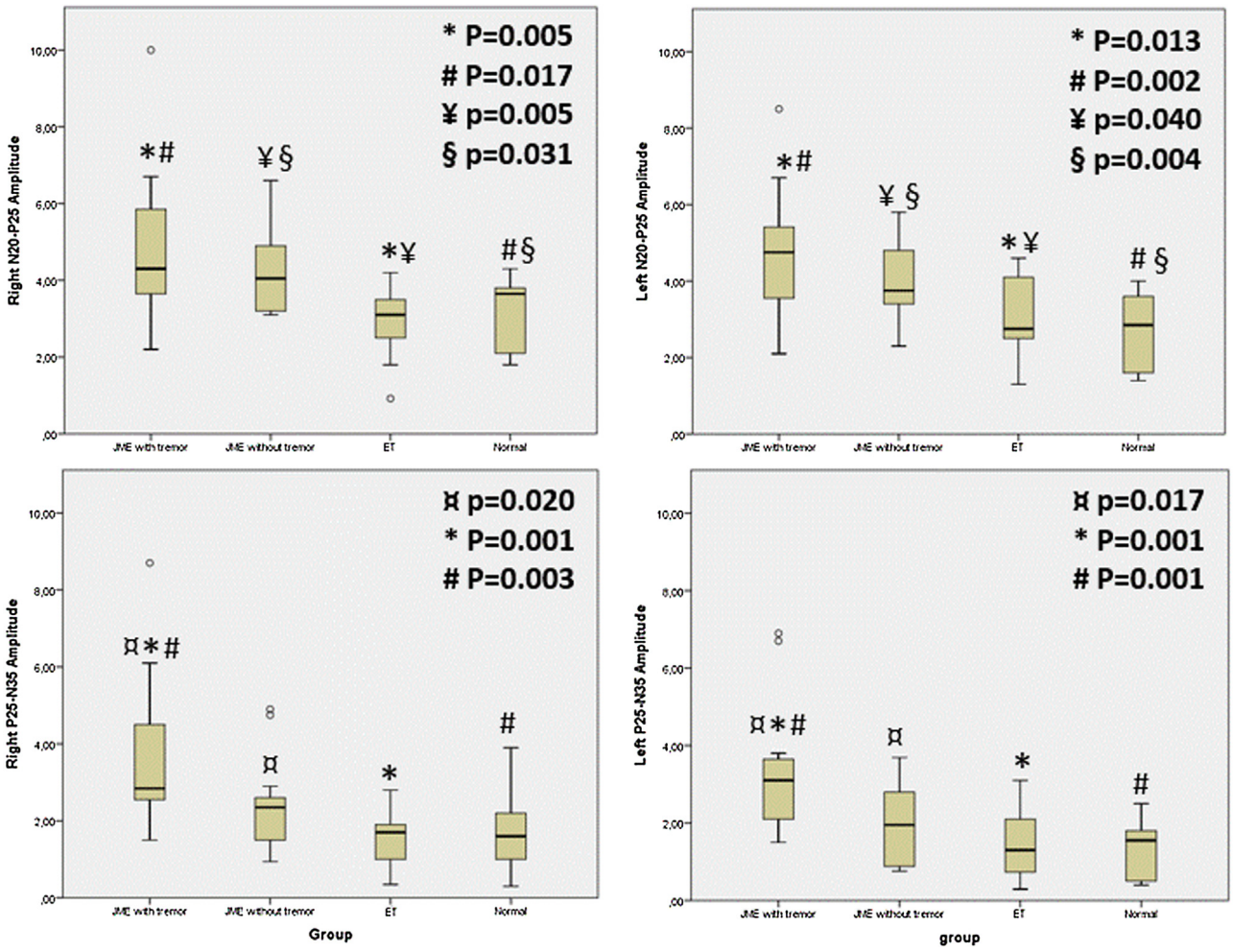

Fig. 4. Comparison of the right and left N20-P25 (a,b), P25-N35 (c,d) amplitudes between the groups. Mann-Whitney-U test results were shown by the symbols for binary group comparisons. JME; juvenile myoclonic epilepsy, ET; essential tremor.

r: −0.579). Also, in the ET group, right N20 latency and left side tremor peak frequency ($p = 0.007$, r: −0.685), as well as left N20 latency and right side tremor peak frequency ($p = 0.005$, r: −0.707) yielded negative correlations.

4. Discussion

Emergence of tremor in some patients diagnosed with JME is a neurological finding which had previously attracted the attention (Panayiotopoulos et al., 1994) but has been neglected thereafter and there were no studies on this subject in the literature yet. Our study suggested that, contrary to the popular belief, these complaints did not have empirical relationships with VPA use (Hyman et al., 1979; Rinnerthaler et al., 2005) or ET comorbidity, but indicated a different sub-group. Emergence of tremor after VPA treatment (Hyman et al., 1979) was not in question in our patients; and it had started either before or at the same time with the epilepsy. Additionally, similar tremor was also observed in 3 patients who did not receive VPA treatment.

Since its definition as a sub-syndrome of idiopathic generalized epilepsy in 1989 by ILAE, clinicians obtained a vast amount of information and experience on JME (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). However, as the knowledge increases, its clinical heterogeneity has caused confusion. Therefore, a standardization study was conducted in 2011 with the contribution of scientists experienced on JME, including two of the present authors (BB and CG), and this consensus report has been published in 2013 (Kasteleijn-Nolst Trenité et al., 2013). The properties of our JME patients are compatible with the criteria of this group (myoclonic jerks usually developing without loss of consciousness in 2 h after waking up from sleep, normal background activity in the EEG and generalized multiple spikes and waves with high amplitudes, normal intelligence, age at onset of 10–25 years). The only difference was the additional myoclonic tremors in hands. Accordingly, our JME patients with tremor presented with two types of myoclonic jerks. One of them was typical myoclonic jerks in proximal parts of the arms of JME with higher amplitudes that lead to the syndrome diagnosis, while the other one was small jerks localized to the fingers which were discussed in this study. It was well-known that medication discontinuation was especially difficult in JME although remission developed easily under appropriate treatment and recurrence rate was high after the discontinuation of medication (Baykan et al., 2013). In the light of our findings, we think that these small myoclonic jerks in the hands should also be taken into consideration during the discontinuation of medication.

In the comparison of JME patients with tremor and without tremor; myoclonic seizures in JME patients with tremor were significantly more frequent in the baseline before treatment, their interictal epileptiform discharges had significantly higher frequencies (>4 Hz) and higher rates of photosensitivity in the EEG was

observed. These findings might suggest a phenotype leading to a further increased hyperexcitability.

4.1. SEP findings

In the comparison of SEP findings, the amplitudes of the waves representing the primary somatosensory cortex on both hemispheres were the highest in the JME group. SEP amplitudes were slightly lower in the JME group without tremor as compared to those of the JME group with tremor; however their results were still higher than those obtained in the two control groups (ET and normal controls). Enhancement of cortical SEP amplitudes might be seen in myoclonic epilepsies. This is more likely seen in patients having sensitivity to IPS (Jones, 1982). This result, partially supporting our hypothesis, indicated an increased excitability level in JME patients with tremor compared to others. However, regarding the enhanced cortical SEP findings which were thought to indicate increased cortical hyperexcitability more clearly, albeit observed more frequently, there was no exact dichotomy and there were no statistically significant differences in the present study between JME group with tremor and without tremor in terms of clinical and EEG findings. Additionally, approximately half of the patients with enhanced cortical SEP results had epilepsy histories in their families. Familial property of SEP findings in JME was previously emphasized in the literature (Atakli et al., 1999). Significant increases were found in P25 and N33 amplitudes in a limited number of SEP studies conducted on JME patients, but the presence of tremor were not questioned in these studies (Atakli et al., 1999; Salas-Puig et al., 1992; Kanazawa and Nagafuji, 1997; Erdem et al., 2001; Sendrowski et al., 2010). Similar to those in the literature, increased SEP amplitudes were also detected in JME patients in our study. Additionally, some SEP studies argued that cortical excitability increased before the treatment in patients with JME and it can be resolved with VPA treatment (Kanazawa and Nagafuji, 1997; Erdem et al., 2001). However all of our patients were under antiepileptic treatment and, SEP amplitudes were found still increased indicating the decrease in tonic inhibitory mechanisms at the brainstem, thalamic or cortical levels, or cortical hyperexcitability in the primary somatosensory cortices in JME patients with or without tremor. However, enhanced C reflex which is another indicator of cortical hyperexcitability was not seen in any group in the present study.

4.2. Comparison of tremor seen in JME and ET groups

The mean age at onset of ET was reported as 35–45 years (Lou and Jankovic, 1991). However the age at onset of tremor in JME patients was much lower (average: 13.75) and showed an overlap with the onset of seizures (Baykan et al., 2008). Similar to ET, mostly postural and occasional resting tremor was observed in JME patients with tremor (Jankovic, 2000). However, other findings reported approximately in half of the ET patients which were related to cerebellar disorders including intentional tremor, ataxia and dysmetria were not observed in our JME patients (Jankovic, 2000; Restuccia et al., 2003). In some patients, ET might show a progressive course in years (Jankovic, 2000), but there was no progression in our JME patients with tremor during their 10 year of follow-up. These clinical findings suggested that tremor observed in JME patients had a different origin and cannot be explained as ET comorbidity.

In this study, we detected that tremor amplitude and frequency were significantly changing in JME group both visually and accelerometrically during recordings, however this was not the case in the ET group. Tremor frequencies of JME patients obtained in accelerometric analyses were similar to those observed in ET patients, however they were slightly faster. Additionally, postural tremor amplitude in the non-dominant hand in ET group was significantly higher compared to that of JME group with tremor, indicating a disturbing tremor in ET together with the FTM-TRS analysis results. Furthermore, clumsiness in small spiral drawings with non-dominant hand (left) was significantly more impaired in ET group. Also, unlike the ET group, short, low amplitude instantaneous jerks in the fingers of the JME patients with tremor, observed both visually and polygraphically on the accelerometric recordings. This finding suggested “cortical myoclonic tremor” with very low amplitudes, rather than tremor in patients diagnosed with JME. Moreover in SEP examinations, carried out to determine whether the pathophysiological origin of the tremor in JME group is different from that of ET's, significantly increased SEP amplitudes were detected in JME group with tremor compared to ET.

4.3. Can these patients having both the diagnosis of JME and tremor Be categorized as a separate entity?

The JME diagnosis in our patients was correct in terms of all criteria, however, differently, these patients had hand trembling complaints before the JME diagnosis or detected simultaneously. There were small myoclonic jerks in the hands mixed into the trembling. Therefore, we might evaluate these small group of patients under the title of familial cortical myoclonic tremor and epilepsy (FCMTE) which was first identified in Japanese people, defined under different names in the literature and characterized with distal tremor-like movements and epileptic seizures (Restuccia et al., 2003; van Rootselaar et al., 2005). In FCMTE, the presenting symptom was usually tremor and the age at onset was 15 (ages 4–60) (Uyama et al., 1985). Age at tremor onset and other clinical features were also similar to our patients. Predominantly proximal multifocal myoclonic seizures were also seen in 80% of these patients and the emergence of these seizures was usually after tremor (the mean age: 17, range 5–60 years). Various clinical properties were detected in different pedigrees. Symptoms started earlier in European pedigrees and atypical symptoms may be observed in addition to the classical ones (Crompton et al., 2012; Depienne et al., 2010; Gardella et al., 2006; Magnin et al., 2009; Bourdain et al., 2006; Manabe et al., 2002).

Clinical characteristics of this syndrome was compatible with those of our patients, however there was no family history in most of our group. The differential diagnosis for FCMTE included ET, progressive myoclonic epilepsy, medication induced tremor (Na-Valproate tremor) besides JME (Bourdain et al., 2006), indicating the possible intersection of these two entities.

There were no reported differential diagnostic patterns in the EEGs of FCMTE patients and the reported findings were similar to those of our cases; background activity was normal and there was frequent photosensitivity (Gardella et al., 2006). GSW or multiple spike-wave complexes were seen in 94% of the patients with FCMTE (van Rootselaar et al., 2005).

In the recordings conducted on FCMTE cases using surface electrodes, short-lasting (<50 ms) arrhythmic or semi-rhythmic low amplitude discharges with irregular high frequencies (8–13 Hz) were shown in distal muscles of the upper extremity triggered by posture or action which can be also seen during resting (Labauge et al., 2002). Our accelerometric recordings showed a similar pattern besides being intensified with posture and weights placed on hands.

MRIs in FCMTE were generally reported to be normal, however mild cerebellar atrophy, non-specific anomalies (for example, slight enlargement in the subarachnoid space, mild enlargement of the lateral ventricles) were reported in some patients (Elia et al., 1998). As the patients with normal MRIs were included in our study to satisfy the initial diagnostic criteria of JME, our cases did not show any pathological MRI findings.

FCMTE is inherited mostly in autosomal dominant manner (de Falco et al., 2003), however, it can also be autosomal recessive (Stogmann et al., 2013). No definite gene has been found yet and different loci have been reported in different pedigrees (Depienne et al., 2010; Gardella et al., 2006; Magnin et al., 2009; Labauge et al., 2002; de Falco et al., 2003; Suppa et al., 2009; Striano et al., 2004, 2005; Deng et al., 2005). Pathophysiology of FCMTE is currently unknown. In addition to the cortical functional changes, cerebellar signs, and cerebellar pathological changes have also been described (Crompton et al., 2012; van Rootselaar et al., 2004). All pedigrees shared evidences of cortical origin for tremor-like movements. It was indicated that tremor-like movements were associated with sensorimotor cortex hyperactivity (van Rootselaar et al., 2006, 2008). This cortical hyperexcitability depended presumably on the changes in the inhibitor activity of GABAergic system (Van Rootselaar et al., 2007). Similar electrophysiological properties which supported cortical hyperexcitability were also detected in our patients.

Our study is the first detailed clinical and accelerometric investigation of the JME patients with tremor complaints, revealing different and similar properties with ET, and we detected findings indicating that origin of this tremor was most likely cortical. On the other hand, the weaknesses are the limited number of patients, inability to evaluate all consecutive JME patients, inability to study back-averaged cortical potentials time-locked to myoclonia, due to the long duration of the study protocol, and also that patients were under treatment. As discussed above most of the properties of these patients were compatible with FCMTE, however, we did not have any genetic analyses yet.

As a result, tremor which is the complaint of some JME patients can be related to comorbid ET in a few of them, whereas it can be VPA-induced tremor in some. However, in most of the patients with JME, tremor complaints may have different electrophysiological and clinical properties, and in fact, this can be a separate syndrome similar to JME, but associated with cortical myoclonic tremor. From this point of view, many findings of our JME patients who have tremor comply with clinically and electrophysiologically defined FCMTE entity. While FCMTE is regarded as a different syndrome, it has not been recognized by ILAE yet. If tremor is not taken into consideration or thought to be related to VPA which is frequently used in JME, FCMTE diagnosis might be skipped or even relapses may occur due to the discontinuation of the medication with presumption of remission for proximal jerks, only. Moreover, the tremor assessment in all JME patients should be performed at diagnosis and during follow-up to guide a better choice of treatment in these patients

In conclusion, our study is the first in the literature that addressed tremor in JME with all dimensions and suggested that these cases may indicate a different genetic entity.

Disclosure of conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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The study protocol was approved by the Istanbul University Faculty of Medicine Ethics Committee (2012/1573-1247) and all subjects were included in the study after giving their informed consents.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eplepsyres.2016.10.010.

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