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The clinical characteristics and related factors of tremor in patients with epilepsy

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ABSTRACT

Purpose: Tremor is frequently observed in patients with epilepsy (PWE), which is generally attributed to the side-effect of antiepileptic drugs (AEDs) particularly valproate (VPA) with largely unknown mechanisms. The study aimed to assess the clinical features and related factors of tremor in PWE with tremor.

Methods: PWE with tremor and a control group of age- and sex-matched PWE without tremor were enrolled. Detailed demographic and clinical information for each individual was recorded. PWE with tremor were evaluated by The Clinical Rating Scale for Tremor (CRST) and Tremor Related Activities of Daily Living (TRADL) questionnaire.

Results: 132 individuals were enrolled, which including sixty-six (36 males) PWE with tremor with mean age of 33 years and epilepsy duration of 12.5 years. Tremor was postural in all, with median duration of four and one year from diagnosis and AED treatment to the onset of tremor respectively. The upper limbs were predominantly affected. VPA had been used in 62 (93.9%) PWE with tremor compared to 31 (47.0%) PWE without tremor ($P < 0.001$). The total CRST score was significantly associated with epilepsy duration and maximum VPA dosage ($B = 0.30$, $p < 0.001$; $B = 0.32$, $p = 0.013$). Patients with VPA dosage over 17.05 mg/kg/d might be more vulnerable to develop tremor.

Conclusions: PWE with tremor were more frequently treated with VPA, however, tremor was mild in most without any functional impairment. Epilepsy duration and maximum VPA dosage were important factors of tremor severity, suggesting mechanisms underlying tremor in PWE may be an elaborate interplay of AEDs and disease itself.

1. Introduction

Tremor is defined as an involuntary, rhythmical, oscillatory movement of a body part produced by either synchronous or alternating contractions of antagonist muscles [1]. As one of the most common neurological symptoms, tremor was frequently seen in patients with epilepsy (PWE). According to the Epilepsy Comorbidities and Health (EPIC) Survey, 9.3% of the respondents with epilepsy reported perceived movement disorder/tremor, more than twice as prevalent as those without epilepsy [2].

Tremor in epilepsy patients is always presumed to be one of the side-effects of antiepileptic drugs (AEDs) particularly valproate (VPA), with the incidence of 45% and 6–64% respectively [3–6]. However, one study on juvenile myoclonic epilepsy (JME) patients tended to assort the tremor as a separate syndrome similar to JME [7]. In previous studies, postural or sometimes resting tremor were both observed, within several months after VPA therapy [8,9]. However, these results were based upon data from over 30 years ago with small sample sizes. Factors of tremor severity may include gender, age, the dosage and formulations of VPA though prior results were not always consistent [8,10–12]. The VPA-induced tremor was reported reversible on reduction or withdrawal of the drug and worsened as the dose increased [9,13,14].

As the limited existing researches were mainly conducted on patients with AEDs treatment for different neurological disorders besides epilepsy or on patients with VPA, there was no large and systemic study assessing the clinical features and functional impact of tremor in PWE taking AEDs. In consideration of the high incidence and impercipient of tremor in epilepsy patients, this study was conducted.

The aim of this study was (1) to analyze the clinical features of

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epilepsy and tremor in PWE with tremor, (2) to characterize the severity and functional impact of tremor in PWE with tremor, (3) to identify epilepsy related factors with tremor severity.

2. Methods

2.1. Subjects

Patients diagnosed with epilepsy as per International League Against Epilepsy (ILAE) criteria [15] were recruited from the Epilepsy Center of West China Hospital between August 2017 and August 2018. For the case group, patients (1) with self-reported complaint of tremor, or (2) directly asked by medical personnel "do you have tremor?" and answered "yes", or (3) tremor found in physical examination by clinicians were enrolled consecutively. The study excluded patients (1) diagnosed with other diseases related to tremor like Parkinson's disease and hyperthyroidism (2) with tremor preceding epilepsy (3) taking other medications with anti-tremor or tremor-induced effect such as beta-blockers and antipsychotics (4) with mental disability or unable to cooperate with the evaluations. As for the control group, we enrolled age- and sex-matched epilepsy patients without self-reported tremor, and "no" to the question "do you have tremor?", and no physical sign of tremor. The study protocol was approved by the Ethical Committee of West China Hospital, Sichuan University, and informed consent was obtained from all participants.

2.2. Clinical data

For each patient, we collected the following clinical data: demographics (age, gender, handedness and body mass index (BMI)); characteristics of epilepsy (age at first unprovoked seizure, epilepsy duration, seizure types, seizure frequency, neuroimaging data, AED types, duration and dosage of each AED, drug response); comorbid medical disorders and other medications besides AEDs.

Seizures were classified according to ILAE 2017 classification as focal onset seizures, generalized onset seizures, and unknown [16]. Details on the VPA formulation, delayed-release VPA (DR-VPA) or extended-release VPA (ER-VPA), was recorded in patients with VPA for further comparisons. Drug response was grouped as drug resistant and drug responsive, in which drug resistant was defined as the failure of adequate trials of two tolerated, appropriately AED schedules to achieve sustained seizure freedom [17]. Otherwise it was counted as drug responsive. Physical examinations (such as tremor, bradykinesia, rigidity, and postural instability) was performed by two neurologists individually, and where there was disagreement a consensus was reached by a senior neurologist.

After the physical examination, patients with tremor were asked to fill the questionnaire about (1) the first exact day/month you perceived tremor, (2) whether the tremor is symmetric; if not, which side is more severe? (3) is there any aggravating or relieving factor of your tremor? (4) Do you think tremor has any influence on your life quality?

2.3. Assessments

Tremor of the patients were evaluated with two validated inventories by a neurologist. The Clinical Rating Scale for Tremor (CRST) is a widely used and validated scale for tremor, which comprising three parts: Part A measures tremor location and amplitude, Part B assesses tremor when performing specific motor tasks (writing, drawing, and pouring liquids), and Part C assesses functional disability due to tremor (speaking, eating, drinking, personal hygiene, dressing, writing, working, and social activities) [18]. Each item was scored from 0 to 4, with higher scores indicating more severe tremor. The maximum possible score of part A, part B, part C and the total CRST were 88, 36, 32 and 156, respectively.

Tremor Related Activities of Daily Living (TRADL) questionnaire was employed to evaluate the degree of tremor-induced disability [19]. It is a self-administered questionnaire composed of 25 items reflecting daily activities. Each item was rated from 1 to 4 according to the difficulty to perform an activity (1, no difficulty to 4, cannot perform the activity by oneself). The possible score of TRADL were 25 to 100.

2.4. Statistics

Data analyses were conducted using IBM SPSS Statistics Software (version 20.0, SPSS, Inc., an IBM company, Chicago, IL, USA). Continuous variables were presented as mean (standard deviation) or median, and categorical variables were shown with counts (%). Independent-sample t-test, the chi-square test and Mann-Whitney U test were used to access the unadjusted differences in continuous or categorical variables between groups. Correction for multiple comparisons was not performed. Multiple linear regression analysis was employed to evaluate the association of epilepsy related factors and tremor severity after adjusting for potential confounding factors, considered as the variables significant ($p < 0.05$) in the univariate analyses. For PWE prescribed with VPA, an optimal cut-off point of maximum dosage per kg was estimated with receiver operating characteristic (ROC) analysis. The null hypothesis was rejected at a p-value < 0.05.

3. Results

3.1. Demographics and clinical characteristics of PWE

A total of 66 epilepsy patients (males: 54.5%) with tremor were recruited in this study. Sixty-six patients without tremor were included as controls. Descriptive information on demographic and clinical features was shown in Table 1.

For PWE with tremor, the mean duration of epilepsy was 12.5 ± 9.5 years, and the mean duration of antiepileptic treatment was 9.4 ± 8.5 years. In the 28 patients with tremor of generalized onset, three were confirmed as JME, compared with two in the control group. One patient with tremor was diagnosed benign epilepsy with centrotemporal spikes (BECTS). All the 66 patients with tremor were on AEDs when examined, with two-thirds (63.6%) of the patients under polytherapy. Sixteen (24.2%) patients were drug resistant, and 17 patients showed brain abnormality by Magnetic Resonance Imaging (MRI). Of these, one patient had undergone a craniotomy and evacuation of hematoma after trauma. We found a significant difference ($p < 0.001$) of the number of PWE who had used VPA between the tremor group (62, 93.9%) and control group (31,47.0%). In the other 4 patients with tremor never used VPA, Levetiracetam (LEV), oxcarbazepine (OXC) and carbamazepine (CBZ) were prescribed. Tendency of differences in the maximum and current VPA dosage were found between the groups ($p = 0.065$ and $p = 0.048$, respectively). There was no significant difference in other parameters between PWE with and without tremor.

3.2. Manifestation of tremor

The median time was 4 years (range 1 month to 50 years) and 1 year (range 1 month to 30 years) from diagnosis and medication to the occurrence of tremor respectively. Five patients claimed that tremor appeared after the first seizure but before medication. No parkinsonism symptoms like resting tremor, rigidity and bradykinesia were detected in this study. Tremor was postural in all patients, predominantly in upper limbs. Tremor was also seen in other body parts: nine patients in legs, three in trunk, one in laryngeal, and one in head. Thirty (45.5%) patients subjectively complained the asymmetry of tremor severity, especially in the non-dominant hand (73.3%). However, objective study of the asymmetry by the scores in Part A of the CRST revealed no statistical difference (data not shown).

Table 1
Demographic and clinical features of PWE with and without tremor.

Parameters	PWE with tremor (N = 66)	PWE without tremor (N = 66)	p
Age (y)	33.0 ± 13.4	32.0 ± 12.9	0.658
Gender (F/M)	30/36	30/36	–
Handedness (R/L)	65/1	66/0	–
BMI (kg/m^2)	22.7 ± 3.5	21.8 ± 3.6	0.149
Age at onset (y)	20.8 ± 14.5	19.0 ± 11.3	0.424
Epilepsy duration (y)	12.5 ± 9.5	13.0 ± 10.4	0.760
Seizure types (No.)			
Focal onset	36	43	0.457
Generalized onset	28	22	
Unknown	2	1	
Seizure frequency (No.)			
Seizure free > 1 year	16	19	0.544
< 1 seizure/month	24	27	
≥1 seizure/month	26	20	
Neuroimaging (No.)			
Normal/Abnormal	49/17	43/23	0.256
AEDs use (No.)			
Monotherapy/Polytherapy	24/42	32/34	0.159
AED medication duration (y)	9.4 ± 8.5	9.3 ± 8.9	0.944
Drug-resistant (No.)	16	15	0.837
Use of VPA (No.)	62	31	**< 0.001**
Maximum dosage of VPA (mg/kg/d)	16.0 ± 6.4	13.6 ± 4.9	0.065
Current dosage of VPA (mg/kg/d)	12.6 ± 8.1	9.2 ± 6.5	**0.048**
Cumulative dose of VPA (kg)	1.0(0.6-2.2)		
Total CRST score	14.2 ± 8.5		
Part A	3.7 ± 2.1		
Part B	7.2 ± 4.4		
Part C	3.3 ± 3.4		
TRADL score	29.2 ± 6.9		

Data are presented as counts, mean ± SD or median (IQR).
The p-Values are obtained from independent-sample t-test, the chi-square test and Mann-Whitney U test.
PWE, patients with epilepsy; BMI, body mass index; AEDs, anticonvulsants; VPA, valproate; CRST, Clinical Rating Scale for Tremor; TRADL, Tremor Related Activities of Daily Living questionnaire.

3.3. Severity and functional impact of tremor

The total score of CRST in the whole sample was 14.2 ± 8.5, with 3.7 ± 2.1 in part A, 7.2 ± 4.4 in part B, and 3.3 ± 3.4 in part C. In the interview, 19 (28.8%) patients complained influence of tremor on daily life. While when measured with the TRADL questionnaire that revealing the ability of daily living, 48 (72.7%) patients were observed an increase on the TRADL score, with the mean score of 29.2 ± 6.9. Most of the patients scored between 25 and 38, with only two patients got higher scores of 53 and 71 respectively.

3.4. Epilepsy related factors associated with tremor severity

Patients under polytherapy had higher scores of CRST than those under monotherapy, significantly in total score (P = 0.026), part B (P = 0.048) and part C (P = 0.05). There was no statistical difference in the groups with gender, seizure types, seizure frequency, drug response or neuroimaging as shown in Table 2.

Univariate linear regression analysis showed significant association between the total CRST scores and number of AEDs, medication duration, epilepsy duration, maximum dosage, current dosage and cumulative dose of VPA. However, multivariate linear regression showed significant association for the total CRST score only with epilepsy duration and maximum dosage per kg of VPA (adjusted $R^2 = 0.301$, $p < 0.001$; Table 3).

An area under the curve (AUC) was 0.625 (95% CI: 0.506-0.744, p = 0.05) in the ROC curve. The optimal value of cut-off point was 17.05 mg/kg/d (sensitivity 45.2%, specificity 83.9%) for the maximum dosage of VPA.

3.5. Tremor in PWE taking different formulations of VPA

Among the 55 patients receiving VPA currently, 9 were treated with DR-VPA formulation and 39 patients with ER-VPA. The other 7 patients experienced changes of VPA formulations were excluded for analysis. No difference was found in age, age at onset, epilepsy duration, medication duration and dosage between the two groups with different VPA formulations, except a higher ratio of men in those taking ER-VPA (Table 4). Though higher scores in three parts of CRST and TRADL were observed in the DR-VPA group, there was no statistical difference in the scores between DR-VPA and ER-VPA groups.

4. Discussion

4.1. Clinical features of tremor in PWE

In our cohort of PWE, no propensity of gender distribution, seizure types, seizure burden, epilepsy duration, AED medication duration, number of AEDs, drug response and abnormal neuroimaging was observed in the occurrence of tremor, except for the high proportion and dosage of VPA medication.

According to previous researches, tremor occurs in 6–64% of patients using VPA [4–6]. Other AEDs like CBZ, phenytoin and tiagabine were also related to tremor though reports were few [4,5,11]. However, the real incidence of VPA-induced tremor might be underestimated as revealed by quantitative methods that the impairment might already exist before tremor perceived [13]. Consistent with prior studies, 93.9% of patients with tremor had been treated with VPA in our study, compared with 47.0% in patients without tremor. Although the exact mechanism of valproate-induced tremor is unknown, several studies

Table 2
Scores of the CRST and TRADL scales in different subgroups.

		total CRST score	Part A	Part B	Part C	TRADL score
gender	male	14.4 ± 6.3	4.1 ± 2.3	7.2 ± 3.6	3.1 ± 2.0	28.2 ± 3.1
	female	13.9 ± 10.7	3.2 ± 1.5	7.1 ± 5.3	3.6 ± 4.6	30.3 ± 9.6
Seizure type	Focal onset	13.1 ± 7.1	3.3 ± 1.4	7.2 ± 4.5	2.7 ± 2.4	28.0 ± 4.9
	Generalized onset	15.6 ± 10.1	4.3 ± 2.6	7.2 ± 4.5	4.1 ± 4.4	30.8 ± 8.8
	Unknown	12.0 ± 5.7	3.0 ± 1.4	6.0 ± 1.4	3.0 ± 2.8	27.0 ± 2.8
Seizure frequency	Seizure free > 1 year	12.1 ± 4.8	3.1 ± 1.0	6.3 ± 2.8	2.7 ± 2.0	28.0 ± 3.3
	< 1 seizure/month	13.2 ± 7.8	3.7 ± 2.1	6.8 ± 4.6	2.8 ± 2.2	28.3 ± 3.0
	≥1 seizure/month	16.4 ± 10.5	4.2 ± 2.4	8.1 ± 5.0	4.2 ± 4.8	30.7 ± 10.2
Drug response	Drug-resistant	15.5 ± 12.9	3.7 ± 1.9	7.5 ± 6.4	4.3 ± 5.5	31.3 ± 12.7
	Drug-responsive	13.7 ± 6.6	3.7 ± 2.1	7.1 ± 3.6	3.0 ± 2.5	28.5 ± 3.4
Neuroimaging	Normal	14.3 ± 9.1	3.7 ± 2.1	7.3 ± 4.7	3.4 ± 3.7	29.6 ± 7.7
	Abnormal	13.7 ± 6.6	3.8 ± 2.1	6.8 ± 3.3	3.1 ± 2.5	27.8 ± 3.2
AEDs	monotherapy	**11.3 ± 6.2***	3.2 ± 1.4	**5.7 ± 3.2***	2.4 ± 2.6	27.5 ± 3.2
	polytherapy	**15.9 ± 9.2**	4.0 ± 2.3	**8.1 ± 4.8**	3.8 ± 3.8	30.1 ± 8.2

Data are presented as mean ± SD.
The p-Values are obtained from Mann-Whitney U test.
AEDs, anticonvulsants; CRST, Clinical Rating Scale for Tremor; TRADL, Tremor Related Activities of Daily Living questionnaire.
* $p < 0.05$.

Table 3
Univariate and multivariate linear regression analysis for the associations of the total CRST score.

parameters	Univariate coefficient (95% CI)	p	Multivariate coefficient (95% CI)	p
Age	0.05 (−0.09 to0.18)	0.495		
Gender	−1.93 (−5.44 to 1.59)	0.278		
BMI	−0.28 (−0.79 to 0.24)	0.285		
Seizure types	−1.16 (−4.36 to 2.04)	0.471		
Seizure frequency	1.45 (−0.77 to 3.68)	0.197		
AEDs use	3.68 (0.16 to 7.19)	**0.041**		
AED medication duration	0.35 (0.17 to 0.54)	**< 0.001**		
Epilepsy duration	0.35 (0.19 to 0.51)	**< 0.001**	0.30 (0.14 to 0.47)	**< 0.001**
Maximum dosage of VPA	0.31 (0.05 to 0.58)	**0.023**	0.32 (0.07 to 0.57)	**0.013**
Current dosage of VPA	0.22 (0.01 to 0.43)	**0.045**		
Cumulative dose of VPA	1.46 (0.53 to 2.39)	**0.003**		

The p-Values are obtained from linear regression analysis.
BMI, body mass index; AEDs, anticonvulsants; VPA, valproate; CRST, Clinical Rating Scale for Tremor; CI, confidence interval.

attributed it to abnormality of neurotransmitters such as γ -amino butyric acid (GABA), dopamine (DA) and catecholamines to some degree [20,21].

Time from medication to the occurrence of tremor was 1 year (range 1 month to 30 years) in our study. Prior studies reported the tremor began 1 to 14 months after starting therapy [8,9,14]. The difference might due to the study design, as some studies with small sample sizes performed prospective approaches and other objective measurements but our results were based on the patients' recall. Moreover, as mentioned above, the impairment might already exist before tremor perceived, it may take a long time from insidious impairment to perceived oneself or detected in physical examination [13].

Generally, the tremor was mild and seldom induced disability by the objective measurements including CRST and TRADL scores, which was in accordance with prior reports [10,22]. Tremor was observed postural in all in the present study, with the clinical features similar to essential tremor (ET). Previous studies with validated scales and electromyographic recordings also reported a ET resembled tremor with similar severity and functional impairment [7,22,23]. Postural tremor was observed in most studies including one performing computerized tremor analysis, while resting tremor was reported in some as well [7,8,10,12,23].

No asymmetry was detected in the CRST test in the present study, however, 45.5% of patients complained different tremor severity between the right and left sides, particularly more severe in the non-dominant hand. One possible reason of the inconsistence could be that even if tremor was bilaterally symmetric, patients might perceive a more obvious influence in the non-dominant hand for it was less flexible in task performing. Two studies focused on the symmetry of tremor in PWE. In one study in JME, no difference was found between the right and left sides by accelerometric analysis [7]. While another study with 10 patients reported a bilateral tremor, prominently in the dominant hand [8]. More researches with objective instrument are demanded for the features of tremor to elucidate the questions of whether the tremor is typical ET and the symmetry of tremor.

4.2. Epilepsy related factors associated with tremor severity

As severity of tremor was measured by CRST and TRADL scores, patients under polytherapy had a higher score than monotherapy in our study, though no relationship was reported between presence of tremor and the number of AEDs in earlier study [3].

Multivariate linear regression analysis revealed that the dosage of maximum VPA instead of current VPA was strongly correlated with higher CRST score, which indicating the severity of tremor. A further analysis suggested PWE under a maximum VPA dosage higher than 17.05 mg/kg/d were more vulnerable to be suffered with tremor. Similarly, prior researches revealed that tremor became more severe with the increasing dosage, especially when the dosage exceeded 750 mg per day [8,10]. One possible explanation was the recovery of tremor might take a long time after drug reduction or withdrawal, but exact mechanism requires further study.

In addition, epilepsy duration also showed a strong correlation with tremor severity in our study, contrary to prior findings [13]. Since the

Table 4
Characters of tremor in PWE treated with different VPA formulations (n = 48).

Parameters	Delayed-release VPA (n = 9)	Extended-release VPA (n = 39)	p
Age (y)	33.0 ± 13.7	31.4 ± 11.7	0.715
Gender (F/M)	7/2	12/27	**0.020***
BMI (kg/m^2)	20.9 ± 2.5	23.2 ± 3.6	0.072
Age at onset (y)	19.8 ± 14.4	21.4 ± 12.5	0.740
Epilepsy duration (y)	13.2 ± 15.5	10.4 ± 7.0	0.419
Medication duration (y)	9.9 ± 15.8	7.6 ± 5.5	0.670
AEDs use			
Monotherapy/Polytherapy	3/6	12/27	1.000
Maximum dosage (mg/kg/d)	16.8 ± 6.1	15.2 ± 6.2	0.477
Current dosage (mg/kg/d)	14.2 ± 6.3	13.5 ± 6.7	0.804
Cumulative dose (kg)	1.2(0.2-3.6)	1.1(0.6-2.2)	0.905
total CRST score	20.7 ± 15.6	13.0 ± 6.0	0.284
Part A	4.9 ± 3.6	3.5 ± 1.6	0.370
Part B	9.9 ± 7.1	6.9 ± 3.8	0.335
Part C	5.9 ± 7.0	2.7 ± 1.8	0.219
TRADL score	35.3 ± 16.3	28.3 ± 3.0	0.989

*$p < 0.05$.
Data are presented as counts, mean ± SD or median (IQR).
The p-Values are obtained from independent-sample t-test, the chi-square test and Mann-Whitney U test.
PWE, patients with epilepsy; VPA, valproate; BMI, body mass index; AEDs, antiepileptic drugs; CRST, Clinical Rating Scale for Tremor; TRADL, Tremor Related Activities of Daily Living questionnaire.

available researches on tremor in PWE were limited, it's hard to explain all the outcomes. It may be influenced by the sophisticated interrelations in medication, epilepsy and individual predisposition, though the nature yet to be identified.

4.3. Tremor in PWE taking different formulations of VPA

Though it did not reach significance, patients receiving DR-VPA treatment showed a higher score in the tremor severity and disability than those receiving ER-VPA. A prospective study quantitatively assessing VPA-induced tremor also revealed that the DR-VPA group exhibited a significant increase in tremor amplitudes [12]. Other studies observed improvement when switching from DR-VPA to ER-VPA [24,25]. The underlying mechanisms were unclear, prior studies ascribed it to the diverse peak–trough variation of different formulations to some extent [26].

4.4. Limitations

There are several limitations in our study. First, potential recall bias existed due to the design of our study. Second, as a cross-sectional design, the study was lack of longitudinal follow-up and comparisons. It was unable to study the change of presumed drug-induced tremor after medicine reduction or withdrawal. Third, we didn't detect plasma concentration of VPA in the present study, however, prior studies showed little relationship between plasma concentration and tremor severity [8,10,12]. Furthermore, by evaluating severity and handicap with scales, the information we got was limited. Other objective measures such as electromyography and accelerometer might reveal more details and be more credible, if applied to the research.

5. Conclusions

Overall, PWE with tremor were more frequently treated with VPA. Tremor was postural in all, with mild functional impairment in daily life. Tremor severity was significantly associated with epilepsy duration and maximum VPA dosage. Patients under a VPA dosage higher than 17.05 mg/kg/d might be more vulnerable to develop tremor. With mechanisms underlying unknown, more investigations are required to uncover the inner connection of epilepsy, VPA and tremor.

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Conflict of interest

The authors report no conflicts of interest in relation to this work.

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