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From tremor to myoclonus associated with valproate: Clinical insights and polymyographic evaluation

Leyla Köse Leba, Ayşegul Gündüz, Çiğdem Özkara, Seher Naz Yeni, Şakir Delil, Meral E. Kiziltan

Istanbul University-Cerrahpasa, Cerrahpaşa Faculty of Medicine, Department of Neurology, Türkiye

Abstract

Objectives: We aimed to perform clinical and polymyography analyses in patients with epilepsy to assess characteristics of involuntary movements associated with valproate. *Method:* All consecutive patients who used valproate for epilepsy were included in the study. We performed a detailed examination and polymyography recordings on the upper extremities at rest, with arms outstretched, during loading, action, and fine hand movements. We determined the type and characteristics of abnormal movements, as well as the clinical findings associated with these movements. *Results:* We included 63 patients in the study, identifying 45 (71.2%) with tremor and 20 (31.7%) with myoclonus. All patients with myoclonus also had tremor. Valproate-induced tremor was postural, mild, and associated with low-dose valproate, compared to patients without tremor (n=18). Although mild to moderate, a positive correlation was found between tremor severity, as measured by the Fahn-Tolosa-Marin tremor rating scale, and the duration of valproate use (p=0.026, r=0.328). Distal myoclonus was prominent and appeared in repetitive bursts (polyminimyoclonus), clinically mimicking tremor. It was equally present in patients with focal epilepsy. Patients with myoclonus had higher serum valproate levels than those without myoclonus.
Conclusions: Tremor was common, primarily mild and postural, and associated with low-dose valproate. The severity increased with the more prolonged use. Higher serum levels of valproate triggered myoclonus, even in patients with focal epilepsy. Polymyography is needed to distinguish tremor and myoclonus.

Keywords: Epilepsy, tremor, valproate, valproate-induced myoclonus, valproate-induced tremor

INTRODUCTION

Valproate has been approved by the Food and Drug Administration (FDA) and is a first-generation, broad-spectrum antiseizure drug. It is commonly administered to treat generalized and focal epilepsies in children and adults.[1] Tremor is a widely known side effect of valproate.[2] The reported percentage of tremor is quite large, 6-45%[3-5], and is mainly influenced by the research method used, such as patient reports, detailed neurological examination, electrophysiological methods, or accelerometers. Among patients with epilepsy, tremor is generally related to valproate.[6] Action or postural tremor is more common than rest tremor.[2] A study revealed more frequent cranial (head/voice) and lower limb involvement, as well as a higher frequency of rest tremor in valproate-induced tremor than in essential tremor.[7] However, parkinsonism is rare despite a higher incidence of rest tremor.[8] According to reports in the literature, tremor generally appears when valproate dosage exceeds 750 mg/day, particularly 1000 mg/day.[2]

However, the prevalence and risk factors are controversial. Furthermore, cultural and genetic factors may influence the occurrence of valproate-related tremor. Therefore, we aimed to investigate the prevalence and risk factors of valproate-induced hyperkinetic movements in our cohort. To determine tremor in our cohort, we performed detailed clinical and polymyography analyses in patients using valproate.

Address correspondence to: Leyla Köse Leba, Department of Neurology, Bursa City Hospital, Bursa, Türkiye. E-mail: leylakos_e@hotmail.com
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METHODS

We recruited consecutive patients with epilepsy taking valproate over the course of a year. The patients have undergone a detailed clinical and electrophysiological workup. Patients taking medications known to cause involuntary movements (such as antipsychotics, antidepressants—especially SSRIs, lithium, beta-adrenergic agonists, and other antiseizure medications), those under the age of 18 years, those unable to cooperate in reporting side effects, or patients who were unwilling to enroll were excluded from the study. Patients with other known causes of tremor, including thyrotoxicosis, Parkinson's disease, and essential tremor, were also excluded based on clinical evaluation and laboratory findings when necessary.

Clinical assessments

All patients were interviewed using a detailed questionnaire prepared by the attending researchers. The questionnaire included assessments of sociodemographic and clinical features regarding tremor and epilepsy. We extracted information on epilepsy type, seizure type, antiseizure medications, duration of tremor reported by the patient, daily valproate dose, serum valproate level, age at seizure onset, age at initiation of valproate use, other side effects, alcohol consumption, and family history of tremor from patient interviews and medical records. The same investigator (L.K.L.) did a detailed neurological examination regarding tremor. To minimize observer bias, tremor findings were further supported by polymyographic recordings. During neurological examination, involuntary movements were assessed in posture, action, and rest. The localization and side were established. The same investigator also administered the Fahn-Tolosa-Marin (FTM) tremor rating scale to each patient. The epilepsy syndromes were diagnosed according to the 1989 ILAE classification, and seizure classification was based on the 2010 ILAE classification. The diagnosis was reassessed by the same neurologist expert in epilepsy (S.N.Y.) according to the 2017 classifications. We also noted the referral diagnosis for involuntary movements of the epilepsy unit: tremor, none, or other. All patients underwent laboratory investigations, including a complete blood count, serum biochemistry, and serum valproate levels, on the same day as their neurological and electrophysiological investigations. Patients were categorized as receiving valproate monotherapy or polytherapy, and concomitant antiseizure medications were recorded.

Electrophysiological assessments

We performed polymyography recordings using surface electrodes and Neuropack Sigma MEB-5504k (Nihon Kohden Medical, Tokyo, Japan) while patients were relaxed and sitting in an armchair. The Ag–AgCl pairs of cutaneous recording electrodes were placed on the biceps brachii, flexor muscles of the wrist, extensor muscles of the wrist, and abductor pollicis brevis muscles. The ground electrode was on the anterior side of the forearm.

We recorded on the predominantly affected side or on the right side if both sides were affected equally. We recorded at rest, with arms outstretched, during loading, during action, and during fine hand movements. The amplitude and frequency of involuntary movements were measured using cursors.

The frequency interval, sweep time, and sensitivity were adjusted to 20 Hz–5 kHz, 50 ms–200 ms/div, and 200–1000 μV/div, respectively.

Statistical analysis

We identified abnormal movement if both neurological examination and polymyography indicated, and determined the frequency of abnormal movement in the group. Involuntary movements were defined according to previous reports.[9] We categorized patients into two subgroups: patients with abnormal movements, such as tremor or myoclonus, and patients without myoclonus. We compared age, sex, clinical features of epilepsy, daily valproate dose, and serum valproate levels between the two groups.

The severity of tremor was presented using the FTM scale. We also used amplitude measurement on polymyography to indicate severity. Any involuntary activity was considered high amplitude when it was more than 500 μV, and moderate and low amplitude between 200-500 μV and <200 μV, respectively. Additionally, the ratio of myoclonus amplitude to interference amplitude was calculated to provide standardization.

Data analyses were performed using the SPSS 15.0 software statistical package. Qualitative data

were presented as percentages, and quantitative data were presented as means ± SD.

Comparisons were made using the t-test when the data were normally distributed, and the Mann–Whitney U test when they were not normally distributed for quantitative data. For qualitative data, comparisons were made using the Chi-square test.

The association between tremor and clinical findings, including epilepsy type, seizure type, use of single or multiple antiseizure medications, daily valproate dose, serum valproate level, age at seizure onset, and age at onset of valproate use, was analyzed using logistic regression.

Correlations between tremor severity measured by the FTM scale and duration of valproate use, duration of tremor declared by the patient, daily valproate dose, and serum valproate level were assessed using Pearson correlation analysis.

A p-value ≤ 0.05 was considered significant.

RESULTS

In the study period, we recruited 63 patients who were using valproate and fulfilled the study criteria. Of these, 26 (41.3%) were receiving valproate monotherapy, while 37 (58.7%) were on polytherapy with other antiseizure medications, including topiramate, lamotrigine, levetiracetam, and carbamazepine.

By clinical examination, we determined involuntary movements in 45 (71.4%) patients: i. tremor or ii. irregular jerks. All patients with irregular jerks also had tremor. However, in all these cases, the referral diagnosis from the epilepsy unit was only tremor. Polymyography showed tremor in an additional seven patients, confirming tremor in 45 patients (71.4%) and myoclonus in 20 patients (31.7%).

Eighteen patients exhibited no abnormal movement and therefore constituted the control group.

Tremor

Tremor characteristics: Clinical examination revealed tremor in 38 patients. All patients had upper extremity tremor, accompanied by voice tremor in two patients, and head tremor in one. No patients had lower extremity tremor. Using polymyography, we determined that seven additional patients had tremor. Therefore, 45 patients were in the tremor group.

Postural tremor was the most common tremor type (n = 40, 89%), followed by action tremor (n = 28, 62%) and rest tremor (n = 13, 29%). There were patients with two or more types of tremors. The tremor was low-amplitude, synchronous, and generally affected the distal parts of the upper extremities. The frequency ranged from 6 to 9 Hz.

The mean FTM tremor rating scale score was 8.7±7.2 points in the tremor group. According to patient reports, tremor developed within 1 month of initiating valproate in 26 (58%) patients. The mean duration from the tremor onset was 2.7 years. Seven (15%) patients did not notice tremor. In these patients, tremor was not subjectively reported but was detected exclusively by polymyography despite being clinically subtle or unrecognized.

Clinical findings: The mean ages of the tremor and control groups were 31.4±13.5 and 31.1±13.1 years, respectively. There were 22 women (48.9%) in the tremor group, whereas there were six women (33.3%) among patients without tremor ($p = 0.262$). Other sociodemographic features, such as alcohol consumption, family history of tremor, seizure types, epilepsy syndrome types, using multiple antiseizure drugs, and the presence of other side effects, were similar (Table 1). Although serum valproate levels were similar between the groups (56.7±30.1 µg/ml vs. 55.4±26.7 µg/ml, $p = 0.876$), the daily valproate dose was lower among patients with tremor compared to the control group (911.1±397.1 mg/day vs. 1166.7±469.7 mg/day, $p = 0.028$). Low-dose valproate was also an independent risk factor for tremor ($p = 0.026$). A positive correlation was found between tremor severity, as measured by the FTM tremor rating scale, and the duration of valproate use ($p = 0.026$, $r = 0.328$).

Myoclonus

Myoclonus characteristics: We determined irregular, high-amplitude, short-duration jerky bursts (positive myoclonus) in 20 patients, all of whom also had tremor. Among them, four patients also exhibited silent periods (negative myoclonus). They did not have C reflexes or high-amplitude long-latency reflexes.

Clinical findings: The mean ages of patients with and without myoclonus were 27.5±10.2 and 31.1±13.1 years, respectively ($p=0.348$). There were 14 women (58.3%) among the patients with myoclonus, and six women

Table 1. Sociodemographic and clinical features of patients with and without tremor

	Patients with tremor n=45	Patients without tremor n=18	p
Age, year	31.4 ± 13.5	31.1 ± 13.1	0.802
Gender M, n (%)	23 (51.1)	12 (66.7)	0.262
Treatment, n (%)			
Monotherapy	18 (40)	8 (44.4)	0.609
Polytherapy	27 (60)	10 (55.6)	
Valproate daily dose, mg/day	911.1± 397.1	1166.7 ± 469.7	***0.028***
Serum valproate level, µg/ml	56.7 ± 30.1	55.4 ± 26.7	0.876
Family history, n (%)	5 (11.1)	4 (22.7)	0.939
Smoking, n (%)	9 (20)	7(38.9)	0.120
Alcohol n (%)	2 (4.4)	2 (11)	0.683
Type of seizure			0.697
Focal	21 (46.7)	10 (55.6)	
Generalized	23 (51.1)	8 (44.4)	
Non-epileptic	1 (1.6)	-	
Duration of valproate use	7.9 ± 8	6.2 ± 6.3	0.368

(33.3%) were in the control group (p = 0.052). Other sociodemographic features, such as alcohol consumption and family history of tremors, seizures, and epilepsy syndromes, the number and the type of the other antiseizure drugs (topiramate, carbamazepine, lacosamide, zonisamide, lamotrigine, levetiracetam) were similar. Patients with myoclonus had higher serum valproate levels. However, it was not significant (67.0±22.4 µg/ml vs 55.4±26.7 µg/ml, p=0.140).

Figure 1 shows representative examples of tremor (A-B), myoclonus (C-D), and both tremor and myoclonus (E-F) in the patients.

DISCUSSION

The major findings of our study indicate that valproate-induced tremor was frequent, mild, and predominantly postural. It was associated with low-dose valproate in our cohort, and its severity correlated with the duration of use. Additionally, myoclonus was common and accompanied tremor in nearly half of the cases.

Tremor in our patient group was mild, and did not cause disability, similar to that reported in the literature.[10,11] Although rest tremor and parkinsonism are known complications of valproate[10,12], almost 15% of patients in our study did not recognize or report tremor. Therefore, it is clear that recognition requires specific examination methods, and spontaneous self-reports are not sufficient to determine prevalence. The tremor characteristics in our cohort were similar to those reported in a recent study. These authors reported bilateral postural and action tremor. However, the frequency was slower than we detected: 5-6 Hz.

Besides being a direct complication of valproate, there may be other causes of tremor in patients with epilepsy using valproate, such as co-existence of essential tremor or misdiagnosis of familial myoclonic tremor and epilepsy.[13] The characteristics of valproate-induced tremor, as identified on surface electromyography, are similar to those of essential tremor.[14] Despite the clinical similarities, essential tremor may occur at a relatively older age[15], often accompanied by high-frequency tremor, alcohol responsiveness, or a family history.[9] We specifically searched for these features in our patient population, and none of the patients in this study matched the criteria for essential tremor. In familial myoclonic tremor and epilepsy, in contrast to our cases, tremor is expected to start simultaneously with seizures and to decrease in severity after administration of valproate.

Previous studies in humans have yielded conflicting findings regarding the relationship between daily valproate dosage and tremor. Some did not find a correlation between the daily

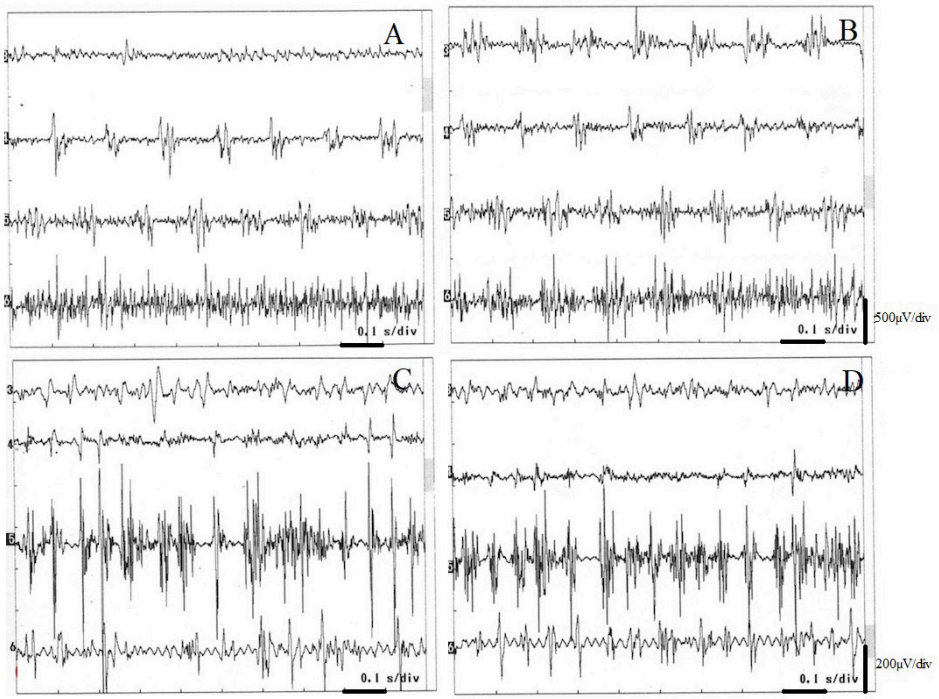

Figure 1. Representative examples of tremor (A-B) and myoclonus (C-D) in the patients using valproate. Please note the repetitive bursts of myoclonus and silent phases in C and D, which illustrate an example of polyminimyoclonus.

valproate dose and tremor.[4] Some suggested that tremor was associated with a higher daily dosage (i.e.,> 750 mg per day).[2] Interestingly, Paparella *et al*. reported a direct relationship between valproate serum concentration and the severity of kinetic tremor.[7] However, an animal study also observed the association with low doses of valproate. Biggs and colleagues reported the dual effect of valproate on GABA levels in rats. Low valproate levels reduced GABA levels, whereas moderate doses exerted no impact, and high doses increased GABA levels in the rat hippocampus.[16] Its dual GABAergic effect may explain the decrease of tremor with high doses and the development of myoclonus instead in our cohort. Mechanisms using GABA may be responsible for the generation of myoclonus since other drugs using GABAergic mechanisms are also known to cause myoclonus. Paparella *et al*. suggested that valproate may trigger tremor through the cerebellum. One study investigated the association of valproate-induced tremor and cerebellar morphology.[17] They found that tremor was associated with high daily dosage, long treatment duration, and a family history of tremor. Interestingly, the same authors suggested that extended-release formulation or combination with carbamazepine was a protective factor. The patients in our cohort were using the extended-release formulation, which may explain why higher daily dosages did not cause tremor.

The most interesting and surprising finding in our study was the recording of myoclonus, even in patients with focal epilepsy, which was not characterized by the presence of epileptic myoclonus. The morphology of myoclonus was similar to that of the cortical or cortico-subcortical type: high in amplitude and short in duration. We do not have analyses of back-averaging, giant somatosensory evoked potentials, or the C-reflex that confirm cortical myoclonus.

Previously, a study investigating motor performance quantitatively in patients using valproate demonstrated irregular finger movements, which were attributed to valproate-induced deterioration of motor performance.[18] They performed an accelerometer but did not report myoclonus. We suggest that reduced motor performance may be related to the development of myoclonus. On the other hand, myoclonus related to valproate has only been reported in cases with toxicity and encephalopathy.[19] In our patient population, no patients exhibited any other toxicities. Sometimes, the myoclonus

in the distal part of the extremities may form clusters mimicking the postural tremor. In these cases, one may misdiagnose it as a postural tremor solely based on clinical examination, particularly if the examiner is not an expert in movement disorders.[20] Therefore, it is crucial to note that a polymyography is necessary to distinguish. In the referral diagnosis, clinicians failed to recognize irregular jerks or even tremor in some cases of our cohort.

Myoclonus is also a well-known manifestation in various types of hereditary or acquired ataxia. However, we should acknowledge that we did not measure the blood ammonium levels. The relatively higher serum valproate levels in patients with myoclonus may suggest a higher probability of toxicity, which could be related to individual enzymatic changes. However, all patients had normal hepatic functions.

We should acknowledge certain other limitations of the study, such as the relatively small number of patients without abnormal movements. Second, this is a cross-sectional study; although clinicians reduced the dosage or stopped the medication in severe cases, we did not repeat the examinations after their antiseizure medications were changed. However, we may say that the treatment was not changed in most patients, as the tremor was mild and not disturbing.

In conclusion, low-dose valproate is mainly related to mild postural tremor in the early period after the administration of the drug. The severity increased with the more prolonged use. Interestingly, valproate, especially in high doses, may also trigger myoclonus. Polymyography is needed to distinguish tremor and myoclonus. We propose that valproate exerts a dual mechanism of action on involuntary movements, postural tremor at lower serum levels, and myoclonus at higher serum levels.

DISCLOSURE

Ethics: The Institutional Review Board approved the study, and all participants provided informed consent (February 3, 2016, 82686).

Data availability: The data supporting this study's findings are available on request from the corresponding author.

Financial support: None

Conflict of interest: None

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