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Short communication

The clinical features and functional impact of valproate-induced tremor

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ABSTRACT

Background: Tremor is a known side-effect of anticonvulsants, particularly of valproate. However, there is a dearth of information regarding detailed clinical features and functional impact of valproate-induced tremor.

Methods: We studied a cohort of patients treated with anticonvulsants for neurological disorders, through blinded evaluations using the Clinical Rating Scale for Tremor (CRST); we compared the frequency, severity and functional impact of drug-induced tremor between patients treated with valproate and those treated with other anticonvulsants.

Results: From a cohort of 218 consecutive patients, 171 were fully evaluated; 118 patients were taking valproate alone or combined with other anticonvulsants and 53 patients were taking other anticonvulsants. Mean age (±SD) at evaluation of the cohort was 32 ± 13 years, females represented 55.6% of cases. Tremor was more frequently observed in patients taking valproate particularly postural upper limb tremor: 49% vs. 15% (right-side) ($P < 0.001$) and 48.3% vs. 13.2% (left-side), ($P < 0.001$); had a higher total CRST score: 12.14 vs. 3.06 ($P < 0.001$), and required more frequently treatment for drug-induced tremor: 23.7% vs. 5.6% ($P=0.005$) compared with patients taking other anticonvulsants. Among 118 patients taking valproate, women had a higher total CRST score compared with men: 14.54 ± 14.9 vs. 9.56 ± 9.55 ($P=0.034$). A weak correlation between the total CRST score, dose per Kg of valproate and serum levels of valproate were observed.

Conclusions: Tremor is frequently observed in patients taking valproate and is severe enough to require treatment in about 24% of cases.

1. Introduction

Tremor is a well-known side effect of anticonvulsants, observed in 45% of patients taking these drugs [1]. Among all anticonvulsants, valproate is the most commonly associated with drug-induced tremor, reported in up-to 80% of subjects taking this drug [2,3]. However, the clinical features, risk factors and functional impact of drug-induced tremor by anticonvulsants, particularly valproate, have not been well defined.

We aimed to characterize the frequency, severity and distribution of drug-induced tremor in patients treated with valproate and other anticonvulsants; we hypothesized that patients taking valproate would have a higher frequency, severity and functional impact of drug-induced tremor, compared to patients taking other anticonvulsants. Primary outcomes were the total score in the Clinical Rating Scale for Tremor (CRST); and treatment-required for drug-induced tremor in patients treated and not treated with valproate; secondary outcomes included scores in Part A (tremor magnitude), Part B (tremor during tasks), and Part C (tremor disability) of the CRST.

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2. Materials and methods

We studied a cohort of 218 consecutive patients taking anticonvulsants for different disorders in a single neurological center. Inclusion criteria included patients older than 14 years-old, both genders, and taking anticonvulsants for at least the previous three months, and within the last 6 h from the clinical assessments. We excluded patients with mental handicap or unable to cooperate with the evaluations, focal or generalized neurological deficits such as spasticity or dystonia, and patients taking medications with a known anti-tremor effect such as beta-blockers, topiramate, primidone, and gabapentine [4]. We eliminated patients endorsing tremor before starting treatment with anticonvulsants or when the tremor had clinical features supporting an alternate etiology such as essential, dystonic or psychogenic tremor; and patients unable to complete the CRST evaluation. Patients taking other drugs with potential tremorigenic effect were not eliminated as this was infrequent. Patients were treated with three valproate preparations: divalproex sodium (with enteric coat) and magnesium valproate with and without enteric coat. Evaluations were carried out by a movement disorders specialist using the CRST which scores range from 0 to 4 per evaluated component, with higher scores indicating more severe tremor [5]. The CRST is a widely used and validated scale [6] composed of three parts: Part A includes items on tremor magnitude in different body parts (maximum possible score: 80); Part B includes items in tremor tasks such as writing, drawing spirals and pouring water, however the latter item was not included in the analysis due to difficulties to carry out this task consistently during the clinical visit (maximum possible score: 28 −excluding item 16: water pouring-) and Part C includes items in tremor disability (maximum possible score: 28).

The evaluations were blinded to the anticonvulsants taken by the examined patient; and patients were not aware of the study hypothesis. At the end of the clinical evaluations, patients were asked whether treatment was necessary for their tremor, in that case, a switch to other anticonvulsant or propranolol up-to 40 mg three times a day was provided, after excluding contraindications for use of beta-blockers. We compared the clinical and demographic features between patients taking and not taking valproate. The Internal Review Board of the University Hospital of Guanajuato approved the study protocol and patients provided informed consent to participate in the study.

2.1. Statistics

Data was summarized in means ± standard deviations, range, and percentages. The independent T-test was used to compare means between groups. The chi-squared test and Fisher's exact test were used to compare proportions between groups. Correlations were carried out using Pearson's R or Spearman's rho tests. The specific weight of independent variables on the total CRST score and "treatment-required for tremor" was analyzed using multivariate linear and logistic regression respectively. All statistical evaluations were carried out using SPSS version 22, a P value < 0.05 was considered significant.

3. Results

From a cohort of 218 consecutive patients, we excluded or eliminated 49 patients due to different reasons. A total of 171 patients fulfilled the inclusion criteria. There were 118 patients taking valproate alone or combined with other anticonvulsants and 53 patients taking other anticonvulsants (supplementary figure S1).

The 171 patients included had a mean (±SD) age of 32 ± 13 years, and most were female n = 95 (55.6%). No differences in gender distribution, age at evaluation and underlying diagnosis was observed between patients treated and not treated with valproate, except for a higher number of anticonvulsants per patient in those taking valproate (Table 1). The number and type of anticonvulsants are summarized in Supplementary Table 1.

Tremor distributed more frequently in assessed body parts in patients taking valproate compared to patients taking other anticonvulsants (Table 1). Frequency of postural upper limb tremor: 49% vs. 15% (right-side) ($P < 0.001$) and 48.3% vs. 13.2% (left-side), ($P < 0.001$). Kinetic upper and lower limb tremor, postural tongue, trunk and lower limb tremor were also significantly more frequent in patients taking valproate compared to patients taking other anticonvulsants (Table 1). When comparing scores in postural tremor, those on valproate had a higher score in the right and left side: 0.60 vs. 0.17, with between-group difference of 0.432 points (95% confidence interval [CI]: 0.219 to 0.645; $P < 0.001$) (supplementary table S2). Upper limb tremor at rest was observed in about 10% of patients taking valproate; however, none of these patients had rigidity or bradykinesia suggesting parkinsonism; a feature also described in patients taking valproate [7]. Total CRST scores were higher in patients taking valproate: 12.14 vs. 3.06, between-group difference: 9.07 points (95% CI: 5.55 to 12.6; $P < 0.001$). Higher scores in Parts A, B and C of the CRST were also observed in patients taking valproate (Table 2).

Treatment for tremor was required in 23.7% of patients taking valproate, compared with 5.6% of patients taking other anticonvulsants ($P = 0.005$). Patients requiring treatment for tremor were older than those not requiring treatment: 36.6 ± 15.4 vs. 30.8 ± 12.2 ($P = 0.026$) even after controlling for gender, number of anticonvulsants and treatment with valproate ($P = 0.030$). All patients requested treatment because of upper limb postural and kinetic tremor and not because other types of tremor. Fifty three patients had serum levels of valproate measured at the time of the evaluation; no differences in such levels were observed between patients requiring treatment for their tremor (n = 12) or not (n = 41): 78.6 ± 36.4 vs. 76.1 ± 26.5 ($P = 0.794$); a weak correlation between serum levels and total CRST score: r = 0.156 ($P = 0.256$) and between the dose per kg and total CRST score: r = 0.183 ($P = 0.047$) were observed.

Among patients treated with valproate, women had a higher total CRST score than men: 14.54 ± 14.9 vs. 9.56 ± 9.55 ($P=0.034$) even after controlling for independent variables (supplementary table 3); and required more frequently treatment for tremor: 31.2% vs. 15.7% ($P=0.050$). The relative risk for upper limb postural tremor was higher in women compared to men; right-side: 1.39 (95% CI: 0.975 to 2.01), left-side: 1.34 (95% CI: 0.946 to 1.91). Besides gender, no other risk factor was associated with tremor among patients taking valproate. When comparing patients taking divalproex sodium with valproate magnesium, the latter had higher CRST scores (10.5 vs. 12.5 points, $P=0.507$) and required treatment for tremor more commonly (18.2% vs. 33.8%, $P=0.667$); although these differences were not significant. Patients taking valproate with enteric-coat had a higher total CRST score: 14.9 ± 15.9 vs. 10.0 ± 9.4, ($P=0.043$); and required more frequently treatment for tremor: 35.3% vs. 14.9%, ($P=0.010$) than those patients taking valproate without enteric coat, even after controlling for dose per kg ($P=0.044$).

4. Discussion

Drug-induced tremor is a common side effect in patients taking anticonvulsants; however such tremor is considerably more frequent in patients taking valproate. Through blinded evaluations; we show that tremor can be frequently observed in patients taking valproate; although in the majority of cases such tremor is mild and

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