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Original article

Valproate in adolescents with photosensitive epilepsy with generalized tonic–clonic seizures only

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ABSTRACT

Aim: To assess the effects of valproate (VPA) on seizure response/control and photosensitivity (PS) in adolescents suffering from photosensitive epilepsy with generalized tonic–clonic seizures only (EGTCS).

Methods: We prospectively evaluated 55 adolescents with newly diagnosed EGTCS and PS at presentation, who received VPA monotherapy. Two phases of the study were defined and analysed separately. In the phase I, the electroclinical data of patients were compared over three time points: T1 (at 6 months of treatment); T2 (at 12 months of treatment); and T3 (at 36 months of treatment). In the phase II, only patients who stopped VPA were evaluated over a period of 12 months.

Results: At both T2 and T3 there was a significant great percentage of seizure-free patients compared with that at T1 (78.2% vs 69.1%, $p < 0.01$; and 85.5% vs 69.1%, $p < 0.001$) and a similar trend was also noted according to PS-free patients (70.9% vs 52.7%, $p < 0.01$; 80.0% vs 52.7% $p < 0.001$). At the end of the phase II, 46.5% and 32.6% out of 43 patients who stopped VPA had seizure relapses and reappearance of PS, respectively. In particular, 78.6% of the 14 patients with PS reappearance presented the same type of EEG response showed at study entry.

Conclusions: VPA monotherapy is very effective for both seizure outcome control and PS reduction in adolescents with EGTCS. Treatment discontinuation induces relapse of seizures and PS in a certain number of patients. PS reappearance presented the same type of EEG response showed before VPA treatment.

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1. Introduction

Photosensitivity (PS) is a genetically determined trait which may or may not be evident in electroencephalogram (EEG) as an abnormal photoparoxysmal response (PPR) activated by intermittent photic stimulation (IPS).[1] Reflex photic EEG activation may be asymptomatic throughout life or manifest with clinical epileptic seizures.

The prevalence of PS in non-epileptic subjects is about 0.5%, whereas that reported in children and adolescents affected by epilepsy ranges from 10 to 20%.[2] PS is commonly associated with idiopathic generalized epilepsies (IGEs) which constitute nearly a third of all epilepsies.[2] Female-to-male ratio for PS is 1.5–2.0.[1] However, males predominate among video game-induced seizures, because many more boys than girls play such games. PS, particularly in IGE, has a higher incidence in adolescence with a peak at 12 or 13 years, while its incidence suddenly decreases after age of 20 years and subsequently decreases further.[3,4]

Photosensitive epilepsy is a broad term comprising numerous heterogeneous epileptic disorders and syndromes with different electroclinical prognosis, characterized by high incidence of photic induced seizures and, more frequently, by PPR without clinical seizures. PS in epileptic children and adolescents has been studied in few longitudinal studies and the available data are not homogeneous because they included many types of epilepsies with different etiologies, therapies and long-term prognosis.[5,6]

Therefore, in order to study a group of patients as homogeneous as possible with a specific epileptic syndrome and therapy, we evaluated prospectively the electroclinical course of adolescents suffering from photosensitive epilepsy with generalized tonic–clonic seizures only (EGTCS) who received monotherapy with valproate (VPA). We hypothesised that VPA, considered an effective antiepileptic drug (AED) for treatment of PS, might improve seizure response/control, reducing or abolishing PPRs to IPS in these patients with photosensitive EGTCS.

2. Subjects and methods

2.1. Participants

Fifty-five adolescents (age range, 10.0–19.0 years) with newly diagnosed EGTCS and evidence of PPRs to IPS were consecutively enrolled between December 2004 and January 2006 from five paediatric neurological centres in Italy: Department of Pediatrics, Chieti ($n = 23$); Department of Pediatrics, I Faculty of Medicine, Rome, ($n = 9$); Chair of Pediatrics, II Faculty of Medicine, Rome ($n = 13$); Department of Pediatrics, Siena ($n = 6$); and Department of Child Neuropsychiatry, Mantova ($n = 4$). All patients started VPA monotherapy increasing dose on standard recommended values (30–40 mg/kg/day).

Informed consent was obtained from parents of the recruited patients and the study was approved by the Ethics Committee of each institution.

2.2. Study design

At epilepsy presentation, patients and parents were systematically questioned for the presence of personal and family history for febrile seizures, epilepsy and PS. Later, participants were followed up with regular clinical examinations and serial EEG recordings.

For the purpose of this study two phases were defined and analysed separately. In the phase I, the electroclinical data of patients were compared over three time points: T1 (at 6 months from the beginning of VPA treatment); T2 (at 12 months from the beginning of VPA treatment); and T3 (at 36 months from the beginning of VPA treatment). The prospective design of the study required discontinuation of VPA in all patients who fulfilled the two followed criteria at T3: (1) seizure-freedom (complete absence of seizures on VPA for at least 24 months); and (2) absence of PS (abnormal PPR activated by IPS at EEG). In the phase II of the study, only patients who stopped VPA treatment at T3, because presented the above reported criteria, were evaluated over a period of 12 months, in order to analyse how many subjects had seizure relapse and PS reappearance after VPA withdrawal.

2.3. EEG evaluation

A standard technique of IPS was used for all recordings, as previously described.[7] Serial 16- or 32 channel EEG recordings were performed for all patients during awake and sleep states. Silver chloride electrodes were placed by using the 10–20 International system with bipolar and referential montages (including the Oz electrode). After a basic standard EEG recording, including hyperventilation, the responses to IPS were recorded on computer. IPS was produced by a photostimulator (Micromed, Mogliano Veneto, Italy) in which the spacing between lines occupied a 20 min visual angle. The photostimulator was placed 30 cm from eyes. The intensity of stimulus was 1363 cd/m^2 (68 cd/s/m), and rates between 1 and 60 flashes per second were tested by using one flash rate at a time. Stimulation sequences of 10 s duration were executed for any frequency. All patients were tested with their eyes open for the first 5 s, focusing on the centre of the lamp; the patient should then close the eyes for the remaining 5 s of stimulation. A free period of at least 7 s was scheduled between the stimulations.

If any paroxysmal activity appeared, the stimulus was promptly stopped to avoid seizure induction. Diagnosis of photosensitivity was based on two routine consecutive EEG recordings in two different days during a week. In particular, patients who had a first PPR to IPS at one EEG, were revaluated for confirmation with a second EEG in a different day during the same week.

After VPA withdrawal, participants were followed with regular EEGs until 12-month time point. Each patient underwent to EEG evaluation at 12-month follow-up.

2.4. VPA analysis

Serum levels of VPA were periodically determined by fluorescent polarization immune assay (Abbott Laboratories