

EEG photosensitivity and response to valproate segregate together in Indians with juvenile myoclonic epilepsy

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Abstract

Objectives and background: Juvenile myoclonic epilepsy (JME) has a similar clinical expression including excellent response to valproate (VPA) across different populations. We aimed to define the clinical and EEG features in patients and their relatives diagnosed to have JME whose seizures best responded to VPA alone versus those who required VPA and another anti-epileptic drugs (AED). **Materials and Methods:** Indian probands and their relatives diagnosed to have JME were divided into 2 groups depending upon the AED to which they finally responded: 1) VPA alone (n=267; 248 probands and 19 relatives), 2) VPA in combination with carbamazepine, diphenylhydantoin or phenobarbitone (n=40; 36 probands and 4 relatives). **Results:** The two groups were comparable with regards to sex distribution, age at seizure onset, seizure types, precipitating factors for myoclonic jerks, EEG being normal or abnormal, history of febrile convulsions and family history of seizures. EEG photosensitivity was observed in 27 probands and 1 relative with JME who responded to VPA alone (28 of 267; 10%) compared to none of the 40 with JME responding to VPA plus other AEDs. **Conclusions:** EEG photosensitivity and response to VPA appear to segregate together in Indians with JME supporting heterogeneity in JME. Responsiveness to VPA should be taken into account in future molecular genetic studies on JME.

Key Words: JME, Valproate, EEG Photosensitivity

INTRODUCTION

Juvenile myoclonic epilepsy (JME) is a well defined idiopathic generalized epileptic syndrome that has been reported to account for 5-11% of all epilepsy cases.¹⁻⁵ Beginning typically in early adolescence, the clinical spectrum of JME is characterized by myoclonic jerks (occurring mainly on awakening and often precipitated by sleep deprivation, stress, alcohol and photic stimulation) that are almost always associated with generalized tonic-clonic seizures, and absence seizures also arise in a variable number of cases.¹⁻⁷ Although hereditary factors have been strongly suspected to be involved in the pathogenesis of this syndrome, neither the exact pattern of inheritance nor the responsible genetic defect(s) have been defined.^{6,8-17}

Despite a large proportion of the world's population today lives in Asian countries, data on JME among Asians are surprisingly scarce. A few series that include a large number of patients have been reported by the present authors from India.^{6,7,18,19} The clinical expression of JME in different populations is remarkably similar

including the excellent response to valproate (VPA) mono-therapy. Despite these reports, some variability in the manifestation of JME among probands and their relatives has been taken to suggest heterogeneity in this syndrome.⁶⁻⁹ For example, JME is a generalized epilepsy but a few studies have reported focal features of both seizures and electroencephalographic patterns among patients with this syndrome.^{5,20}

The situation with regards to pathogenesis of seizures in most of the idiopathic generalized epileptic syndromes seen among humans is still not clear. Despite this, it has been the experience world-wide that majority of patients with JME become seizure-free with appropriate anti-epileptic drugs (AED) and VPA is currently the drug of choice. However, among all series reporting the drug response in JME, there is a small fraction of patients that have not responded to VPA alone.^{5,18,19,21-24}

In our ongoing effort aimed at defining the phenotypic spectrum of JME, we have collected data on 301 Indian probands and their relatives. With an aim to define some of the unreported

aspects of the disease expression, we report the similarities and differences among the clinical and EEG features in patients and their relatives diagnosed to have JME who finally responded to VPA alone versus those who required another AED besides VPA. It is expected that analysis of clinical data aimed at defining the unusual/unreported features of JME may provide further clues towards a better understanding of the pathogenesis of this syndrome.

MATERIALS AND METHODS

The study material has been taken from 301 JME probands attending the out-patient clinics of the Neurosciences Centre, All India Institute of Medical Sciences, New Delhi and 38 relatives of these probands, the relatives also having been diagnosed to have JME. The detailed method of clinical evaluation and construction of family pedigrees has been described earlier.^{6,18} To summarize, the inclusion criteria for JME were: a) unequivocal clinical (historical) evidence of bilateral myoclonic jerks with or without generalized tonic-clonic seizures and/or absence seizures; b) no evidence of neurologic or intellectual deficit; and c) normal CT/MRI scan (if performed). Patients with evidence of myoclonic jerks secondary to brain hypoxia, metabolic disease, and degenerative disease were excluded.

Detailed family pedigrees to include all the first- and second-degree relatives of the probands were constructed by a trained person. One author (SJ) examined all JME probands and the affected relatives. The entire family data was reviewed and reconfirmed (SJ). The seizure types and the epileptic syndromes in affected family members were classified according to the International Classification of Epileptic Syndromes.²⁵ All probands and the relatives diagnosed to have JME had at least one conventional scalp EEG with hyperventilation and intermittent photic stimulation (IPS) without modification of their current anti-epileptic treatment, if any. Video-EEGs were not done. The same person with the knowledge of the patient's diagnosis (SJ) analyzed EEGs.

In untreated patients, the EEG was considered 'abnormal' only when it showed generalized spike and/or multiple spike wave discharges. EEGs with background abnormalities other than well-defined spike wave discharges in patients on treatment were classified as "borderline abnormal". Photosensitivity in the EEGs was defined as occurrence of generalized spike, spike-

wave or polyspike-wave discharges not frequency-locked with the stimulus, consistently elicited by IPS and on occasions outlasting the IPS stimulus.

In newly diagnosed cases with JME and in those whose seizures are not controlled despite other AEDs, we routinely initiate treatment with VPA in the dose of 200-400 mg twice daily. If required, VPA is then increased slowly over the next few months until complete seizure control is achieved or unacceptable adverse reactions develop. Once complete seizure control is achieved, other AEDs are tapered slowly and ultimately withdrawn. In cases lacking complete seizure control with VPA alone, other AEDs are added after ensuring serum VPA levels in the therapeutic range (50-100 mg/l). In those with unacceptable adverse reactions with VPA, other AEDs are substituted even without the estimation of serum VPA levels. In cases presenting with seizures that are completely controlled with AEDs other than VPA, the drug schedule is not altered.

Individuals diagnosed to have JME (probands as well as relatives) were divided into 2 groups depending upon the AEDs to which they finally responded: 1) VPA alone, and 2) VPA in combination with carbamazepine (CBZ), diphenylhydantoin (DPH) or phenobarbitone (PB). These 2 groups with JME were compared for sex of individuals, age at first seizure, seizure types, precipitating factors for seizures, EEG features, whether CT/MRI scans were done, past history of febrile convulsions, and a family history of seizures.

RESULTS

Information was available on 339 individuals (301 probands and 38 relatives) with JME. Among these, 32 persons with JME who were never treated with VPA (17 probands and 15 relatives) have not been included in this analysis. Of the remaining, 267 finally responded to VPA alone (Group 1) while 40 to VPA in combination with DPH, CBZ, and/or PB (Group 2). These 307 persons are the subjects of this study.

The details of the comparative clinical and other features of persons with JME in Group 1 (n=267; 248 probands and 19 relatives) and Group 2 (n=40; 36 probands and 4 relatives) are as in Table 1. There was no difference when the two groups were compared with regards to: sex distribution, age at first seizure, presence of generalized tonic-clonic seizures and absences in association with myoclonic jerks, myoclonic

TABLE 1: Clinical and EEG details of JME patients responding to VPA alone and VPA in combination with other anti-epileptic drugs

	Sex distribution Male: Female	Age at onset of seizures (yrs) Mean (± SE)	Seizures other than Myoclonic Jerks		Precipitating Factors for seizures		EEG Details			History of febrile convulsions	Family History of seizures in 1° & 2° relatives
			Generalized tonic-clonic seizures	Absence seizures	Awakening/soon after awakening	Sleep deprivation	Abnormal	EEG Photosensitivity	EEG on anti-epileptic drugs		
Responded to VPA alone											
Probands (n= 248)	103:145	- (94%)	233	22 (9%)	218 (88%)	182 (73%)	208 (84%)	271 (11%)	169 (68%)	13 (5%)	82 (33%)
Relatives (n= 19)	12:7	-	16 (84%)	1 (5%)	15 (79%)	13 (68%)	18 (95%)	1 (5%)	10 (53%)	0	-
Total (n= 267)	115: 152	13.61 (0.197)	249 (93%)	23 (9%)	233 (87%)	195 (73%)	226 (85%)	28 (10%)	179 (67%)	13 (5%)	-
Responded to VPA in combination with CBZ/DPH/PB											
Probands (n= 36)	15: 21	- (94%)	35	4 (9%)	31 (88%)	26 (73%)	29 (84%)	0 (11%)	29 (68%)	0 (5%)	15 (33%)
Relatives (n= 4)	3 : 1	- (94%)	4	0 (9%)	2 (88%)	3 (73%)	4 (84%)	0 (11%)	4 (68%)	2 (5%)	- (33%)
Total (n= 40)	18 : 22	14.32 (0.533)	39 (98%)	4 (10%)	33 (83%)	29 (73%)	33 (83%)	0	33 (83%)	2 (5%)	-

VPA: Valproate, CBZ: Carbamazepine, DPH: Phenytoin, PB: Phenobarbitone

jerks precipitated by awakening and sleep deprivation, EEG being normal or abnormal, history of febrile convulsions, and a family history of seizures among first- and second-degree relatives.

Although there was no statistical difference among the 2 groups in terms of EEG being normal versus abnormal, more patients among responders to VPA plus other AEDs (Group 2) had EEG done while on treatment compared to Group 1 (83% vs. 67%, $p < 0.05$). Similarly, imaging of the brain (CT/MRI scan) was done more often in those responding to multiple drugs (Group 2) compared to the group responding to VPA alone (23 of 40 vs. 88 of 267, $p < 0.01$). The brain imaging was normal in all the patients in whom it was performed.

EEG photosensitivity was observed in 27 probands and 1 relative with JME who had responded to VPA alone (28 of 267; 10%) as compared to none of the 40 persons with JME responding to VPA in combination with other AEDs ($p=0.03$). In all, 28 of 307 (9%) persons with JME included in this analysis had EEG photosensitivity. Although these 28 with EEG photosensitivity had finally responded to VPA alone, 13 had EEGs done while they were initially on different AEDs: VPA (5), CBZ (5), DPH (1), and DPH plus CBZ or PB (2). The remaining 15 had their EEGs done while they received no treatment. The mean age at onset of first seizure was 13.6 years, the mean age when EEG was done was 16.8 years.

DISCUSSION

Despite being a common type of idiopathic generalized epilepsy, no definite diagnostic test is currently available to overcome the difficulties in accurate diagnosis of JME. JME was not initially recognized even in the epilepsy clinic in one-third of cases.⁵ The factors associated with incorrect diagnosis are not only responsible for the inaccurate estimations of the proportion of epilepsy patients exhibiting a syndrome like JME but may also be contributing to the variations and contradictory reports of linkage studies till-date.^{5,11,13,16-17}

It has been the standard practice to use well-defined clinical criteria along with the EEG abnormalities to classify JME probands and their family members as "affected" for inclusion into linkage studies. We have used standard clinical criteria to diagnose JME. Although at least one EEG was done in all patients, EEG abnormality was not included as a necessary

diagnostic criteria. This was because many persons with JME had their EEGs done while on treatment and AEDs are known to influence the EEG abnormality. We have previously reported the rate of abnormal EEG in our JME patients not on treatment as 100%, whereas it was 63% for those while on treatment.¹⁸ We have included patients with only myoclonic jerk in this study. Myoclonic jerks may precede generalized tonic clonic seizure by more than 20 years. Myoclonic jerks only are reported to occur in 7-17% cases of JME. It accounted for 7% of the JME in our earlier report.¹⁸

Various phenotypic and genetic evidences supported the heterogeneity of JME. We have earlier suggested that those individuals with only myoclonic jerks may represent a milder form of the syndrome.⁷ We also reported the reduced occurrence of absence seizure among Indian compared to JME probands from the United States.^{6,19} Although linkage in or near the HLA region of chromosome 6 were reported in two population groups, another study has ruled out this linkage, and a minor susceptibility locus for JME has also been reported on chromosome 15q.^{8-11,13,16,17}

In this study, 267 of 307 (87%) of JME probands and their relatives responded to VPA alone. This is similar to other reported series, where VPA has been successful in treating 90% of JME.^{5,18-24} Additionally, we report for the first time the association between response to VPA and EEG photosensitivity in JME.

Photosensitivity on intermittent photic stimulation has long been thought to be a genetically determined EEG phenotype.²⁶ The prevalence of EEG photosensitivity in epileptics has varied from 0.6% to 9.9% in different populations studied.²⁷ The pathophysiologic mechanisms of the photoparoxysmal response on the EEG have been extensively studied and have been related to the classification of the epilepsy syndrome.²⁸ The association between VPA responsiveness and EEG photosensitivity suggest that VPA responsiveness may also be a genetic trait and the genes involved in these two features may be closely related.

In linkage studies till-date, response to VPA has not been considered as a separate criterion for classification of JME probands and their relatives. The 10% of cases that do not respond to VPA alone may be another example of genetic heterogeneity within JME. Responsiveness to VPA should be taken into account in future studies.

The clinical implication of our findings is that when EEG photosensitivity is seen in JME, the clinicians may be more persistent with their use of VPA. This study has shown that all patients with EEG photosensitivity had eventually responded to VPA.

A new era of better understanding of the idiopathic generalized epilepsy has just begun with the identification of mutations in a few genes responsible for some of the rare syndromes. All 4 genes identified till date for human idiopathic generalized epilepsies have been shown to code for ion channel sub-units, mostly voltage-gated (KCNQ2, KCNQ3, SCN1B) and one ligand-gated (CHRNA4). The concept of idiopathic generalized epilepsy being a group of "channelopathies" is fast emerging.²⁹⁻³² Molecular genetic techniques are expected to throw further insights into the pathogenesis of idiopathic generalized epilepsy and other epilepsies, lead to the development of better AEDs, novel therapeutic strategies, and prevention of the disease. In view of these recent developments in molecular biology and the newer AEDs attempting novel antiepileptic mechanisms that include enhancing the inhibitory GABAergic function, clinical data on patients with idiopathic generalized epilepsy in respect to the response to AEDs becomes all the more important.

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