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Pharmacological outcomes in juvenile myoclonic epilepsy: Support for sodium valproate

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ABSTRACT

Purpose: Juvenile myoclonic epilepsy (JME) is one of the most frequently diagnosed of the idiopathic generalised epilepsy syndromes, but long term outcome data still remain sparse.
Methods: A retrospective audit was undertaken in 186 patients (male: $n=78$; female: $n=108$) diagnosed with JME at the Epilepsy Unit at the Western Infirmary in Glasgow, Scotland between July 1981 and July 2012. Median age at treatment start was 16 years (range 13–44), with median follow-up of 14 years (range 2–32).
Results: Overall, 171 patients (92%) achieved remission with antiepileptic drug (AED) treatment (median 9.5 years; range 1–31). After discontinuing treatment in 28 patients, only 11 remained seizure-free off medication. Fifteen patients (8%) continued to have seizures despite having tried up to 8 AED regimens: (5 male, 10 female), 7 of whom had psychiatric comorbidities. AEDs most commonly prescribed included sodium valproate (VPA; $n=142$), lamotrigine (LTG; $n=66$) and levetiracetam (LEV; $n=22$). More male patients than female attained remission with their first or second AED schedule (88% versus 56%). More male patients (44%) received VPA than female (31%) overall. Fewer male patients than female received LTG (26% versus 74%) and LEV (22% versus 78%). Of the monotherapies, remission was achieved using VPA ($n=74$; 52%), LTG ($n=21$; 32%) and LEV ($n=12$, 55%). A total of 76 (25%) of AED schedules resulted in intolerable side-effects, including 29 with VPA, 12 with LTG and 4 with LEV.
Conclusion: Overall, JME showed a high rate of seizure freedom with AED treatment. VPA appeared to be the most effective AED. Women tended to have a worse outcome than men, since they were increasingly less likely to receive VPA. Patients with psychiatric comorbidities also had a poorer prognosis.

1. Introduction

Juvenile myoclonic epilepsy (JME) is one of the most frequently diagnosed idiopathic generalised (genetic) epilepsy syndromes (IGES) in teenagers with a prevalence of around 18% of IGES and 5–10% of all epilepsies (Jallon and Latour, 2005). It is characterised by myoclonic jerks, tonic–clonic seizures and, on occasion, generalised absences (Camfield et al., 2013). JME has a slight female predominance, with a peak age of onset between 12 and 18 years. Around 30% of patients show photoparoxysmal responses on a surface electroencephalogram (EEG). Young patients with JME may have lifestyle issues that have the potential to increase the likelihood of further seizures, such as sleep deprivation, exposure to stroboscopic flashes, bout drinking of alcohol and recreational drug use, all with the potential of contributing to suboptimal adherence to antiepileptic drug (AED) therapy (Kasteleijn-Nolst Trenité et al., 2013) and an increased propensity to develop psychiatric co-morbidities (Tellez-Zenteno et al., 2007).

Patients with JME tend to respond well to medication (Striano and Belcastro, 2013). Several hospital-based studies have considered long term outcomes in adolescents with JME, reporting five-year seizure remission rates ranging between 60% (Senf et al., 2013) and 86% (Geithner et al., 2012). In particular, sodium valproate (VPA) is regarded as the most effective AED, but concerns remain regarding teratogenicity (Hitiris and Brodie, 2005; Marson et al., 2007; Crespel et al., 2013). Official guidelines issued by the Medicines and Healthcare Products Regulatory Agency (MHRA) warn against the use of VPA in female patients unless all other appropriate treatments have failed (MHRA, 2015). This study considered whether any differences in gender outcomes arose as a result in a cohort of adolescents and adults with JME diagnosed, treated and followed up at a single centre over a 30-year period.

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2. Materials and methods

Patients included in the analysis had a clinical diagnosis of JME, sometimes supported by an abnormal routine electroencephalogram (EEG), made at the Epilepsy Unit at the Western Infirmary in Glasgow between July 1982 and July 2012 with a minimum of two years of follow-up. The patient was excluded from the analysis if there was any subsequent doubt as to the correctness of the diagnosis. Those who consistently missed clinic appointments and/or were persistently non-adherent with medication were also excluded from analysis. Overall, 186 patients diagnosed with JME at the Epilepsy Unit at the Western Infirmary in Glasgow satisfied the requirements for inclusion in the study. At their first clinic attendance, a structured interview and protocol were used to gather information regarding seizure type, lifestyle factors and family history. At each subsequent visit, changes to the AED regimen, as well as number of seizures and side-effects noted by the patient were recorded in research case-notes, which were stored on-site (Brodie, 2013).

Those patients, who had no further seizures for at least the previous 12 months on an unchanged AED regimen, were classified as being in remission. In some of these, treatment was withdrawn at the patient's request. If seizures recurred in a patient who initially achieved a 12-month or more seizure-free period, they were regarded as having relapsed. Patients were categorised as being uncontrolled if they continued to experience seizure activity of any kind, including myoclonic jerks, despite taking their latest AED treatment schedule appropriately. Other endpoints included years of remission, responses to different drug schedules, and numbers of patients whose medication was changed due to side-effects. Drug choices and treatment responses were compared between male and female patients. A further area of interest was outcomes in patients with treated psychiatric comorbidities at first presentation and over the course of follow-up.

3. Results

Of the 186 patients included this analysis, 42% were male and 58% were female (Table 1). The median age at commencement of treatment was 16 years (range 12–44 years). Median duration of follow-up was 14 years (range 2–32 years). The most common presenting seizure type was generalised tonic–clonic in 72% of patients, with 17% reporting just myoclonic jerks and 11% initially diagnosed with absence seizures before developing myoclonic jerks and/or generalised tonic–clonic seizures. Overall, 32% patients had a first degree relative with epilepsy, while 11% had a history of birth trauma. Febrile convulsions in infancy had occurred in just 6% of patients. Over the course of follow-up, 26% of the population admitted to bout drinking of alcohol while 12% took recreational drugs. A total of 174 patients had a routine EEG, 126 (68%) of whom demonstrated clear epileptiform discharges. Only 64 (34%) patients displayed a photoparoxysmal response. In 12 cases, the patient declined an EEG, and in 27 cases photoparoxysmal response was not tested because of the patient's concern regarding the possible triggering of a seizure. At the time of presentation, 19 patients (10%) had treated psychiatric comorbidities, rising to 41 patients (22%) over the course of follow-up (Fig. 1). The most common diagnoses were anxiety (5% rising to 11%), depression (3% rising to 12%) and schizophrenia (1% rising to 3%). These co-morbidities sometimes coexisted with the original 19 patients having 24 psychiatric diagnoses. The final 41 affected patients had had a total of 57 psychiatric diagnoses made.

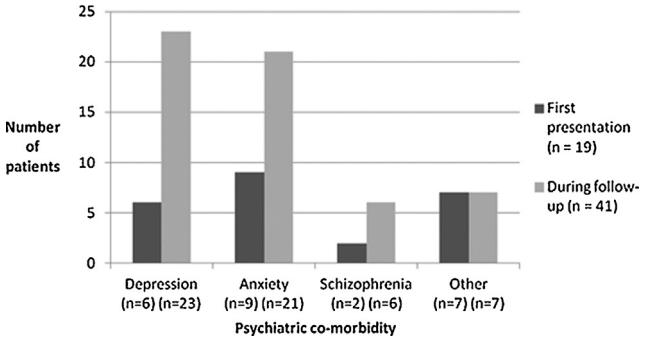

Fig. 1. Psychiatric comorbidities requiring pharmacological intervention at first presentation and during follow-up.

In total, 171 patients (92%) achieved remission (Table 2) with a median seizure-free period of 9.5 years (range 1–31 years). Overall 81 patients achieved seizure freedom on their first AED. A further

Table 1
Patient demographic data.

Demographic data	Patients (n = 186)
Gender	
Male	78 [42%]
Female	108 [58%]
Median age at treatment start (years)	16 (range 12–44)
Median duration of follow-up (years)	14 (range 2–32)
First seizure type	
Generalised tonic–clonic	134 [72%]
Myoclonic	31 [17%]
Absence	21 [11%]
Family history of epilepsy	59 [32%]
Birth trauma	20 [11%]
History of childhood absences	17 [9%]
History of febrile convulsions	12 [6%]
Bout drinking of alcohol	49 [26%]
Recreational drug use	22 [12%]
Epileptiform discharges on electroencephalogram	
Present	126 [68%]
Absent	48 [26%]
Not tested	12 [6%]
Photoparoxysmal response on electroencephalogram	
Present	64 [34%]
Absent	95 [51%]
Not tested	27 [15%]

Table 2
Remissions and remission rates (%) for each drug schedule.

Antiepileptic drug/Combination	Number of remissions [%]
Sodium valproate	74 [52%]
Lamotrigine	21 [32%]
Levetiracetam	12 [55%]
Topiramate	6 [67%]
Lamotrigine/Levetiracetam	5 [42%]
Phenobarbital	3 [60%]
Tiagabine	3 [75%]
Zonisamide	3 [50%]
Clonazepam	3 [60%]
Ethosuximide	2 [67%]
Phenytoin	1 [50%]
Valproate/Lamotrigine	14 [52%]
Lamotrigine/Zonisamide	3 [60%]
Topiramate/Lamotrigine	3 [50%]
Valproate/Levetiracetam	3 [23%]
Valproate/Topiramate	3 [38%]
Valproate/Zonisamide	3 [43%]
Valproate/Clobazam	2 [67%]
Levetiracetam/Rufinamide	1 [100%]
Levetiracetam/Zonisamide	1 [33%]
Valproate/Clonazepam	1 [50%]
Valproate/Lamotrigine/Levetiracetam	1 [100%]
Valproate/Zonisamide/Clobazam	1 [100%]
Valproate/Levetiracetam/Topiramate	1 [100%]
Zonisamide/Lamotrigine/Levetiracetam	1 [100%]