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Relapse after treatment withdrawal of antiepileptic drugs for Juvenile Absence Epilepsy and Juvenile Myoclonic Epilepsy

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ABSTRACT

Purpose: Conventional teaching is that juvenile myoclonic epilepsy (JME) and juvenile absence epilepsy (JAE) require lifelong antiepileptic drug (AED) treatment. We therefore wanted to determine how many patients attending our epilepsy service with JAE or JME went into 2 year remission, and then relapsed, both off and on AEDs.

Method: This was a retrospective case-notes review. Patients with JAE and JME were systematically ascertained from clinic lists and databases at one teaching hospital. Data was extracted systematically. Simple descriptive statistics were used.

Results: JAE: 14/36 (39%) were seizure free on AEDs for at least 2 years. Of the 6 (43%) attempting AED withdrawal, all (100%) relapsed, compared with only 25% of those who did not withdraw AEDs. Only 2/5 who relapsed and restarted AEDs regained remission.

JME: 32/145 (22%) were seizure free on AEDs for at least 2 years. Of the 10 (31%) attempting AED withdrawal, 8 (80%) relapsed, compared with only 36% of those who did not withdraw AEDs. Only 2/8 who relapsed and restarted AEDs regained remission.

Conclusion: Remission rates for JAE and JME was lower than expected. Higher proportions of seizure free patients underwent physician-supervised withdrawal than anticipated. Relapse rates off AEDs were similar for JAE and JME, and at least twice as high as for those remaining on AEDs, and a further remission was not invariable on restarting AEDs. Our experience, comparing relapse in those withdrawing to those staying on AEDs will help in discussions with patients keen to try AED withdrawal.

1. Introduction

The objective of this clinical audit was to assess current practice and experience of remission, antiepileptic drug (AED) withdrawal, and relapse in young people and adults with Juvenile Absence Epilepsy (JAE), and Juvenile Myoclonic Epilepsy (JME).

1.1. Background

JAE and JME are Genetic Generalised Epilepsy syndromes (GGE) [1], previously known as Idiopathic Generalised Epilepsy syndromes (IGE) [2]. Epilepsies in this group occur principally in patients with otherwise normal brain structure and function. They are generally of shared complex inheritance with reduced penetrance, sharing susceptibility alleles at more than one locus [3]. There is some controversy over what criteria should be used to diagnose individuals as having JAE or JME [2,4,5]. Furthermore, as well as sharing clinical features e.g. age of onset, lack of associated encephalopathy, EEG features, there is overlap in the seizures expressed. In JAE all have typical absence seizures (AS) and most have generalised tonic-clonic seizures (GTCS). In JME awakening myoclonus is the hallmark, but most patients also have GTCS and many have AS.

The phenotypic similarities and overlaps in GGEs, especially juvenile (adolescent) onset GGEs, are reflected in segregation and twin studies [6–8]. So given the clinical, EEG, and underlying genetic commonalities, we might expect JME and JAE to share treatment responsiveness and prognosis. Indeed it has been argued that they could be regarded as one type of epilepsy [9].

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1.2. Rates of JME remission previously reported

There is a range of remission rates reported for JME. A retrospective review of 50 patients with JME on treatment found 86% were seizure free for at least one year [10]. A similarly high rate of remission was reported in a cohort of 66 patients followed up prospectively for 5 years, with 88% becoming seizure free for at least three years [4]. A questionnaire study of 43 JME patients found 79% had experienced no GTCS in the previous year, but a more modest 41% were entirely seizure free [11]. A clinic based study of 13 patients showed only 38% were seizure free [12]. A large prospective study of 257 JME patients reported remission in 58% of the 186 patients considered to have classical JME, but a much lower rate of remission of 7% in the subtype which had evolved from an earlier CAE type epilepsy [13]. Two additional retrospective studies of 200 patients [14] and 55 patients [15], found similar rates of seizure freedom, 75% and 73% respectively. 78% of a cohort of 24 patients followed up for mean of 25 years achieved seizure freedom at some point [5]. A recent study used both review of records and interviews of 31 patients after a minimum follow-up of 25 years and reported that 67% were seizure-free on treatment; no correlation was found in this study between seizure freedom and prior history of CAE [16]. Another study using interviews of 42 patients after 20 years follow-up found 21 were in remission of at least 5 years [17]. A further retrospective cohort study of 66 patients with follow-up of between 20 and 69 years reported that 59% were seizure-free for over 5 years [18]. A recent cross-sectional observational study of 175 patients with minimum 2 years follow-up reported that 62% were seizure-free for at least one year, and 54% for at least two years [19]. In a study of 105 JME patients who had been in remission for at least 1 year, only 29% maintained seizure freedom after 2–3 years with the majority showing relapse strongly associated with provoking factors such as missed medication and sleep deprivation [20].

1.3. Rates of JAE remission previously reported

A meta-analysis of 23 study cohorts of 2303 patients with absence epilepsy found that 78% of patients with AS alone, and 35% of patients with AS and GTCS became 'seizure free' [21]. Remission rates varied in studies from 21% to 89%. This meta-analysis was not specific to JAE and included any absence seizure syndromes. The criteria for being 'seizure free' also varied in these papers. However, there have been a small number of studies that have looked specifically at JAE patients. A study of 64 patients with JAE found that 62%, on treatment, were completely seizure free for at least two years [22]. A retrospective study of 21 JAE patients found that 43% on treatment had achieved seizure freedom [23]. In a further retrospective study 8/17 (44%) patients with JAE were seizure free on treatment [24]. A lower rate of longer 5-year remission was reported in a study of 46 patients where only 7 (15%) were seizure-free, and 22 patients (48%) were felt to have very poor control despite AED treatment [25]. Little is reported about the natural course of epilepsies without treatment, but one such study followed up 15 patients who had refused all AED treatment, of whom 5 had absence seizures and 5 had both absence and GTCS; the duration of follow-up was 7–27 years and 80% of those with absence seizures alone were in remission, compared to 20% with both seizure types [26].

In summary, there has been a range of reported remission rates from 33 to 88% for JME and 21–89% for JAE. These studies were heterogeneous in terms of methodology, patient groups and criteria for assessing remission.

1.4. Seizure relapses in JAE and JME patients after treatment withdrawal

A recent study specifically addressed this issue in 59 patients with IGE, who were assessed and diagnosed in two hospitals over 8 years [27]. Subjects were in remission on AEDs for at least 2 years and then had at least two years follow up. 7/17 with JME and 3/11 with JAE had AEDs reintroduced because of a deteriorating EEG before seizures could relapse; of those remaining off AEDs, 10/10 with JME and 4/8 with JAE relapsed. Ninety-five percent of all relapses in the study were within 24 months of AED withdrawal. This contrasts with a similar study from the same team of 52 patients with juvenile onset cryptogenic focal epilepsies withdrawn from AEDs after at least 2 years remission and followed for at least 2 years [28]. The relapse rate in these was only 38%, although again the vast majority (over 90%) who relapsed did so within 2 years of withdrawal. Three studies of 12, 4, and 130 JME patients respectively, have reported relapse rates of 100% after withdrawing AED treatment [14,29,30]. In a study of 43 JME patients, 90% of patients who had treatment withdrawn later relapsed [11]. Another study found that 9/11 (82%) JME patients who had valproate withdrawn relapsed [4]. Similar rates have been reported in two studies, one of 186 patients with JME in remission [13], and one of 175 JME patients overall [19], where for both only 9% remained seizure-free off treatment. Slightly more optimistic outcomes are reported in recent papers. One study found that 6 out of 9 JME patients in remission who stopped AED treatment remained seizure free after follow-up of 8–30 years, and in the three patients where seizures relapsed, reintroduction of medication gave seizure freedom again [16]. Of 39 seizure-free JME patients, out of a cohort of 66, 11 remained seizure free off treatment [18]. In 21 of 42 JME patients in remission, 7 remained so off treatment [17].

Two studies of JAE patients have found that all attempts to withdraw treatment led to relapse [22,23]. One prospective study of AED discontinuation in childhood epilepsies found that 9 seizure free patients with JAE had treatment withdrawn and only 3/9 relapsed [30].

In summary, many studies report a high relapse rate for both JME and JAE patients who had been in remission, after AED withdrawal, but this review suggests that a significant minority do retain seizure freedom off treatment.

1.5. Rational for and aims of this clinical audit

Although there is literature documenting the high relapse rate for JME on AED withdrawal, the literature for JAE is sparser, based on smaller numbers, and not so persuasive. We wanted to assess: 1) how often our patients with JAE or JME become seizure free on AEDs; 2) how often we withdrew AEDs; 3) how many relapsed if and when treatment was withdrawn; and 4) how many relapsed if they stayed on treatment beyond 2 years of remission. We wanted to gather data about the variance in our practice and outcomes of drug withdrawal, to inform future discussions with our patients.

2. Methods

This was a retrospective clinical chart review of young persons' and adults' epilepsy clinic visits, focusing on seizure freedom, AED withdrawal, and seizure relapse after AED withdrawal. Clinical practice and outcomes were compared to the literature. This clinical audit was approved and registered with our hospital Clinical Audit Department.

Cases with JAE and JME were identified systematically and consecutively using clinic lists and databases from both a Young