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

Running title: Relapse after AED withdrawal for JAE and JME

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Highlights

- A high number of patients with JME and JAE in remission withdrew from AEDs.
- All patients with JAE and 80% of patients with JME relapsed after AED withdrawal.
- 25% of patients with JAE continuing on AEDs relapsed.
- 36% of patients with JME continuing on AEDs relapsed.

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.

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Key words: absence seizures, generalised seizures, myoclonic epilepsy, adolescent, juvenile, adult, antiepileptic drugs

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).

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].

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 20-69 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].

Rates of JAE remission previously reported

A meta-analysis of 23 study cohorts of 2,303 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 33-88% for JME and 21-89% for JAE. These studies were heterogeneous in terms of methodology, patient groups and criteria for assessing remission.

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.

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.

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 Person (Transition) Epilepsy Clinic and an Adult Epilepsy Clinic. The patients were all diagnosed by a consultant paediatric neurologist or adult neurologist with expertise in epilepsy diagnosis and management (WPW, MFO'D, SS), in accordance with the 1989 classification[2]. It is our practice to diagnose JME in patients with features of both JME and JAE.

Data was extracted by LH and RA and entered onto Excel spreadsheets. Cases were then grouped into 'two years seizure free' or 'not two years seizure free', 'treatment withdrawn' or 'not withdrawn', and 'relapsed' or 'not relapsed'. Only descriptive statistics were used.

Results

The study identified 36 patients with JAE and 145 with JME. All diagnoses were found to be in accordance with ILAE 1989 criteria[2]. At the time of audit, the JAE patients were aged 16-59 years (mean 26) and JME patients were aged 13-92 years (mean 32). 27/36 (75%) of the JAE patients were female, as were 87/145 (60%) with JME. For the majority of patients, age of first seizure onset was 1-18 years (figure 1), including those with previous childhood absence epilepsy (CAE) and febrile seizures (FS). They had specific seizure combinations (see table 1), and compatible interictal or ictal EEG features, and normal or only non-specific and incidental abnormalities on neurological examination, or brain MRI when done: MRI or CT was only done in 16/36 (44%) and 68/145 (47%) cases with JAE and JME respectively.

The proportions of patients who were completely seizure free of all seizure types for two years were 14/36 (39%) with JAE, and 32/145 (22%) with JME. After this period of remission, AED withdrawal was attempted in 6/14 (43%) with JAE, and in 10/32 (31%) with JME (figure 2).

Juvenile Absence Epilepsy (JAE) outcomes

For the 6/14 seizure free JAE patients who had AED withdrawal, relapse occurred in 6 (100%), at between 1 month and 3 years (mean 11 months): 5 had GTCS with or without AS, 1 AS alone (table 1).

In the 8/14 seizure free JAE patients who did not undergo AED withdrawal (figure 2a), relapse occurred in 2 (25%), at between 2 and 4 years (mean 3 years) after 2 years of seizure freedom. For the 6/8 patients who did not relapse, follow up time was between 1 and 6 years (mean 2 years) after the first 2 years of seizure freedom (table 2).

Juvenile Myoclonic Epilepsy (JME) outcomes

For the 10/32 seizure free JME patients who had AED withdrawal, relapse occurred in 8/10 (80%) at between 1 month and 15 years (mean 5 years, 11 months) of AED withdrawal, 4/8 (50%) within 2 years of treatment withdrawal (table 2). Seven had GTCS with or without myoclonic seizures, 1 had myoclonic seizures alone. For the 2 patients who did not relapse, follow up time was at least 3 years.

In the 22/32 seizure free JME patients who did not have AED withdrawal, 8/22 (36%) relapsed at between 2 and 12 years (mean 5 years) of being 2 years seizure free (figure 2b). For the 14 patients who did not relapse, follow up time was between 1 year and 11 years (mean 4 years), after the first 2 years seizure freedom (table 2).

Other outcomes

There were some patients who did not fit the criteria of remission from all types of seizure but in whom treatment did control GTCS. This was true for 17/145 (12%) patients with JME. Furthermore, 25/145 (17%) JME patients were lost to follow up.

Outcomes after reinstating AEDs

All 6 JAE patients resumed AED treatment with no re-attempted withdrawals. Two have returned to remission, 1 has been lost to follow up and 3 have continuing seizures. All 3 patients who continue to have seizures have GTCS after previously being in remission from GTCS and absences.

All 8 JME patients were restarted on AED treatment and none had withdrawal re-attempted. Two returned to remission, 4 were lost to follow up, and 2 continued to have seizures after resuming AED treatment. Both patients who continue to have seizures have GTCS and myoclonus after previously being in remission from these types of seizure.

Discussion

The remission rate for JME in this study was low compared to previous studies. This may partly be explained by patient selection. Patients in our study were likely to be difficult cases of JME and JAE that had been referred to specialist clinics, rather than being managed in the community by General Practitioners (GPs), family physicians, and in non-specialist paediatric clinics. It is plausible that those lost to follow-up were more likely to be in remission and returned to community follow-up by their GP, than to have continuing seizures. However it is unlikely that all those lost to follow-up were in remission so the real remission rate is likely to be between 22% (32/145 seizure free patients) and 39% (32/145 seizure free patients and 25/145 patients lost to follow up) for JME. Also, the length of follow up in this study was relatively short (up to 14 years). Some previous studies followed patients for up to 25 years, giving more time for

remission to occur [5, 10-12]. This shorter follow-up may have contributed to the low remission rate we observed.

This study is notable, compared to the previous literature, in using patients from the same background population with the same clinicians and the same methods of analysis to compare JAE and JME patients. JAE and JME patients had similar high rates of relapse after treatment withdrawal (JAE 83%; JME 80%). This study is unique in comparing the relapse rates following withdrawal of AEDs after remission, to relapse rates in those with at least 2 years remission but not withdrawn (JAE 25%; JME 36%) (figure 3).

Our relapse rates for JAE and JME are similar and within the ranges previously reported. In counselling patients however it is important to relate this risk of relapse to the risk of relapse if they stay on AEDs. Our data suggest that about 20% of those with JME can withdraw AEDs successfully after a 2 year remission on treatment. We had no successful withdrawals in patients with JAE, in agreement with some previous reports[22, 23]. However, our numbers were small, and the literature dose suggest that some patients may withdraw AEDs after 2 years remission without relapse[21, 27]. Some patients will want to try this. For these patients it is important to let them know that if they do relapse then recommencing AEDs has a reasonable chance of leading to remission again, but not necessarily in all.

We were surprised that as many as 43% patients with JAE, and 31% of JME attending our epilepsy clinics attempted the withdrawal of their AEDs after 2 years of remission. Most doctors are wary of withdrawing drugs in JME, but many patients hope or believe they have outgrown

their epilepsy and express a desire to try withdrawal. It is interesting to speculate that these opposing views tended to side with "patient preference" over "doctor's orders" in our cohort, perhaps reflecting the increasing move towards patient-centred medicine. Their doctors listened to and supported them in attempting to come off AEDs, even though the relapse rates turned out to be 100% for JAE (compared to 25%), and 80% (compared to 36%) for JME.

It was also pertinent that re-introduction of AEDs did not always lead to a further remission.

Our audit results will not only enable us to council patients more realistically in the future, but will be useful for patients attending other clinics, especially for those with JAE. We hope that future audits will show fewer patients with JAE and JME electing to try AED withdrawal.

Limitations of the study

This was not hypothesis driven clinical research, but a systematic and objective clinical audit of our practice concerning patients with JAE and JME reaching a 2 year remission on AEDs, and the decisions made about AED withdrawal and their consequences. It is an accurate description of what happened. However, while it may inform others' practice, it was not designed to answer the questions: how many patients with JAE and JME will relapse off AEDs after a 2 year remission, and how easily will it be to re-establish remission by reinstating the AEDs if needs be? It necessarily lacked sufficient power and study design to answer these questions confidently.

These questions could be addressed potentially, though with considerable difficulty, by a randomised controlled trial: similar to the Medical Research Council (MRC) study[31], but with syndrome diagnoses. However, it is doubtful that a large enough number of physicians and

patients would be willing to randomise such choices, and we doubt the feasibility of controlling both placebo and nocebo effects, e.g. using a placebo controlled design. In short an observational study, like this clinical audit, but including a larger multicentre patient population, may be the only feasible way of convincingly addressing this important issue.

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Acknowledgements

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Disclosures

This was a non-intervention study, a systematic retrospective medical notes review, and all data was anonymized, registered with our hospital clinical audit department, as part of our service quality control, and research ethics committee approval was not required.

Informed consent was not required.

All authors have no conflicts of interest to declare relevant to this study. The paper does not comment on any particular antiepileptic drug.

No external funding was obtained to undertake this study.

This study was not a clinical trial or intervention study.

Table 1 Seizure types

JAE seizure types	Number
Absence only	9
Absence + GTC	25
Absence + GTC + Myoclonic#	1
Absence + Unspecified	1

JME seizure types	Number
Myoclonic only	4
Myoclonic + GTC	61
Myoclonic + GTC + Absence	64
Myoclonic + Absence	4
Myoclonic + GTC + Absence + Atonic	1
Myoclonic + Unspecified	12

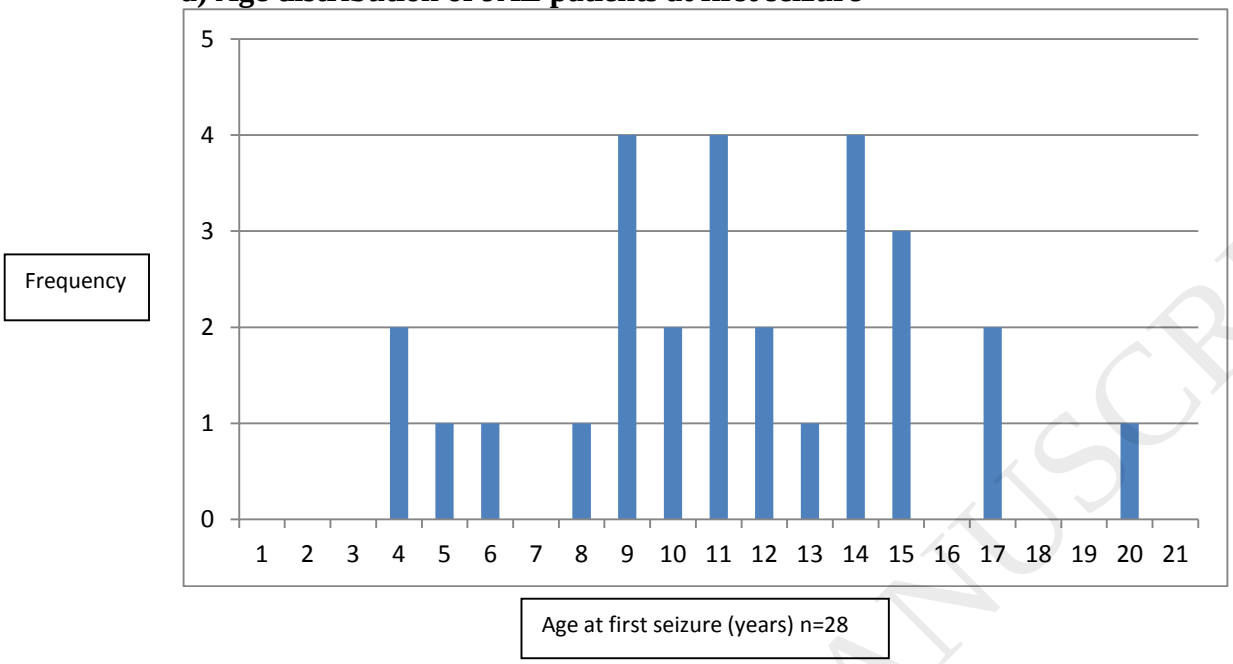
JAE = Juvenile Absence Epilepsy; GTC = generalised tonic-clonic; JME = Juvenile Myoclonic Epilepsy; #the myoclonus reported in this case was not captured on EEG, occurred very rarely, and was not awakening typical of JME.

Table 2 Important time lengths in JAE and JME patients who were seizure free for at least 2 years

			Time between **EVENT A** (in treatment not withdrawn group EVENT A is 2 year seizure free date) and **EVENT B** (in did not relapse group event B is last follow up date)	
	EVENT A	**EVENT B**	Mean	Range
Seizure free JAE patients (14)	Treatment withdrawn (6/14)	Relapsed (6/6) (100%)	11 months	1 month – 3 years
		Did not relapse (0/6)	N/A	N/A
	Treatment not withdrawn (8/14)	Relapsed (2/8) (25%)	3 years	2-4 years
		Did not relapse (6/8) (75%)	2.2 years	<1 year – 6 years
Seizure free JME patients (32)	Treatment withdrawn (10/32)	Relapsed (8/10) (80%)	5.9 years	1 month – 15 years
		Did not relapse (2/10) (20%)	> 3 years	Unknown
	Treatment not withdrawn (22/32)	Relapsed (8/22) (36%)	5 years	2 years to 12 years
		Did not relapse (14/22) (64%)	5 years	1 month – 14 years

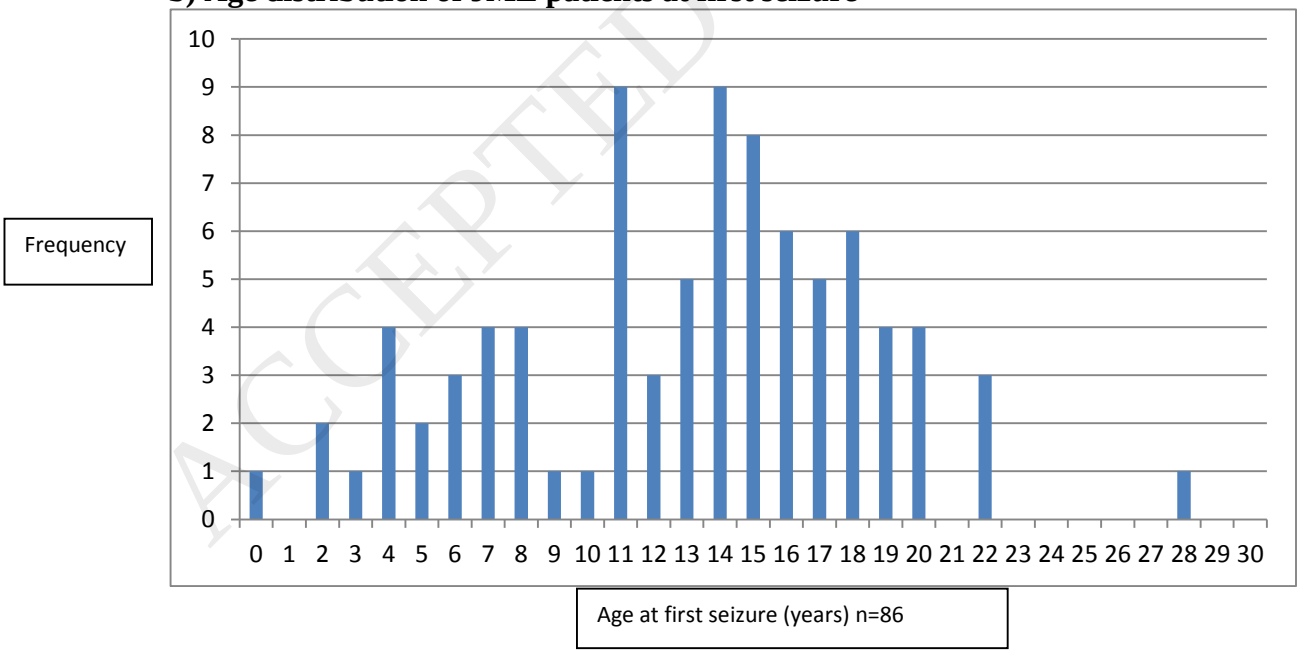
Figure 1 Age at first seizure

a) Age distribution of JAE patients at first seizure



8/36 (22%) patients with JAE did not have the age at first seizure recorded.

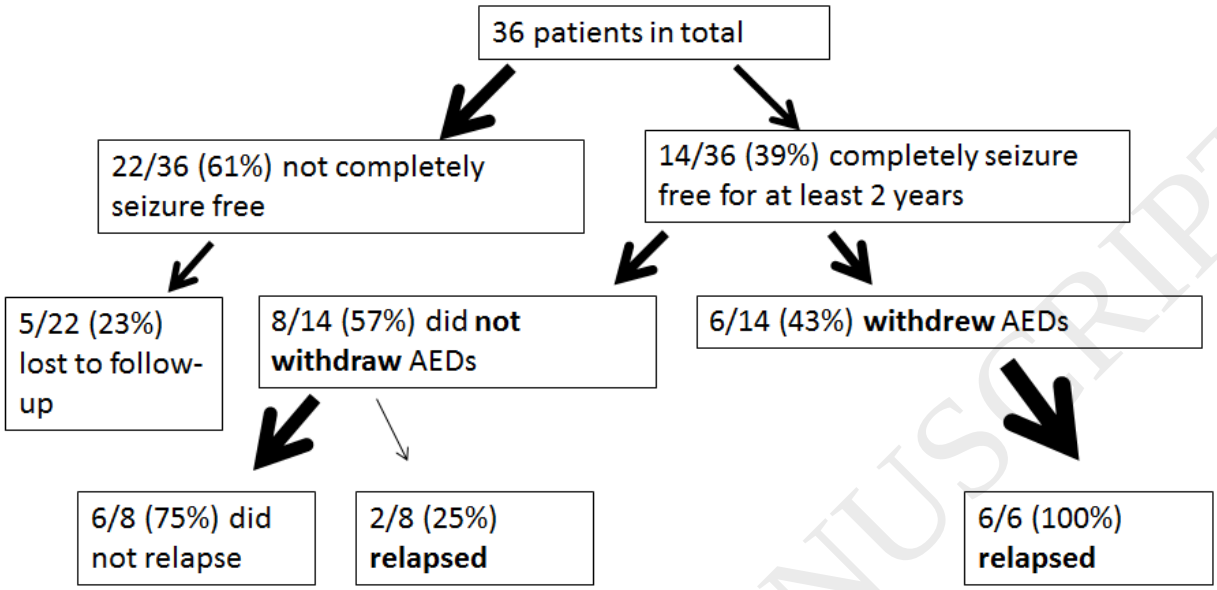
b) Age distribution of JME patients at first seizure



59/145 (41%) with JME did not have the age at first seizure recorded

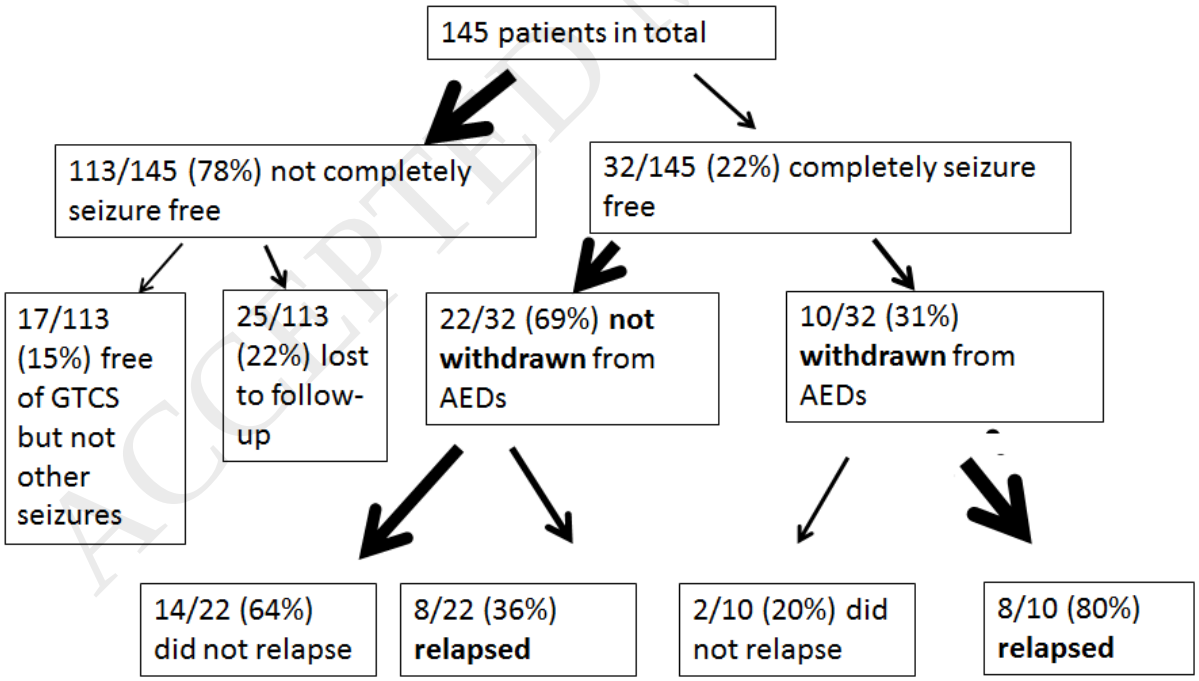
Figure 2 Flow diagram of patient outcomes

a) JAE results



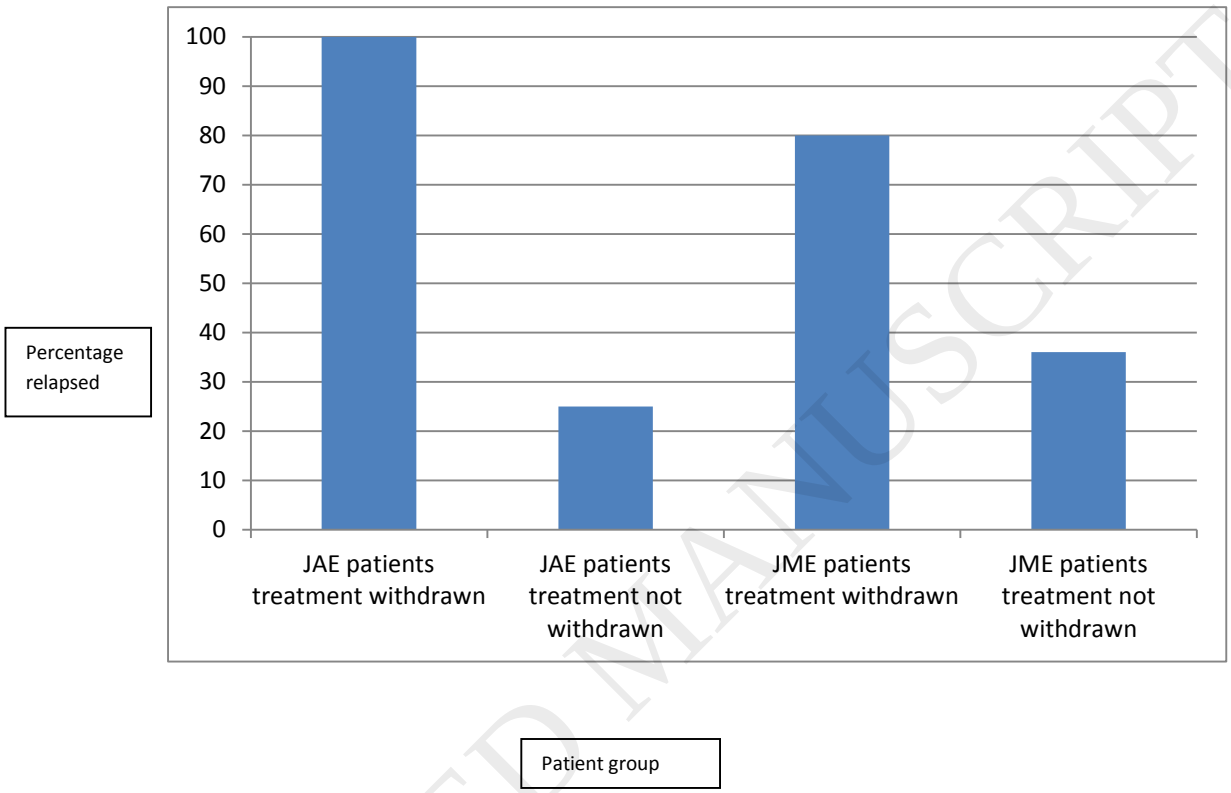
JAE = Juvenile Absence Epilepsy; AEDs = antiepileptic drugs.

b) JME results



JME =Juvenile Absence Epilepsy; GTCS = generalised tonic-clonic seizures; AEDs = antiepileptic drugs

Figure 3 Relapse % observed in those withdrawn and not withdrawn from AEDs, after at least 2 years seizure freedom



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