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ORIGINAL ARTICLE

Long term prognosis of juvenile absence epilepsy ☆

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KEYWORDS
Juvenile absence epilepsy;
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Abstract
Introduction: Juvenile absence epilepsy (JAE) is a generalized form of epilepsy, characterized by absence seizures (AS) initiated in adolescence, with a typical EEG showing generalized spike-wave discharges. Apart from absences, other seizure types may be observed such as myoclonia and generalized tonic-clonic seizures (GTCS). Its long-term prognosis is uncertain.
Material and methods: We retrospectively selected all patients who met the 1989 ILAE diagnostic criteria for JAE. We analysed clinical variables, pharmacological treatment, and seizure remission with medical treatment and seizure relapse after stopping medical treatment.
Results: We identified 21 patients, 17 women and 4 men, 86% of whom had suffered GTCS and 14% myoclonias. Mean age at AS onset was 17 years old (range 10-44), 4 patients debuted with AS in adulthood. Mean follow up duration was 25 years (range 10-43). Ninety per cent of the patients were treated with valproate and 62% needed polytherapy. Currently 43% have achieved seizure freedom under medical treatment. All attempts to stop treatment failed, in some cases after long periods of seizure remission.
Conclusions: Less than fifty per cent of patients with JAE achieve remission, antiepileptic treatment is mandatory during all life, despite having long periods of remission.

PALABRAS CLAVE
Epilepsia ausencia juvenil;
Ausencias;
Pronóstico;

Pronóstico a largo plazo de la epilepsia ausencia juvenil

Resumen
Introducción: La epilepsia ausencia juvenil (EAJ) es un tipo de epilepsia generalizada idiopática que se caracteriza por la presencia de crisis de ausencia (CA) que comienzan

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Tratamiento;
Edad adulta

en la adolescencia, con un EEG típico de punta-onda generalizada, y que puede acompañarse de mioclonías y crisis tónico-clónicas generalizadas (CTCG). El pronóstico a largo plazo es incierto.

Material y métodos: Seleccionamos de manera retrospectiva todos los pacientes que cumplían los criterios diagnósticos de EAJ de la ILAE 1989, analizamos las variables clínicas, el tratamiento farmacológico, el estar libre de crisis y la posibilidad de retirar el tratamiento.

Resultados: Encontramos 21 pacientes, 17 mujeres y 4 varones, el 86% presentó también CTCG y el 14% mioclonías. La edad de inicio de las CA fue de 17 años (rango: 10-44). Cuatro pacientes comenzaron con CA en la edad adulta. El seguimiento medio fue de 25 años (intervalo: 10-43). El 90% recibió tratamiento con valproato y el 62% requirió politerapia. El 43% de los pacientes están actualmente libres de crisis, aunque todos ellos en tratamiento farmacológico. Todos los intentos de retirar la medicación fracasaron, pese a largos períodos sin crisis.

Conclusiones: Menos de la mitad de los pacientes con EAJ están libres de crisis. El tratamiento antiepiléptico es necesario durante toda la vida a pesar de largos períodos de remisiones.

Introduction

Typical absence seizures (AS) are defined as sudden episodes of altered consciousness with generalised spike-wave discharges at 3Hz or more in an EEG.[1] These AS, myoclonus and primarily generalised tonic-clonic seizures (GTCS), alone or in combination, are the kinds of crises that form part of idiopathic generalised epilepsy (IGE).[1,2] Representing around 15% to 20% of all epilepsies,[3] IGE is characterised by: being genetically determined, beginning during childhood or adolescence in patients with normal psychomotor development, normality in neuroimaging tests and an EEG with generalised spike-wave discharges.[2] According to the 1989 International League Against Epilepsy (ILAE) classification,[1] the most notorious types due to their prevalence are childhood absence epilepsy (CAE), juvenile myoclonic epilepsy (JME), epilepsy with GTCS on awakening (which was subsequently renamed as only GTCS in the 2001 ILAE classification[4]) and juvenile absence epilepsy (JAE). A new update of the ILAE classification of 1989[5] has recently been published; in it, the dichotomy between "epileptic syndrome" and "epileptic disease" has evolved into "electroclinical syndrome", "epileptic constellation", "epilepsy with a structural/anatomical origin" and "epilepsy of unknown cause", based on a better knowledge of the aetiology and especially of the genetic origin of epilepsy. The IGE mentioned previously are all recognised as electroclinical syndromes, given their clinical homogeneity and electroencephalographic characteristics.

The most frequent forms of IGE are CAE and JME; they are, therefore, the best studied. The prevalence of JME is 5% to 10%[3] of all epilepsies with an excellent long-term prognosis if adequate drug treatment is followed, but with a high rate of recurrence if this is discontinued.[6,7] Depending on the series,[3] CAE has a prevalence of 1.5% to 12% with a variable remission rate, depending on the diagnostic criteria used. According to the latest criteria by Loisseau and Panayiotopoulos,[8] which are more restrictive than those gathered in the ILAE classification of 1989,[1] the remission rate can reach 90%. In contrast, JAE is a less common entity, much less known and probably underdiagnosed. According to the ILAE classification of 1989,[1] JAE is characterised by the appearance of AS in adolescent patients, where AS are less frequent and present a lower level of altered consciousness compared to CAE. The presence of GTCS is common, and can occur even earlier than AS. Patients may also suffer myoclonus. It affects women and men equally. Its estimated prevalence is of 0.2% to 2.4% of all epilepsies,[3] but there are many questions about it, because its natural history is not accurately known. Few studies have examined the long-term prognosis of this entity.[9-12] In this series, between 37% and 62% of patients were free from seizures, but none of the previous studies analysed the possibility of withdrawing the drug treatment.

The main objective of our work was to analyse the long-term prognosis of JAE. To this end, we studied clinical variables, pharmacological treatment, the patient being free from crises or not, the possibility of withdrawing the treatment and, finally, the variables that may influence prognosis.

Table 1 Diagnostic criteria for juvenile absence epilepsy according to the 1989 ILAE

Onset during puberty. Similarity across genders
AS are the main type of crises, with a lower frequency than in CAE, but the alteration of consciousness is not as severe
Frequent association with GTCS, and these may occur earlier than the AS
May occur with myoclonus
The EEG is characterised by generalised spike-wave discharges greater than or equal to 3Hz
Good response to medical treatment

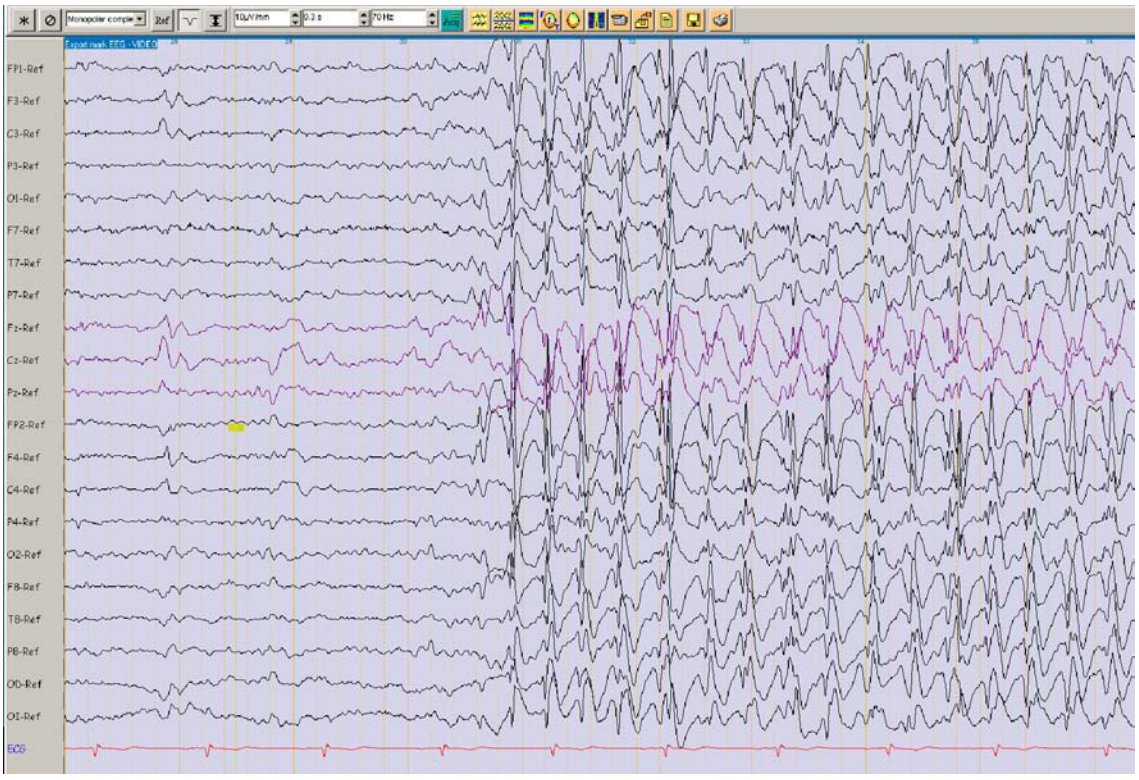

Figure 1 EEG (monopolar recording): generalised spike-wave discharges of 3Hz.

Material and methods

Patients

We retrospectively selected all patients who met the JAE diagnostic criteria by ILAE from 1989[1] (table 1) seen at the Hospital de Bellvitge and the Hospital de Sant Boi between 2005 and 2008. In our centres, all patients are seen at least once a year, despite having a good clinical control of epilepsy, whether or not they continue drug treatment. We also included patients who began to suffer epilepsy in adulthood (although ILAE defines puberty as age of onset, we decided to include patients with age of onset up to 30 years because that is the maximum age at which there may still exist brain maturation, especially in the frontal lobes).

Methods

The EEGs were performed with electrode placement according to the international 10/20 system, including activations by opening/closing eyes, photic stimulation, hyperventilation and, in some patients, sleep deprivation. We reviewed the EEG of all patients included in the study and all showed generalised spike-wave discharges (fig. 1). In some doubtful cases, we carried out a prolonged video-EEG.

Exclusion criteria

We excluded patients with a family history of febrile seizures and generalised epilepsy, due to the possibility of including epilepsy with febrile seizures. In addition, we excluded patients with exclusively photosensitive crises and the cases in which, despite displaying highly suggestive symptoms, we could not review the EEG that were diagnostic at the beginning of the disease.

Variables

Clinical variables

For each patient we collected gender, age at onset of AS and GTCS. We also separated the patients into two groups depending on their age at first crisis: those with onset at puberty (from 10 to 17 years) and those with late-onset (18 years or more). We considered it necessary to make this distinction, given that the ILAE classification of 1989[1] recognises as JAE only those patients who started crises at puberty, and not more belatedly. We also included the duration of the disease, the presence of GTCS and whether or not it was the first manifestation, the presence of myoclonus, the frequency of AS and GTCS at the onset, the development of status epilepticus and family history of epilepsy.

Therapeutic variables

We included the use of valproate (VPA), its levels, the number of drugs used throughout the disease and the need for combination therapy, the attempt to withdraw the treatment and, in this case, whether seizures recurred.

Prognostic variables

We collected the crisis-free status, defined as the absence of crises in the last two years[9,12] (depending on the

perception of the patient and the family), presence or absence of drug treatment and the maximum period without seizures. All these variables were analysed in terms of crisis-free status, to assess their possible relationship with disease prognosis. We did not include the EEG variable in the prognosis because evolution EEGs were not available for all patients.

Statistics

The results were analysed with the statistical package SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA). Univariate analysis was performed. Qualitative variables were analysed by unilateral Chi-square (with Yates correction when necessary) and continuous variables with the Student t test and the ANOVA test. As this was a descriptive study that included all patients with JAE and with no exclusion criteria, there was no sample size estimation.

Table 2 Results

	Number or mean (percentage or range)
Clinical variables	
Males	4 (19%)
Age of onset of AS	17.7 years (10-44)
Age of onset of GTCS	17.3 years (10-27)
Presence of GTCS	18 (85.7%)
GTCS as first manifestation	5 (23.8%)
Presence of myoclonus	3 (14.3%)
Frequency of AS at start of disease	
Sporadic	5.9%
Monthly	58.8%
Daily	35.3%
Frequency of GTCS at start of disease	
Sporadic	83.3%
Monthly	16.7%
Family history of epilepsy	9 (42.9%)
Time of evolution	24.6 years (10-43)
Status of absences	2 (9.5%)
Late start	4 (19%)
Therapeutic variables	
Treatment with VPA	19 (90.5%)
Levels of VPA in therapeutic range	71.4%
Need for combination therapy	13 (61.9%)
Number of drugs tested	3.3 (1-7)
Prognostic variables	
Mean period without crises	5.48 years (0-20)
Crisis-free at present	9 (42.9%)

AS: absence crises; GTCS: generalised tonic-clonic seizures; VPA: valproate.

Results

From a total of 26 patients who met the ILAE diagnostic criteria for JAE, we excluded one case with a family history of febrile seizures and generalised epilepsy, one case with exclusively photosensitive epilepsy, another case with symptom onset at age 55 and two cases in which the pathological EEG were not available for review. Consequently, we obtained a total of 21 patients, representing 1.9% of all our patients with epilepsy.

We found a clear female predominance, with 17 females and 4 males (table 2). The mean ages of onset of AS and GTCS were 17.7 and 17.3 years respectively (range: 10-44 and 10-27 years respectively). A total of 81% of patients were in puberty at onset, while the rest suffered a late onset, after 18 years of age. A total of 43% had a family history of epilepsy. The vast majority of patients presented GTCS at some point during their evolution (86%); in 24% of the patients, GTCS were the first clinical manifestation. Of all patients, 14% presented a history of myoclonus. In 59% of patients, AS at the time of diagnosis were mostly monthly; they were daily in 35% and sporadic in 6%. In 83% of patients, the frequency of GTCS was sporadic (less than one episode per year) and they were monthly in 17%. The duration of the disease was very long, about 25 years, with a maximum of 43 and a minimum of 10 years. Two cases reported absence status.

The vast majority of patients, up to 90%, had completed treatment with VPA at some point in their evolution, the majority (71%) with therapeutic levels. Of the two patients who did not receive VPA, one was without crises after the first treatment, and we could not confirm whether there had been treatment with VPA or not in the second case, as controls had initially taken place at another hospital. Most seizure-free patients were treated with VPA in monotherapy, with doses ranging between 300 and 1,500mg per day, in some patients even with lower-than-therapeutic levels. Seizure-free patients who did not receive VPA in monotherapy were treated with topiramate, carbamazepine or a combination of VPA and lamotrigine. Patients who were not seizure-free tried combinations of VPA with lamotrigine, topiramate, benzodiazepines, phenobarbital, zonisamide, and combinations thereof. All patients had received drug treatment and 62% of cases required combination therapy at some point during the disease.

Medication withdrawal was attempted in 8 patients after several years without crisis. In two cases, it was not achieved, because the crises reappeared before the medication was completely removed. In the 6 patients in whom it was achieved, in one case it became necessary to restart the medication due to an EEG with very frequent bursts of generalised spike-wave without apparent clinical manifestation; the remaining 5 patients presented crises once again after a variable time interval (between one month and 8 years), making it necessary to reinstate the medication in all cases.

A total of 43% of patients are currently seizure-free, that is, who have not suffered crises in the past two years, all with drug treatment. The mean period without seizures during the course of the disease was 5.5 years (range 0-20).

Table 3 Clinical and therapeutic variables according to status of seizure-free or not

	Seizure free (n=9)	Not seizure free (n=12)	*P*
Clinical variables			
Males	100%	0%	0.01
Females	30%	70%	
Age of onset of AS	15.2 (SD 3.4)	19.5 (SD 9.9)	Ns
Age of onset of GTCS	18 (SD 3.2)	17 (SD 6.1)	Ns
Presence of GTCS	77.7%	91.6%	Ns
Presence of myoclonus	11.1%	16.6%	Ns
Frequency of AS at start of disease			
Sporadic	100%	0%	0.04
Monthly	60%	40%	
Daily	0%	100%	
Frequency of GTCS at start of disease			Ns
Sporadic	84.8%	81.8%	Ns
Monthly	14.2%	18.1%	
Status of absence	0	16%	Ns
Age of late onset	22.2%	16.6%	Ns
Therapeutic variables			
Treatment with VPA	88.8%	100%	Ns
Levels of VPA in therapeutic range	57.1%	85.7%	Ns
Need for combination therapy	33.3%	83.3%	0.02
Number of drugs tested	2 (SD 1.1)	4.2 (SD 1.6)	0.02
Adverse effects of treatment	66.6%	41.6%	NS

AS: absence seizures; GTCS: generalised tonic-clonic seizures; NS: not significant; SD: standard deviation.

We compared the patients in terms of seizure control and analysed all previous variables (table 3). We found statistically-significant differences by gender and frequency of AS at the onset of the disease. Males showed a better prognosis than females, with a seizure-free rate of 100% and 30% respectively ($P=.01$). Patients with daily AS at the onset of the disease had a worse prognosis than those with monthly AS, with 0% and 60% of patients being free from crisis respectively ($P=.04$). In connection with medication, we found that patients who continued to suffer crises presented a greater need for combination therapy and had tried a greater number of drugs ($P=.02$). In relation with the presence of GTCS, although 66.6% of patients without GTCS were free of seizures and only 35.2% of patients with GTCS were seizure-free, these results were not statistically significant.

We also compared the patients according to age at onset of the first crisis. The groups were quite homogeneous, although patients with late onset showed a lower risk of developing GTCS than those with early onset (33% and 92% respectively; $P=.04$).

Discussion

The mean age of onset of AS in our study was 17.7 years, similar to the mean age of onset of GTCS, which was 17.3 years; although it is possible that JAE starts with GTCS, this is not very common.[1] These findings were due to the inclusion in our sample of 8 patients who started with AS in adulthood (4 of them with GTCS in adolescence and subsequent appearance of AS in adulthood, and 4 patients with no history of crises with a start of AS in adulthood). When we calculated the mean ages of onset of AS and GTCS in the rest of patients, we observed that they were 13 and 17.9 years respectively, similar to those obtained in other studies. Determining the age of onset of AS can be difficult, as these seizures can sometimes be so mild that the patient does not identify them as pathological. There was a clear female predominance in our series (81%). Although no difference between genders has been described in JAE,[1] it seems to be present in other IGE such as CAE, where there is a predominance of the female gender.[2]

Less than half of the patients in our sample are currently free of seizures (43%) with a mean follow-up of 25 years. There are other studies examining the long-term prognosis of JAE in the literature: Loiseau et al[9] obtained a sample of 62 patients with a very variable follow-up (minimum age of 20 years at the completion of the study) and found that 37% of patients were seizure-free; Bartolomei et al[10] achieved 60% seizure-free patients with a sample of 27 patients, who were followed for approximately 12 years; Tovia et al,[11] in a series of 17 patients, reported 43.7% to be seizure-free after a follow-up of 6 years; and Trinka et al[12] (with the largest series and the longest follow-up) collected 64 patients with a mean follow-up of 25 years and obtained 62% of remissions. Bouma[13] conducted a meta-analysis of 16 studies, which established a highly variable remission

rate, from 21% to 89% depending on the series, although it included patients with CAE and JAE. In view of these studies and our own results, it appears that JAE, despite also being a form of IGE, has a worse prognosis than CAE and JME. The 2001 ILAE classification[4,14] postulated that patients with JME, GTCS and JAE should be grouped under the single set of generalised epilepsies of variable phenotype with onset during adolescence, despite probably encompassing patients with different prognoses. We must remember that patients with JME who follow correct drug treatment with VPA become seizure-free in 90% of cases.[6,7]

Most seizure-free patients are currently being treated with VPA and, as in the case of JME patients, some receive lower doses compared with other focal epilepsies, with even lower-than-therapeutic doses.[7,15]

In our study, 62% of patients required combination therapy at some point during the course of their disease. Although this must be associated with a poor disease prognosis, it could also be related to an improper use of some antiepileptic drugs contraindicated in AS, such as carbamazepine and phenytoin. Many authors agree that an incorrect diagnosis, and therefore a wrong treatment of IGE, is the most common cause of drug resistance in these types of epilepsies.[2,4,6]

The presence of GTCS in JAE is very common, around 85% of cases,[2] and is associated with a worse disease prognosis.[9-12] In his meta-analysis, Bouma[13] found that 78% of patients without GTCS were seizure free, compared to only 35% of patients with GTCS. Other authors who have studied AS agree with this finding, both in the case of CAE and JAE.[8-12] In our series, we had only 3 patients without GTCS and also found the same trend, as 2 of the 3 patients without GTCS (66.6%) were seizure free compared to only 6 of 17 (35.2%) patients with GTCS. However, this difference was not statistically significant. On the other hand, the presence of myoclonus has also been postulated as an indicator of poor prognosis;[12] we found no differences in our series. Similarly, it has also been shown in JME that patients suffering the 3 types of crises (AS, myoclonus and GTCS) are more likely to display drug resistance.[16]

According to the ILAE, IGEs begin in childhood or adolescence by definition, although there are several authors who describe their appearance at later ages.[17-19] In our study, 4 patients (19% of the total) displayed AS after the age of 18 years, with no history of other types of crises. These late forms present the same clinical features as classical forms, and perhaps a better prognosis.[18] In our series, the late-onset group had a lower tendency to present GTCS (33% compared to 92% in the group with onset at puberty), a fact which could be correlated with a better prognosis. Although other authors also point to the existence of syndromes initiated only in adulthood, (such as IGE with pseudo-absence seizures),[20] our view is that patients who started AS at later ages form part of the same clinical spectrum as JAE.

In patients with episodes of disconnection from the environment with an adult onset, it is very important to always perform the differential diagnosis with focal seizures (with a frontal or temporal origin) and AS. This is because they may be cases of undiagnosed CAE or JAE (especially in JAE, where the AS may be more subtle[17]) or genuine cases of AS with onset in adulthood. We wish to note that the only patient who was not treated with VPA was a patient who suffered onset during adulthood (19 years). This patient was diagnosed with focal epilepsy and was treated with carbamazepine, although the electroclinical features were clearly those of IGE, including a neuroimage without epileptogenic lesions. Despite this, the patient remains seizure free with the medication.

IGE is a diagnosis to be considered even in adult-onset epilepsy. Consequently, obtaining an EEG (if necessary with sleep deprivation) is essential for correct diagnosis. We found one patient who started to suffer AS at age 55, with a generalised spike-wave EEG at 3Hz, and with an excellent response to VPA; we decided to exclude her from the study, but we feel that this was a very late form of JAE (even though the ILAE would not recognise it as a case of JAE due to the very late age of onset).

None of the studies mentioned previously discussed the possibility of withdrawing antiepileptic treatment in JAE. In our series, the medication was withdrawn in 6 patients after a variable crisis-free period and it was necessary to reintroduce it in all cases due to the recurrence of crises (except in one case, which was due to a severely pathological EEG). Consequently, it seems that JAE, like JME, and unlike CAE, requires treatment to be maintained for life.

The most important limitations of our study were the small sample of patients and especially the fact that it was retrospective, as we may have lost the more benign spectrum of the disease (patients with no follow-up due to being crisis free). We should also mention that most of our patients came from a tertiary centre, which could lead to a selection bias (by the inclusion of a subgroup of patients with worse prognosis). There was no control EEG available in all cases, especially in those subjects who were free of crises. Finally, not all of our patients received the best treatment for IGE from the onset of the disease, which may have conditioned a worse long-term prognosis.

In conclusion, JAE is a disease that persists throughout life, like JME and some other types of IGE with onset in adolescence, and which therefore requires indefinite antiepileptic treatment. The response to treatment in JAE, even with VPA, is far more modest than in JME and CAE, with combination therapy being necessary in many cases. All these results should be confirmed in larger prospective studies, to make the right decisions with this group of patients.

Conflict of interest

The authors declare no conflict of interest.

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