J Neurol (2004) 251 : 1235–1241
DOI 10.1007/s00415-004-0521-1

ORIGINAL COMMUNICATION

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Long-term prognosis for childhood and juvenile absence epilepsy

Abstract *Purpose* To analyse prognostic factors for long term seizure remission in patients with childhood (CAE) and juvenile absence epilepsy (JAE). *Study design* A retrospective analysis of a hospital based prevalence cohort. *Methods* The cohort consisted of 163 patients (104 females, 59 males) treated at the Universitätsklinik für Neurologie, Innsbruck between 1970 and 1997. All had absences according to the ILAE classification. Follow up was in 1999 to 2000. We assessed multiple clinical and EEG factors as predictors of outcome and compared a classification according to the predominant pattern of seizure recurrence (pyknoleptic, PA or non pyknoleptic absence, NPA) with the ILAE classification with respect to prognosis. *Results* The mean age at seizure onset was 10.9 years (range, 3 to 27); age at follow up was 36.7 years (range, 13 to 81); duration of follow up was 25.8 years (range, 3 to 69). Sixty four patients (39 %) had CAE and 64 (39 %) JAE, while 35 (22 %) had typical absences but could not be clearly defined as either CAE or JAE, and were therefore called "the overlap group". Patients with JAE or patients in the overlap group developed more often generalized tonic clonic seizures (GTCS) ($p < 0.001$) and myoclonic attacks ($p < 0.05$) during the course of the disease. At follow up 36 (56 %) of patients with CAE, 40 (62 %) with JAE and 19 (54 %) of the overlap group were seizure free for at least two years (p = ns). When classified according to the predominant absence pattern at seizure onset 42 (51 %) patients with PA and 53 (65 %) with NPA were in remission (p = ns). In a stepwise binary logistic regression analysis the pattern of absence (PA or NPA) together with the later development of additional seizure types (myoclonias or GTCS), but not the CAE/JAE classification was predictive for long term lack of remission with a correct prediction of 66 % of all patients. *Conclusion* Only 58 % of patients with absences were in remission after a long term follow up. CAE and JAE are closely related syndromes with large overlap of the age of onset. A classification according to the predominant seizure pattern at onset, together with later development of myoclonic attacks or GTCS is useful in predicting seizure remission in absence epilepsies.

Key words childhood absence epilepsy · juvenile absence epilepsy · absence seizure · epilepsy · prognosis

Received: 26 June 2003
Received in revised form: 20 April 2004
Accepted: 28 April 2004

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Introduction

Childhood absence epilepsy (CAE) and Juvenile Absence Epilepsy (JAE) are both recognized as distinct epilepsy syndromes by the ILAE [2]. The definition of the syndromes is based on frequency of absences or pattern of recurrence, and age at seizure onset. In CAE multiple absences occur daily, often up to hundreds (i. e. they are pyknoleptic, PA) with a younger age of onset around 6 to 8 years, while in JAE the absences occur at a later age, around 10 to 12 years with a frequency less than daily (i. e.

non-pyknoleptic, NPA) [11, 17, 21]. There may be a considerable overlap between the two syndromes and the cutoff age remains controversial [15, 18].

Andermann and Berkovic re-examined the definitions and criteria of idiopathic generalized epilepsies (IGEs) with generalized tonic clonic seizures (GTCS) in adolescence in a *"special article"* [3] and alluded to the question whether one should attempt to classify the IGE syndromes on the basis of predominant seizure type and pattern, age at onset or clinical disability and prognosis. Though the exact number is not known, many of the patients with GTCS in adolescence had absences before the onset of GTCS but on the other hand many children with absences during childhood never develop other seizure types and therefore have a favorable prognosis. However, at present it is not clear, whether the ILAE classification or a new classification based on predominant seizure pattern is more appropriate to predict seizure remission.

In the present study we analysed multiple clinical and electroencephalographic (EEG) factors to predict the outcome of patients with absences and tried to clarify whether the ILAE classification or a classification based on predominant seizure pattern (i. e. pyknoleptic and non-pyknoleptic absences) is most suitable with respect to prognosis.

Methods

All patients with absences fulfilling the ILAE criteria [1] (n = 255) treated at the Universitätsklinik für Neurologie, Innsbruck, Austria between 1970 and 1997 were reviewed. Fifty five patients were excluded for the following reasons: unknown seizure frequency and semiology before antiepileptic drug (AED) treatment (n = 16), incomplete demographic patient data (n = 10), death (n = 15), additional non epileptic seizures (n = 5), unclassifiable seizures (n = 7), unknown age of onset (n = 2). Thirty seven patients were lost to follow up. A total number of 163 patients meeting the broad criteria of CAE and JAE according to the definitions of the ILAE classification [2] were included in the study and had a follow up interview in 1999 to 2000.

We analysed clinical information including age, sex, birth history, neurological examination, age of seizure onset, pattern and frequency of seizure recurrence before treatment, history of status epilepticus, additional seizure types (myoclonic attacks and/or GTCS) and when they began, AED treatment, and treatment response. EEG findings (spike wave frequency, background rhythm abnormalities, focal abnormalities) were re-examined and brain CT or MRI records were reviewed when available. Information was obtained by chart review for those patients who had their last visit in our seizure clinic no longer than six months before study inclusion, and by personal follow up interview in the others. Seizure freedom was defined as complete absence of seizures with or without AEDs for 2 years or more.

Seizure classification was defined as follows

Pyknoleptic absences (PA)

Characterized by abrupt severe impairment of consciousness only or combined with mild clonic, atonic, tonic, and automatic components and automatisms occurring frequently, many per day up to hundreds in an otherwise normal patient.

Non-pyknoleptic absences (NPA)

Characterized by impairment of consciousness only or combined with mild clonic, atonic, tonic, and automatic components and automatisms occurring infrequently, not every day, in an otherwise normal patient.

Syndrome classification was defined as follows

CAE

- Onset of frequent (daily, pyknoleptic) absences (PA) in an otherwise normal child at age ≤ 10 years
- Pyknoleptic absences (PA) as the predominant seizure type at time of diagnosis
- Absences accompanied by bilateral, symmetric, and synchronous discharge of regular 3 to 4Hz spike wave discharges with normal or mildly abnormal background activity.

JAE

- Onset of absences less frequent than daily (non-pyknoleptic, NPA) in an otherwise normal child at age > 10 years
- Non-pyknoleptic absences (NPA) as predominant seizure type at time of diagnosis
- Absences accompanied with bilateral, symmetric, and synchronous discharge of regular 3 to 4Hz spike wave or polyspike wave discharges with normal or mildly abnormal background activity.

Overlap group

Because age of onset shows a considerable overlap we further defined an overlap group using the following criteria:

- Patients with PA and an age at onset > 10 years and
- patients with NPA starting at an age at 10 years or younger.

Patients initially classified as CAE, JAE, or overlap group with continuing seizures at the time of follow up who developed additional myoclonic attacks in association with the characteristic EEG changes of fast generalized spike wave or polyspike wave discharges with or without GTCS were classified as juvenile myoclonic epilepsy (JME). Evolution of the EEGs to show the characteristic changes were considered confirmatory but not necessary for diagnosis of JME.

In addition to the syndrome classification we divided patients into 2 groups according to their predominant pattern of absence recurrence at the time of diagnosis: (1) patients with pyknoleptic absences (PA) and (2) patients with non-pyknoleptic absences (NPA) [18] and compared clinical data and outcome in these groups.

Statistical analysis

Data processing and analysis were performed with SPSS for Windows 11.0. We used chi-square and Fisher's exact tests for group comparisons at nominal-data level. A stepwise binary logistic regression analysis was computed to predict the influence of independent variables, including the syndrome classification (CAE, JAE, overlap group) and the classification by seizure pattern (PA and NPA) on the outcome measurement (seizure free versus not seizure free).

Results

Clinical data and epilepsy syndromes

One hundred and sixty-three patients were studied. The cohort consisted of 104 women (64%) and 59 men (36%). Mean age at seizure onset was 10.9 years (SD 4.64; range, 3 to 27) and at follow up 36.7 years (SD 13.96; range, 13 to 81) resulting in a mean follow up duration of 25.8 years (SD 14.67; range, 3 to 69). At follow up 95 (58%) of all patients were seizure free; 42 (44%) of the seizure free patients were treated with AEDs at the time of follow up.

Eighty-two patients (50.3%) had pyknoleptic absences (PA) whereas 81 (49.7%) patients had non-pyknoleptic absences (NPA). Age of onset in patients with PA was earlier than with NPA ($p < 0.001$). The age distribution of both groups is illustrated in Fig. 1. Using a strict definition of syndromes with a cutoff age of 10 years [18], 64 (39%) patients were classified as CAE and 64 (39%) as JAE, while 35 (22%) patients ("overlap group") could not be defined as either CAE or JAE. Clinical and demographic data are summarized in Table 1.

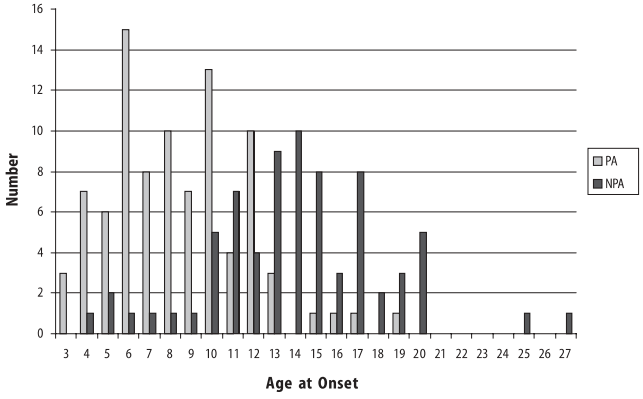

Fig. 1 Distribution of age of seizure onset in patients with pyknoleptic absences (grey bars) and non-pyknoleptic absences (black bars) (*NPA* non-pyknoleptic absences; *PA* pyknoleptic absences)

Evolution of seizure types and epilepsy syndromes

Absences were the initial seizure type in 79% of patients with PA but only 48% of those with NPA ($p < 0.001$). Only three patients (4%) with PA but 11 patients (14%) with NPA experienced GTCS ($p < 0.05$) as the initial seizure type. In 44 patients (14 with PA and 31 with NPA) both seizure types (GTCS and absences) began at approximately the same age (within six months). In both patient groups only a minority (7 of 82 with PA and 6 of 81 with NPA, p = ns) experienced convulsive or non-convulsive status epilepticus. During the course of the disease 74 (91%) patients with NPA developed GTCS compared with 60 (73%) of patients with PA ($p < 0.005$). The myoclonic attacks developed more often in patients with NPA than in those with PA (21% vs. 5%, $p < 0.005$). In 21 patients (26%) with PA and six (7%) with NPA no other seizure types developed during the follow up period (Table 2).

Patients in the overlap group or those with JAE experienced more often additional myoclonic attacks ($p < 0.05$) or GTCS ($p < 0.001$) during the course of the disease. At follow up 36 (56%) patients with CAE, 40 (62%) with JAE and 19 (54%) of the overlap group were seizure free for at least two years (p = ns). Only 3 (5%) patients initially defined as CAE but 12 (19%) with JAE and 6 (17%) patients of the overlap group (ANOVA; $p < 0.05$) evolved to juvenile myoclonic epilepsy (JME).

Table 1 Clinical and demographic data of patients with childhood absence epilepsy (CAE) and juvenile absence epilepsy (JAE)

	CAE (n = 64)	JAE (n = 64)	Overlap group n = 35	p =
sex (m/w)	23/41	22/42	14/21	ns
age at onset, years mean ± SD	7 ± 2.2	15 ± 3.3	10.6 ± 3.4	< 0.001
duration of FU, years mean ± SD	30 ± 14.1	22 ± 14.9	24.9 ± 13.4	< 0.05
positive FHx	41 (64%)	47 (73%)	26 (74%)	ns
Hx of SE	5 (8%)	5 (8%)	1 (3%)	ns
development of myoclonias	3 (5%)	12 (19%)	6 (17%)	< 0.05
development of GTCS	44 (69%)	61 (95%)	29 (83%)	< 0.001
seizure free at follow up	28 (43%)	24 (37%)	16 (46%)	ns

CAE childhood absence epilepsy; *positive FHx* positive family history in first degree relatives; *FU* follow up; *GTCS* generalized tonic clonic seizure; *Hx* history; *JAE* juvenile absence epilepsy; *m* men; *ns* not significant; *p* Pearson's chi-square or ANOVA; *SE* status epilepticus; *w* women

Table 2 Evolution of seizure types and outcome in patients with pyknoleptic and non-pyknoleptic absences

	PA (n = 82)	NPA (n = 81)	p =
sex (m/w)	32/50	27/54	
age at onset, years	Median 8 (range, 3–19)	Median 14 (range, 4–27)	< 0.001
duration of FU, years mean ± SD	28 ± 14.4	23 ± 14.7	ns
seizure type at onset			
ABS	65 (79%)	39 (48%)	< 0.001
GTCS	3 (4%)	11 (14%)	< 0.05
ABS + GTCS	14 (17%)	31 (38%)	ns
Hx of SE	7 (6%)	6 (5%)	ns
development of myoclonias	4 (5%)	17 (21%)	< 0.005
development of GTCS	60 (73%)	74 (91%)	< 0.005
persisting seizure types			
ABS	19 (47%)	7 (25%)	ns
GTCS	10 (25%)	9 (32%)	ns
ABS + GTCS	9 (22%)	7 (25%)	ns
myoclonic	1 (2%)	2 (7%)	ns
other*	1 (2%)	3 (11%)	ns
seizure free at follow up	42 (51%)	53 (65%)	ns
duration of remission (years)			
≤ 5	13 (31%)	31 (60%)	ns
6 to 10	9 (21%)	5 (9%)	ns
11 to 15	6 (14%)	6 (11%)	ns
16 to 20	8 (19%)	6 (11%)	ns
21 to 25	4 (10%)	4 (8%)	ns
≥ 25	2 (5%)	1 (2%)	ns

ABS absences; *FU* follow up; *GTCS* generalized tonic clonic seizures; *Hx* history; *m* men; *NPA* non-pyknoleptic absences; *PA* pyknoleptic absences; *SE* status epilepticus; *w* women; * various combinations of absences, generalized tonic clonic seizures, and myoclonic seizures; *p* Pearson's Chi-square

Seizure types, EEG and imaging findings

A total of 478 EEGs were analysed (Table 3). There was a tendency towards a faster spike wave frequency in NPA than in PA which did not reach significance.

A hundred and forty-eight patients had brain CT or MRI with normal findings in 128 patients. Nine patients had diffuse brain atrophy and small cerebrovascular lesions, one had a prepontine epidermoid cyst and one hippocampal asymmetry with a smaller hippocampus on the left and a normal T2-signal. Posttraumatic gliosis or lesions from a remote stroke were seen in nine patients. All imaging findings were regarded as unrelated to the seizure disorder, or were definitely acquired after the seizure onset. Fifteen patients had no brain CT or MRI.

Seizure types and outcome

Forty-two (51%) patients with PA and 53 (65%) with NPA were seizure free at follow up (p = ns). Sixty (73%) patients with PA and 61 (75%) with NPA were on AEDs at follow up. The majority in both groups (35 with PA and 42 with NPA) were on valproate monotherapy. 13 patients with PA and 11 with NPA were treated with valproate in combination with other AEDs (lamotrigine, ethosuximide, primidone or topiramate). Duration of seizure freedom ranged from 2 to 42 years in patients with PA and 2 to 28 years in those with NPA (Table 2). Twenty six (38%) of the patients who were not in remission had absences, 19 (28%) had rare GTCS, 16 (24%) had absences and GTCS, three (4%) myoclonic seizures, and 4 (6%) had combinations of GTCS, absences and myoclonic seizures at follow up. There were no differences in persisting seizure types between patients with PA and NPA (Table 3). Patients with PA who developed GTCS during the course of the disease (n = 60) were less often in remission than those with NPA and GTCS (n = 74; 58% vs 36%; Pearson chi-square, p < 0.05). More than half (12 of 21, 57%) of patients who developed myoclonic epilepsy and 46% (62 of 134) who developed GTCS during their disease were not seizure free at follow up (Pearson chi-square, p = ns.)

Table 3 Electroencephalographic findings in patients with PA and NPA

EEG findings n = number of EEGs	PA n = 240	NPA n = 238	p =
normal	2	0	ns
normal background rhythm	69 (84%)	75 (92%)	ns
mild diffuse slowing	13 (16%)	6 (7%)	ns
paroxysmal theta	71 (87%)	72 (89%)	ns
3 Hz Spike Wave	50 (46%)	30 (32%)	ns
3–4 Hz Spike Wave	5 (6%)	14 (17%)	ns
4 Hz Spike Wave	7 (8%)	8 (9%)	ns
> 3Hz Spike Wave	5 (6%)	5 (6%)	ns
irregular Spike Wave	15 (18%)	20 (25%)	ns
polyspike Wave	13 (16%)	13 (16%)	ns
photosensitivity	3 (4%)	9 (11%)	ns

NPA non-pyknoleptic absence; *PA* pyknoleptic absence; *p* Pearson's Chi-square

Predictors for seizure remission

A forward stepwise logistic regression analysis with dependent variables *seizure free* and *not seizure free* at follow up was calculated. The clinical factors *pattern of absence (PA or NPA), epilepsy syndrome (CAE, JAE or overlap group), development of myoclonic attacks, or GTCS, history of absence status, age at seizure onset ≤ 10 or > 10 years, positive family history, and history of febrile convulsions* were used as independent variables. Only the pattern of absence (PA or NPA), and a development of myoclonic attacks or GTCS served as a significant predictor for persistence of seizures and explained

13.7 % of the variance (Table 4). Using this model, in 66 % of all patients seizure remission was correctly predicted.

Discussion

The subclassification of absence epilepsies in CAE and JAE has caused much controversy since it was first established in 1985 and it is still debated. The nosological concepts of the absence epilepsies vary between forming a biological continuum and representing distinct entities [3, 6, 15, 18, 23]. Previous studies reported a large overlap of the age at seizure onset between the patient groups studied [11, 15, 17, 18] yielding age as an unreliable discriminator between the two syndromes.

We used a strict definition with a cutoff age of 10 years as a criterion to distinguish between CAE (predominantly PA with age at onset younger than 10 years) and JAE (predominately NPA with age at onset after 10 years). Using these criteria we found significant clinical differences between the syndromes to justify a syndrome-based delineation: in CAE the absences start *per definitionem* at a younger age, and are less often associated with other seizure types (GTCS and myoclonic attacks) than in patients with JAE. However, not all patients could be assigned to one or the other group without effort, leaving a large proportion of patients overlapping the boundaries between these syndromes. Thus, we alternatively classified the patients according to their predominant pattern of absence recurrence (PA or NPA) at onset of disease. In our study approximately 60 % of all patients with absence epilepsy were seizure free after a long follow up. The percentage of seizure free patients did not differ whether we classified them according to their predominant absence pattern and seizure type, or according to the ILAE classification. Though most of the patients with absences will enter remission, a considerable number of patients will develop additional seizure types and will not be seizure free for a long period of time. The remission rates vary depending on the length of follow up and the various inclusion criteria used over the time [7]. A meta-analysis of 26 publications on the prognosis of absence epilepsies has shown remission rates between 21 % and 89 % with development of GTCS in about half of the patients included in the studies. The proportion of seizure free patients was 78 % for those with absence seizures only and 35 % for the ones who developed GTCS [7]. There was a strong correlation between mean duration of follow up and outcome indicating a lower proportion of seizure free patients with longer follow up periods [7]. A study on prognosis of CAE reported similar remission rates (65 %) and found a high proportion (15 %) of their patients who progressed to juvenile myoclonic epilepsy (JME) [29]. Moreover, of those patients who were not in remission, 44 % had progressed to JME. In our study a smaller proportion (4.7 %) of patients with CAE progressed to JME, whereas 18.8 % of the patients with JAE and 17.1 % of the overlap group progressed to JME ($p < 0.05$). In addition only 17 % of our patients who were not in remission at follow up had myoclonic attacks, but 91 % had developed GTCS. The disparities between the studies are possibly due to a selection bias with different definitions of the syndromes or – more likely – a genetic difference in the investigated population [8]. Nevertheless the development of myoclonic attacks or GTCS during the disease course had an adverse influence on the rate of seizure free patients in both studies.

The assumption that CAE is a self limited benign disease in contrast to JAE, which is probably a lifelong condition [15, 21, 23] is not supported by currently available data including the results from the present study [4, 5, 9, 10, 16, 22, 25]. In our study with a very long follow up we found 56 % of the patients with CAE and 62 % with JAE in remission. The remission rate is perhaps influenced by a selection of more severe patients, since it does not reflect an incidence, but a prevalent cohort. However, similar remission rates were found in a retrospective analysis of a smaller cohort comparing CAE and JAE [4]. Because of the small number of JAE patients no statistical correlation was made in that study and for CAE patients only the presence of polyspikes and polyspike waves during sleep was associated with a poor outcome [4]. In our study none of the analysed EEG findings were found as a predictor of poor outcome.

At the time of diagnosis only the pattern of absence recurrence (PA or NPA), and development of additional myoclonic attacks or GTCS, but not the syndromic CAE/JAE classification predicted lack of remission. Consequently lack of remission can only be predicted by the course of the disease. Therefore it may be meaningful to describe syndromes according to their predomi-

Table 4 Binary logistic regression analysis of clinical factors predicting lack of remission of absence epilepsies

Variable	Regression coefficient EXP β	Wald coefficient	Significance p	EXP β (95 % CI)
absence pattern (PA or NPA)	1.042	8.105	0.004	2.836 (1.384–5.811)
development of myoclonias	–1.001	3.850	0.05	0.367 (0.135–0.999)
development of GTCS	–1.512	8.511	0.004	0.220 (0.80–0.699)

GTCS generalized tonic clonic seizure; *EXP* exponent; *NPA* non-pyknoleptic absence; *PA* pyknoleptic absence

nant seizure types and recognize idiopathic generalized epilepsy syndromes with GTCS and other seizure types as has been recently suggested [3]. According to this classification patients who had PA or NPA in young life or adolescence and later develop GTCS could then be considered as having *idiopathic generalized epilepsy with GTCS and pyknoleptic or non-pyknoleptic absences*, which corresponds more to reality than to classify an adult patient who had absences during childhood and rare GTCS in later life still as CAE.

Conversely there are many patients who had absences only during childhood or adolescence (in the present study 26 % of patients PA and 7 % of those with NPA) who will never have other seizures during later life. Recent studies discovered two gene mutations in CAE probands with further epileptic or other neurological features [19, 27] and several susceptibility loci [8, 12, 13, 14, 20, 24, 26, 27] supporting genetic heterogeneity and the hypothesis of fundamental biological differences within IGE syndromes and even CAE subsyndromes. These findings may account for the different prognostic scenarios for a child with CAE, namely either entering remission of absences or evolving into other IGE syndromes (e. g. JME) either with later development of GTCS or myoclonic seizures or both [8, 13, 28, 29].

Considering the clinical differences between patients with absences, they are sufficient to delineate distinct subsyndromes within the idiopathic generalized epilepsy classification. However, CAE and JAE are closely related within the spectrum of IGE, which is underlined in this study by their similar long term prognosis. Thus they may be regarded as age-dependent variants of a biological continuum. But as long as the genes responsible for different phenotypes are far from clear it is reasonable to concentrate on the clinical differences and form stringent clinical criteria within the classifications of IGE subsyndromes based on seizure types. It would then make it more difficult to select suitable probands for genetic analysis, but could also make it easier to detect genetic traits, which in turn would validate a syndromic classification of the idiopathic generalized epilepsies.

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