DOI: 10.1093/brain/awh151 *Brain* (2004), **127,** 1343–1352

Idiopathic partial epilepsy with auditory features (IPEAF): a clinical and genetic study of 53 sporadic cases

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Summary

The purpose of our study was to describe the clinical characteristics of sporadic (S) cases of partial epilepsy with auditory features (PEAF) and pinpoint clinical, prognostic and genetic differences with respect to previously reported familial (F) cases of autosomal dominant partial epilepsy with auditory features (ADPEAF). We analysed 53 patients (24 females and 29 males) with PEAF diagnosed according to the following criteria: partial epilepsy with auditory symptoms, negative family history for epilepsy and absence of cerebral lesions on NMR study. All patients underwent a full clinical, neuroradiological and neurophysiological examination. Forty patients were screened for mutations in *LGI1*/epitempin, which is involved in ADPEAF. Age at onset ranged from 6 to 39 years (average 19 years). Secondarily generalized seizures were the most common type of seizures at onset (79%). Auditory auras occurred either in isolation (53%) or associated with visual, psychic or aphasic symptoms. Low seizure frequency at onset and good drug responsiveness were common, with 51% of patients seizure-free. Seizures tended to recur after drug withdrawal. Clinically, no major differences were found between S and F patients with respect to age at onset, seizure frequency and response to therapy. Analysis of *LGI1*/epitempin exons failed to disclose mutations. Our data support the existence of a peculiar form of non-lesional temporal lobe epilepsy closely related to ADPEAF but without a positive family history. This syndrome, here named IPEAF, has a benign course in the majority of patients and could be diagnosed by the presence of auditory aura. Although *LGI1* mutations have been excluded, genetic factors may play an aetiopathogenetic role in at least some of these S cases.

Keywords: temporal lobe epilepsy; auditory aura; *LGI1* gene; epilepsy prognosis; IPEAF

Abbreviations: ADPEAF = autosomal dominant partial epilepsy with auditory features; AED = anti-epileptic drug; CI = confidence interval; DHPLC = denaturing high-performance liquid chromatography; F = familial; FS = febrile seizure; *LGI1* = leucine-rich, glioma-inactivated 1 gene; MTS = mesial temporal sclerosis; PEAF = partial epilepsy with auditory features; S = sporadic; SGTCs = secondarily generalized tonic or tonic–clonic seizures; TLE = temporal lobe epilepsy

Received October 27, 2003. Revised January 25, 2004. Accepted January 27, 2004. Advance Access publication April 16, 2004

Introduction

Temporal lobe epilepsy (TLE) is the most common form of partial epilepsy and is frequently associated with mesial temporal sclerosis (MTS). Intensive research on refractory cases, stimulated by interest in surgical treatment, has documented common aetiologies and clinical characteristics of lesional cases of TLE. Otherwise, little is known about the aetiologies and outcome of non-lesional cases. From epidemiological reviews, it appears that non-lesional TLE is not

a uniform disorder, but includes patients with severe refractory epilepsy and cases with a mild epileptic disorder who enter remission with or without antiepileptic medication (Hauser, 1992; Aguglia *et al*., 1998).

In recent years, growing evidence has indicated that a genetic predisposition appears to be an important causal factor of TLE and familial clustering of the disorder has been reported (Ottman *et al*., 1995; Scheffer *et al*., 1995; Berkovic *et al*., 1996; Cendes *et al*., 1998). According to seizure semiology, familial TLE can be divided into two main categories, one with mesial temporal lobe symptoms (Berkovic *et al*., 1996) and one with lateral symptoms (Ottman *et al*., 1995). Whereas familial mesial TLE is a heterogeneous condition (Berkovic *et al*., 1996; Cendes *et al*., 1998), familial lateral TLE appears to be more homogeneous, characterized by simple partial seizures with mainly auditory hallucinations (Winawer *et al*., 2002).

In 1995, Ottman described the first pedigree in which most of the affected members reported seizures with acoustic symptoms usually followed by secondary generalization and named the syndrome autosomal dominant partial epilepsy with auditory features [ADPEAF (OMIM 600512)]. To date, another 20 families have been reported (Poza *et al*., 1999; Ikeda *et al*., 2000; Mautner *et al*., 2000; Michelucci *et al*., 2000, 2003; Brodtkorb *et al*., 2002; Santos *et al*., 2002; Wallace *et al*., 2002; Winawer *et al*., 2002; Fertig *et al*., 2003; Pizzuti *et al*., 2003) with similar phenotype, clarifying the main features of the syndrome that are characterized by autosomal dominant transmission with high penetrance, onset in the second and third decades of life, recurrent auditory aura usually followed by generalized seizures, low seizure frequency and benign outcome with good drug response. Recently, mutations causing ADPEAF have been found in the leucine-rich, glioma-inactivated 1 gene, *LGI1,* (Kalachikov *et al*., 2002; Morante-Redolat *et al*., 2002). The gene is located on chromosome 10q24 and was renamed 'epitempin' (Morante-Redolat *et al*., 2002). The function of this gene is unknown, but a role in neuronal migration has been postulated (Cowell *et al*., 2002; Gu *et al*., 2002). The exclusion of linkage to 10q24 in one ADPEAF family and the absence of *LGI1* mutations in a few other families suggest that this syndrome may be genetically heterogeneous (Bisulli *et al*., 2002; Michelucci *et al*., 2003). Evidence that patients with familial aphasic seizures have mutations in the same gene, first shown in a Norwegian family (Gu *et al*., 2002), further widens the clinical spectrum of this condition. Thus, the term autosomal dominant lateral temporal epilepsy (ADLTE) rather than ADPEAF has been proposed (Poza *et al*., 1999; Michelucci *et al*., 2003), focusing on seizure onset from the lateral portion of the temporal lobe and therefore including other symptoms (visual and aphasic) which recurred in these families in isolation or associated with auditory auras.

Although interest in auditory auras has recently been aroused by the discovery of these ADPEAF cases, auditory symptoms are well known in partial epilepsy of any aetiology and have always been considered a characteristic of temporal lobe seizures (Wunderlich *et al*., 2000). Auditory seizures were first reported by Holmes as early as 1927 (Holmes, 1927). Lennox reported a 2.4% incidence of auditory aura among 1359 epileptic patients (Lennox, 1960). This percentage rose to 16% in Currie's series of 666 patients with temporal lobe seizures (Currie *et al*., 1971). Moreover, Penfield and Kristiansen found only three patients out of 222 surgical cases, suggesting the rarity of this condition in refractory epilepsies (Penfield and Kristiansen, 1951). Therefore, auditory aura is a rare epileptic symptom if we consider only lesional TLE but perhaps more frequent in cryptogenetic cases even if the exact incidence is not reported.

The purpose of our study was to describe the clinical characteristics of sporadic (S) cases with partial epilepsy with auditory features (PEAF) and pinpoint clinical, prognostic and genetic differences with respect to previously reported familial (F) cases with autosomal dominant partial epilepsy with auditory features (ADPEAF).

Methods

Present series

Diagnosis of PEAF was made according to a clinical history of at least two lifetime seizures with auditory features: a single cluster of seizures was considered as a single episode. Possible candidates with PEAF were identified both with (i) a prospective observation of patients admitted for the first time to epilepsy centres participating in the study from January 1999 to March 2003, and (ii) retrospectively from the databases of the centres and reviewing all clinical records. All candidates of the latter group, with long-lasting disease followed at our centres for many years, had a seizure diary and clinical evaluation visits at least every 6 months. Moreover, they were recalled and re-examined personally.

The study population therefore included both patients with newly diagnosed epilepsy and some patients with long-standing disease. Among these patients, we selected those responding to the following inclusion criteria: (i) absence of first- and second-degree relatives (siblings, offspring, parents, grandparents, aunts and uncles) with epileptic seizures; (ii) absence of clear-cut neuroradiological abnormalities, including MTS. Exclusion criteria were an insufficient or doubtful family history and lack of neuroimaging data.

The data from each patient were tabulated with full details of seizure type, auras, seizure frequency, response to therapy, antiepileptic drug (AED) used, ictal and interictal EEG recording, and neuroradiological findings. Other clinical items tabulated were sex, dominant hand, personal antecedents, family history, age at seizure onset, follow-up duration, delay between seizure onset and diagnosis, delay between onset of partial seizures with auditory symptoms and secondarily generalized tonic or tonic–clonic seizures (SGTCs).

Three investigators (F.B., R.M., P.S.) undertook personal interviews with the patient and at least one relative, usually the mother, to establish the family history (for febrile seizures, epilepsy, mental retardation and neurological diseases) and potential personal antecedent events such as severe asphyxia, severe head injury, viral encephalitis, bacterial meningitis or cerebral abscess, and

complicated febrile seizures. Febrile seizures (FS) were diagnosed when convulsions associated with fever occurred between the age of 3 months and 5 years (Consensus development conference on febrile seizures, National Institutes of Health, 1981).

All patients underwent repeated EEG recordings during wakefulness and, when possible, during diurnal sleep induced by sleep deprivation (18 patients). Each patient underwent high-resolution NMR or CT scanning of the brain. Twenty millilitres of blood for DNA extraction were collected from 40 patients after written informed consent had been given.

Literature review

Previously reported cases of ADPEAF were identified searching articles in the National Library of Medicine's MEDLINE database (from 1966 to 2003), focusing on the terms 'ADPEAF' OR '*LGI1*' OR 'familial temporal lobe epilepsy' OR 'auditory aura', and checking the reference lists of identified articles to find additional references.

We did a retrospective analysis of 119 cases of ADPEAF belonging to the 19 families described so far (Table 1). Clinical details were only accepted when unambiguous. Case numbers therefore differ slightly among the parameters assessed. Other reported families, mentioned in abstract form or with scant clinical and electrophysiological data, were not included in our analysis (Picard *et al*., 2000; Santos *et al*., 2002; Wallace *et al*., 2002). Moreover, we excluded cases in which the pattern of inheritance was not autosomal dominant (Bisulli *et al*., 2002) and the Kanemoto family, in which affected members reported only aphasic seizures without any auditory auras (Kanemoto *et al*., 2000).

Statistical analysis

Clinical data about S and F cases (the latter by each single study) were reported as relative frequency (dichotomous data) and mean (continuous data), with the 95% confidence interval (CI). Comparison of some clinical data was made by means of the forest plot graphic presentation (Lewis and Clarke, 2001). According to this method, the results are shown as squares (S patients) and circles (F studies) centred on the point estimate of the result of each study. A vertical line runs through the point estimate to show its 95% CI.

Mutation analysis

Genomic DNA was extracted using standard methods and all *LGI1* exons were PCR-amplified. Some PCR primer sequences have already been reported (Michelucci *et al*., 2003); the others will be made available on request. PCR fragments specific for exons 1, 6, 7 and 8 were analysed by denaturing high-performance liquid chromatography (DHPLC; Transgenomic) at the appropriate temperatures. This method has a sensitivity >90%. PCR fragments for exon 2, 3, 4 and 5 turned out to be unsuitable for DHPLC analysis and were therefore analysed by direct sequencing with the BigDye Terminator Cycle Sequencing kit (Perkin Elmer Applied Biosystems).

Results

Clinical data

We collected data on 119 PEAF cases out of 8000 epileptic patients admitted for the first time to the centres. Among them, 53 fulfilled the inclusion criteria; 18 were identified with the prospective observation and 35 from the databases and by reviewing clinical files of the epilepsy centres. The remaining 66 patients were excluded because of insufficient clinical and neuroradiological data (10 patients), positive family history for epilepsy (41 patients) and symptomatic aetiology (15 patients).

Clinical and EEG findings compared with previously reported ADPEAF families are shown in Table 1.

A family history of FS in second- and third-degree relatives was noted in two patients. Medical histories were unremarkable with respect to structural or metabolic insults. FS were reported in five patients, but none of them experienced prolonged or complicated episodes. Neurological examination was normal.

Type of seizure

At onset, SGTCs were the most common type of seizures occurring in 42 patients (79%). Some of these patients were referred to us with a diagnosis of idiopathic generalized epilepsy (11%). On the basis of a detailed epileptological interview, 36 of these 42 patients were also found to suffer from clear-cut focal, elementary (22 patients) or complex (14 patients) seizures (according to the international classification of seizures: Commission on Classification and Terminology of the International League Against Epilepsy, 1989) other than SGTCs, while six had only SGTCs. Eleven patients had only focal seizures (elementary two, complex six, both elementary and complex three). Seizures occurred only during wakefulness in 60% of patients and also during sleep in 40%.

Auditory auras

The focal seizures (either elementary, complex or secondarily generalized) were characterized by prominent auditory symptoms in all patients because of the inclusion criteria. Auditory auras were isolated in 53% of patients and associated with other symptoms in the remainder. Three patients with auditory symptoms also reported visual features during the same attacks or in isolation. Psychic symptoms such as dreamy state sensation, déjà vu, déjà vecu and negative thoughts (like a feeling of dying) followed the auditory auras in three cases. Difficulty in speaking or loss of speech comprehension accompanied the auditory symptoms in five patients. Only one patient described olfactory auras and the remaining patients experienced auras characterized by several symptoms in different associations.

Most of the patients (58.4%) described simple hallucinations characterized by unformed sounds, like hissing, buzzing and acoustic vibration. Other patients (40%) reported complex auditory hallucinations characterized by well-formed and occasionally quite specific acoustic symptoms, like music or well-defined human voices. Negative auditory symptoms, described as loss of hearing (as if they had become

Table 1 *Data from the literature and the present series*

No. of families	Ottman 1	Poza 1	Michelucci 1	Mautner 1	Ikeda 1	Winawer 4	Brodtkorb 1	Pizzuti 1	Fertig 1	Michelucci 7	Present series 53
Affected members	11	11	6	10	3	19	12	5	8	34	53
Alive/dead	10/1	11/0	3/3	7/3	3/0	17/2	12/0	3/2	7/1	24/10	53/0
LGI mutation	+	+	–	–	nt	+	+	+	+	4+/3–	–
Sex distribution											
Male	8	6	3	4	2	na	6	1	4	18	29
Frequency	72.7	54.5	50	40	66.7	na	50	20	50	52.9	54.7
95% CI	39–94	23–83	11–88	12–74	9–99	na	21–79	1–72	17–83	35–70	40–68
FS (no./total no.)	–	–	na	na	1/3	–	–	na	–	–	5/53
Age at observation (years)											
Mean	na	54.5	56.3	19.0	31.3	na	42.9	41.3	53.3	48.7	26.5
Range	na	34–75	32–80	12–26	19–51	na	16–72	28–64	34–70	27–64	12–52
95% CI	na	44–65	0–114	0–108	0–74	na	33–53	0–90	39–67	1–97	24–29
Follow-up (years)											
Mean	na	na	na	na	na	na	na	na	na	na	6.1
Range	na	na	na	na	na	na	na	na	na	na	0.5–22
Age at seizure onset (years)											
Mean	13	22	8	22	16	14	18	13	24	21.8	19
Range	8–19	11–40	6–12	2–50	15–16	9–30	4–42	9–15	8–42	8–50	6–39
95% CI	10–15	17–27	7–10	0–55	14–17	10–19	11–25	9–18	13–34	19–25	17–21
Type of seizure at onset											
SGTCs (no. of patients)	10/10	9/10	3/3	9/9	3/3	10/10	11/11	2/3	7/7	26/26	42/53
EPS and/or CPS (no. of patients)	9/10	2/10	–	–	3/3	4/10	11/11	3/3	3/7	15/26	47/53
UOTC (no. of patients)	1/11	1/11	3/6	1/10	–	1/17	1/12	1/4	–	8/34	–
Type of auras											
Auditory	6	4	3	8	3	14	6	3	8	23	53
Visual	2*	6*	–	–	–	4*	–	–	1*	2*	3*
Aphasic	–	–	–	–	1*	1	8*	2*	–	4*	5*
Other	8*	1*	–	1*	2*	10*	7*	1*	3*	3*	17*
Reflex seizures	1	–	–	–	1	1	7	na	na	4	5
Outcome											
Seizure-free patients	7/11	7/11	5/6	10/10	3/3	na	6/12	na	0/1	24/24	27/53
SGTCs after therapy	na	1/3	na	–	–	na	1/5	na	1/1	na	5/25
Seizure freq. after therapy											
Rare (<3/year)	na	3/3	na	–	–	na	3/3	na	1/1	–	19/25
Frequent (⩾1/month)	na	–	na	–	–	na	–	na	–	–	6/25
Drug withdrawal	na	5/9	3/3	na	na	na	2/11	na	na	3/24	15/51
Relapses	na	4/5	2/3	na	na	na	1/2	na	na	3/3	13/15

Table 1 *Continued*

No. of families	Ottman 1	Poza 1	Michelucci 1	Mautner 1	Ikeda 1	Winawer 4	Brodtkorb 1	Pizzuti 1	Fertig 1	Michelucci 7	Present series 53
EEG											
Epileptiform abnormalities	–	2	–	3	–	1	3	2	1	3	18
Mild temp. slow activities	–	–	2	2	2	1	3	1	–	10	27
Normal	8	5	1	2	1	–	6	1	5	7	8
Not done	3	4	3	3	–	17	–	–	1	8	–
Seizure recording	–	–	–	–	–	–	–	–	–	13	7
NMR/CT											
Negative	3	5	2	6	1	3	10	na	3	19	47
Mild abnormalities	–	1	1	–	1	–	1	na	–	2	6
Not done	8	5	3	3	1	16	1	na	4	13	–

Ottman = Ottman *et al*., 1995; Poza = Poza *et al*., 1999; Michelucci = Michelucci *et al*., 2000; Mautner = Mautner *et al*., 2000; Ikeda = Ikeda *et al*., 2000; Winawer = Winawer *et al*., 2002; Brodtkorb = Brodtkorb *et al*., 2002; Pizzuti = Pizzuti *et al*., 2003; Fertig = Fertig *et al*., 2003; Michelucci = Michelucci *et al*., 2003. Number and percentage of sporadic and familial PEAF patients are shown. For ADPEAF cases clinical details were only accepted when unambiguous and data were not always available. Case numbers therefore differ slightly among assessed parameters. *Some of the clinical data regarding this family were also reported by Winawer *et al*., 2000. Pts = patients; N = number; nt: not tested; FS = febrile seizures; SGTCs = secondarily generalized tonic-clonic seizures; UOTC = tonic-clonic seizures of unknown origin (whether partial or generalized); EPS = Elementary Partial Seizures; CPS = Complex Partial Seizures; *these symptoms could be isolated or associated with the auditory symptoms; – = absent; type of auras 'other' includes autonomic, psychic and the other type of sensory auras (olfactory, vertiginous, gustatory).

deaf) or blocked ears, were reported by 24.5% of patients and in four of them they were the only ictal manifestation. Few patients (11.3%) described a distorted perception of sound. These different types of auditory symptoms could be isolated or coexist in the same seizures.

Asking patients if they were able to lateralize the origin of auditory auras, only 28.3% of patients reported the symptom confined to one ear while most of them (56.6%) were not able to localize the origin of aura exactly. In 15% of patients, aura was bilateral. Five patients reported specific triggering stimuli of seizures. Sudden noises (two patients), flowing water (e.g. toilet flushing; two patients) or answering the phone (one patient) could precipitate the seizures, which also occurred spontaneously.

Seizure frequency

Seizure frequency was generally low: before treatment SGTCs were sporadic or occurred a maximum of three times per year in 90.5% of patients (Fig. 1B), whereas elementary or complex partial seizures were more frequent, occurring more than once per month in 38.3%. When both seizure types were present, partial seizures usually preceded SGTCs by some years (mean 5.6 years). However, given the mild intensity of the auditory auras, these could continue unrecognized for several years, causing delayed diagnosis (mean 4.4 years) because of no medical counselling (five patients) or misdiagnosis (six patients).

Outcome after therapy

The outcome after therapy was good in the majority of patients, with a reduction of seizures by more than 50% in 44 out of 51 patients who started therapy (86.2%) (Fig. 2A). Twenty-seven patients (51%) have been seizure-free for at least 1 year, with an average period of 8.3 years (Fig. 2C). In a further 49% of cases, attacks became milder, usually represented by the auditory auras, and less frequently with sporadic seizures or a few seizures per year in 77% of patients (Table 1). Only six patients still have SGTCs (mean follow-up 2.8 $\pm$ 3 years).

Monotherapy was usually effective, sometimes at low doses, in the majority of patients (66%) (Fig. 2B); only 26% of patients used two or more AED. Carbamazepine was the most common AED used (55%). Two patients refused antiepileptic medication as their ictal symptoms were mild. Thirteen patients interrupted the treatment after a few years of seizure-freedom: seizure recurrence was high (87%) and after resumption of therapy four patients failed to regain control of seizures, experiencing rare episodes of auditory auras (Table 1).

Neuroimaging

A high-resolution NMR scan was available in 47 patients; the other six individuals had a CT scan. All the investigations were reviewed and were normal in all except six patients, who had a slight, not significant asymmetry of the temporal horns (one patient), lateral ventricles (two patients) and hippocampus without clear-cut evidence of MTS (three patients).

Sporadic versus familial

The distributions of sex, age at onset, the absence of relevant antecedent events and other electroclinical features in our S patients did not differ from those in the ADPEAF cases (Table 1). A history of FS was reported in five patients of the S group, whereas within the literature cases only one member of Ikeda's family experienced FS (Ikeda *et al*., 2000). SGTCs at onset occurred in a high percentage of patients in both groups but were more common in ADPEAF cases (Fig. 1A). Moreover, the frequency of this type of seizures at onset was similar in the two groups, with no more than a few attacks per year in the majority of patients (Fig. 1B).

The focal seizures (either elementary, complex or secondarily generalized) were characterized by prominent auditory auras in all S cases because of the inclusion criteria, whereas not all F cases had auditory symptoms (Table1).

Good drug response, with reduction of seizure frequency of more than 50%, was common in both groups (Fig. 2A). Usually monotherapy was sufficient to control seizures in most patients (Fig. 2B). The percentage of seizure-free subjects was higher in the F cases, though the difference was not statistically significant as the 95% CIs overlapped (Fig. 2C). The relapse rate after drug withdrawal, which was high in both groups, was slightly higher in the S cases (Table 1). Moreover, all familial cases became seizure-free again after resuming therapy, whereas only 69% of the sporadic cases regained control.

Genetic data

To test whether *LGI1* mutations might occur in sporadic PEAF cases, possibly as *de novo* mutations, we screened the eight *LGI1* exons by DHPLC or direct sequencing. No mutations were found in our series of sporadic patients, nor were other types of sequence alterations or polymorphic variations detected in the coding region of the gene.

Discussion

Non-lesional TLE is not a uniform disorder since it encompasses both patients with a severe refractory form and cases with a mild epileptic disorder achieving remission with or without antiepileptic medication (Hauser, 1992; Aguglia *et al*., 1998). As most studies on TLE have originated from groups with a special interest in surgical treatment, information to date has mostly concerned patients with refractory TLE (French *et al*., 1993; Williamson *et al*., 1993; Jack *et al*., 1994). Conversely, the mild form of non-lesional TLE remains an undefined entity from an aetiological and electroclinical point of view. In 1998, Aguglia *et al*.,

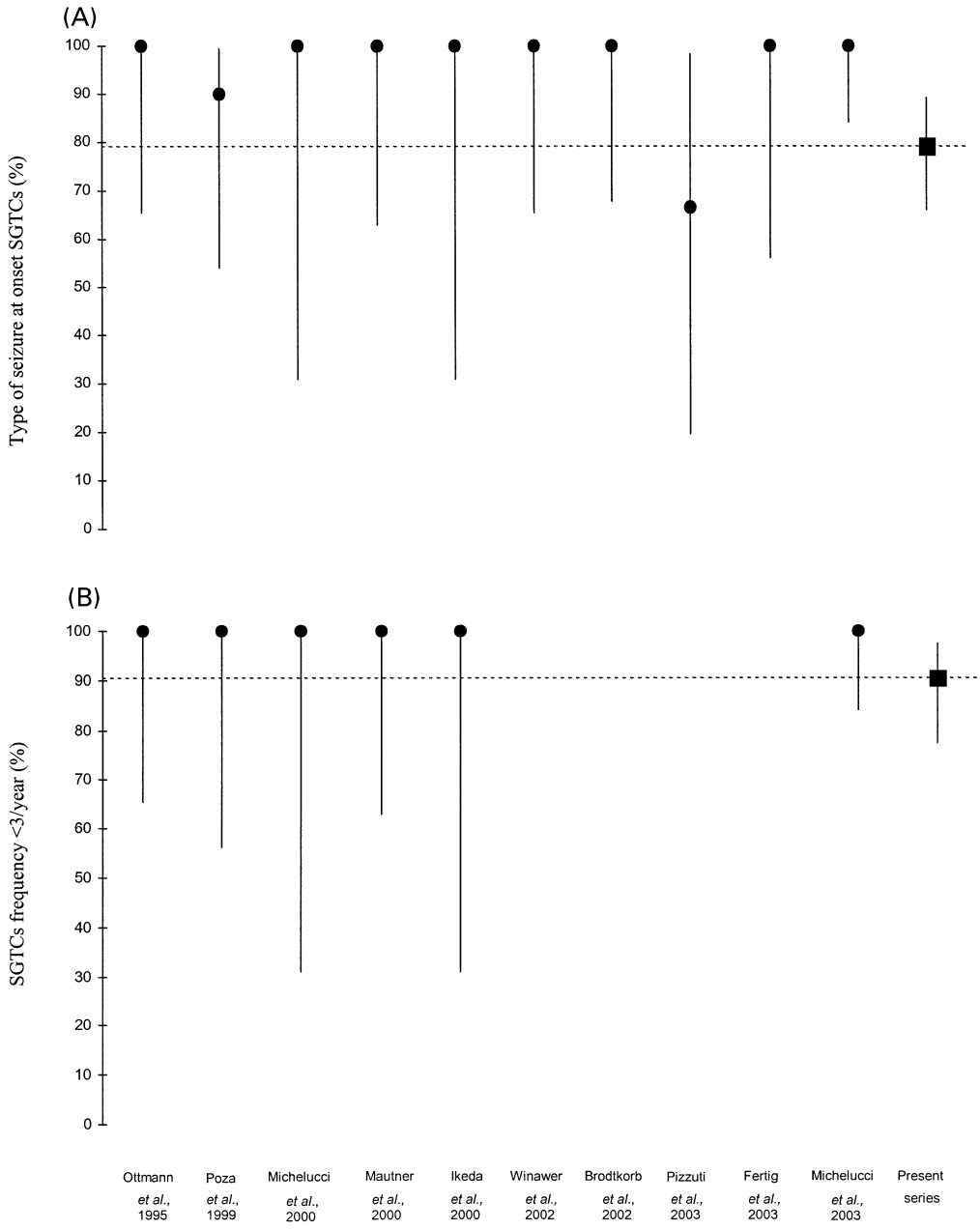

Fig. 1 Forest plot comparing the relative frequencies (95% CI) of patients with SGTCs at onset (**A**) and patients with SGTCs occurring fewer than three times per year (**B**). The results are shown as squares (present series) and circles (F studies) centred on the point estimate of the result of each study. A vertical line runs through the point estimate to show its confidence interval. In calculating the relative frequencies of patients with SGTCs (**A**), we excluded patients in whom focal ictal onset of tonic–clonic seizures could not be established (see Table 1, UOTC). The results are shown as squares (present series) and circles (F studies) centred on the point estimate of the result of each study. A vertical line runs through the point estimate to show its CI.

comparing mild non lesional TLE with severe cases, concluded that the mild form is characterized by a higher prevalence of familial history of epilepsy and a much less common association with MTS, suggesting a major aetiopathogenetic role of genetic factors (Aguglia *et al*., 1998). Finally, they suggested that onset of seizures during adulthood indicates a good prognosis in non-lesional TLE, which is confirmed by our findings. No other prognostic factor was identified to distinguish between a favourable or unfavourable outcome from the beginning.

The present study describes a homogeneous population of patients with TLE selected on the basis of auditory auras and absence of a familial trait and symptomatic aetiology. This entity is probably underestimated and may often pass undiagnosed: because of the mild nature of the seizures many patients had a diagnosis delayed by months or years,

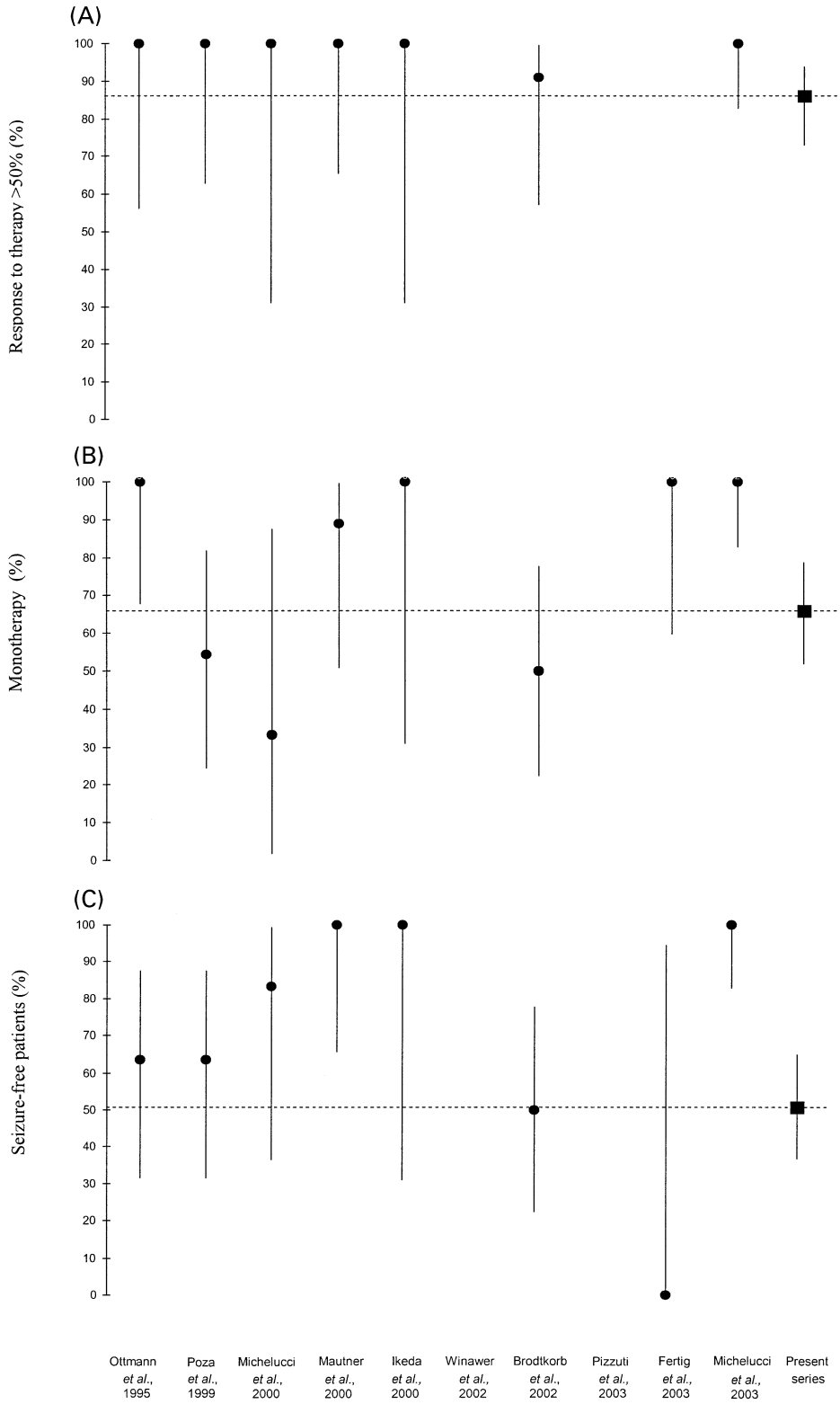

Fig. 2 Forest plot comparing the relative frequencies of response to therapy >50% (**A**), monotherapy (**B**) and seizure-free patients (**C**) in ADPEAF cases and in the present series.

often with the onset of the first SGTCs. On the other hand, the high incidence of SGTCs in our population, as in literature reports, and their frequent occurrence during sleep without any conscious auditory aura prompted the misdiagnosis of idiopathic generalized epilepsy in 11% of our patients. For these reasons, auditory symptoms must be specifically

investigated by the clinician also in those patients presenting with apparently generalized seizures.

Our data suggest that PEAF could represent a benign clinical entity within the larger group of non-lesional TLE and that auditory auras can represent a predictor of good outcome. In all our cases, the diagnosis of ADPEAF was firmly excluded by interviewing more than one family member and constructing the patient's family tree. In addition, our definition of sporadic cases was more rigid than Briellmann's criteria as we also excluded patients having a second-degree relative with epilepsy (Briellmann *et al*., 2001). However, in our S cases some clinical features, such as the age at onset, seizure patterns and the favourable outcome, are very similar to those of ADPEAF. We found only a few possible, but not statistically significant, differences between the two groups: a higher incidence of FS in S cases, a more common incidence of SGTCs at onset in familial cases (meaning a more invalidating type of seizures), a higher number of seizure-free patients and a slightly better response to therapy in F cases compared with S cases. The latter two differences may be explained, however, by a difference in the diagnostic work-up between the two series. First, our patients were instructed to carefully record the elementary auditory auras in their seizure diaries, producing a lower number of seizure-free patients. Secondly, we directly investigated all our patients whereas literature cases sometimes were not seen directly by the physician and information even included data on deceased patients. Another reason could be that the mean age at observation was lower in our group of patients. Similarly, the EEG findings provided more paroxysmal abnormalities in S than in F patients, due to a more accurate and detailed neurophysiological study in our cohort. If these differences are disregarded as partly due to differences in the evaluation of clinical items and in the diagnostic work-up, there were no major clinical differences between the S and F groups and both have a benign prognosis.

The similarities with ADPEAF, the benign outcome and absence of lesions suggest that at least some of these cases have a genetic aetiology. To date, 15 *LGI1* mutations have been reported in ADPEAF families, resulting in either protein truncation or amino acid substitution (Gu *et al*., 2002; Kalachikov *et al*., 2002; Morante Redolat *et al*., 2002; Wallace *et al*., 2002; Fertig *et al*., 2003; Kobayashi *et al*., 2003; Michelucci *et al*., 2003; Hedera *et al*., 2004). None of these mutations were detected in our series. We also failed to detect other types of nucleotide sequence alterations or polymorphic variations in the coding *LGI1* exons. Recently, a GABA(B) receptor 1 polymorphism resulting in the amino acid substitution Gly489Ser was found to be a strong risk factor for non-lesional TLE in an Italian series of sporadic TLE cases (Gambardella *et al*., 2003). Another association study implicated a functional polymorphism of the prodynorphin gene promoter in the aetiology of TLE (Stogmann *et al*., 2002). In the light of these studies, it is conceivable that genetic factors, particularly gene polymorphisms, contribute to susceptibility to sporadic PEAF.

Finally, in the current ILAE classification of epilepsy syndromes (1989), the term 'idiopathic' is reserved for syndromes of presumed genetic origin, and the term 'cryptogenic' for conditions presumed to be non-genetic but with insufficient evidence to assign a specific aetiology. Because of the complexity in the genetic contribution to the epilepsies, clinical syndromes cannot be divided into two broad classes based on genetic susceptibility. For these reasons, Ottman suggested addressing the question of genetic susceptibility separately from the correct definition of 'idiopathic' rather than 'cryptogenic' (Ottmann *et al*., 1995). According to Engel, we believe it more appropriate to use the term 'idiopathic' only on a clinical basis, referring to a syndrome with no underlying structural brain lesion or other neurological sign or symptoms presumed to be genetic (Engel, 2001). For this reason it could be meaningful to consider the majority of our patients as idiopathic cases and use the term 'IPEAF' (idiopathic partial epilepsy with auditory features).

We conclude that IPEAF is a benign, non-age-related clinical entity within non-lesional TLE. Because of its peculiar clinical picture, however, it may often pass unrecognized or be misdiagnosed for a long time. Even if *LGI1* mutations have been excluded, genetic factors may play an aetiopathogenetic role in at least some of these S cases. A separate analysis of non-lesional TLE with auditory symptoms is useful and S cases should be included in molecular genetic studies, as proposed by Briellmann and colleagues for generalized epilepsy (Briellmann *et al*., 2001).

Acknowledgements

We wish to thank Mrs Elena Zoni for help in manuscript editing, Mrs Roberta Bellini for performing blood samples, Mrs Annalia Cesare for keeping in touch with patients, and Dr Mirella Mochi and Mrs Sabrina Farnè for their help in DNA extraction. The mutation analysis was supported by grants from the Italian League Against Epilepsy and Telethon-Italy (grant GGP02339 to C. N. and R. M.).

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