Age At Onset Predicts Good Seizure Outcome In Sporadic Non-Lesional and Mesial Temporal Sclerosis Based Temporal Lobe Epilepsy

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Umberto Aguglia, MD, Ettore Beghi MD, Angelo Labate MD, Francesca Condino, PhD, Vittoria Cianci, MD, Laura Mumoli, MD, Sara Gasparini MD, Aldo Quattrone, MD, Antonio Gambardella MD.

From the Institute of Neurology (Drs. Aguglia, Cianci, Gambardella, Gasparini, Labate, Mumoli, Quattrone) University Magna Græcia, Catanzaro, Italy; Institute of Neurological Sciences (Drs. Condino, Gambardella, Labate, Quattrone), National Research Council, Piano Lago - Mangone, Cosenza, Italy; Regional Epilepsy Center (Dr. Aguglia), Reggio Cal., Laboratory of Neurologic Diseases, Mario Negri Institute, Milan (Dr. Beghi), Italy.

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Address correspondence to:

Angelo Labate MD

Cattedra ed U.O. di Neurologia; Università degli Studi “Magna Græcia,” Campus Universitario Germaneto; Viale Europa, 88100 Catanzaro, Italy; Email: a.labate@isn.cnr.it

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Abstract

Purpose. To study prognosis and prognostic predictors of sporadic, non-lesional temporal lobe epilepsy (TLE).

Method. Four hundred seventy-four patients with TLE were consecutively seen from April 1987 to April 2004. One hundred-ninety had a sporadic, non lesional TLE and a follow-up longer than two years. Two hundred eighty four patients were excluded because of family history for TLE, incomplete history, poor compliance with treatment, psychogenic seizures, no brain MRI study, presence of intracranial lesions except for scattered T2-hyperintense spots on hemispheric white matter or mesial temporal sclerosis (MTS). The following prognostic predictors were considered: age at onset of epilepsy, gender, family history of non-TLE or febrile seizures, perinatal factors, history of febrile seizures, ictal phenomena, MTS, and interictal EEG. The end point was time to 24-month seizure freedom after treatment onset. Chi-square test, Student's t test, Kaplan–Meier survival curves with log-rank test (univariate analysis) and Cox proportional-hazards regression models (multivariate analysis) were used to assess seizure prognosis and prognostic predictors.

Results. At univariate analysis, patients achieving 24-month seizure freedom had significantly older age at onset of epilepsy (33.5 $\pm$19.9 vs. 17.2 $\pm$14.4 years), lower occurrence of febrile seizures (11.0% vs 24.4%) and MTS (19.0% vs. 35.6%). The chance of remission was directly correlated to the age at onset of seizures and inversely correlated to a history of febrile seizures and to the presence of MTS. At multivariate analysis, age at onset of epilepsy was the only significant prognostic predictor.

Conclusion. Older age at onset predicts better prognosis in sporadic, non-lesional TLE.

Introduction

Temporal lobe epilepsy (TLE) represents the most common type of partial epilepsy. From a neuropathological point of view, TLE may be divided into "lesional" and "non lesional" subtypes. In epilepsy surgery series, the most frequent causes of lesional TLE are tumors, vascular malformations, cortical dysplasia or gliosis/scar due to remote etiologies, traumatic lesions and less commonly immune mediated condition such as limbic encephalitis. [1,2,3] Conversely, non lesional TLE represents the most common subtype and comprises patients with mesial temporal sclerosis (MTS). [4,5] It is a heterogeneous disorder since there are patients with a severe refractory form, while many others have a mild epileptic disorder and they enter remission with or without antiepileptic medication. [5,6] Indeed, in this type of epilepsy the prediction of the clinical course would help both physicians and patients. Because many studies on TLE have originated from groups with a special interest in surgical treatment, the available information mostly concerns patients with refractory non lesional TLE. [4,7-10] In such cases, antecedent factors for epilepsy, such as febrile seizures (FS) or cerebral infections are very common, [9] and MTS represents the most common substrate as demonstrated by magnetic resonance imaging (MRI) studies. [4,7-10] In a previous cross-sectional study comparing mild to severe non-lesional TLE, [6] we found that mild non-lesional TLE is an unrecognized disorder characterized by onset in adulthood and frequent family history of epilepsy, including TLE. Familial TLEs include autosomal dominant lateral TLE (ADLTLE) and familial mesial TLE (FMTLE). Most patients with familial TLE have a benign course, [11,12,13] and refractory seizures have been reported only in a minority of patients. [14] The prognosis of sporadic non-lesional TLE has not been investigated by prospective studies; moreover, a recent longitudinal study conducted in children with new-onset epilepsy demonstrated that MRI lesions predict poor seizure outcome. [15] Based on this knowledge, our aim was to

evaluate predictive prognostic factors in a cohort of patients with well defined non-lesional, sporadic TLE regardless of the age of onset.

Methods

Initial assessment. 473 patients with clinical diagnosis of partial seizures of temporal lobe origin were consecutively seen in from April 1987 to April 2004 in two twin University Epilepsy Centers located in Reggio Calabria and Catanzaro, Calabria, Southern Italy, sharing protocol, study design, and research objectives. Patients were ascertained from different sources, including general practitioners, pediatricians, emergency departments (Reggio Calabria hospital), and patients. Criteria for inclusion in the study were a history of two or more unprovoked seizures of temporal lobe origin, regardless of the age of onset, being resident in Calabria, and having a follow-up of two years or longer. Data collected at enrolment included patient's demographics, perinatal factors (encephalitis, brain anoxia, trauma, ischemia or hemorrhage), family history of non-TLE or febrile seizures (FS), personal history of FS, age at onset of TLE, seizure semiology and frequency, neurological and cognitive findings, antiepileptic drugs (AEDs), interictal EEG and imaging. Ictal phenomena were coded with reference to the 1981 international classification. [16] In subjects with normal neuroimaging and interictal EEG, the following semiological criteria were considered reliable to make a diagnosis of TLE: déjà-vù, stereotyped flashbacks or olfactory hallucination and a rising epigastric aura. Three of us (A.G., A.L., U.A.) reviewed, double blind, the interictal EEGs acquired in each patient at first investigation. The interictal EEGs were recorded according the 10-20 International system with supplementary T1 and T2 electrodes. The EEG abnormalities (spikes, spike-waves, sharp theta/delta waves, runs of temporal intermittent rhythmic delta activity over one temporal region) were labeled as unilateral if confined to one temporal side at least 95% of the

time. MTS was diagnosed by MRI and coded as present or absent. Excluded were patients without TLE, patients with familial TLE, patients with incomplete clinical history, poor compliance, psychogenic seizures, and patients with only EEG or imaging documentation suggestive of TLE. MRI evidence of MTS, simultaneous presence of FLAIR hyperintensity and IR atrophy or scattered T2-hyperintense spots on hemispheric white matter were not considered reasons for exclusion. [17] In the whole group carbamazepine (CBZ) or oxcarbazepine (OXC) were the most utilised AEDs and they were usually in monotherapy (51% of the patients) in the seizure-free group and in polytherapy (74% of the patients) in the non seizure-free group, in combination with topiramate (36% of these patients), phenobarbital (28%), levetiracetam (10%) or other AEDs (3%).

Follow-up study. Follow-up examinations were performed every 2-12 months only in patients who fulfilled the inclusion criteria and were managed in person by trained epileptologists (A.G., A.L., U.A.) of the two University Centers. Follow-up data included family history of epilepsy, seizure frequency and semiology, behavioral and clinical findings. MRI study was performed at the Institute of Neurologic Science of National Research Council, Piano Lago, Cosenza, following a methodology extensively described by our group elsewhere. [5] Imaging done before 2000 was repeated. All imaging was evaluated by a neuroradiologist blind to patient identity, initial imaging findings, seizure localization and outcome. The last follow-up examination was performed in May 2006.

Diagnosis of patients. All diagnoses were re-evaluated every 3-6 months by a panel consisting of two epileptologists who were not blinded to previous reviews. Although EEG and imaging data were not obligatory, the diagnosis was changed according to different clinical, EEG or imaging findings achieved during follow up.

Statistical analysis. The end point was time to 24-month seizure freedom (no seizures with or

without AED treatment). We classified patients according to tertiles of age at onset of epilepsy(<13.7 years, 13.7 to 32.0 years, >32.0 years) and then determined the effect of the tertiles on the endpoint. For continuous variables, mean, SD and range were calculated and the Student's t test for unpaired samples was used to assess differences between groups. Categorical variables were expressed as percentages and differences among group distributions were assessed using the chi-square test. Survival curves were generated according to the Kaplan–Meier (KM) method and compared with the log-rank test. With reference to 24-month seizure freedom, prognosis was coded into two categories (0=good; 1=poor) and assessed by univariate and multivariate analysis. Tested covariates included age at onset of epilepsy, gender, family history of epilepsy, FS, perinatal factors, ictal manifestations, MTS, and interictal EEG (Table 1). First, we identified by univariate analysis variables that resulted associated to poor prognosis at a 5% level of significance. These variables were then included into a Cox proportional-hazards regression model. Data have been expressed as hazard ratios with 95% confidence intervals. All calculations were done by SPSS version 13 (Chicago, Illinois, USA).

Results

Patients' recruitment and follow-up. A total of 473 patients were assessed. Two hundred fourteen (45%) fulfilled our inclusion criteria whereas 259 were excluded for one or more of the following reasons: familial TLE (n= 32); extratemporal seizures or uncertain seizure localization (n=103); psychogenic or other nonepileptic seizures (n=26), poor compliance (n=20); unavailable MRI study (n=10); brain lesions diagnosed by CT or MRI (n=95). Twenty-four additional patients were excluded during follow-up because of extra-temporal epilepsy (n=13), major stroke (n=2), generalized epilepsy (n=4), or drop-out (n=5). Thus, 190 patients were ultimately diagnosed with

sporadic non-lesional TLE. The sample was followed for 2116.5 person-years (mean 11.1 years; range 2-75 years). Follow-up interictal EEGs were performed in 98 patients, video-EEG monitoring in 25 with daily seizures, and neuropsychological examination in 84. Follow-up MRI scans were performed in 25 patients and reviewed with knowledge of seizure localization and previous MRI findings.

Clinical and instrumental findings. The sample included 104 women and 86 men. Mean age at study entry was 45.2±17.6 years, and age at onset of epilepsy was 33.0±19.7 years. Family history of epilepsy was identified in 58 patients (30%) whereas 33 (17%) had febrile seizures and nine (4.7%) had perinatal events. MRI scans at enrollment showed signs of MTS in 57 patients (30%) that were confirmed on unblinded re-evaluation in 51 (26.8%). One hundred and 13 patients (53.5%) had epigastric aura, 67 (35.3%) autonomic phenomena (flushing, whitening, tachycardia, diaphoresis, hyperthermia, or pilomotion), 41 (21.6%) unilateral dystonic movements, 23 (12%) dysfasia (impaired comprehension, anomia or paraphasia), 19 (10%) drop attacks, 17 (8.9%) auditory features, 14 (7.4%) dejà/jamais or vu-veçu, and seven (3.7%) olfactory seizures. Complex partial seizures (loss of consciousness or unresponsiveness preceded by aura and/or associated with oro-alimentary or hand automatisms) were found in 145 patients (73.3%), and secondarily generalization (major motor seizures) was present in 115 (60.5%). Patients with MTS differed from those without MTS in terms of history of febrile seizures (47.1 vs. 6.5%), mean age at onset of epilepsy (15.7 vs. 29.5 years), epigastric aura (70.6 vs. 55.4%), dysphasic seizures (19.6 vs. 9.4%), and interictal EEG abnormalities (94.1 vs. 78.4%). Epileptiform abnormalities were found in 147 patients (77.4%) unilaterally and in ten patients (5.2%) bilaterally. Normal interictal EEG was found in 33 patients (17.4%). A strong correlation between EEG epileptiform activity and MRI features of MTS has been previously reported elsewhere. [5] Carbamazepine (CBZ) or

oxcarbazepine (OXC) were the commonest AEDs given as monotherapy in seizure-free patients (51%) or in polytherapy in non seizure-free patients (74%) in combination with topiramate (36%), phenobarbital (28%), levetiracetam (10%), or other drugs (3%).

Cumulative probability of remission and prognostic predictors. As shown in Table 1, 100 patients (53%) achieved 24-month seizure freedom. The cumulative probability of remission was 42.2% at 2 years, 48.1% at 5 years, and 49.4% at 10 years. The chance of remission was unaffected by seizure type (data not shown), but was directly correlated to the age at onset of seizures (Figure 1) and inversely correlated to a history of febrile seizures and to the presence of MTS (Table 2). Compared to patients with normal interictal EEG, those with abnormal tracings had a lower, non-significant chance of remission. However, only age at disease onset was confirmed by multivariate analysis to be an independent predictor of seizure remission (Table 3).

Discussion

TLE is the commonest type of partial epilepsy and MTS the commonest underlying pathology. Indeed, TLE is considered predominantly intractable and seizures are very often physically and socially disabling. In such cases, an abnormal EEG, the presence of MTS, and an unsuccessful response to first AED treatment predict long-term prognosis and seizure relapse. [18,19] Furthermore, in approximately one-third of children or adults with TLE, MRI lesions, specially MTS or dual pathology, are predictors of intractable epilepsy and pharmacoresistance. [15,20,21] Conversely, many patients with sporadic or familial TLE have well controlled epilepsy, regardless of seizure semeiology and presence of MTS. [5,6,13,17,24] However, early prognostic predictors are still limited to acquired refractory TLE, with little attention to the more benign drug-responsive TLE variants. [5,6,22]

Our group has recently described clinical, genetic, neuroimaging features and outcome of benign sporadic TLE who were not selected for surgical purposes. In a previous cross-sectional study of 73 nonsurgical adult patients with non-lesional TLE (with or without MTS), about two-thirds were found to have a good prognosis after a follow-up ranging from 36 to 96 months. [6] The identification of MRI evidence of MTS in many of these cases has shown that MTS itself does not necessarily mean intractable epilepsy and bad outcome as previously thought. [5,22] Interestingly, in the present study we found that epilepsy remitted in approximately half (100 out of 190; 53%) of patients with non-lesional, sporadic TLE, after a mean follow-up of 11 years.

Although at univariate analysis predictors of seizure freedom included older age at onset (33 vs 17 years), lower occurrence of FS (11% vs 24%), and MTS (19% vs 35%), only age at seizure onset was an independent prognostic predictor. Our data cannot be entirely explained by selection bias nor by defects in the study design. In fact, although one may expect that only patients with persisting seizures tend to remain under surveillance, subjects with difficult-to-treat epilepsy are frequently seen in secondary and tertiary epilepsy centers regardless of their age at onset of seizures. Other possible explanations include the lower tendency of seizures to relapse in adult and elderly individuals compared to children. Seizure recurrence has been correlated to younger age at onset by several investigators. [23-27] In a study of mostly adult surgical patients, more than half of participants had their onset of epilepsy during childhood and early adolescence. [28] In another study in patients undergoing temporal lobectomy, younger age at seizure onset was significantly correlated to the presence and grade of hippocampal sclerosis even after controlling for disease duration and history of febrile seizures. [29] In this series, the relationship between hippocampal sclerosis and history of febrile seizures was no longer significant when controlling for age at onset. On this basis, the authors concluded that an earlier age at onset of epilepsy predisposes to the

development of childhood febrile seizures and the younger hippocampus is more susceptible to insults causing hippocampal sclerosis than that of more mature individuals. The same explanation can be offered for our findings.

We did not find seizure type or focal abnormal EEG to predict prognosis in our sample. Déjà vu was a very common ictal phenomenon in family members with benign mesial TLE mapping to chromosome 4q13.2-q21.3. [30] Intriguingly, in our study experiential phenomena, such as déjà - jamais vu/veçu, were slightly (but non significantly) more frequent in patients who achieved seizure freedom. As déjà vu experience is also common in normal subjects, this ictal phenomenon may have been misinterpreted and underestimated. Some of our patients also developed drop attacks, usually long after the onset of epilepsy, a finding that was already described in patients with TLE. [31] The fact that about 7% of our patients reported auditory auras, which are suggestive of a lateral temporal origin, further reinforces the view that idiopathic TLE with auditory features represents a benign clinical entity within the larger group of non-lesional TLE. [32] Accordingly, also in these patients with mild lateral TLE, seizures started around the age of 20 years of age, which is later than that observed in refractory TLE.

Of interest, in our series this type of aura was much more rare than viscero-sensory or affective auras, a finding that is strikingly similar to what seen in autosomal dominant familial TLE. [12] It is therefore reasonable to speculate that benign sporadic and familial TLE are part of a biological continuum in which familial TLE inherited in an autosomal dominant manner is much more rare. [33] This is not surprising, since TLE is mainly a heterogeneous disorder with complex genetics where putative susceptibility genes and environmental factors are believed to act together to produce the disease phenotype. We also found that the presence of EEG abnormalities, since the vast majority of patients (regardless of seizure freedom) showed focal interictal EEG abnormalities.

Moreover, EEG abnormalities were usually unilateral (more than 70%) and located over one temporal region. Thus, the interictal EEG was not helpful to predict benign versus intractable course of TLE.

Our study has some limitations. First of all, the diagnosis of sporadic non lesional TLE was based predominantly on seizure description and interictal EEGs; however the diagnosis was made by trained epileptologists and confirmed through repeated follow-up assessment. Second, only 25 patients with frequent seizures underwent video-EEG monitoring thus preventing exclusion of extratemporal TLE in other cases. It must be addressed, however, that in all our patients the diagnosis of TLE was made on the basis of the constellation of clinical, MRI and EEG criteria, which are considered to be reliable interictal indicators of TLE. [16] Third, during the period of patients' enrolment (1987-2004), major improvements in MR technology occurred and it is possible that non-lesional patients (ie, without MTS) were more rarely encountered in the last years of recruitment.

In conclusion, this study provides new information in support of clinical decision making because we showed that older age at onset predicts good seizure outcome and more likely remission in patients with sporadic non-lesional TLE despite the presence of complex partial or secondary generalized seizures, focal EEG abnormalities and signs of MTS. Few questions still remain unsolved: Can patients with sporadic non-lesional TLE spontaneously remit? How long AEDs should be continued? Can genetic predisposition and susceptibility contribute to determine remission? For example, we recently observed that the A/G genotype of the $GABA_B$ receptor was associated with a 6.45 odds ratio to develop drug resistance in patients with TLE, [34] findings not replicated in different ethnic populations. Prospective epidemiological population based studies are needed to address these questions.

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Table 1. Patient data

Clinical and laboratory data	**Seizure-free n=100**	**Non seizure-free n=90**	**p-value**
Age at epilepsy onset, years: mean (±SD)	33.5 (19.9)	17.22 (14.42)	0.003
Sex:Female (%)	55 (55.0)	49 (54.4)	NS
Family history (%)	33 (33.0)	27 (30)	NS
Perinatal factors (%)	5 (5.0)	4 (4.4)	NS
Febrile seizures (%)	11 (11.0)	22 (24.4)	0.0001
Ictal phenomena:			
auditory (%)	10 (10.0)	7 (7.8)	NS
autonomic (%)	30 (30.0)	37 (41.1)	NS
complex partial (%)	75 (75.0)	70 (77.8)	NS
déjà-jamais vu/vecu (%)	10 (10.0)	4 (4.4)	NS
dysphasic (%)	9 (9.0)	14 (15.6)	NS
dystonic (%)	20 (20.0)	21 (23.3)	NS
drop attacks (%)	11 (11.0)	8 (8.9)	NS
epigastric aura (%)	63 (63.0)	50 (55.6)	NS
olfactory (%)	4 (4.0)	3 (3.3)	NS
secondarily generalized (%)	58 (58.0)	57 (63.3)	NS
Interictal EEG:			NS
normal (%)	22 (22.0)	11 (12.2)	NS
abnormal, unilateral (%)	73 (73.0)	74 (82.2)	NS
abnormal, bilateral (%)	5 (5.0)	5 (5.6)	NS
Mesial temporal sclerosis (%)	19 (19.0)	32 (35.6)	0.001

Table 2. Cumulative time-dependent 24-month seizure freedom at 2, 5 and 10 years by selected prognostic predictors.

Results of univariate analysis

Variable	24-month seizure freedom (%)		
	2 years	5 years	10 years
Gender			
Women	42.6	47.8	48.9
Men	41.9	48.6	50.2
Age, years (tertiles)			
<13.7	17.5	20.8	20.8
13.7-32.0	47.4	52.8	55.0
>32.0	61.9	71.3	73.5
Family history of epilepsy			
No	41.0	47.9	48.9
Yes	45.0	48.5	50.3
Perinatal factors			
No	42.2	48.3	49.7
Yes	44.4	44.4	44.4
History of febrile seizures			
No	47.4	52.3	54.0
Yes	18.2	27.6	27.6
EEG			
Normal	63.6	63.6	63.6
Abnormal, unilateral	38.3	44.3	45.9
Abnormal, bilateral	30.0	50.0	50.0

Mesial temporal sclerosis			
No	47.7	54.4	55.4
Yes	27.5	31.5	33.6

(●) Log-rank test

Table 3. Multivariate analysis (●) of prognostic predictors found to be of (borderline) significance at univariate analysis

Variable	Hazard ratio	95% CI	P value
Age, years (tertiles)			
<13.7	1		
13.7-32.0	2.5	1.3-4.7	0.004
>32.0	4.2	2.3-8.0	0.000
History of febrile seizures			
No	1		
Yes	0.8	0.4-1.9	0.673
EEG			
Normal	1		
Abnormal, unilateral	0.6	0.4-1.0	0.074
Abnormal, bilateral	1.2	0.4-3.8	0.697
Mesial temporal sclerosis			
No	1		
Yes	0.8	0.5-1.5	0.604

CI = Confidence interval

(●) = Cox proportional-hazards regression model