Original article

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How many adults with temporal epilepsy have a mild course and do not require epilepsy surgery?

Lizbeth Hernández-Ronquillo [1], Samantha Buckley [1], Lady Diana Ladino [2], Adam Wu [3], Farzad Moien-Afshari [1], Syed AA Rizvi [1], Jose F. Téllez-Zenteno [1]

[1] Saskatchewan Epilepsy Program, Department of Medicine, University of Saskatchewan Saskatoon, SK, Canada
[2] Neurology Section, Hospital Pablo Tobón Uribe, Medellín, Colombia
[3] Saskatchewan Epilepsy Program, Department of Surgery, University of Saskatchewan Saskatoon, SK, Canada

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ABSTRACT – *Aims.* Temporal lobe epilepsy (TLE) is the most common type of drug-resistant epilepsy in adults and commonly requires surgical treatment. While an overwhelming preponderance of literature supports the notion that a large percentage of patients with TLE benefit from surgery, there is a paucity of outcome data on patients who demonstrate a sustained response to pharmacological treatment. In this study, we present an adult cohort of patients with TLE, with the purpose of identifying the proportion of patients with a mild course of the disease, as well as potential risk factors.
Methods. A prospective cohort study of all patients with TLE assessed and followed by the Saskatchewan Epilepsy Program, from 1 March 2007 to Jan 29th 2014. Patients were dichotomized as having a mild (seizure freedom without surgical intervention) or severe (surgical intervention required and/or failure to achieve seizure remission) course. Descriptive statistics, odds ratios and confidence intervals were calculated to identify predictors of seizure freedom.
Results. The cohort consisted of 159 patients. Mean patient age at last follow-up visit was 46±14.4 (range: 19-88) years. Mean follow-up period was 43.4±22.6 (6 to 84) months. Forty-six patients (29%) demonstrated mild-course TLE while 113 (71%) had a severe course of TLE. Patients with a mild course of TLE were more likely to be older ($p = 0.002$), have late-onset epilepsy ($p < 0.001$) with shorter evolution ($p < 0.001$). A good response to the first antiepileptic drug (OR: 6.8; 95% CI: 2.5-19; $p < 0.001$) was associated with a mild course of TLE.
Conclusions. Although a majority of patients with TLE eventually require surgery, operative treatment is not necessary for all patients. This study identifies prognostic factors that may help patients and clinicians characterize long-term outcome.

Key words: prognosis, temporal lobe epilepsy, mild course, severe course, adult epilepsy, benign temporal epilepsy

Correspondence:
José F. Téllez-Zenteno
Department of Medicine,
Division of Neurology Royal University Hospital,
Saskatoon, SK, S7N 0W8 Canada
<jftellez@yahoo.com>
<jose.tellez@usask.ca>

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Temporal lobe epilepsy (TLE) has been defined by the League Against Epilepsy (ILAE) as a localization-related symptomatic epilepsy, characterized by simple partial, complex partial, and secondary generalized seizures in the presence of supportive ictal and interictal electroencephalogram (EEG) findings (Proposal for revised classification of epilepsies and epileptic syndromes, 1989). Among the localization-related epilepsies, TLE is the most common subtype (Téllez-Zenteno and Hernandez-Ronquillo, 2012), and the subject of intense research with respect to surgical outcomes for mesial temporal sclerosis (MTS) (Berg, 2008). However, comparatively little is known about the long-term evolution and prognosis of patients with TLE who do not require surgery, although the literature suggests that seizure freedom is possible in these cohorts. In 1999, Kim and Cols (Kim *et al*., 1999) analysed 104 patients with MTS, of whom 25% achieved complete control of seizures on medication. Similarly, another study of 110 patients from a referral hospital in Ecuador (Sanchez *et al*., 2014) found that 31% of patients with MTS were seizure-free after two years of follow-up, and all of them were on either mono- or dual-therapy. Both studies were limited to patients with MTS, and neither analysed the impact of age at seizure onset (*i.e*. childhood versus adult-age). In contrast to studies of the adult population, for cohorts of patients with paediatric TLE, higher seizure remission rates are reported, ranging from 30-50% (Josephson and Pohlmann-Eden, 2012). It is conjectured that the divergent rates of seizure freedom between paediatric and adult populations with TLE may reflect the possibility that adult-onset TLE is a different disease entity with distinct prognostic outcomes versus paediatric-onset TLE.

The present study analyses a prospective cohort of patients with TLE, with the aim of identifying the proportion of patients with a mild course as well as prognostic variables of patients controlled only by medication.

Material and methods

Type of study and setting

This is a nested case-control study based in a prospective cohort that included all patients with TLE assessed and followed by the Saskatchewan Epilepsy Program (SKEP) since 2007 to 2014. The SKEP is the sole epilepsy centre in the province of Saskatchewan, Canada, which serves a catchment population of 1.1 million. The SKEP is staffed by two epileptologists, two neurosurgeons, neuroradiologists, a psychiatrist, neuropsychologist, and a dedicated epilepsy nurse. Routine investigative practices include scalp EEG, 3-Tesla magnetic resonance imaging (MRI), in-patient video-EEG epilepsy monitoring (VEM), functional MRI (fMRI), and positron emission tomography (PET). If clinically indicated, intracranial investigation (*e.g*. placement of depth electrodes) and electrocorticography can be performed. All diagnostic work-up and post-surgical follow-up occurs under the supervision of the two adult epileptologists. The SKEP also operates a single seizure clinic where patients with early diagnosis of epilepsy, including TLE, are identified. As the only provincial epilepsy programme, the SKEP is unique in its ability to capture all patients with TLE, evaluate all potential epilepsy surgery (ES) candidates, and follow-up patients with TLE over time. Our sample is representative of the province of Saskatchewan, as the SKEP is the only centre in the province that has the capability to investigate these patients. The case-control study was nested in a prevalent cohort that has been followed since 2007.

Subjects

All study participants diagnosed with TLE epilepsy from 2007-2014 were identified by searching the SKEP database. TLE diagnosis was based on Williamson's criteria (Williamson and Engel, 2008), according to seizure activity provided by non-invasive or invasive electrophysiology monitoring and a typical description of seizures suggesting temporal lobe onset, such as staring, unresponsiveness, automatism or aura. Seizure localization was inferred through other neurophysiology testing, such as, EEG, VEM, neuropsychological testing, and imaging such as a PET scan and MRI. We excluded patients with familial temporal lobe epilepsy. Patients with any other epilepsy syndrome distinct from TLE, or documented seizure onset outside of the temporal lobe, were excluded from the study. TLE patients with follow-up of less than six months were also excluded; it was considered a short period of time to assess prognosis.

Data collection

Sociodemographic, clinical variables, and treatment outcomes were analysed. Based on clinical experience and literature review, it was surmised that five main variables would prognosticate outcomes of patients with TLE: age at epilepsy onset, years of evolution, risk factors for epilepsy (*i.e*. febrile seizures [FS], central nervous system (CNS) infections such as meningitis or encephalitis, head trauma with loss of consciousness, neonatal seizures and family history of epilepsy in a first-degree relative), lesions/temporal lobe abnormalities on MRI, and outcome after the first

antiepileptic drug (AED) trial. Other variables included in the analysis were history of status epilepticus, frequency of seizures per month, presence of psychiatry comorbidity, developmental delay, and death. Lesions were defined by radiologists and epileptologists as being directly relevant to the epileptogenic process (Téllez-Zenteno *et al*., 2010). Neocortical and mesial epilepsy were defined using ILAE criteria (Proposal for classification of epilepsies and epileptic syndromes, 1985; Proposal for revised classification of epilepsies and epileptic syndromes, 1989; Téllez-Zenteno and Hernandez-Ronquillo, 2012). An AED trial was considered a failure if seizures persisted at the maximally tolerated dose. The aetiology and classification of epileptic syndromes were defined according to the criteria proposed by the ILAE in 1989 (Proposal for revised classification of epilepsies and epileptic syndromes, 1989). For this study, early-onset epilepsy was defined as the diagnosis of epilepsy made before the age of 18 years old.

Definition of mild course and severe course TLE

Patients were dichotomized as having either a mild or severe course of TLE. Mild-course TLE (case) was defined as patients who were well controlled (no seizures) with or without AEDs at last follow-up visit. A severe course (control) of TLE was considered when patients either:

– experienced persistence of any type of seizure involving impairment of consciousness, despite at least two maximally tolerated AED trials and with possible indication of surgery by the epileptologists;

– required ES;

– were candidates for ES, but declined intervention and continued to have seizures;

– or manifested drug-resistant epilepsy (DRE), but were not surgical candidates and continued to have seizures (*e.g*. bi-temporal cases, medical contraindications, *etc*.).

The Engel classification was used to categorize post-operative outcomes after ES (Engel, 1993).

Statistical analysis

Analyses were performed with SPSS software version 22 (IBM, Chicago, IL, USA). The data are presented as means, standard deviations, and percentages. A bivariate analysis was also conducted. Two by two tables using χ^2 test or Fisher's exact test were used to analyse categorical data. Odds ratios and confidence intervals were calculated. Student's *t*-test was used to find differences between numerical variables. Two-tailed p values of < 0.05 were considered

Table 1. General characteristics of the cohort (n=159).

Characteristics	Mean + SD (range) n (%)
Age of patients	46.0+ 14.4(19-98)
Age at onset of epilepsy (years)	23.9+ 19.3(0-79)
Female/Male	83(52)/76(48)
Years of evolution	22.1+ 15.1 (1-63)
Last seizure frequency	2.8+ 6.6(0-30)
First AED used	
Phenytoin	27(34)
Carbamazepine	16(20)
Lamotrigine	13(16.5)
Phenobarbital	8(10)
Levetiracetam	6(8)
Valproic	5(6)
Clobazam	2(2.5)
Other	2(2.5)
Unknown	80 (50)
AEDs tried	4.38 + 2.2 (1-12)
Actual # of AED	2.1+ 0.9 (1-12)
Aetiology of epilepsy	
MTS	58(36.5)
Unknown	46 (29)
Mild course tumour	15 (9.5)
Cranial trauma	10(6)
Cerebral infections	6(4)
Vascular malformation	6(4)
Cortical dysplasia	5(3)
Stroke	3(2)
Congenital Malformation	3(2)
Asphyxia during birth	3(2)
Other	4(2.5)
Epileptic syndromes	
Symptomatic	101(63.5)
Cryptogenic	58(36.5)
Lesional (MRI)	95 (60)

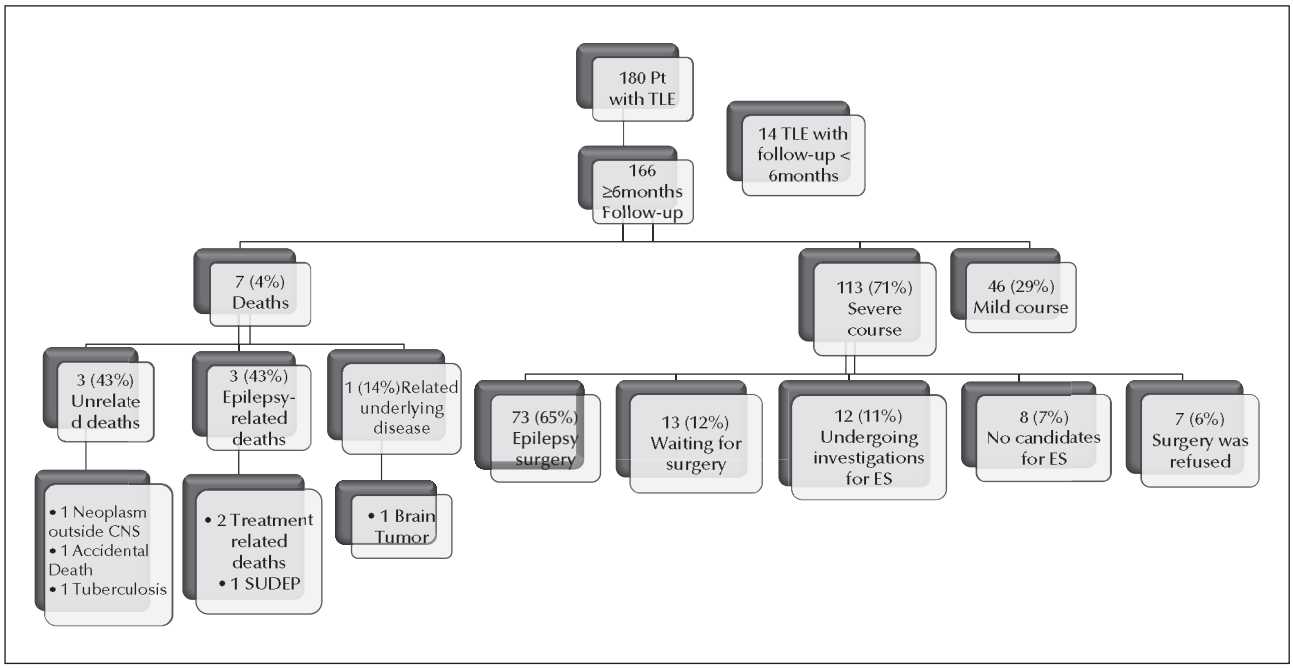

Figure 1. The main outcomes of our cohort (*n*=180).

statistically significant. A multiple logistic regression analysis was performed with the most significant variables.

Results

Description of the cohort

Of 180 patient records reviewed, 166 patients met inclusion criteria (*table 1*). We excluded 14 patients because they had less than six months of follow-up (*figure 1*). Of 166 patients, seven (4%) patients died during follow-up due to the following causes: three patients had deaths unrelated to epilepsy (one accidental stair fall, one death from complications of tuberculosis, and one from a neoplasm outside the CNS); one death occurred as a result of a brain tumour (related to underlying disease); and three patients with epilepsy-related deaths (two patients had sudden unexpected death in epilepsy [SUDEP], and one patient died due to a pulmonary embolism after ES). Consequently, 159 patients were included in the final analysis (*figure 1*).

Of the 159 patients, 83 were female (52%). Fifty-one (32%) had right temporal and 77 (48.5%) had left TLE, and 31 (19.5%) had bi-temporal seizure onset. Eighty-five (53%) patients had mesial epilepsy, 35 (22%) had neocortical epilepsy, 17 (11%) patients had characteristics of both (mesial/neocortical), and it was not possible to classify the specific syndrome in 22 (14%) cases.

Outcomes at last follow-up visit

Mean patient age at last follow-up visit was 46.0±14.4 (range: 19-88) years. Seventy-three per cent of patients (46%) started having seizures before the age of 18. Mean follow-up period was 43.4±22.6 (6 to 84) months. Forty-six (29%) patients were seizure-free with AED therapy (mild course TLE) and 113 (71%) patients developed a severe course of TLE of whom: seven (6%) patients declined ES, eight (7%) were not candidates for ES (five bi-temporal cases and three multifocal cases with previous resections in the temporal region), 12 (11%) patients had DRE and were being assessed for ES, 13 (12%) patients were surgical candidates waiting for ES, and 73 (65%) had undergone ES.

Surgical outcomes

Of 73 patients who underwent ES, all had at least six months of follow-up, 63 had one-year, 48 had two-year, and 34 had five-year follow-up data. At six months, (*n* = 73) 54 (74%) achieved Engel class I, nine (12%) class II, seven (10%) class III, and three (4%) class IV. At one year (*n* = 63), 41 achieved class I (65%), 10 (16%) class II, eight (13%) class III, and four (6%) class IV. At two years (*n* = 48), 30 (62.5%) attained class I, four (8%) class II, nine (19%) class III, and five (10%) class IV. At five years (*n* = 34), 19 (56%) patients achieved Engel class I, four (12%) class II, five (15%) class III, and six (17%) class IV.

Table 2. Comparison between mild and severe course of TLE (*n*=159).

Prognostic factors	**Mild TLE (29%) *n*=46**	**Severe TLE (61%) *n*=113**	**OR (intervals)**	***p* value**
Female	27(59%)	56(50%)	1.45 (0.7-2.9)	0.4
Age at last follow-up Years (± SD)	51.5(16.1)	43.8(13.1)	NA	0.002
Mean age at onset of epilepsy in years (± SD)	36.5(21.5)	18.74(15.7)	NA	0.001
Means year of epilepsy evolution (± SD)	14.9(15)	25.1(14.2)	NA	0.001
Number of AEDs tried	2.5(1.46)	5 (2)	NA	0.001
Currently mean number of AEDs on (± SD)	1.6(0.7)	2.2(0.9)	NA	0.001
Seizure frequency Median (mean last 12 months)	0.26	1	NA	0.002
Mean follow-up (months)(± SD)	36.3(22.4)	46.4(22.1)	NA	0.01
Family history of epilepsy	4(9%)	17 (15%)	0.54(0.2-1.7)	0.28
Good response to first AED	24(63%)	8(20%)	6.8 (2.5-19)	0.001
A period of >2y of sz freedom (any time)	30(65%)	28 (25%)	5.7 (2.72-11.95)	0.001
Any risk factor for epilepsy	22(48%)	64(57%)	0.7(0.35-1.4)	0.31
History of status epilepticus	3(6.5%)	30(26.5%)	0.19 (0.06-0.67)	0.005
History of FS	1(2%)	11(10%)	0.20 (0.02-1.6)	0.1
Developmental delay	3(6.5%)	16(14%)	0.42 (0.1-1.5)	0.18
Any psychiatric comorbidity	13(28%)	41(36%)	0.7 (0.3-1.5)	0.33
Aetiology of epilepsy				
• Unknown	19(41%)	27(24%)	2.2(1.8-4.6)	0.028
• MTS	4(9%)	54(49%)	0.10(0.03-0.31)	0.001
Epileptic syndrome				
Symptomatic	25(54%)	76(67%)	0.58(0.29-1.17)	0.12
Cryptogenic	21(46%)	37(33%)	1.72(0.85-3.5)	0.12
Complex partial seizures	29(63%)	103(91%)	0.16 (0.07-0.4)	0.001
Partial seizures with secondary generalization	31(67%)	99(88%)	0.29 (0.13-0.67)	0.003
Lesion on MRI	21(49%)	74(67%)	0.47 (0.23-0.98)	0.04
Mesial epilepsy	14 (30%)	71 (63%)	0.25 (0.11-0.49)	0.0001
Neocortical	31 (67%)	37 (33%)	2.34 (1.0-5)	0.02

Comparison between mild and severe courses of TLE

Table 2 shows a comparative analysis between mild- and severe-course TLE. Patients with mild-course TLE were older (*figure 2A*) (p = 0.002), with a late onset of epilepsy (p = 0.001) and their evolution of epilepsy was shorter (*figure 2B*) (p = 0.001). Patients with a mild course of TLE were using fewer AEDs (p = 0.001) and had lower seizure frequency (p = 0.006) relative to patients with severe-course TLE. Other factors associated with mild-course TLE were: a good response to the first AED

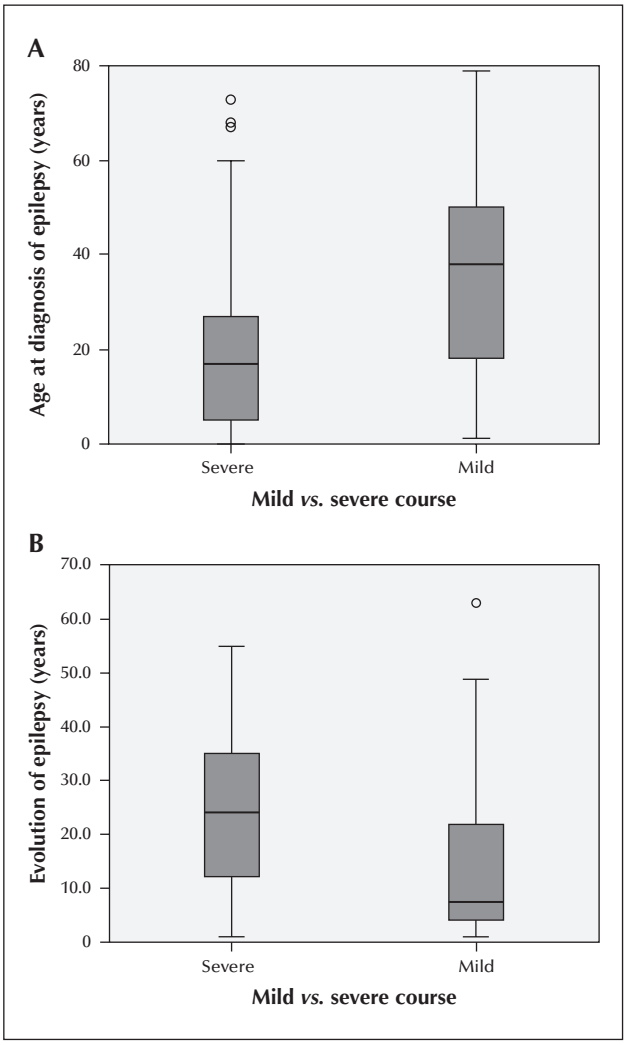

Figure 2. A. Boxplot displaying the age at onset in patients with a mild *vs.* severe course of temporal lobe epilepsy. B. Boxplot displaying the duration of epilepsy (years) in patients with a mild and severe course of temporal lobe epilepsy.

(OR: 6.8; 95% CI: 2.5-19: $p = 0.001$), a period of two years of seizure freedom (anytime) (OR: 5.7; 95% CI: 2.7-11.9; $p = 0.001$), and unknown aetiology (OR: 2.2; 95% CI: 1.8-4.6; $p = 0.001$).

Factors associated with severe-course TLE were: history of status epilepticus (OR: 0.19; 95% CI: 0.06-0.67; p=0.005), mesial temporal sclerosis pathology (OR: 0.10; 95% CI: 0.03-0.31; p=0.001), mesial temporal lobe epilepsy (OR: 0.25; 95% CI: 0.11-0.49; p=0.0001), any lesion on MRI (OR: 0.47; 95% CI: 0.23-0.98; p=0.04), clinical presentation with complex partial seizures (OR: 0.16; 95% CI: 0.07-0.4; $p = 0.001$), and presence of partial seizures with secondary generalization (OR: 0.29; 95% CI: 0.13-0.67; p=0.003).

Multivariate analysis

Table 3 shows the results of multivariate analysis. The following variables were entered in a logistic regression model: age at diagnosis of epilepsy, years of evolution of epilepsy, good response to first AED, and a period of two years or more with no seizures during evolution. The variables which remained significant in the multivariate analysis were a good response to the first AED (OR: 6.8; 95% CI: 1.79-25.9; $p < 0.005$) and any period of seizure freedom for at least two years (OR: 14.6; 95% CI: 3.7-57.64; $p<0.001$).

Table 4 provides a comparative analysis of seizure-free rates in other published cohorts. We calculated seizure freedom rates (weighted average) of patients using AEDs at last follow-up visit. The weighted average in the referenced paediatric studies was 35% (range: 32-39%; n = 473). The weighted average for the adult studies was 20% (range: 18-22%) (n = 2007). For patients with MTS, the weighted average was 12% (range: 9-14%; n = 266). The weighted mean for all patients with TLE (with unspecified aetiology) was 28% (range: 26-30%; n = 1,860).

Discussion

In this cohort, 28% of patients exhibited mild-course TLE, that is, they achieved seizure freedom with pharmacotherapy alone. As demonstrated in *table 4*, the weighted average for seizure freedom in non-surgical cohorts ranged from 35% (range: 32-39%) in paediatric populations to 20% in adult cases (range: 19-21%). Specifically, in patients with MTS, the weighted average was only 14% (range: 11-16%) and in all types of TLE without specific pathology, the weighted mean was 26% (range: 26-30%). The proportion of mild-course TLE in this study is higher than previously reported and may be due to differences in population characteristics. For instance, previous reports may have included a predominance of patients with MTS, in whom non-surgical outcomes tend to fare worse. However, the frequency of a mild course of MTS is higher in this cohort than previously published and may reflect the inclusion of both mesial and neocortical cases.

This study lends credence to the hypothesis that TLE in adult patients may represent a different entity compared with paediatric populations. In this cohort, 28% of adult patients with TLE achieved seizure freedom which is considerably lower than the rates reported in some paediatric studies, notably those of Dlugos *et al.* (2001) (62.5%) and Aguglia and colleagues (1998) (59%). This observation is further supported by the mean averages tabulated in *table 4*, in which 35% of paediatric but only 20% of adult cohorts achieved seizure freedom. It has been suggested that the development

Table 3. Logistic regression model.

	Coefficient	SE	Wald Chi-squared	OR	95% CI	*P* value
Age at diagnosis of epilepsy	0.021	0.021	1.059	1.022	0.98-1.06	0.30
Years of evolution of epilepsy	-0.047	0.035	1.787	0.954	0.89-1.02	0.181
Good response to first AED	1.92	0.68	7.92	6.8	1.7- 25.9	0.005
Seizure freedom for 2 years (Any period)	-1.91	1.1	2.97	14.6	3.7-57.6	<0.001

Table 4. Published studies analysing seizure freedom rates in patients with TLE.

Author	Year	Type of population	Type of study	Number of patients	Type of pathology*	% of patients that well controlled with medications
Lindsay *et al*.	1979	Children	Cohort study	100	TLE	33%
Harbord and Manson	1987	Children	Retrospective cohort	65	TLE	35%
Aguglia *et al*.	1998	Children	Retrospective cohort	104	Non lesional	59%
Dlugos *et al*.	2001	Children	Retrospective Cohort	162	TLE	62.5%
Cersosimo *et al*.	2011	Children	Retrospective cohort	42	MTS	5%
Sanchez *et al*.	2014	Children and adults	Cohort	110	MTS	31%
Currie *et al*.	1971	Adults	Cohort	666	TLE	40%
Kim *et al*.	1999	Adults	Cohort study	104	MTS	25%
Kumlien *et al*.	2002	Adults	Retrospective case	83	MTS	13%
Semah *et al*.	2002	Adults	Retrospective study	535	TLE	20%
Helmstaedter *et al*.	2003	Adults	Cohort	102	TLE	12%
Varoglu *et al*.	2009	Adults	Retrospective cases	287	MTS	9%
Pittau *et al*.	2009	Adults	Incident and retrospective cases	230	TLE	20.6%
Aguglia *et al*.	2011	Adults	Prospective	474	Non lesional	21%
Falip *et al*.	2003	Adults	Retrospective	51	MTS	29.2%
Park *et al*.	2014	Adults	Retrospective	234	Lesional TLE	17.8%
Sanchez *et al*.	2014	Children and adults	Retrospective	110	MTS	29%
Spooner *et al*.	2006	Children	Retrospective	77	TLE	31%

Weighted average for paediatric studies: *n*=473, 35% (32-39%); weighted average for studies including adult patients: *n*=2,007, 20% (19-21%); weighted average for studies with patients with MTS: *n*=266, 14% (11-16%); weighted average for studies including all patients with TLE without specific pathology group: *n*=1,271, 26% (24-28%). We identified studies including only cases of MTS (mesial temporal sclerosis), series with non-lesional cases, series with all kinds of pathologies specified as TLE, and series of cases of lesional TLE.

of DRE may be a function of time, such that the threshold for intractability may occur once adulthood is reached. An alternative explanation is that some paediatric patients may have been misclassified as having TLE when in fact a more favourable epilepsy syndrome, such as benign rolandic epilepsy, may have been causative. Although further inquiry is necessary, the present study adds to previous evidence that discrepant seizure remission rates between adult and paediatric patients are a consistently observed trend, which may reflect differences in aetiopathogenesis.

A key outcome of this study is the elucidation of an interaction between duration of epilepsy and age at seizure onset. Seizure onset in patients with mild-course TLE occurred significantly later (average: 36.5 years) compared with the severe course (average: 18.7 years). Putative explanations include the possibility that the threshold for intractability may reflect a time-dependent process, which may suggest that mild-course TLE patients may regress to a severe course over longer-term follow-up. This suggestion is supported by Berg and colleagues (Berg *et al*., 2006) who published a cohort of 613 children and demonstrated that intractability is a delayed effect, often preceded by a quiescent phase.

Alternatively, it could be surmised that mild- and severe-course TLE reflect two diverse phenotypes, such that patients with relatively early age at seizure onset (*i.e*. seizure onset in their twenties) and longer evolution may portend a more malignant (*i.e*. severe) course of TLE, likely requiring surgical intervention, versus the relatively mild course of TLE observed in patients with shorter evolution times and late age at seizure onset (*i.e*. seizure onset in forties) that can be satisfactorily managed with pharmacotherapy alone. A similar observation was reported by Sanchez *et al* (2014) in a retrospective cohort of 110 patients with TLE, in which patients who developed seizures later in life had a better prognosis than patients who had earlier age at seizure onset. Mesial TLE is the most common form of partial epilepsy in adolescents and adults, and some studies have estimated that it represents about 40% of all epilepsies in this age range (Cendes, 2004). Typically, patients have known risk factors, such as perinatal injury, central nervous system (CNS) infection, FS, head trauma, and family history of epilepsy (Cendes, 2004). Up to 60% of patients with MTS may have a previous history of FS before developing seizures. In contrast, neocortical TLE (NTLE) has a different clinical profile than mesial TLE. A history of FS, CNS infection, perinatal complications, or head injury is less common (Gil-Nagel and Risinger, 1997). Seizures in patients with NTLE appear five or ten years later than in MTS (Gil-Nagel and Risinger, 1997; Bercovici *et al*., 2012). This study reveals that the presence of mesial epilepsy is a risk factor for severe-course TLE and a protective factor for mild-course TLE. This observation correlates with previous reports (Ladino *et al*., 2014). Many cases in this cohort with mesial TLE had MTS, therefore it was expected that the absence of this finding could be a predictor of mild-course TLE. Additionally, the majority of patients in this cohort had mesial TLE, which is also consistent with previous literature (Ladino *et al*., 2014).

Response to first AED was a significant prognostic factor for mild-course TLE. This observation has been substantiated in studies of other types of epilepsy (Brodie *et al*., 2013) and in studies of paediatric TLE (Dlugos *et al*., 2001b). Moreover, this study demonstrated that patients with mild-course TLE use less medication than patients with severe-course TLE. This observation indicates that patients with mild-course TLE require fewer AED trials to demonstrate seizure control, a finding supported in the literature (Dlugos *et al*., 2001). All patients who achieved mild-course TLE required AED therapy, which is discordant with the findings of Currie *et al*. (1971) who reported seizure freedom in the absence of AED therapy in paediatric patients with TLE. This observation is interesting because some patients who were classified with a mild-course in our study could have been candidates for medication withdrawal, although this management was not undertaken for our patients because of the very strict driving restrictions in Canada. For paediatric TLE patients, discontinuation of AEDs is more feasible since driving is less of an issue. We believe that more studies are needed to reveal the frequency of patients with TLE who are free of seizures and medication.

An interesting observation is the demonstration based on bi- and multivariate analyses, that the presence of a seizure-free period of two or more years predicts mild-course TLE. Previously, it was suggested that some patients with MTS experience a seizure-free "honey moon" period (no seizures) after early seizures and subsequently progress to intractability (Berg, 2008). A more fitting explanation for the observation in this study is that patients with mild-course TLE are more amenable to pharmacotherapy and therefore generate longer periods of seizure freedom than patients with severe-course TLE, and this is likely a reflection of AED responsiveness.

This study helps establish the concept of mild-course TLE; a concept hitherto lacking systematic inquiry. The authors recognize that the concept of mild-course TLE is inherently controversial in the face of literature debating high rates of intractability of patients with TLE. The results of this investigation indicate, however, that a significant minority of patients will achieve seizure freedom on pharmacotherapy, which supports the genesis of the nosological categorizations of mild and severe courses of TLE. Labate *et al*. (2011) have attempted to characterize an approach to

mild-course TLE, suggesting that benign mesial TLE should be defined as at least 24 months of seizure freedom with or without medications. By their definition, seizure onset should occur in adolescence or adulthood with the accompaniment of a family history of FS and evidence of MTS (Labate *et al*., 2011). This viewpoint stands in contradistinction to the results of the present investigation which elaborate a better prognosis for patients who experience seizure-onset in their forties and lack MTS. The inclusion of both mesial and neocortical epilepsy in this study broadens the concept of a benign TLE to all subsets and suggests that response to the first AED, age at onset, time of evolution, and specific MRI-visualized lesions prognosticate severe or mild phenotypes. It is the opinion of the authors that the concept of benign mesial TLE is too restrictive and fails to account for the many patients with TLE who have neocortical epilepsy.

The key strengths of the present investigation include the longitudinal assessment of a large cohort of patients, which includes subsets of both surgically and medically managed patients. The study methodology is complemented by a clear case definition. Our study has some limitations. First, a potential point of controversy concerns the classification of patients who undergo ES and then become seizure-free as those with a severe course. It is the investigators' contention that patients eventually requiring surgery manifest features of intractability by virtue of failure of AED therapy and that this represents a different phenotype relative to patients who achieve long-term seizure remission on AED therapy alone. Another limitation in our study is the inclusion of patients with a minimal follow-up of six months. Some authors have suggested that intractability may take more time to develop and some cases with short follow-up could be misclassified. We recognize this limitation although one of our main purposes was also to show the results of a cohort of patients followed over time and have a full picture of the prognosis of TLE. Finally, it is possible that some patients with TLE who started before the age of 18 years old, and who were rendered seizure-free over time, were not assessed in our adult programme and potentially not included in our study, producing a selection bias.

Conclusions

One of the most important contributions of this study is the potential application of findings to individual patient prognostication. The present analysis suggests that patients with TLE with older age at onset, good response to first AED, and shorter disease duration are more likely to adhere to a mild-course. Conversely, the presence of MTS, mesial TLE, and potentially seizure type (complex partial with secondary generalization) are prognostic factors for intractability. The disclosure of these findings may aid epileptologists and patients in providing long-term counselling for patients newly diagnosed with TLE.

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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TEST YOURSELF

(1) From the following variables, which one is a risk factor associated with a mild course in patients with temporal lobe epilepsy?

A. Response to first antiepileptic drug
B. Normal MRI
C. Early onset of seizures
D. Developmental delay

(2) From the following variables, which one is a risk factor associated with a severe course in patients with temporal lobe epilepsy?

A. Idiopathic aetiology
B. Stroke as an aetiology
C. Female
D. Early onset of seizures

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".