Mild Non-lesional Temporal Lobe Epilepsy

A Common, Unrecognized Disorder with Onset in Adulthood

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ABSTRACT: ***Objective:*** To compare mild vs. severe non-lesional temporal lobe epilepsy (TLE). ***Methods:*** Data from 104 consecutive patients with non-lesional TLE were reviewed. Seventy-three of the 104 fulfilled the criteria for inclusion in this study of a follow-up period longer than three years at our Institute. Patients were considered to have a mild TLE if they were seizure free for at least three years after appropriate antiepileptic medication, or had rare (≤ 2/year) complex partial or secondarily generalized seizures for at least three years with or without appropriate antiepileptic therapy. Clinical, EEG and MRI data of mild vs. severe non-lesional TLE patients were compared on the basis of a cross-sectional study design. ***Results:*** Of the 73 patients with non-lesional TLE included in the study, 43 (59%) had mild TLE, and 30 (41%) had severe TLE. Duration of epilepsy was significantly shorter (mean 15.2 ± 10.5 years vs. 26.4 ± 13.2 years) and age at onset was significantly higher (mean 34.3 ± 15.3 years vs. 7.8 ± 6.8 years) in mild than in severe TLE group. Patients with mild TLE had also a significantly higher prevalence of positive family history of epilepsy (37.2% vs. 10%), and a significantly lower occurrence rate of febrile convulsions (FC) (4.7% vs. 33.3%), mesial temporal sclerosis (MTS) (6.9% vs. 36.7%), and intelligence deficiency (0% vs. 20%). In mild TLE there was also a significantly high rate (58.1% vs. 0%) of delayed diagnosis (from 1 to 28 years), because of misdiagnosis (39.5%) or no medical counseling (18.6%). ***Conclusions:*** Mild non-lesional TLE is a common, unrecognized disorder mainly characterized by both onset in adulthood and high prevalence of familial history of epilepsy. The present findings suggest that mild non-lesional TLE may represent a clinical entity different from severe non-lesional TLE.

RÉSUMÉ: Épilepsie temporale légère sans lésion - une affection fréquente, méconnue, de l'âge adulte. ***But:*** Comparer l'épilepsie temporale (ÉT) légère et sévère, sans lésion du lobe temporal. ***Méthodes:*** Nous avons révisé les dossiers de 104 patients consécutifs atteints d'ÉT sans lésion. Soixante-treize des 104 remplissaient le critère d'inclusion de cette étude, soit un suivi de plus de trois ans à notre Institut. Les patients étaient considérés comme souffrant d'ÉT légère s'ils n'avaient pas eu de crise depuis au moins 3 ans sous médication antiépileptique appropriée ou avaient eu très peu de crises partielles complexes ou secondairement généralisées (≤ 2/année) pendant au moins 3 ans, avec ou sans traitement antiépileptique approprié. Nous avons comparé les données cliniques, électroencéphalographiques et de RMN des patients avec ÉT légère et sévère, sans lésion, selon un plan d'étude transversale. ***Résultats:*** Parmi les 73 patients inclus dans l'étude, 43 (59%) avaient une ÉT légère et 30 (41%) avaient une ÉT sévère. La durée de la maladie était significativement plus courte (moyenne 15.2 ± 10.5 ans vs. 26.4 ± 13.2 ans) et l'âge de début était significativement plus élevé (moyenne 34.3 ± 15.3 ans vs. 7.8 ± 6.8 ans) dans les cas d'ÉT légère par rapport aux cas sévères. Les patients atteints d'ÉT légère avaient également une prévalence significativement plus élevée d'une histoire familiale d'épilepsie (37.2% vs. 10%) et une fréquence plus élevée de convulsions fébriles (4.7% vs. 33.3%), de sclérose temporale mésiale (6.9% vs. 36.7%) et de déficit intellectuel (0% vs. 20%). Dans l'ÉT légère, il y avait également un taux significativement élevé de diagnostic tardif (58.1% vs. 0%, de 1 à 28 ans), à cause de diagnostics erronés (39.5%) ou d'absence de consultation médicale (18.6%). ***Conclusions:*** L'ÉT légère sans lésion est une affection fréquente, méconnue, caractérisée principalement par un début à l'âge adulte et une prévalence élevée d'une histoire familiale d'épilepsie. Nos constatations suggèrent que l'ÉT légère sans lésion pourrait représenter une entité clinique différente de l'ÉT sévère sans lésion.

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Temporal lobe epilepsy (TLE) represents the most common type of partial epilepsy.[1-2] According to the underlying pathology, TLE may be divided into two broad categories: "space-occupying lesions" and "non-lesional" cases.[3] The latter is the most common subtype and comprises also patients with mesial temporal sclerosis (MTS).[3]

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From a review of the epidemiological studies,[4] it appears that non-lesional TLE is not a uniform 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. Because many studies on TLE have originated from groups with a special interest in surgical treatment, information up to now has concerned mostly patients with refractory non-lesional TLE.[3,5-8] In such cases, antecedent factors for epilepsy, such as febrile convulsions (FC) or cerebral infections are very common,[5] and MTS represents the most common substrate as demonstrated by magnetic resonance imaging (MRI) studies,[3,5-8] and confirmed at autopsy and in histological material after temporal lobe resection.[9]

Conversely, the mild form of non-lesional TLE still remains an undefined entity from an etiological and electroclinical point of view. Some authors have also suggested that this entity may often pass undiagnosed, since many patients only rarely have major seizures or brief partial attacks.[10]

In the present study, we compared clinical, EEG and MRI findings of mild vs. severe non-lesional TLE.

Patients

The patient population consisted of 735 consecutive referrals to our secondary care epilepsy service from January 1988 to March 1997. Five-hundred-thirty out of 735 patients (72.1%) had a partial epilepsy, which was intractable in 182/530 (34.3%). From 530 patients with partial epilepsy, we selected 104 (19.6%) with non-lesional TLE. According to the International Classification of Epileptic syndromes,[11] the clinical diagnosis of TLE was based on seizure semiology[12-17] suggestive of onset in the temporal lobe (i.e., simple partial seizures with autonomic and/or psychic symptoms or sensory phenomena, such as olfactory and auditory, including illusions, with or without complex partial seizures), and if there were no clinical or investigatory features indicating an extratemporal partial epilepsy. The diagnosis of TLE was also based on the interictal scalp EEG characteristics, including: slight or marked asymmetry of the background activity, temporal spikes, sharp waves and/or slow waves, or no abnormality.[11] Based on MRI studies, we considered TLE as non-lesional if no epileptogenic foreign tissue lesion, also including cortical dysplasia,[3] was detected. TLE patients with neuroimaging evidence of MTS[6-8] were included in the non-lesional group. The criteria for inclusion was also a follow-up at our epilepsy center longer than three years. Exclusion criteria were history of epilepsy less than three years, insufficient or doubtful clinical or imaging data, and a poor compliance as assessed by periodic monitoring of the plasma concentrations of antiepileptic drugs (AED).

The patients were divided into two groups. Group 1 or the mild TLE group consisted of patients who had ≤ 2 complex partial or secondary generalized seizures per year for at least three years with or without appropriate antiepileptic therapy. Group 2 or the severe TLE group consisted of patients with resistant partial or secondarily generalized seizures despite an optimal regimen of antiepileptic medication for at least three years.

Methods

Clinical, EEG and MRI data of mild vs. severe non-lesional TLE patients were compared on the basis of a cross-sectional study design.

Clinical data. A detailed history of the type and frequency of seizures was obtained from patients, parents and other relatives at the time of the investigation, and from a review of the patients' medical records. Special attention was paid to discovering a familial history of FC or epilepsy, personal medical history, age at onset of epilepsy, classification and frequency of each type of seizure, and evolution and response to treatment. Neurological, neuropsychological (WAIS), psychiatric, and general examinations were always performed.

Follow-up. In all patients, we scheduled at least one follow-up visit every 3-6 months after the AED treatment was initiated. Each visit included: neurological examination, survey of seizure frequency by means of a purpose-made calendar, routine blood chemistries, and monitoring of AED plasma concentrations.

EEG study. A routine waking EEG study was carried out in all patients. EEG recordings during sleep induced by sleep deprivation, i.m. chlorpromazine[18] or chloral hydrate were obtained whenever possible. EEGs were recorded with a 21-channel polygraph. Electrodes were placed according to the International 10-20 system and usually included T1 and T2 electrodes.

MRI study. In all patients, standard MRIs were performed with a GE Vectra 0.5-Tesla scanner, and included T2-weighted images (TE 100, TR 2,800 msec), proton density-weighted images (TE 25 TR 2,800 msec) and T1-weighted images (TE 320, TR 10 msec) obtained utilizing sagittal, coronal and axial planes. Coronal images were made parallel to the long axis of the brain stem and axial images were taken orthogonally to this axis, using 5 mm-thick sections and a 1-mm gap between the slices.

Statistical analysis. Comparisons of normally distributed interval data were made using the Student's *t*-test. Categorical data were compared using the chi-square test or, where appropriate, Fisher's exact test.

Results

Thirty-one of the 104 non-lesional TLE patients were excluded from this study because of insufficient or doubtful clinical or imaging data (11 patients), a follow-up period (15 patients) shorter than three years, lost to follow-up (3 patients), or poor compliance (2 patients). No patient died from sudden unexplained causes. The remaining 73/104 non-lesional TLE patients were eligible for the study. The past medical histories of these 73 patients were unremarkable with respect to head injury, cerebrovascular disease, and alcohol or drug abuse. Forty-three of the 73 (59%), 19 men and 24 women, ranging in age from 20 to 80 years (mean 49.5 and SD 16.2 years; median 47.0 years), had a mild non-lesional TLE, while 30 of the 73 (41%), 11 men and 19 women, ranging in age from 10 to 73 years (mean 34.1 and SD 13.9 years; median 34.0 years), had a severe non-lesional TLE.

The results of the comparative study are summarized in the Table. No significant differences between the two groups were found with respect to sex distribution, duration of the follow-up period, type of seizure, or incidence of psychiatric disturbances, and lateralization of the interictal epileptiform and background EEG abnormalities, which always involved the temporal regions

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Table: Comparison between severe and mild non-lesional TLE groups.

	Severe TLE (N = 30 patients)	**Mild TLE** (N = 43 patients)	**Statistics**
FOLLOW-UP			
- range	36 - 74 months	36 - 96 months	
- mean (± SD); median	45.6 (±12.9); 39.5	48.3 (±14.5); 42.0	NS
SEX RATIO			
- Male/Female	11/19	19/24	NS
AGE AT ONSET			
- range	2 months - 23 years	5 years - 69 years	
- mean (± SD); median	7.8 (±6.8); 6.0	34.3 (±15.3); 36.0	p < .0000001
DURATION OF EPILEPSY:			
- range	6 - 67 years	3 - 56 years	
- mean (± SD);	26.4 (±13.2);	15.2 (±10.5)	p < .0005
PERSONAL ANTECEDENTS			
- febrile convulsions	10 (33.3%)	2 (4.7%)	p = .0016
- perinatal anoxia	2 (6.6%)	1 (2.3%)	NS
- infantile meningoencephalitis	3 (10.0%)	0	NS
FAMILY HISTORY OF FC/EPILEPSY	3 (10.0%)	16 (37.2%)	p = .0080
LOW IQ	6 (20.0%)	0	p = .0035
TYPE OF SEIZURES			
viscerosensory auras	23 (76.7%)	32 (74.4%)	NS
secondary generalized tonic-clonic	25 (83.3%)	29 (67.4%)	NS
complex partial	24 (80.0%)	26 (60.5%)	NS
fear	11 (36.7%)	11 (25.6%)	NS
structured hallucinations	5 (16.7%)	9 (20.9%)	NS
dysphasia	2 (6.7%)	2 (4.7%)	NS
vertiginous	0	3 (7.0%)	NS
déjà-vu/jamais vu	0	2 (4.7%)	NS
olfactory	0	2 (4.7%)	NS
dreamy status	0	1 (2.3%)	NS
acoustic	1 (3.33%)	0	NS
somatosensory	1 (3.33%)	0	
PSYCHIATRIC DISTURBANCES			
- anxiety, depression	11 (36.7%)	12 (27.9%)	NS
- other disturbances	4 (13.3%)	1 (2.3%)	NS
DELAYED DIAGNOSIS			
- misdiagnosis	0	17 (39.5%)	p < .000001
- no medical counseling	0	8 (18.6%)	p = .011
ANTIEPILEPTIC TREATMENT			
- monotherapy	11/30 (36.7%)	35/40 (87.5%)	p < .000001
- polytherapy	19/30 (63.3%)	5/40 (12.5%)	p < .000001
- no treatment	0	3/43 (6.9%)	NS
INTERICTAL EEG			
- normal	0	10/43 (23.3%)	p = .0031
- unilateral abnormalities	24/30 (80.0%)	29/33 (87.9%)	NS
- bilateral abnormalities	6/30 (20.0%)	4/33 (12.1%)	NS
MTS on MRI	11 (36.7%)	3 (6.9%)	p = .002

LEGEND TO TABLE

FC = febrile convulsions; IQ = intelligence quotient (WAIS); MRI = magnetic resonance imaging; MTS = mesial temporal sclerosis; NS = no significant difference; SD = standard deviation; TLE = temporal lobe epilepsy.

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(data not shown). The most common ictal manifestations were viscerosensory auras (i.e., rising epigastric sensation, abdominal or chest pressure, nauseous feeling, flushing, sweating or pallor), but other experiential phenomena such as fear, structured hallucinations, olfactory hallucinations (bad smell), déjà vu, jamais vu, dysphasia, dreamy status, vertigo with or without oroalimentary, verbal or gestural automatisms also occurred in both groups. Complex partial seizures occurred in either group and consisted of behavioral arrest or staring with or without automatisms, followed by dystonic posturing and occasionally by slow slumping to the floor. Secondary generalized tonic or tonic-clonic seizures (SGTCs) occurred in 25 (83.3%) patients with severe TLE and in 29 (67.4%) patients with mild TLE (Table). In the latter, pre-treatment SGTCs were rare (< 4/year) and tended to occur during sleep.

In comparison with severe TLE, patients with mild TLE had significantly shorter duration of epilepsy (mean 15.2 ± 10.5 years vs. 26.4 ± 13.2 years) as well as older age at onset of epilepsy (mean 34.3 ± 15.3 years vs. 7.8 ± 6.8 years) and a significantly lower occurrence rate of FC (4.7% vs. 33.3%), intelligence deficiency (0% vs. 20%) and MTS (6.9% vs. 36.7%). Specifically, only three patients with mild non-lesional TLE had MRI abnormalities suggestive of unilateral MTS, such as an increased T2 signal in mesial temporal structures in two patients, or right mesial temporal atrophy in the remaining patient, always concordant with the EEG focus. Mild TLE-patients had a significantly higher prevalence (37.2% vs. 10%) of familial histories of FC or epilepsy. In detail, 14 mild TLE-patients had a first-degree relative with epilepsy. Three out of these 14 patients belonged to the same family with autosomal dominant TLE, recently reported by us.[19] Six out of these 14 patients stated that their relatives had a similar seizure pattern to the one they presented. Unfortunately, we were unable to contact them, so we could not confirm the diagnosis of TLE. The relatives of the remaining five out of the 14 patients have been followed at our clinic because of childhood absence epilepsy (1 patient), benign rolandic epilepsy (2 patients), cryptogenic fronto-temporal epilepsy (1 patient), remote-symptomatic partial epilepsy (1 patient). Mild TLE patients had also a significantly higher prevalence of normal interictal EEG recordings (23.3% vs. 0%), treatment by monotherapy (87.5% vs. 36.7%) and delayed diagnosis (58.1% vs. 0%). Specifically, eight out of the 25 patients with delayed diagnosis of mild non-lesional TLE refused any medical counseling for one to 12 years (median 4 years). The remaining 17 patients had misdiagnosis of panic attacks (9 patients), gastrointestinal disturbances (6 patients), syncopal attacks (1 patient), or ischemic heart disease (1 patient), for 1 to 28 years (median 10.5 years). All of these 17 patients underwent several and repeated diagnostic procedures, including upper and lower gastrointestinal endoscopies, abdominal ultrasonographies, barium enema, or 24-hours Holter electrocardiography and electrocardiographic stress tests, which were always normal. They had been treated with benzodiazepines, gastric antisecretory drugs, antispasmodic drugs, or nitrates without any beneficial effects. The advent of disabling seizures (i.e., complex partial or secondary generalized tonic-clonic seizures) or an increase in the frequency of the habitual seizures led all of these patients to seek neurological counseling as a solution to their disturbances. Finally, three patients with mild non-lesional TLE refused antiepileptic medication because of the very mild ictal symptomatology.

Discussion

Our data illustrate that mild non-lesional TLE represents a common and often unrecognized clinical entity which should be differentiated from severe non-lesional TLE. In fact, in mild non-lesional TLE seizures usually start in adulthood and genetic factors seem to play a major etiopathogenetic role, while the association with MTS, as detected by MRI study, is much less common than that observed in severe non-lesional TLE. In accordance with the latter finding, we also found a much lower incidence of etiological factors known to be capable of causing MTS, such as FC or severe cerebral insults.[20] Our study also suggests that an age at onset of seizures later than 30 years of age indicates a good prognosis in non-lesional TLE. Moreover, since our study was not truly "cross sectional" with respect to epilepsy duration (patients with severe TLE had significantly longer duration of epilepsy) one may question if the duration of epilepsy may be a factor in intractability. We believe this is not the case, since it has been shown that remission of seizures within a few years from the onset of epilepsy is a reliable indicator of long-term good outcome.[21,22]

In our mild TLE patients, auras with autonomic or psychic symptoms were the leading ictal manifestation and epileptiform abnormalities were confined to temporal regions, suggesting that the epileptogenic disorder affects a very small territory within the mesial temporal structures.[5,12-17] Consistent with this hypothesis, recent studies have demonstrated that seizure symptoms and the extent of interictal EEG abnormalities correlate well with the degree and extent of temporal lobe damage.[23] A restricted epileptogenic region is associated with rare or absent major seizures, and predominantly mesiobasal interictal spiking activity. In contrast, more diffuse temporal lobe damage correlates with larger interictal EEG foci and more frequent secondary generalized seizures.[23]

The clinical features, seizure patterns, interictal EEG, and benign nature of the mild non-lesional TLE are very similar to those of familial TLE.[10,24] It is noteworthy that such a diagnosis could be ascertained or suspected in nine of the patients presented here. Moreover, it is possible that more familial cases may have occurred, but they may have passed unrecognized because of the very mild nature of this epilepsy in other family members. As stated by Berkovic et al.,[10,24] in fact, we also noted that viscerosensory auras or other simple partial seizures were often ignored by our patients, who did not seek medical counseling for a long time after the onset of epilepsy. Nevertheless, epileptic disorders different from TLE were found in the first-degree relatives of five individuals with mild TLE. The latter finding raises the question of whether a phenotypic heterogeneity may occur in familial TLE.

On MRI study, the lack of recognizable MTS in most mild TLE patients reinforces the hypothesis that a genetic predisposition appears to be an important causal factor in this epileptic disorder. However, the possibility cannot be excluded that at least some of our mild TLE patients may have had subtle damage or cell loss in the mesial temporal structures which was below the detection threshold of our MRI scans. In fact, some authors reported a relatively high occurrence of MTS in cryptogenic non-refractory TLE, as detected with a more powerful 1.5 Tesla MRI machine.[25] Nonetheless, even with more sophisticated MRI techniques, such as volumetric study,[26] relaxometry[27] or

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spectroscopy,[28] it is reasonable to hypothesize that there would still be a significant lower incidence in mild compared with severe cases of non-lesional TLE.

Finally, because of the mild nature of the seizures, many mild TLE-patients had a delayed diagnosis for several months or years. Indeed, these patients refused medical counseling or had a misdiagnosis, such as gastrointestinal disturbances, syncopal attacks, ischemic heart disease or panic attacks, which in turn led to repeated and fruitless investigations and treatments. Consistent with these findings, other authors have found that the diagnosis of adult-onset seizures is often delayed, because of the later requirement of medical counseling or misdiagnosis.[29] Furthermore, it was illustrated that simple partial seizures of temporal lobe origin may simulate panic attacks[30] and that adult patients referred to a psychiatry unit because of "panic disorders" were found to have focal epileptiform abnormalities in their EEG recordings, usually involving temporal lobe.[31]

We conclude that mild non-lesional TLE is a common epileptic disorder, starting in adult life. Because of its peculiar clinical picture, however, it may often pass unrecognized or misdiagnosed for a long time. In contrast to severe non-lesional TLE, genetic factors rather than prolonged FC or severe cerebral insults leading to MTS seem to play an important etiopathogenetic role.

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