Seizure 20 (2011) 163–166

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Is Temporal Lobe Epilepsy with childhood febrile seizures a distinctive entity? A comparative study

Kjell Heuser [a,*], Milada Cvancarova [b], Leif Gjerstad [a,c], Erik Taubøll [a,c]

[a] Department of Neurology, Oslo University Hospital, Rikshospitalet, Sognsvannsveien 20, N-0027 Oslo, Norway
[b] Cancer Registry of Norway, Oslo, Norway
[c] Faculty of Medicine, University of Oslo, Norway

ARTICLE INFO

Article history:
Received 19 July 2010
Received in revised form 5 November 2010
Accepted 22 November 2010

Keywords:
Temporal Lobe Epilepsy
Hippocampal sclerosis
Mesial Temporal Lobe Epilepsy
Febrile seizures
Phenotype

ABSTRACT

Objective: Pharmacoresistance continues to be a major challenge in Temporal Lobe Epilepsies (TLE). A key to overcome pharmacoresistance is to identify subgroups among the TLE and disclose their specific molecular pathways. This will facilitate a tailored pharmacological treatment and improve outcome. There is growing evidence in favor of the theory that TLE with childhood febrile seizures (TLE-FS) may represent one distinctive subgroup among the TLE.

Material and methods: We compared clinical features from 102 TLE-FS patients with 105 TLE patients without FS. We also conducted a logistic regression analysis to adjust for possible confounders caused by overrepresentation of patients with Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis (MTLE-HS) in the TLE-FS group.

Results: MTLE-HS was overrepresented in patients with TLE-FS ($p = 0.043$). Age at epilepsy onset was lower in patients with TLE-FS ($p < 0.001$). TLE-FS patients had a higher frequency of first grade family members with FS ($p = 0.003$, adjusted for MTLE-HS: $p = 0.002$). They were more frequently plagued with simple partial seizures ($p = 0.015$, adjusted: $p = 0.038$), and especially with vertiginous symptoms ($p = 0.004$ adjusted: $p = 0.006$). They also had the higher frequency of autonomic symptoms ($p = 0.003$; adjusted: $p = 0.012$), and more generalized tonic–clonic seizures (0.034; adjusted $p = 0.038$).

Conclusion: We identified TLE-FS as a phenotype that can be delineated from other TLE. None of the characteristics are specific, but we disclosed a set of features also when adjusted for MTLE-HS.

1. Introduction

Temporal Lobe Epilepsies (TLE) are fascinating conditions as they raise fundamental questions about brain development, neuroplasticity, molecular- and genetic pathways of epileptogenesis and mechanisms of pharmacoresistance. The term TLE simply refers to the location where seizures arise and does not allude to a common pathogenesis. Yet, TLE consist of several entities with different etiological backgrounds.

Despite recent medical advances patients with TLE continue to frequently display pharmacoresistance and often require temporal lobectomy to achieve seizure control.[1] Thus there is an urgent need to develop new therapy strategies for TLE. One of the most important future tasks to overcome medical intractability is to identify distinguishable entities among the TLE and tailor pharmacological treatment to the respective. Delineation of subgroups is however challenging as they exhibit similar phenotypes and are determined by complex polygenetic inheritance and largely unidentified environmental factors.

There is a growing list of indications in literature that TLE patients who suffered from febrile seizures in early childhood (TLE-FS) constitute a unique entity distinct from afebrile TLE.[2–4] In fact, studies on several large pedigrees suggest that TLE and FS may have a common genetic basis, whether hippocampal sclerosis is present or not.[5–7] These studies are reinforced by data from our recent association study that indicates genetic variants in TLE-FS.[8] In this respect the question arises whether TLE-FS display a phenotype that can be distinguished from other TLE. To address this issue, we here perform a comparative analysis of two TLE patient cohorts – one cohort with FS and one without FS – in order to identify phenotypic characteristics associated with TLE-FS. This is the first study to systematically investigate clinical characteristics of patients with TLE-FS.

* Corresponding author. Tel.: +47 230 70472; fax: +47 230 70490.
E-mail addresses: kjell.heuser@oslo-universitetssykehus.no, dr.heuser@gmail.com (K. Heuser).

1059-1311/$ – see front matter © 2010 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.seizure.2010.11.015

2. Materials and methods

2.1. Patient collection

Patient data were collected between 2000 and 2004 in a cooperative project (GenEpA), involving only tertiary Norwegian centers with high competence in the field of epileptology. 207 patients with TLE (according to the ILAE criteria, see www.ilae.org) were included. Inclusion criteria for all individuals were: age > 18 years; Caucasian race, with at least 3 of 4 grandparents of Scandinavian origin. Patients filled out standardized evaluation forms together with the treating physician or epilepsy nurse. These forms were controlled by the treating epileptologist and lacking information was added based on the medical records. MRI (typically 1 or 1.5 T, with sagittal and axial T1, axial and coronal T2 and FLAIR) was performed in all patients in order to identify abnormalities such as hippocampal sclerosis, temporal lobe atrophy and mass lesions. TLE patients with FS were compared with those patients without FS. We analyzed patient data as age, sex, age at epilepsy onset, incidence of FS in first grade family members, incidence of hippocampal sclerosis or other abnormalities in MRI, and clinical characteristics as seizure semiology and other ictal and interictal symptoms.

2.2. Data analysis

Categorical variables were described with proportions, continuous with median and range. Associations between variables were studied using Chi-square tests or Fisher's exact tests (when number of observations was too small for one or both variables). Crude association between the two patient subgroups and age of epilepsy onset were assessed using Cochran–Armitage test for trend.[9] To correct for possible confounding caused by overrepresentation of MTLE-HS in TLE-FS, multiple logistic regression models were adjusted for MTLE-HS and the results expressed as odds ratios (OR) with 95% confidence intervals (CI). p-Values < 0.05 were considered statistically significant. All analyses were computed using SPSS, ver.16.

3. Results

3.1. Patient characteristics

Age at epilepsy onset was lower in patients with TLE-FS ($p < 0.001$) (Fig. 1). Patients with MTLE-HS were overrepresented in the TLE-FS group ($p = 0.043$). TLE-FS patients had more than three times higher frequency of first grade family members with childhood febrile seizures ($p = 0.003$, adjusted for MTLE-HS: OR 3.85; 95% CI 1.66–8.9). Further patient characteristics are summarized in Table 1.

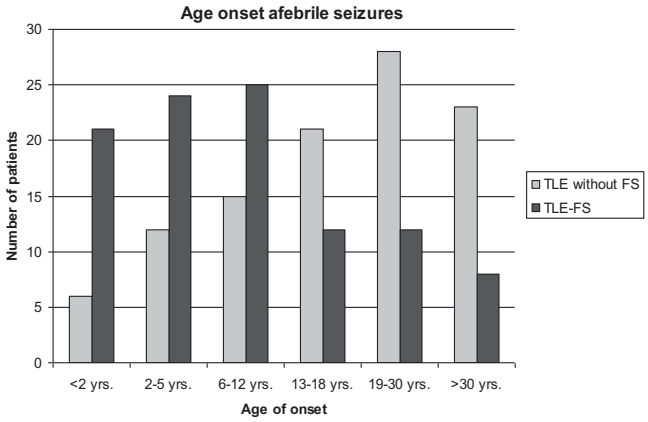

Fig. 1. Age at epilepsy onset in TLE-FS patients compared with TLE patients without FS. p-Value < 0.001.

Table 1
Patient characteristics of TLE-FS patients compared with TLE patients without FS.

		TLE-FS	TLE without FS
Patients n		102	105
Sex	Female	50	65
	Male	52	40
Median age (years) when entering the study		39 (18–70)	41 (18–66)
Median duration (years) of epilepsy when entering the study		23 (1–55)	22 (1–55)
Patients with Hippocampal Sclerosis (MTLE-HS)		33	21
Surgery	Vagal nerve stimulator	7	3
	Temporal lobectomy	30	22
First grade family members with FS		24	9
Seizure-free period of at least 5 years within the last 10 years before entering the study		28	23

3.2. Ictal and interictal features

TLE-FS patients were more frequently plagued with simple partial seizures ($p = 0.015$, adjusted OR 1.87; 95% CI 1.04–3.37), and especially with vertiginous symptoms ($p = 0.004$ adjusted OR 6.04; 95% CI 1.66–21.92) and psychic symptoms as déjà vu, jamais vu and ictal fear ($p = 0.047$). They also had the higher frequency of ictal autonomic symptoms ($p = 0.003$; adjusted OR 2.2, 95% CI 1.2–4.1), and displayed more often generalized tonic–clonic seizures (0.034; adjusted OR 2.5, 95% CI 1.1–6.4). Ictal features are summarized in Table 2. Interictally, TLE-FS patients showed borderline more often abnormal psychiatric or cognitive behavior (mood disturbance, psychosis, anxiety, cognitive impairment or memory disturbance) ($p = 0.046$), but reached no statistical significance when corrected for MTLE-HS.

4. Discussion

It is a contemporary phenomenon that diseases from traditionally having been subdivided on the basis of their clinical features increasingly become defined by their genetic background. Therefore, current disease classifications often appear confusing due to inclusion of both clinical and genetic information. The TLE usually have been subdivided on the basis of their electroclinical pattern into neocortical TLE (NTLE) and mesial TLE (MTLE), the latter further in MTLE with (MTLE-HS) and without hippocampal sclerosis. The latest proposal for classification of epileptic syndromes by the International League Against Epilepsy (ILAE) highlights only two distinctive subgroups among the TLE, which are familial MTLE (FMTLE) and MTLE-HS[10]; the first is defined by its specific genetic background, the second on the basis of its typical clinical presentation. Additionally the classification exhibits a third term, "MTLE defined by specific etiologies", to encourage further subdivision. As mentioned in the introduction, subdivision may contribute to challenge pharmacoresistant TLE.

The present study was motivated by findings from our recent association study that indicated genetic variation among TLE patients who have had febrile seizures in childhood (TLE-FS) when compared with TLE without FS.[8] As a result of our findings we wanted to test the hypothesis that TLE-FS may display another subgroup among the TLE. This hypothesis is supported by other studies that have indicated TLE-FS to constitute a unique entity distinct from afebrile TLE.[2–4] In this respect the question arises whether TLE-FS present clinical characteristics that allow a

Table 2
Seizure type and ictal symptoms in TLE-FS patients compared with TLE patients without FS.

	TLE-FS ($n=102$)	TLE without FS ($n=105$)	p-Value	Adjusted for MTLE-HS		
				p-Value	OR	95% CI
Simple partial seizures (SPS)	58	47	0.015	0.038	1.87	1.0–3.4
SPS with autonomic symptoms	44	25	0.003	0.012	2.2	1.2–4.1
SPS with vertiginous symptoms	14	3	0.004	0.006	6.04	1.7–21.9
SPS with motor symptoms	20	12	n.s.	n.s.		
SPS with somato-sensory symptoms	36	29	n.s.	n.s.		
SPS with psychic symptoms (déjà vu, jamais vu, ictal fear)	35	23	0.047	n.s.		
Complex partial seizures (CPS)	93	97	n.s.	n.s.		
Generalized tonic–clonic seizures	89	80	0.034	0.038	2.5	1.1–6.4

distinction from other TLE. Surprisingly we could not detect any previous study in which the phenotype of TLE-FS has been systematically investigated.

Our study shows that age at afebrile seizure onset is significantly lower in TLE-FS than in the other TLE patients. Generally, age at disease onset is an important indicator that facilitates delineation of disorders. Early epilepsy onset is consistent with particular biological features in the maturing brain that contribute to its hyperexcitability.[11–13] In certain epileptic conditions, such as probably in TLE-FS, a pathological reinforcement of these age-specific factors may predispose to seizure susceptibility in an early phase of development.

TLE patients with FS also seem to have a more serious condition than those without FS, as they display higher seizure frequency for both partial and generalized seizures, and surgery (vagus nerve stimulator and temporal lobectomy) tended to be more often conducted. Additionally we observed the higher incidence of ictal autonomic symptoms, vertiginous symptoms, psychic symptoms, but we have no good explanation for these observations.

Not surprising, we found that patients with MTLE-HS were overrepresented in the TLE-FS group. As patients with MTLE-HS are known to present a typical clinical picture,[14] we conducted logistic regression analysis (LRA) to adjust for probable confounders caused by the overrepresentation of MTLE-HS in the TLE-FS group. LRA confirmed our original findings and thus strengthened the idea of TLE-FS to represent a distinctive phenotype.

Certainly, one could ask whether it makes sense to divide TLE-FS from MTLE-HS as it is supposed that there is a large overlap. On the other hand it is still one of the most controversial topics whether febrile seizures are associated with TLE; some studies confirm such a link,[15–17] while others proof the opposite.[18,19]

At least, TLE-FS patients had the higher frequency of first grade family members with childhood febrile seizures. Febrile Seizures have principally been regarded as genetically determined, as twin- and family studies have pointed to an important genetic component[20,21] and epidemiological studies have shown a regional variation in prevalence.[22,23] TLE on the other hand has been traditionally regarded as an acquired condition. However, lately several lines of evidence have pointed towards an important role of genetics in TLE, such as observations of familial monogenic forms,[24,25] the frequent presence of positive familial antecedents for epileptic events,[26] the discovery of autosomal dominant partial epilepsy with auditory features (ADLTLE)[27] and also, if somewhat controversial, the high association with febrile seizures.[28]

The most recent findings have added important information to the rigid concepts of the TLE field and should be taken into consideration: First, boundaries between simple- and complex FS are more fluid than earlier predicted and the assumption that only complex FS may lead to hippocampal injury followed by TLE is no longer adequate, as even simple FS may cause hippocampal abnormalities and TLE.[29,30] Second, it became more obvious that only a fraction of patients with complex FS develop TLE[31]; and third, patients with FMTLE may not only develop complex, but also simple FS. The last finding, even originating only from a few families, fits nicely into the scope of our study as it demonstrates a coupling between a reliable genetic background responsible for both complex and simple febrile seizures and a clear relation to TLE.[32,33]

Our data were collected from a relatively small and homogenous population from Norway, which is usually considered an advantage. However, there may be geographical variations of FS etiology, based on different genetic and environmental factors around the world. Additional trials are therefore required to verify our results. Furthermore, the type of epilepsy that develops after FS depends on a variety of factors, of which some may be genetic; others may include characteristics of the FS themselves. Recent studies on animal models have demonstrated that FS seem to activate cellular and molecular mechanisms that may have an impact on the clinical characteristics of the TLE phenotype.[34] Furthermore, pathogenic factors of FS such as *inflammation* "at a certain time in a certain place" in the brain doubtlessly have an influence on the phenotype by affecting anatomy and physiology, regardless genetics.[35]

Although no genes have been found for the vast majority of FS and TLE, there is a growing consensus that genetics plays a role in both conditions. As containing two strong clinical features, the combination of TLE *plus* childhood FS may be a predictor for a genetic basis itself, and it is therefore reasonable to search for susceptibility genes and also phenotypic characteristics in the intersection of both conditions. Indeed, we identified TLE-FS as a phenotype that can be delineated from other TLE. None of the characteristics are specific, but we disclosed a subset of features. Further research including genetic, clinical and animal studies, are however needed to settle our results.

Conflict of interest

None declared.

Acknowledgements

We are grateful to the Norwegian GenEpA Group: Leif Gjerstad (principal investigator), Eylert Brodtkorb, Bernt Engelsen, Morten Lossius, Karl Otto Nakken, Erik Taubøll, and Erik Sætre. This study was supported by GlaxoSmithKline, The Nordic Centre of Excellence Program, and the Research Council of Norway (STORFORSK and NevroNor grants).

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

1. Semah F, Picot MC, Adam C, Broglin D, Arzimanoglou A, Bazin B, et al. Is the underlying cause of epilepsy a major prognostic factor for recurrence? *Neurology* 1998;**51**(November):1256–62.

2. Umbricht D, Degreef G, Barr WB, Lieberman JA, Pollack S, Schaul N. Postictal and chronic psychoses in patients with temporal lobe epilepsy. *Am J Psychiatry* 1995;**152**(February (2)):224–31.
3. Abou-Khalil B, Krei L, Lazenby B, Harris PA, Haines JL, Hedera P. Familial genetic predisposition, epilepsy localization and antecedent febrile seizures. *Epilepsy Res* 2007;**73**(January (1)):104–10.
4. Wieshmann UC, Larkin D, Varma T, Eldridge P. Predictors of outcome after temporal lobectomy for refractory temporal lobe epilepsy. *Acta Neurol Scand* 2008;**118**(November (5)):306–12.
5. Gambardella A, Messina D, Le Piane E, Oliveri RL, Annesi G, Zappia M, et al. Familial temporal lobe epilepsy autosomal dominant inheritance in a large pedigree from southern Italy. *Epilepsy Res* 2000;**38**(February (2–3)):127–32.
6. Baulac S, Picard F, Herman A, Feingold J, Genin E, Hirsch E, et al. Evidence for digenic inheritance in a family with both febrile convulsions and temporal lobe epilepsy implicating chromosomes 18qter and 1q25–q31. *Ann Neurol* 2001; **49**(June (6)):786–92.
7. Schulz R, Ebner A. Prolonged febrile convulsions and mesial temporal lobe epilepsy in an identical twin. *Neurology* 2001;**57**(July 24 (2)):318–20.
8. Heuser K, Nagelhus EA, Taubøll E, Indahl U, Berg PR, Lien S, et al. Variants of the genes encoding AQP4 and Kir4.1 are associated with subgroups of patients with temporal lobe epilepsy. *Epilepsy Res* 2010;**88**(January (1)):55–64.
9. Armitage P. Tests for linear trends in proportions and frequencies. *Biometrics* 1955;**11**(3):375–86.
10. Engel Jr J. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE task force on classification and terminology. *Epilepsia* 2001;**42**:796–803.
11. Sanchez RM, Jensen FE. Maturational aspects of epilepsy mechanisms and consequences for the immature brain. *Epilepsia* 2001;**42**:577–85.
12. Galanopoulou AS. Developmental patterns in the regulation of chloride homeostasis and GABA(A) receptor signalling by seizures. *Epilepsia* 2007; **48**(Suppl. 5):14–8.
13. Velísková J, Claudio OI, Galanopoulou AS, Lado FA, Ravizza T, Velísek L, et al. Seizures in the developing brain. *Epilepsia* 2004;**45**(Suppl 8):6–12.
14. Wieser HG. ILAE commission report. Mesial temporal lobe epilepsy with hippocampal sclerosis. *Epilepsia* 2004;**45**(6):695–714.
15. Annegers JF, Hauser WA, Shirts SB, Kurland LT. Factors prognostic of unprovoked seizures after febrile convulsions. *N Engl J Med* 1987;**316**:493–8.
16. Cendes F, Andermann F, Dubeau F, Gloor P, Evans A, Jones-Gotman M, et al. Early childhood prolonged febrile convulsions, atrophy and sclerosis of mesial structures, and temporal lobe epilepsy: an MRI volumetric study. *Neurology* 1993;**43**(6):1083–7.
17. Kuks JB, Cook MJ, Fish DR, Stevens JM, Shorvon SD. Hippocampal sclerosis in epilepsy and childhood febrile seizures. *Lancet* 1993;**342**(8884):1391–4.
18. Berg AT, Shinnar S, Levy SR, Testa FM. Childhood-onset epilepsy with and without preceding febrile seizures. *Neurology* 1999;**53**(8):1742–8.
19. Bower SP, Kilpatrick CJ, Vogrin SJ, Morris K, Cook MJ. Degree of hippocampal atrophy is not related to a history of febrile seizures in patients with proved hippocampal sclerosis. *J Neurol Neurosurg Psychiatry* 2000;**69**(6):733–8.
20. Hauser WA, Annegers JF, Anderson VE, Kurland LT. The risk of seizure disorders among relatives of children with febrile convulsions. *Neurology* 1985;**35**(September):1268–73.
21. Tsuboi T, Endo S. Genetic studies of febrile convulsions: analysis of twin and family data. *Epilepsy Res Suppl* 1991;**4**:119–28.
22. Hauser WA. The prevalence and incidence of convulsive disorders in children. *Epilepsia* 1994;**35**(Suppl. 2):1–6.
23. Tsuboi T. Epidemiology of febrile and afebrile convulsions in children in Japan. *Neurology* 1984;**34**:175–81.
24. Berkovic SF, McIntosh A, Howell RA, Mitchell A, Sheffield LJ, Hopper JL. Familial temporal lobe epilepsy: a common disorder identified in twins. *Ann Neurol* 1996;**40**(August (2)):227–35.
25. Ward N, Evanson J, Cockerell OC. Idiopathic familial temporal lobe epilepsy with febrile convulsions. *Seizure* 2002;**11**(January (1)):16–9.
26. Briellmann RS, Torn-Broers Y, Jackson GD, Berkovic SF. Seizures in family members of patients with hippocampal sclerosis. *Neurology* 2001;**57**(November 27 (10)):1800–4.
27. Berkovic SF, Izzillo P, McMahon JM, Harkin LA, McIntosh AM, Phillips HA, et al. LGI1 mutations in temporal lobe epilepsies. *Neurology* 2004;**62**(April 13 (7)):1115–9.
28. Baulac S, Gourfinkel-An I, Nabbout R, Huberfeld G, Serratosa J, Leguern E, et al. Fever, genes, and epilepsy. *Lancet Neurol* 2004;**3**(July (7)):421–30.
29. Colosimo E, Gambardella A, Mantegazza M, Labate A, Rusconi R, Schiavon E, et al. Electroclinical features of a family with simple febrile seizures and temporal lobe epilepsy associated with SCN1A loss-of-function mutation. *Epilepsia* 2007;**48**(September (9)):1691–6.
30. Auer T, Barsi P, Bone B, Angyalosi A, Aradi M, Szalay C, et al. History of simple febrile seizures is associated with hippocampal abnormalities in adults. *Epilepsia* 2008;**49**(September (9)):1562–9.
31. Chungath M, Shorvon S. The mortality and morbidity of febrile seizures. *Nat Clin Pract Neurol* 2008;**4**(November (11)):610–21.
32. Kobayashi E, D'Agostino MD, Lopes-Cendes I, Andermann E, Dubeau F, Guerreiro CA, et al. Outcome of surgical treatment in familial mesial temporal lobe epilepsy. *Epilepsia* 2003;**44**(August (8)):1080–4.
33. Kobayashi E, D'Agostino MD, Lopes-Cendes I, Berkovic SF, Li ML, Andermann E, et al. Hippocampal atrophy and T2-weighted signal changes in familial mesial temporal lobe epilepsy. *Neurology* 2003;**60**(February 11 (3)):405–9.
34. Notenboom RG, Ramakers GM, Kamal A, Spruijt BM, de Graan PN. Long-lasting modulation of synaptic plasticity in rat hippocampus after early-life complex febrile seizures. Eur J Neurosci 2010;July 7 [Epub ahead of print].
35. Dubé CM, Ravizza T, Hamamura M, Zha Q, Keebaugh A, Fok K, et al. Epileptogenesis provoked by prolonged experimental febrile seizures: mechanisms and biomarkers. *J Neurosci* 2010;**30**(June 2 (22)):7484–94.