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Title: Age at onset in patients with medically-refractory temporal lobe epilepsy and mesial temporal sclerosis: impact on clinical manifestations and postsurgical outcome.

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Abstract:

Purpose: To evaluate the demographic and clinical manifestations and postsurgical outcome of childhood-onset mesial temporal sclerosis and temporal lobe epilepsy (MTS-TLE) and establishing the potential differences as compared to the patients with adult-onset MTS-TLE.

Method: In this retrospective study all patients with a clinical diagnosis of medically refractory TLE due to mesial temporal sclerosis, who underwent epilepsy surgery at Jefferson comprehensive epilepsy center, were recruited. Patients were prospectively registered in a database from 1986 through 2014. Post-surgical outcome was classified into two groups; seizure-free or relapsed. Clinical manifestations and outcome were compared between patients with childhood-onset MTS-TLE (i.e., age at onset of the first afebrile habitual seizure below 10 years) and those with adult-onset MTS-TLE (i.e., age at onset of the first afebrile habitual seizure 20 years or above).

Results: One hundred and twelve patients had childhood-onset MTS-TLE and 76 had adult-onset MTS-TLE. Demographic, clinical, EEG and MRI characteristics of these two groups were similar. Postoperative outcome was not statistically different between these two groups of patients ($P = 0.9$).

Conclusion: Temporal lobe epilepsy due to mesial temporal sclerosis is a common cause of epilepsy that can start from early childhood to late adulthood. The etiology of MTS-TLE may be different in various age groups, but it seems that when mesial temporal sclerosis is the pathological substrate of TLE, clinical manifestations and response to surgical treatment of patients are very similar in patients with childhood-onset MTS-TLE compared to those with adult-onset disease.

Introduction

Focal epilepsies account for about two-thirds of all adult epilepsy patients, and temporal lobe epilepsy (TLE) is the most common type of focal epilepsy^{1,2}. Mesial temporal sclerosis (MTS) is the most common pathological substrate of TLE³. Temporal lobe epilepsy (TLE) with MTS is one of the most common types of medically-refractory epilepsy referred for epilepsy surgery; it is often refractory to antiepileptic drugs (AEDs), but responds favorably to surgery^{1,4}.

In children, MTS is considered an infrequent etiology of epilepsy, but with the advances in diagnostic technologies, it has started to be diagnosed at an increasingly younger ages^{5,6}. Besides, even in many adults with MTS-TLE a detailed clinical history will clarify that the age at onset of the habitual seizures was in childhood⁷. It has been previously reported that, older age at onset of epilepsy predicts better prognosis in patients with TLE⁸.

The aim of this study was to evaluate the demographic and clinical manifestations of childhood-onset MTS-TLE and establishing the potential differences as compared to manifestations observed in adult-onset MTS-TLE. We also investigated the surgery outcome in childhood-onset MTS-TLE in comparison with that in adult-onset MTS-TLE.

Methods

In this retrospective study all patients with a clinical diagnosis of medically refractory TLE due to mesial temporal sclerosis, who underwent epilepsy surgery at Jefferson comprehensive epilepsy center, were recruited. Patients were prospectively registered in a database from 1986 through 2014. The diagnosis of MTS-TLE was made by the epileptologists working at this institution and based on clinical grounds (semiology), electroencephalographic (EEG) findings and imaging [magnetic resonance imaging (MRI)]. There was no age limit to enter the study. For all patients, a comprehensive presurgical evaluation including a 1.5 Tesla brain MRI (epilepsy protocol) was performed. Magnetic resonance imaging studies were analyzed by neuroradiologists with expertise in epilepsy. Electroencephalographic (EEG) localization was considered unilateral if interictal and ictal EEG findings pointed to one side and considered as bilateral if either interictal or ictal EEG was bilateral or they were discordant. We classified patients as having childhood-onset MTS-TLE, if the age at onset of the first afebrile habitual seizure was below 10 years and adult-onset MTS-TLE, if the age at onset of the first afebrile habitual seizure was 20 years or above. We classified patients as having MTS if they had clear signs of mesial temporal atrophy and/or sclerosis in their MRI. Patients with normal MRI and those with dual pathology were excluded from this study.

All patients were submitted to surgical treatment (i.e., anterior temporal lobectomy). They all had to be under the care of an epileptologist at our institution for at least one year, postoperatively. They were followed for up to five years after their surgery. Post-surgical outcome was classified into two groups; seizure-free or relapsed. Aura was not considered as a relapse; only postoperative tonic-clonic seizures and complex partial seizures were considered as relapse.

Age, gender, race, epilepsy risk factors (e.g., febrile seizure, family history of epilepsy, etc.), age at seizure onset (i.e., the first afebrile habitual seizure), seizure type(s), EEG findings and MRI findings, date of surgery, date of the first relapse (if any) and date of the last contact with all patients were registered routinely.

Demographic variables and relevant clinical variables were summarized descriptively to characterize the study population. All variables were compared between patients with childhood-onset versus those with adult-onset MTS-TLE. Pearson Chi-Square, Fisher's Exact, Mantel-Cox and t- test were used for statistical analyses. Time to event analysis was used to produce a Kaplan-Meier estimate of seizure recurrence. Odds ratio and 95% confidence interval (CI) were calculated. P value less than 0.05 was considered as significant. This study was conducted with the approval by Thomas Jefferson University Review Board.

Results

Two-hundred eighty-one patients in our database had MTS-TLE with at least one year of postoperative follow-up. Age at onset of their habitual afebrile seizures is shown in figure 1. One hundred and eighty-eight patients were eligible for this study (89 males and 99 females). One hundred and twelve patients had childhood-onset MTS-TLE and 76 had adult-onset MTS-TLE. Demographic characteristics of these two groups are shown and compared in table 1. Clinical characteristics of these two groups are shown and compared in table 2. Odds ratio of having history febrile seizures in patients with childhood-onset MTS-TLE compared to those with adult onset disease was 3.1 (95% CI: 1.6-6). Electroencephalographic (EEG) characteristics of these two groups are shown and compared in table 3. The EEG localization of the epileptogenic zone was not differently distributed in these two groups of patients ($P = 0.2$). Imaging (MRI) characteristics of these two groups are shown and compared in table 4. The MRI localization of the epileptogenic zone was not differently distributed in these two groups of patients ($P = 0.07$). Finally, postoperative outcome was not statistically different between these two groups of patients ($P = 0.9$) (Figure 2). The duration of postoperative follow-up was 4.2 ± 1.2 years in the first group and 4 ± 1.4 years in the second group; it was not statistically different between these two groups ($P = 0.2$). Epilepsy duration before surgery in patients with childhood-onset disease was 30 ± 12 years and in those with adult-onset epilepsy was 13 ± 9 years ($P = 0.0001$). However, this is a biased comparison as we had already dichotomized the patients based on their age at the disease onset.

Discussion

Mesial temporal sclerosis is a major etiology for epilepsy in adult populations, but it has been reported to be an uncommon finding in children with epilepsy⁹. However, there is enough evidence to conclude that the age at onset of habitual seizures in MTS-TLE is earlier compared to that for TLE due to other etiologies; it is often in childhood or early adolescence⁷. In our study, age at onset of MTS-TLE was in childhood (i.e., below 10 years of age) in 39.8% of the patients. Therefore, the syndrome of MTS-TLE is not rare and may be identified adequately even in young children¹⁰. But, adult onset MTS-TLE was not uncommon either and in 27% of patients the age at onset of habitual seizures was in their adulthood (i.e., 20 years or above).

Interestingly, demographic and clinical manifestations of medically-refractory temporal lobe epilepsy and mesial temporal sclerosis were very similar between patients with childhood-onset and those with adult-onset disease, in our study. The syndrome of MTS-TLE in childhood often presents with a different semiology compared with that in adults, which is strongly related to brain maturation and neuropsychological development¹⁰. Aura is rarely observed in very young children, probably because they are not able to describe their subjective feelings. However, when children grow, their semiology becomes similar to that in adults. In our study, age at surgery spanned from 12 to 68 years, so the youngest patient had a mature brain and was already grown enough to describe his symptoms. We observed that, not only the seizure types, but also the types of auras that patients experienced were similar between patients with childhood-onset and those with adult-onset disease. Even, electroencephalography or imaging findings were very similar between these two groups of patients.

With regard to surgery outcome, patients with childhood-onset MTS-TLE and those with adult-onset disease fared almost similarly and both groups responded well to epilepsy surgery. In

a previous study of surgery for temporal lobe epilepsy with hippocampal involvement in preadolescent children ¹¹, outcomes at the last follow-up examination were categorized as Engel Class I-II in 20 (76.9%) of 26 children with confirmed MTS, which is comparable to adult studies. This finding is in contrast with the findings in a previous study, in which 190 patients with TLE were analyzed and older age at onset predicted better post-surgical prognosis ⁸. However, their inclusion criteria were different from ours, as they included patients with normal MRI in addition to those with MTS. Besides, they excluded those with family history of TLE and we did not. Their end point was time to 24 month seizure freedom after surgery.

One significant difference that we observed between patients with childhood-onset MTS-TLE and those with adult-onset disease was higher frequent of history of childhood febrile convulsions in the former group. The frequency of febrile convulsions was more than twice in patients with childhood-onset MTS-TLE compared to those with adult-onset MTS-TLE. This increased frequency of febrile convulsions in patients with childhood-onset MTS-TLE might be partly due to reporting bias (e.g., parents were present at the interview and febrile convulsion happened more recently). However, there is evidence that prolonged febrile seizures may cause hippocampal changes. In one study, MRI findings of a markedly hyperintense hippocampus in children with febrile status epilepticus was highly associated with subsequent mesial temporal sclerosis ¹². There is also evidence that suggests a subtle, pre-existing hippocampal malformation may exist in some patients that may facilitate febrile convulsions and contribute to the development of subsequent MTS ¹³. In any way, the observed difference of frequency of history of febrile convulsions between patients with childhood-onset MTS-TLE and those with adult-onset disease may suggest that the cause of MTS-TLE could be different in these two groups of patients. This should be explored in future studies.

Conclusions

Temporal lobe epilepsy due to mesial temporal sclerosis is a common cause of epilepsy that can start from early childhood to late adulthood. The etiology of medically-refractory MTS-TLE may be different in various age groups, but it seems that when mesial temporal sclerosis is the only detectable pathological substrate of TLE, clinical manifestations and response to surgical treatment of patients are very similar in childhood-onset MTS-TLE compared to those with adult-onset disease.

Study limitations

This was a clinic-based series of patients with medically-refractory MTS-TLE and may not represent the full spectrum of MTS-TLEs. Besides, this study was retrospective and uncontrolled in design. **Lastly, epilepsy duration may be considered as a confounder in this study. However, it could have been true if the outcome results were different in those two groups of patients.**

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Conflict of interest

Ali A. Asadi-Pooya, M.D., reports no disclosures. Michael R. Sperling, M.D., Consulting: UCB Pharma; Research: contracts with Thomas Jefferson University, Eisai, UCB Pharma, Sunovion, SK Life Sciences, Marinus, Lundbeck, Medtronic, Visualase, Accordia, Upsher-Smith, Brain Sentinel, Glaxo, Research support from DARPA and NIH to Thomas Jefferson University.

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Figure 1 legend. Mean age at onset of all 281 patients was 15 ± 13 years. Minimum age at onset was the neonatal period and maximum age was 64 years.

Figure 2 legend. Postoperative outcome was not statistically different between these two groups of patients ($P = 0.9$).