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Treatment outcome in patients with mesial temporal sclerosis

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The long-term prognosis of pharmacological therapy in patients with mesial temporal sclerosis (MTS) is generally considered poor. On the contrary, successful surgical therapy is frequently reported. We performed a retrospective case record survey of patients with MTS in a comprehensive epilepsy center between 1993 and 1999 in order to develop treatment strategies. The time period allowed access to high-resolution qualitative magnetic resonance imaging (MRI) and a minimum of 1-year outcome assessment. Eighty-three patients with intractable partial epilepsy with MRI and electroencephalograph (EEG) abnormalities and seizure semiology consistent with temporal lobe epilepsy were identified. Thirty-six patients were treated pharmacologically and surgically and 47 patients received only pharmacotherapy. The number of patients who became seizure free was in total 37 (45%); in the surgical group 26 and in the non-surgical group 11. The proportions of seizure-free patients in each group were 72% (surgical) and 23% (non-surgical). Clinical factors such as age, gender, lesion side, previous medical history, duration of illness, seizure frequency and IQ did not correlate to prognosis. A good seizure outcome was associated with early age of seizure onset, low number of previously used antiepileptic drugs (AEDs) and surgical treatment. There is a better long-term outcome in patients with MTS receiving surgical therapy in comparison with medical therapy.

Key words: mesial temporal sclerosis; treatment; outcome; AED; surgery.

INTRODUCTION

Mesial temporal sclerosis (MTS), the most common lesion underlying temporal lobe epilepsy (TLE)[1,2], is generally associated with medical intractability. However, it is difficult to know how resistant to pharmacotherapy the syndrome is because the majority of clinical trials of antiepileptic drugs (AEDs) report outcome from a seizure type-based perspective, which has not been stratified for etiology. Studies assessing prognosis for seizure control in patients with MTS have shown one-year follow-up seizure freedom in 10% to 25% of patients receiving medical treatment[3–6]. Surgical outcome following surgery ranges from 62% to 96% in patients with MTS confirmed with MRI[7–11].

High-resolution MRI is at present the most reliable technique for the detection of MTS[12]. In the current study we examined seizure outcome in TLE patients with MTS verified by MRI and, in surgical cases, pathology.

METHODS

This was a retrospective study of patients with MRI-verified MTS in a comprehensive epilepsy center (Minneapolis Epilepsy Group, P.A.) between January 1993 and January 1999. Practicing general neurologists, who thought they had exhausted their therapeutic capabilities, had referred the patients. Inclusion criteria were seizure semiology and abnormal EEG consistent with TLE and MRI determinants of hippocampal sclerosis. We excluded patients with a history of non-epileptic seizures or non-compliance, ambiguous EEG-findings and dual pathology on MRI-scans. Furthermore, surgically treated patients who became seizure-free post-operatively after introduction of a new AEDs were excluded.

Medical records were reviewed to establish seizure frequency and former medical history including occurrence of febrile seizures, head trauma and cerebral infections. In addition previous AED treatment was documented. Seizure control was assessed based on frequency 3 months preceding the MRI investigation in comparison with 1 year preceding the last follow-up and expressed as average monthly seizures. Seizure outcome was expressed as seizure free or refractory.

MRI was performed on a GE or Siemens 1.5 T scanner using an epilepsy protocol. This protocol included a volume acquisition SPGR T1-weighted oblique coronal sequence with 1.6-mm thick slices orthogonal to the long axis of the hippocampus. For detection of signal changes a coronal FSE-T2 weighted series was used. Since 1997, both coronal and axial FLAIR sequences were added to the protocol. MTS criteria were: (1) hippocampal atrophy demonstrated with coronal T1-weighted images, (2) signal hyperintensity within the hippocampus on T2-weighted or FLAIR images, and/or (3) disruption of the internal hippocampal architecture on T1 weighted images.

Each patient had been evaluated with long-term video-EEG with surface and sphenoidal electrodes. Abnormal EEG was defined as interictal slowing; sharp, sharp slow wave, spike, and/or spike–slow wave; and a combination of these[13]. In addition focal ictal events characterized by temporal epileptiform fast activity; sharply contoured theta; spike and wave, rhythmic delta; or a combination of these were recorded from all patients. All patients had neuropsychological testing[14, 15].

Patients in whom surgery was considered had been further investigated with intracranial EEG-recordings, and the intracarotid amobarbitual procedure. Eligible patients subsequently underwent anterior temporal resection including amygdalahippocampectomy and tissue was sent for histopathological examination.

Seizure outcome was related to age, sex, MRI-lesion side, medical history of trauma, cerebral infection or febrile seizure, age of onset and duration of epilepsy, seizure frequency and previous AED treatment. Comparison of surgical and non-surgical patients was performed.

Statistical analysis was executed using SPSS 10.05 (1999) for Windows, (SPSS Inc., Chicago, IL). The Student t-test, Mann–Whitney U-tests, Fisher's exact test (two-tailed) and Pearson's chi-square were used. The level for statistical significance was set at $P < 0.05$.

RESULTS

Eighty-three adult patients (42 women, 41 men) met the inclusion criteria for our study. For a detailed summary of clinical data, see Table 1. Thirty-six patients received a temporal lobe resection (18 women, 18 men) and 47 (24 women, 23 men) received solely antiepileptic medication treatment. The average age in the surgical group was 36 years and in the non-surgical group 39 years. On the basis of the MRI investigations, 41 patients had right (24 surgical and 17 non-surgical), 35 left (10 surgical and 25 non-surgical) and seven bilateral pathology (two surgical and five non-surgical). There was a significantly higher proportion of right lesions in the surgical group ($P < 0.001$). Histopathologic examination confirmed MTS in all surgical cases.

Prior risk factors were identified in 24 patients (29%). Three patients in the surgical group and nine patients in the non-surgical group had experienced a prolonged febrile seizure. Furthermore, five patients in each group reported cerebral infection and one patient in each group had experienced significant head trauma preceding onset of seizures. The age of onset (9.0 vs. 11.5 years) and the duration of epilepsy (26.0 vs. 27.8 years) did not differ significantly between the surgical and the non-surgical group. The average number of AEDs tried prior to MRI investigation was 6.3 and 6.5 for the surgical and non-surgical groups, respectively. The mean monthly seizure frequency of complex partial seizures with or without secondary generalization was higher in the surgical group (9.1) vs. the non-surgical group (6.6), although this difference did not reach statistical significance. Mean follow-up time after MRI was significantly ($P < 0.05$) longer in the surgical (4.4) vs. non-surgical group (3.4 years). Mean full scale IQ scores for the surgical (92) and the non-surgical (91) were not statistically different.

The total number of patients who became seizure-free was 37 (45%); in the surgical group 26/36 (72%) and in the non-surgical groups 11/47 (23%). For a detailed summary of outcome data, see Table 2. There was strong evidence that seizure outcome varied by method of treatment ($\chi^2 = 22.5, P < 0.001$). The observed difference in seizure outcome between the surgical and the non-surgical group was not attributed to the side of pathology. After controlling for side, there was still a significant effect of operation ($\chi^2 = 13.9, P < 0.005$). Age, sex, duration, seizure frequency and general intellectual status (i.e. /IQ) did not influence seizure outcome. Age of onset ($P < 0.05$) and number of previous AEDs ($P < 0.05$) were significantly lower in the seizure-free patients.

DISCUSSION

Seizure freedom is the ultimate goal in the treatment of patients with epilepsy[16]. Previous studies have shown that health-related quality of life is scored as a continuum in relation to seizure frequency[17–19]. Few studies have assessed clinical factors and outcome in patients receiving medical treatment. Outcome after

Table 1: Demographic data of patients with mesial temporal sclerosis.

	All patients (n = 83) (100%)	Surgical group (n = 36) (43%)	Non-surgical group (n = 47) (57%)
Age (years)	38 ± 11.2	36.6 ± 10.8	39.1 ± 11.6
MR lesion side			
right[a]	41	24	17
left	35	10	25
bitemporal	7	2	5
Prior medical history	24	9	15
Age at onset (years)	10.5 ± 8.5	9.1 ± 8.5	11.5 ± 8.5
Duration (years)	27.0 ± 13.1	27.7 ± 13.1	26.0 ± 13.1
Seizure frequency	7.7 ± 5.8	9.1 ± 6.2	6.6 ± 5.3
Mean number of AED	6.4 ± 1.7	6.4 ± 1.5	6.5 ± 1.9
Full scale IQ	91.40 ± 14.6	91.7 ± 15.1	91.2 ± 14.5
Mean follow-up (years)[b]	3.8 ± 1.9	4.4 ± 1.9	3.4 ± 1.9

Values are means ± SD. [a]A larger proportion of right MTS than left MTS in the surgical group ($P < 0.001$). [b]Mean follow-up was significantly longer in the surgical group ($P < 0.05$).

Table 2: Outcome in patients with mesial temporal sclerosis.

	Seizure-free patients (n = 37)	Intractable patients (n = 46)
Age (years)	36.03 ± 11.5	40.4 ± 10.4
MRI lesion side		
right[a]	23	16
left	13	23
bitemporal	—	7
Prior medical history	2.8 ± 0.6	2.4 ± 0.9
Age at onset (years)[b]	8.1 ± 6.5	11.9 ± 9.5
Duration (years)	26.6 ± 12.3	28.2 ± 13.1
Seizure frequency	8.8 ± 6.86	6.8 ± 5.0
Mean number of AED[c]	6.0 ± 1.5	7.0 ± 1.8
Full scale IQ	91.2 ± 14.8	91.0 ± 14.1
Mean follow-up (years)[d]	4.4 ± 2.1	3.4 ± 1.8
Surgery		
yes[e]	26	10
no	11	36

Values are mean ± SD. [a]The effect of operation on seizure outcome cannot be attributed to side. After controlling for side, there is strong evidence that operation has an effect on outcome. Binary logistic regression: $\chi 2 = 13.1$, P value < 0.001. [b]Age at onset significantly lower in seizure-free patients ($P < 0.05$). [c]Mean number of AEDs significantly lower in seizure-free patients ($P < 0.05$). [d]Mean follow-up longer in the seizure-free group ($P < 0.05$). [e]Seizure outcome varies by operation: $\chi^2 = 22.5$, P value < 0.001.

surgery in patients with well-defined MTS has on the other hand been frequently addressed. Only a few studies have yet assessed clinical factors and outcome in patients receiving medical treatment. This study was undertaken in order to explore factors that could determine the optimal treatment for patients with MRI-verified MTS. Epilepsy surgery is not easily assessed by randomized trials and the retrospective nature of this study enabled any randomization.

In our series of 83 patients with difficult-to-treat epilepsy, 45% eventually became seizure free for 1 year or longer (mean 3.8 years). In the group of surgically treated patients, 72% had an excellent postoperative outcome which is in parity with earlier published results[20]. Moreover, 23% of the non-surgical patients had seizure remission consistent with an earlier report by Kim and co-authors[4]. No particular combinations of AEDs were found to be more effective in our study. The long duration of epilepsy and the large number of previous AED treatments are indicative of notorious therapy resistance. It is therefore possible that our results do not reflect the actual natural history of MTS. There may be patients with this condition who are easily controlled with medication and accordingly never referred to an epilepsy unit. However, in a MRI study of newly diagnosed partial seizures the presence of MTS was associated with worse the prognosis in comparison to other MRI findings[21] supporting the view that this group of patients is difficult to treat pharmacologically and are in need of expert knowledge.

This study found no relation between good seizure outcome and age, gender, duration of illness or seizure frequency. This is consistent with previous studies that have shown that clinical factors do not significantly influence seizure outcome after surgery[22] or medical treatment[4]. Seizures associated with MTS typically begin early in life. The mean age of seizure onset was 10 years in our study, consistent with previous reports[22,23]. Age of onset has not been unequivocally linked to prognosis in MTS. In two previous studies identification of a younger age of seizure onset was not associated with successful surgical outcome[22,24].

Conversely, in a study of medically treated patients, earlier age of onset was associated with a worse prognosis assuming that there was an inverse correlation between age and grade of MTS[4]. However, the presumption that the degree of hippocampal damage would correlate with the duration of epilepsy may not be tenable[25] and furthermore, the onset age in the study by Kim and co-authors[4] was notably high (16.9 years) for a MTS population.

There is no clear evidence from the literature that there is a relation between laterality and outcome after surgery[22,26] or medical treatment[4]. In our study there was a larger proportion of patients with right MTS in the surgical group probably reflecting a more restrictive practice of dominant temporal lobe resections. However, results from the present study found no significant relationship between side of pathology and methods of treatment.

Prior cerebral injury or medical illness including febrile seizures in association with hippocampal sclerosis has been much debated in the literature. It has been suggested that epilepsy caused by extensive pathology, such as encephalitis or head trauma, would have a worse prognosis[27]. On the other hand, a positive relationship between febrile seizures and good surgical outcome has been reported[23], while others reports have failed to recognize this association[4]. In one previous investigation[4], medically treated patients with a history of febrile convulsions had poorer prognosis than those without. In the present study, a relation between the existence of any risk factor including febrile seizure and seizure intractability was not found. However, it is possible that our sample was too small to make any definite conclusions regarding individual clinical risk factors.

An increased availability of new AEDs during the last years has led to a more restrictive surgical approach. Studies of long-term retention rates of new AEDs suggest that the impact of these new drugs on partial epilepsy is modest[28]. The patients in our study were using a variety of old and new drugs, which prohibited any conclusions regarding the benefits of new AEDs in MTS. Finally, it has been established that the success of epilepsy surgery does not preclude discontinuation of AED treatment. In accordance with experience from other epilepsy surgery centers[29–31] a minority of our patients (20%) were able to withdraw all AEDs, and in an additional 26% the medication was tapered to monotherapy.

CONCLUSION

In this study of a select group of patients with MTS, a larger proportion of patients who had epilepsy surgery were seizure free in comparison with medically treated patients. Clinical factors such as age, gender, duration of illness, seizure frequency, general cognitive capacity, and laterality were not risk factors for seizure occurrence in either group. Good seizure outcome was related to an early age of seizure onset and low number of previously tried AEDs. The results further support the view that epilepsy surgery should be considered early in patients who are discovered to have MTS on MRI.

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