Turkish Neurosurgery 2008, Vol: 18, No: 4, 374-379

# Surgical Outcome in Hippocampal Sclerosis Following Selective Amygdalo-Hippocampectomy

## Hippokampal Sklerozda Amigdalo-Hippokampektomi Sonrası Cerrahi Sonuçlar

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### ABSTRACT

**OBJECTIVES:** Temporal lobe epilepsy is the most common form of intractable partial epilepsy in adults with hippocampal sclerosis accounting for the majority of cases. Selective amygdalo-hippocampectomy (SEAH) is suggested as a safe and effective surgical procedure with the advantage of a better cognitive outcome.

**METHODS:** We prospectively documented 56 consecutive patients with medically refractory medial temporal lob epilepsy. Candidates for surgery were determined as those with characteristic clinical and imaging findings, ictal recordings, and neuropsychological evaluation. A standard SEAH was performed and hippocampal sclerosis was histologically confirmed.

**RESULTS:** In our study 76.7% of patients were classified as Engel I and 62.2% as ILAE I at their last follow up. Overall, at the last follow-up, 51.8% of patients were seizure-free since surgery (Engel 1a and ILAE 1a), 25% had stopped antiepileptic treatment, and another 52% had decreased either the dosage or number of antiepileptic drugs. 86.3% of the patients with abnormality on neurocognitive tasks showed improvement at the end of the 6 months post surgery.

**CONCLUSION:** SEAH is a safe and effective surgical procedure without the necessity of a larger resection and further invasive methods.

**KEY WORDS:** Amygdalo-hippocampectomy, Hippocampal sclerosis, Intractable epilepsy, Medial temporal lobe epilepsy

### ÖZ

**AMAÇ:** Temporal lob epilepsisi erişkin çağında en sık görülen dirençli parsiyel epilepsi olup, olguların çoğunda hippokampal skleroz bulunmaktadır. Selektif amigdalo-hippokampektomi, bu olgularda daha iyi kognitif sonuçlar gösteren, güvenli ve etkin cerrahi bir yöntem olarak önerilmektedir.

**YÖNTEM VE GEREÇLER.** İlaca direçli mesial temporal lob epilepsili 56 ardışık hasta prospektif olarak kaydedilmiştir. Klinik özellikleri, görüntüleme bulguları, iktal kayıtları ve nörokognitif testleri uyumlu bulunan hastalar cerrahi adayları olarak belirlenmiştir. Bu hastalara standart SEAH uygulanmış ve histolojik olarak hippokampal skleroz doğrulanmıştır.

**BULGULAR:** Çalışmamızda son kontrollerinde hastaların %76.7'si Engel I, %62.2 si ILAE I olarak değerlendirilmiştir. Hastaların %51.8'inde operasyon sonrasında hiç nöbet gözlenmemiştir (Engel Ia ve ILAE Ia). %25 hasta antiepileptik ilaçlarını tamamen kesmiş, %52'si de antiepileptik ilaç dozlarını veya ilaç sayısını azaltmışır. Preoperatif dönemde nörokognitif testlerinde bozulma saptanan hastaların postoperatif 6. aylarında yapılan kontrollerinde %86.3'ünde düzelme saptanmıştır.

**SONUÇ:** SEAH geniş cerrahi rezeksiyon ve ileri invazif metodlar gerektirmeyen güvenli ve etkin cerrahi bir yöntemdir.

**ANAHTAR SÖZCÜKLER:** Amigdalo-hippokampectomi, Hippokampal skleroz, Dirençli epilepsi, Mesial temporal lob epilepsi

Received : 07.10.2008
Accepted : 30.10.2008

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## INTRODUCTION

Temporal lobe epilepsy is the most common type of intractable partial epilepsy. The typical substrate associated with medial temporal lobe epilepsy (MTLE ) is hippocampal sclerosis (HS) accounting for 60% to 70% of cases (1,29). The etiology of HS remains unclear. Histologically, severe neuronal loss and gliosis are observed, especially in the CA1, CA3, and CA4 subfields of the hippocampus (3). Recurrent sprouting of mossy fibers is also seen. In most patients, the epileptogenic focus involves the mediobasal structures of the temporal lobe. These structures include the hippocampus, amygdala, uncus and parahippocampal gyrus. Antiepileptic drugs usually suppress secondary generalized seizures successfully, but 50% of patients or more will continue to have partial seizures (9). When seizures persist, surgery is an effective treatment for MTLE associated with hippocampal sclerosis (8), either anterior temporal lobectomy (6) or selective amygdalohippocampectomy (SEAH) (25) is the treatment of choice .

The surgical results in HS are gratifying; seizure freedom is achieved in 70% to 90% of patients, with low morbidity and the findings of HS, both preoperatively by MRI and postoperatively by histology and electrophysiology, predict higher seizure-free outcomes (5,13,14,18,23,24,27).

In this study we report the surgical outcome of patients with MTLE due to HS, who underwent standard pre and postoperative evaluations and a relatively uniform surgical procedure, mainly selective amygdalo-hippocampectomy. The possible risk factors influencing surgical outcome were also evaluated.

Our hypothesis was that SEAH is a safe and effective surgical procedure without the necessity of a larger resection with a good and stable surgical outcome provided it is carried out on carefully selected patients with supporting clinical, radiological, electrophysiological and neurocognitive characteristics.

## MATERIALS and METHODS

We prospectively documented 56 consecutive patients, with medically refractory MTLE due to hippocampal sclerosis, assessed at Bakırköy Hospital for Psychiatric and Neurological Diseases, who underwent SEAH by the same neurosurgeon between 2001 and 2007. Candidates for surgery were determined after a comprehensive presurgical evaluation. Clinical features, seizure semiology and antiepileptic treatment were noted before and after surgery. Long term video EEG monitoring (VEEGM) was performed on all patients and ictal seizures were recorded to confirm the location of ictal onset. All patients underwent pre and postoperative high resolution (1.5-Tesla) MR imaging with an epilepsy protocol (Proton and T1-weighted axial and coronal, and T2-weighted and flair axial and coronal).

A detailed neuropsychological evaluation was applied to all patients with the exception of one who could not complete the tests due to mental retardation before and 6 months after surgery.

Intellectual capacity, hand dominance, attention, verbal, logical and nonverbal memory were assessed by WAIS IQ Test, Edinburgh Hand Dominance Test, Digit Span Test, Verbal Memory Processing Test, Weschler Memory Scale (WMS) story subtest and WMS visual memory subtest. Language skills were evaluated to investigate left hemisphere function. Visuospatial skills and construction ability was assessed by Benton facial recognition test and line orientation test, and frontal functions by Wisconsin card sorting, stroop, and verbal fluency tests. Surgery outcome was assessed according to Engel (7) and ILAE classifications (26).

SEAH was performed via a transslyvian approach as described by Yasargil, entering the temporal horn of the lateral ventricle through the temporal stem. A major portion of the amygdala, the anterior 2/3 of the hippocampus, the uncus and the anterior parahippocampal gyrus were resected (30).

Histopathological analysis of the resection specimen from all patients was carried out at the neuropathology department of the Istanbul Medical Faculty, Istanbul University. Patients were followed-up monthly for 6 months and then yearly afterwards. Antiepileptic drugs were discontinued in patients who were seizure free for at least 2 years.

Surgery-related complications were grouped as minor or major according to the system of Rydenhag and Silander (21). Minor complications are defined as those resolving without sequelae within 3 months and major complications were defined as affecting activities of daily living and lasting longer than 3 months.

One sample t-test, independent sample t-test, Fisher's exact test and chi-square tests were used for statistical analysis.

## RESULTS

56 patients underwent SEAH for refractory MTLE associated with hippocampal sclerosis between 2001 and 2007. Of these patients, 23 (41.1%) were woman and 33(58.9%) were men with a mean age of 30.39±8.95 years (yrs) at follow-up time. The mean age of seizure onset was 9.7 (ranging between 1-36 yrs) and the mean duration of the disease was 16.36 years (ranging from 2-36yrs). Of the patients, 22 (39.3%) had right, and 34 (60.7%) had left hippocampal sclerosis. 91.1% had an initial precipitating incident (IPI) and 90.2% had IPI exposure before the age of 3. In addition, 37 patients had only one, 13 had 2, and only 1 patient had 3 IPI's. Febrile convulsions were the most common IPI (80%), followed by head trauma (25.5%), perinatal hypoxia (13.7%) and central nervous system infection (9.8%). Eight patients had no latent period, and the mean latent period was 7.8±5.12yrs (range 0.5-21 yrs).

In 69.6% of the patients, secondary generalized seizures (SGS) were either reported or detected during VEEGM and 83.9% of patients had limb dystonia. All patients had interictal discharges and seizure onset concordant with their HS lateralization. Eleven patients (19.6%) had bilateral interictal discharges. None of the patients required invasive evaluation.

All of the patients had unilateral MRI features concordant with their HS; either hippocampal atrophy or T2/flair hyperintensities, or both. One patient had left parietal encephalomalasia in addition to left HS.

Thirty-eight of the 55 patients (69%) had neurocognitive deficiency concordant with their lesion and 13 (23.6%) had bilateral involvement. Of those patients with abnormality, 86.3% showed improvement at the end of 6 months after surgery. Four patients (7.8%) showed no change and 3 patients (5.9%) had mild deterioration of neurocognitive tasks.

The demographic data and preoperative characteristics of patients are summarized in (Table I).

The mean age at surgery was 26.21±8.6 years (ranging between 7-46 yrs). The patients were followed-up for a mean duration of 47.09±17.6 months (range 12-84 months) after surgery. Nine patients (16.1%) had early postsurgical seizures (within 28 days after surgery).

**Table I.** Demographic data and clinical characteristic of patients

| | |
|---|---|
| **Sex (female/male)** | **23 (41.1%) / 33 (58.9%)** |
| **Mean age at last follow-up (yrs)** | **30.39± 8.95 (11-51)** |
| **Mean age at seizure onset (yrs)** | **9.7± 6.37 (range 1-36)** |
| **Lateralization (left/right)** | **34(60.7%) /22(39.3%)** |
| **IPI** | **51 (91.1%)** |
| **FS** | 41 (80%) |
| **CNS infection** | 5 (9.8%) |
| **Head trauma** | 13 (25.5%) |
| **Perinatal asphyxia** | 7 (13.7%) |
| **IPI <3 yrs** | 46 (90.2%)37 |
| **IPI (1 / >1)** | (72.5%)/ 14 (27.5%) |
| **Presence of latent period** | **48 (85.7%)** |
| **Duration of LP(month)** | **7.8±5.12(0.5-21)** |
| **SGTCS** | **39 (69.6%)** |
| **Ictal limb dystonia** | **47 (83.9%)** |
| **Bilateral interictal discharges** | **11 (19,6%)** |
| **Neurocognitive assessment (normal/abnormal)** | **4 (7.3%)/51 (92.7%)** |
| **Unilateral /bilateral neurocognitive abnormality** | **38 (69.1%)/13 (23.6%)** |
| **Mean age at surgery (yrs)** | **26.2± 8.6 (range 7-46)** |
| **Mean duration of disease (yrs)** | **16.36±8.6 (range 2-36)** |
| **Mean follow-up time (mths)** | **47.09±17.6 (range 12-84)** |

At the end of the first year, 76.7 % of the patients were classified as Engel I and 69.6% as ILAE I. At the last follow up, 76.7% of patients were Engel I and 62.2% ILAE I. The detailed seizure outcomes according to Engel and ILAE classifications are shown in (Tables II and III).

Only one patient reported no change in the frequency of her seizures (Engel 4b and ILAE 5) after surgery. She was operated upon at a relatively older age of 38 and she had disease duration of 33 years. She had preoperative SGS and postoperative early seizures. She was reoperatedå at the end of the first year and temporal lobectomy was performed. After the second operation she was classified as Engel IIB and ILAE 3.

Nine (23.1%) of the 39 patients were seizure-free at the end of the first year and had seizure recurrence at a mean of 28.22±9.8 (range 15-48) months during follow-up. Four of them (44.4%) were associated with antiepileptic drug discontinuation.

**Table II.** Engel classification of patients.

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **IA** | 69.6 | 63 | 54 | 45 | 34.6 | 36.4 | 33.3 | **51.8** |
| **IB** | 7.1 | 9.3 | 10 | 12.5 | 15.4 | - | - | **10.7** |
| **IC** | - | 5.6 | 6 | 7.5 | 11.5 | 9.1 | - | **7.1** |
| **ID** | - | - | 6 | 10 | 11.5 | 27.2 | 50 | **7.1** |
| **IIA** | 1.8 | 3.7 | 6 | 5 | 3.8 | 9.1 | - | **5.4** |
| **IIB** | 16.1 | 14.8 | 14 | 15 | 15.4 | 18.2 | 16.7 | **16.1** |
| **IIC** | - | 1.8 | 2 | 2.5 | 3.8 | - | - | - |
| **IID** | - | - | - | - | - | - | - | - |
| **IIIA** | 3.6 | 1.8 | 2 | 2.5 | 3.8 | - | - | **1.8** |
| **IIIB** | - | - | - | - | - | - | - | - |
| **IV B** | 1.8 | - | - | - | - | - | - | - |
| **No of patients** | **56** | **54** | **50** | **40** | **26** | **11** | **6** | **56** |

**Table III.** ILAE classification of patients.

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **1** | 69.6 | 66.7 | 56 | 55 | 50 | 63.6 | 83.3 | **62.5** |
| **1a** | 69.6 | 63 | 54 | 45 | 34.6 | 36.4 | 33.3 | **51.8** |
| **2** | 7.1 | 11.1 | 16 | 17.5 | 23.1 | 9.1 | - | **16.1** |
| **3** | 17.9 | 18.5 | 26 | 22.5 | 23.1 | 27.3 | 16.7 | **19.6** |
| **4** | 3.6 | 3.7 | 2 | 5 | 3.8 | - | - | **1.8** |
| **5** | 1.8 | - | - | - | - | - | - | **-** |
| **No of patients** | **56** | **54** | **50** | **40** | **26** | **11** | **6** | **56** |

Overall, 51.8% of patients were seizure-free (Engel and ILAE 1a) at the last follow-up, 25% had ceased antiepileptic treatment, and another 52% had decreased either the dosage or number of their antiepileptic drugs. Only 23% remained on their presurgical antiepileptic treatment.

The prognostic factors for seizure recurrence were analyzed according to ILAE and Engel classification at the end of first year and at the last follow-up. Only SGS and postoperative early seizures were statistically significant for predicting recurrences according to Engel and ILAE outcomes at the end of the first year and at the last follow-up. These results are summarized in (Table IV).

There was no death associated with the surgery. There were no major surgical complications and all of the minor complications were reversible with no consequential neurological deficit. One patient had oculomotor palsy and 2 patients had mild hemiparesis.

**Table IV.** The significance of risk factors on surgical outcome (p value)

| | | | |
|---|---|---|---|
| **Age at seizure onset** | **NS** | NS | NS |
| **Age at surgery** | **NS** | NS | NS |
| **Duration of disease** | **NS** | NS | NS |
| **Duration of latent period** | **NS** | NS | NS |
| **Presence of IPI** | **NS** | NS | NS |
| **IPI before 3yrs** | **NS** | NS | NS |
| **FS** | **NS** | NS | NS |
| **SGS** | **p=0.038** | **p=0.043** | **p=0.058** |
| **Ictal Limb Dystonia** | **NS** | NS | NS |
| **Interictal bilat. EEG discharges** | **NS** | NS | NS |
| **Bilateral cognitive involvement** | **NS** | NS | NS |
| **Presence of complications** | **NS** | NS | NS |
| **Postoperative early seizures** | **p=0.003** | **p=0.003** | **p=0.002** |

## DISCUSSION

The data regarding the surgical outcome for TLE are confusing due to variances in etiopathogenesis, presurgical evaluation, surgical procedures and the different outcome measures used. This study provides the surgical outcome of a very homogeneous group with MTLE due to

histologically confirmed HS. These patients were investigated with a standard non-invasive pre and postsurgical evaluation and underwent the standard surgical technique SEAH by the same neurosurgeon.

In Wieser's amygdalohippocampectomy study (27) 63% of patients with MTLE due to HS were free of disabling seizures (Engel 1) 5 year post surgery. The percentages for the same group reduced slightly to 56% and 54% for the 10th and 15th postoperative years. The percentage of patients with MTLE-HS in ILAE 1a at 5th, 10th and 15th postoperative years were 28%, 17% and 13%, respectively. Paglioli et al. reported a slightly better outcome with ATL, publishing figures of 89% and 81% Engel I and 85% and 66% ILAE 1 at the end of first and 10th year after surgery (18). There is limited data comparing the two surgical techniques in terms of seizure control. Selective amygdalohippocampectomy (SAHE) was suggested with advantages of reduced risk of cognitive side effects and injury to the optic radiation (25). A poorer psychosocial outcome for ATLE was reported compared to more selective techniques (4). Two recent studies have also compared seizure outcomes for ATLE and SAHE (2,17). A better outcome (Engel I and II) was reported more frequently in ATLE than SEAH, giving 66% improvement versus 44% (2). Özkara et al. reported an overall seizure outcome of 72.1% in Engel I and 56.4% in ILAE I at the last available follow-up in a patient group operated on either by SEAH or ATLE and the prognosis was found to be better with ATLE surgery according to Engel, but not according to ILAE classification (17). A recent study reviewed 53 studies addressing the extent of resection in surgery for TLE and concluded that SEAH appears to have similar seizure outcome but a better cognitive outcome than temporal lobectomy (22). In our study 51.8% of patients were seizure and aura free since surgery (Engel Ia), and 76.7% were classified in Engel I and 62.2% in ILAE I with SEAH at the last follow up. It is also encouraging to note that only 1.8% of the patients were either Engel 3 or ILAE 4. Our reported results are slightly better than other studies which could be accounted for by the fact that the cases were carefully selected according to characteristic seizures and ictal recordings, mostly with a history of febrile seizures, clear hippocampal sclerosis findings on MRI, and concordant neurocognitive findings.

Although Rasmussen reported a running-down phenomenon after temporal lobe resections in 16% of the patients (19), recent studies have reported lower rates such as 12-13% (27,17). It was speculated that this phenomenon might be more prominent and might occur later after SEAH. However in Wieser's SEAH series this phenomenon was reported in only 12% of patients and seizure remission was found to be earlier in the nonlesional group (2.6±1.8 years) compared to lesional group (3.3±2.2 years) which is slightly later compared to 2 years, reported for temporal lobe resection (20). In our series only 3 of our patients (5.4%) had running down phenomenon and all of them achieved remission within their second year.

Antiepileptic treatment cessation was reported in 42.7% of patients at the sixth year (17) for both ATE and SEAH and 36.1% five years after SEAH (28). This was achieved in 25% of our patients at the last follow-up however this figure increases to 35% when we focus on the fourth follow-up year as some of our patients had a short postoperative duration and some were afraid to stop their medication although they were seizure-free. An additional 52% had a reduction in their treatment. Similarly, Wieser et al reported an overall treatment reduction in 70% of their patients (27).

Although several studies have investigated the prognostic factors for surgery outcome, no clear risks have been identified. Several studies have shown that epilepsy duration and age at surgery seem to be the most important predictors for surgical outcome (10,11,12). However, after statistical adjustments were made for other factors, duration of the disease and age at surgery had no significant effect on the outcome (14,15). In addition, the age at onset was not found to be associated with seizure recurrence (10,12,15). However, a lack of obvious abnormality, or the presence of diffuse pathology, and SGS were shown to be risk factors for recurrence after ATLE (15). Early postoperative seizures are another factor that has been shown to be associated with relapses (16). In our series both preoperative SGS and postoperative early seizure seem to be prognostic factors indicative of seizure recurrence.

Excessive manipulation of the branches of the middle cerebral arteries and compromise of the anterior or posterior choroidal artery or the posterior cerebral artery are the most likely causes of major complications in SEAH. Rydenhag et al reported

rates of 8.9% for minor and 3.1% for major complications due to epilepsy surgery (21). The rates were found to be even lower, 3.75% for minor and 0.88% for major complications with SEAH in Wieser's series (27). Concordant with the literature (2,17,27), our surgical morbidity was very low with no major complications and no deaths.

This study shows that SEAH is a safe and effective surgical procedure, without the necessity of larger resection and further invasive and expensive methods, to achieve successful surgical outcome for a selected patient group with characteristic seizures, prominent IPI history, mostly febrile seizures, with clear MRI features, ictal recordings and concordant neurocognitive findings.

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