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Acute postoperative seizures and long-term seizure outcome after surgery for hippocampal sclerosis

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ABSTRACT

Purpose: To assess the incidence and the prognostic value of acute postoperative seizures (APOS) in patients surgically treated for drug-resistant temporal lobe epilepsy due to hippocampal sclerosis (TLE-HS).
Methods: We studied 139 consecutive patients with TLE-HS who underwent epilepsy surgery and were followed up for at least 5 years (mean duration of follow-up 9.1 years, range 5–15). Medical charts were reviewed to identify APOS, defined as ictal events with the exception of auras occurring within the first 7 days after surgery. Seizure outcome was determined at annual intervals. Patients who were in Engel Class Ia at the last contact were classified as having a favorable outcome.
Results: Seizure outcome was favorable in 99 patients (71%). Six patients (4%) experienced APOS and in all cases their clinical manifestations were similar to the habitual preoperative seizures. All patients with APOS had unfavorable long-term outcome, as compared with 35 (26%) of 133 in whom APOS did not occur ($p < 0.001$).
Conclusions: Our study suggests that APOS, despite being relatively uncommon in patients undergoing resective surgery for TLE-HS, are associated with a worse long-term seizure outcome. Given some study limitations, our findings should be regarded as preliminary and need confirmation from future larger, prospective, multicenter studies.

1. Introduction

Acute postoperative seizures (APOS) are defined as ictal events occurring during the first week after resective surgery for drug-resistant focal epilepsy.[1–5] These seizures usually are of serious concern to patients and their families, as they suggest that surgery has failed.[6]

The studies examining the prognostic value of APOS in patients undergoing resective epilepsy surgery yielded inconsistent results, both in patients with temporal lobe epilepsy (TLE) and in those with extra-temporal lobe epilepsy (ETLE). While some studies reported an association between APOS and poor long-term seizure outcome,[1,2,7–10] other studies suggested that these seizures did not preclude a favorable outcome,[2,4] especially when APOS are semiologically different from the patient's habitual seizures.[1–3,11,12] Most of these studies had a relatively short follow-up period[2,3,7,9] and, especially those performed on patients with TLE, were often not homogenous for age at surgery, etiology of epilepsy and surgical approach.[1–5,9,13]

Aiming at further clarifying the prognostic significance of APOS in TLE surgery, we examined the association between APOS and long-term seizure outcome in patients who underwent anterior temporal lobectomy (ATL) for drug-resistant TLE due to hippocampal sclerosis (HS) and were followed up for at least 5 years.

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2. Methods

2.1. Patient population

The study was performed at the Epilepsy Surgery Unit (ESU) of the Neuromed-IRCCS neurological institute, Pozzilli, IS, Italy. We retrospectively included all patients affected by drug-resistant TLE-HS who undergone resective surgery (ATL) between 1999 and 2008, had histologically proven HS, and were followed up for at least 5 years. Before surgery, all patients underwent a non-invasive diagnostic work-up described in detail elsewhere.[14,15] Medical charts were systematically reviewed to identify and semiologically characterize APOS, defined as ictal events with the exception of auras occurring within the first 7 days after surgery.

2.2. Surgical approach and neuropathological examination

For each case, the decision for ATL was made after discussion in a multidisciplinary case conference aimed at evaluating the concordance between electro-clinical and anatomical data. ATL was carried out by the same neurosurgeon in all cases. The removed brain tissue was submitted for pathological examination; hippocampal sclerosis was defined as a loss of neuronal cells of 30% or more in the CA1 region of hippocampal formation with or without neuronal loss or gliosis involving other mesial temporal structures.[16]

2.3. Outcome

The follow-up visits were scheduled at 2 months, 1 year, and then annually. At the 2-month follow-up, a brain MRI scan was obtained in all patients. In patients who experienced APOS, the following aspects were retrospectively evaluated by visual inspection of scans: the extent of hippocampal resection; the presence of identifiable amygdala; the presence of periresection gliosis and of previously undetected lesions, such as small tumors or a malformation of cortical development in the neocortex or periventricular heterotopia. We chose to regard a hippocampal resection as complete if, on visual inspection of the MRI, the resection extended to the level of the middle of the midbrain posteriorly, at least to the level of the posterior margin of the crus cerebri.[17] Seizure outcome was determined by patient and family reports to the neurologist during each visit. At the last follow-up visit, the patients who were in Engel class Ia (complete freedom from seizures and auras after surgery)[18] were classified as having a favorable outcome.

2.4. Statistical analysis

First, a descriptive analysis was performed to calculate frequencies and means, as appropriate, of all variables of interest. Then, we calculated the sensitivity, specificity, and predictive values for the presence of APOS with respect to outcome. Subsequently, statistical analysis was carried out using SPSS for Mac, version 20.0 (IBM Corporation, Armonk, NY). Fisher's exact test was used to test for the association between seizure outcome and APOS. The low number of patients who experienced APOS prevented us to perform a multivariate analysis in order to adjust for potential confounders.

3. Results

3.1. Patient characteristics

A total of 243 patients affected by drug-resistant TLE who underwent ATL between 1999 and 2008; histopathology was available for all patients and certified the diagnosis of HS in 142 patients. Two of these patients died for epilepsy-unrelated reasons during the first 5 years of follow-up, while another patient who was lost to follow-up after the first year. Therefore, a total of 139 patients were included in the study. Eighty-two (59%) of them were male and 57 (41%) female. Their mean age was 36.2 years (SD = 10.4, range 18–62), and the mean duration of epilepsy was 22.6 years (SD = 11.1, range 2–49). Seventy-two (52%) had right TLE, and 67 (48%) left TLE. All patients attended all scheduled follow-up visits, with a mean follow-up period of 9.1 years (SD = 3.0, range 5–15). The preoperative neurological examination was remarkable for focal signs only in four patients (3%). Thirty-two patients (23%) had mental retardation (IQ $<$ 70 at the Wechsler Adult or Children Intelligence Scale), while 34 (24%) had a history of sGTCS. Preoperative seizure frequency was monthly in 57/139, weekly in 73/139, and daily in 9/139 patients; preoperative brain MRI studies documented mesial temporal sclerosis in 124/139 (89%) cases.

3.2. APOS

Six patients (4%) (mean age at onset of epilepsy 14.1 years, range 4–27; mean epilepsy duration 21.6 years, range 3–39) experienced APOS; in all cases, they were semiologically similar to the habitual preoperative seizures. None of the patients experiencing APOS had auras in the first seven days after surgery. Four other patients experienced auras in the first postoperative week. The visual inspection of postoperative MRI showed that all patients who experienced APOS underwent complete resection of the hippocampus and the amygdala. No previously undetected lesion was visible, while periresection gliosis was noted in one case. Table 1 reports the demographic and clinical characteristics of each patient who experienced APOS, and summarizes the demographic and clinical characteristics of patients who did not experience APOS.

3.3. Outcome

At the last follow-up visit, 99 patients (71%) were in Engel's Class Ia, seven (5%) in Class Ib, nine (6%) in Class Ic, nine (6%) in Class Id, one (1%) in Class II, two (1%) in Class IIa, four (3%) in Class IIb, seven (5%) in Class IIIa, and one (1%) in Class 4a. Therefore, 99 patients (71%) were classified as having a favorable outcome, whereas the remaining 40 (29%) were classified as experiencing an unfavorable outcome.

3.4. Association between APOS and outcome

The findings were quite similar when considering the outcome 2 years after surgery, as 5 out of 6 (83%) patients who experienced APOS had unfavorable outcome, as compared with 28 (21%) of 133 in whom APOS did not occur ($p < 0.001$).

We found a significant association between APOS and unfavorable seizure outcome after 5 years of follow-up: all the six patients who experienced APOS had poor outcome, as compared with 35 (26%) of 133 in whom APOS did not occur ($p < 0.001$). The sensitivity was 15% (95% C.I. 6–30), specificity 100% (95% C.I. 95–100), positive predictive value 100% (95% C.I. 52–100), and negative predictive value 74% (95% C.I. 65–81).

With regard to the four patients who experienced only postoperative auras in the first week after surgery, two of them obtained sustained freedom from seizures and auras, while the remaining two continued to experience auras during the entire follow up period.

4. Discussion

Seizures occurring in the early postoperative period after epilepsy surgery may be very disturbing emotionally for patients

Table 1
Demographic and clinical characteristics of each patient with APOS and of the group of patients without APOS.

Patients with APOS	Age (yrs)	History of FC	Age at epilepsy onset (yrs)	Epilepsy duration (yrs)	sGCTS	Seizure frequency	Preoperative MRI	Preoperative neurological examination	Side of surgery	Postoperative neurological deficits	Engel's class ≥5 years follow-up
DC	38	No	15	23	1	Weekly	Normal	Normal	Left	No	Ib
AL	22	No	4	18	1	Monthly	MTS	Abnormal	Left	No	IIIa
MC	35	Yes	6	29	0	Weekly	MTS	Normal	Left	No	IIIa
MCM	29	No	27	3	0	Weekly	MTS	Normal	Left	Yes	IIIa
CS	41	No	23	18	1	Weekly	MTS	Normal	Right	No	IIb
LDT	49	No	10	39	0	Weekly	MTS	Normal	Left	No	IIb
Patients without APOS ($N=133$)	(Mean, SD) 36.1 ± 10.4 (range) 18–62	Yes: 67 (50%) No: 66 (50%)	(Mean, SD) 13.4 ± 9.2 (range) 1–38	(Mean, SD) 22.7 ± 11.07 (range) 2–49	Yes: 31 (23%) No: 102 (77%)	Monthly: 56 Weekly: 68 Daily: 9	MTS: 119 (89%)	Abnormal 3 (2%)	Right: 71 (53%) Left: 62 (47%)	Yes: 2 (1,5%)	Ia 99; Ib 6; Ic 9; Id 9; IIa 3; IIb 2; IIIa 4; IVa 1

APOS, acute postoperative seizures; FC, febrile convulsions; sGTCS, secondarily generalized tonic–clonic seizures; MTS, mesial temporal sclerosis.

and their families, as they raise concerns that the operation failed, either for an incomplete removal of the seizure focus or for a surgical complication.[1–3] These feelings of fear and disappointment are most frequent in patients who underwent temporal lobe resections, as they have greater expectations for success[14,19,20] and lower risk of postoperative neurological deficits as compared undergoing extra-temporal resection.[21–23] In the literature there is considerable disagreement as to whether APOS predict poor long-term seizure outcome, possibly because of differences between studies in APOS definition, patients' age range, site of resection, and intracranial investigation methods.

Several studies examined the prognostic significance of APOS in patients who underwent resective epilepsy surgery, most of them focusing specifically on TLE. On the one hand, some studies reported that seizures occurring during the early postoperative period are not associated with poor long-term outcome.[2,11,23,25–27] It has been suggested that these seizures, often of focal motor type or GTCS and named "neighborhood seizures",[11,12,24–26,28] may result from the effects of acute surgical injury. The notion that APOS are related to surgery itself is also reflected in the new ILAE outcome classification, which excludes seizures occurring over the entire first month after surgery as they "do not predict long term outcome".[29]

On the other hand, several studies found a significant association between APOS and TLE surgery failure,[1–3,5,7–9,13] especially when they were semiologically similar to patient's habitual seizures.[1–3,11,12] Garcia et al.[1] reported that APOS, which occurred in 27 (49%) of 55 pediatric and adult patients who underwent temporal lobectomy, were associated with a poor outcome only if there was more than one event and it occurred more than 24 h after surgery. In this study, APOS semiology was found not to be a reliable predictor of outcome. Malla et al.[2] studied 160 pediatric and adult patients who underwent ATL for intractable non-lesional TLE and were followed up for at least 1 year (mean follow-up time 3.1 years). At the last visit, 72.5% of patients were seizure-free. APOS occurred in 32 patients (20%) who had poorer seizure outcome at the last follow-up examination as compared with patients without APOS (Engel's Class I: 62.5% and 83.6%, respectively). The type of APOS was found to be of prognostic importance; patients whose APOS were similar to their preoperative habitual seizures had a worse outcome than those whose APOS were auras or focal motor and/or generalized tonic–clonic seizures (Engel's Class I: 14.3%, 77.8%, and 75%, respectively). Radhakrishnan et al.[7] studied 175 patients who underwent ATL (mean follow up: 3.6 years). APOS occurred in 7% of these patients and they were associated with worse seizure outcome. Recently, two studies on pediatric patients who underwent resective epilepsy surgery, in most cases ATL, confirmed the association between APOS and worse outcome.[5,13]

As compared with previous studies on this topic, our study is similar in terms of sample size, while it had a longer mean duration of follow-up (9.1 years) and found a lower incidence of APOS (4%). Differences between studies in sample composition and APOS definition may account for the lower incidence of APOS in our sample. In fact, most previous studies included both adults and children[1,2,5,7] or only children,[13] whereas we included only adult patients. Moreover, while our study, consistently with most previous studies,[1,5,7] considered as APOS only the seizures occurring in the first 7 days after surgery, Malla et al.[2] included also the auras occurring in the first week after surgery, while Greiner et al.[13] considered all the seizures occurring in the first month after surgery. It should also be noted that seizure outcome was classified in different ways in the various studies. In some studies, patients were considered as having a favorable seizure outcome when they were in Engel Class I,[1,5,7] in another study if they were in Engel Class I-II[2], and in another study if they were in ILAE class 1–3 (up to 3 seizure days/years).[13]

We observed a significant association between APOS following TLE resective surgery and poor long-term seizure outcome. Given that the APOS were semiologically similar to the habitual preoperative seizures, this association suggests that, rather than reflecting transient peri-operative factors, they may represent an immediate postoperative correlate of residual epileptogenicity following an incomplete removal of the epileptogenic zone.[30]

We did not identify any preoperative or postoperative factor associated with APOS; no patient with APOS experienced complications such as infection, fever, or intraparenchymal hematoma. A reduction in AED plasma levels immediately after epilepsy surgery was described[31] and might be a postoperative precipitating factor for APOS. Unfortunately, we could not test this hypothesis, as we did not monitor AED blood levels immediately after surgery.

This study has several limitations. First, the low number of patients who experienced APOS prevented us to perform a multivariate analysis in order to adjust for potential confounders. Furthermore, the retrospective nature of data collection reduced the reliability of the assessment of APOS. In addition, people who described APOS not always had adequate training and experience to correctly classify the seizure type. In fact, the patients were first placed in an intensive care unit and then in a general neurosurgery ward; also, the initial observer of the patient's APOS was frequently a family member or friend. Moreover, patients did not undergo video-EEG monitoring in the immediate postoperative period; thus, we cannot exclude that some patients experienced APOS that were not recognized as seizures. However, APOS semiology was available for all cases and was judged as typical of the habitual preoperative seizures. Also, as already mentioned, AED blood levels in the immediate postoperative period were not measured. Finally, all patients came from a single site and the findings may not generalize to other epilepsy centers.

5. Conclusions

In conclusion, our study suggests that APOS, though relatively uncommon, are associated with poor long-term seizure outcome in patients undergoing resective surgery for TLE-HS. Our findings should be regarded as preliminary and need confirmation from future larger, prospective, multicentre studies with standardized postoperative protocols including video-EEG monitoring and determination of early postoperative AED plasma levels. If confirmed, our findings suggest that caution may be required in the management of maintenance AED treatment for patients experiencing APOS[32] because these seizures, when their semiology is similar to the habitual seizures, would seem to be best regarded as an early seizure recurrence that is unlikely to benefit from the running down phenomenon.[33]

Conflict of interest statement

The authors have no conflict of interest to declare.

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References

1. Garcia PA, Barbaro NM, Laxer KD. The prognostic value of postoperative seizures following epilepsy surgery. *Neurology* 1991;**41**:1511–2.
2. Malla BR, O'Brien TJ, Cascino GD, So EL, Radhakrishnan K, Silbert P, et al. Acute postoperative seizures following anterior temporal lobectomy for intractable partial epilepsy. *J Neurosurg* 1998;**89**:177–82.
3. Park K, Buchhalter J, McClelland R, Raffel C. Frequency and significance of acute postoperative seizures following epilepsy surgery in children and adolescents. *Epilepsia* 2002;**43**:874–81.
4. Tigaran S, Cascino GD, McClelland RL, So EL, Richard Marsh W. Acute postoperative seizures after frontal lobe cortical resection for intractable partial epilepsy. *Epilepsia* 2003;**44**:831–5.
5. Alfstad K.Å., Lossius MI, Røste GK, Mowinckel P, Scheie D, Borota OC, et al. Acute postoperative seizures after epilepsy surgery: a long-term outcome predictor? *Acta Neurol Scand* 2011;**123**:48–53.
6. Abou-Khalil BW. Do immediate postoperative seizures predict surgical failure after frontal lobe epilepsy surgery? *Epilepsy Curr* 2004;**4**:51–2.
7. Radhakrishnan K, So EL, Silbert PL, Cascino GD, Marsh WR, Cha RH, et al. Prognostic implications of seizure recurrence in the first year after anterior temporal lobectomy. *Epilepsia* 2003;**44**:77–80.
8. McIntosh AM, Kalnins RM, Mitchell LA, Berkovic SF. Early seizures after temporal lobectomy predict subsequent seizure recurrence. *Ann Neurol* 2005;**57**:283–8.
9. Jayalakshmi S, Panigrahi M, Kulkarni DK, Uppin M, Somayajula S, Challa S. Outcome of epilepsy surgery in children after evaluation with non-invasive protocol. *Neurol India* 2011;**59**:30–6.
10. Di Gennaro G, D'Aniello A, De Risi M, Quarato PP, Mascia A, Grammaldo LG, et al. Prognostic significance of acute postoperative seizures in extra-temporal lobe epilepsy surgery. *Clin Neurophysiol* 2013;**124**:1536–40.
11. Falconer MA, Serafetinides EA. A follow-up study of surgery in temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry* 1963;**26**:154–65.
12. Bengzon AR, Rasmussen T, Gloor P, Dussault J, Stephens M. Prognostic factors in the surgical treatment of temporal lobe epileptics. *Neurology* 1968;**18**:717–31.
13. Greiner HM, Horn PS, Arya R, Holland K, Turner M, Alsaidi MH, et al. Acute postoperative seizures and long-term outcome following pediatric epilepsy surgery. *Seizure* 2014. S1059-1311(14)00061-2.
14. Quarato PP, Di Gennaro G, Mascia A, Grammaldo LG, Meldolesi GN, Picardi A, et al. Temporal lobe epilepsy surgery: different surgical strategies after a noninvasive diagnostic protocol. *J Neurol Neurosurg Psychiatry* 2005;**76**:815–24.
15. Di Gennaro G, Picardi A, Sparano A, Mascia A, Meldolesi GN, Grammaldo LG, et al. Seizure clusters and adverse events during pre-surgical video-EEG monitoring with a slow anti-epileptic drug (AED) taper. *Clin Neurophysiol* 2012;**123**:486–8.
16. Blümcke I, Pauli E, Clusmann H, et al. A new clinico-pathological classification system for mesial temporal sclerosis. *Acta Neuropathol* 2007;**113**:235–44.
17. Hennessy MJ, Elwes RD, Binnie CD, Polkey CE. Failed surgery for epilepsy. A study of persistence and recurrence of seizures following temporal resection. *Brain* 2000;**123**(Pt 12):2445–66.
18. Engel Jr J. Outcome with respect to epileptic seizures. In: Engel Jr J, editor. *Surgical Treatment of the Epilepsies*. New York: Raven Press; 1987. p. 553–71.
19. Janszky J, Janszky I, Schulz R, Hoppe M, Behne F, Pannek HW, et al. Temporal lobe epilepsy with hippocampal sclerosis: predictors for long-term surgical outcome. *Brain* 2005;**128**:395–404.
20. Téllez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. *Brain* 2005;**128**:1188–98.
21. Laskowitz DT, Sperling MR, French JA, O'Connor MJ. The syndrome of frontal lobe epilepsy: characteristics and surgical management. *Neurology* 1995;**45**:780–7.
22. Ferrier CH, Engelsman J, Alarcón G, Binnie CD, Polkey CE. Prognostic factors in presurgical assessment of frontal lobe epilepsy. *J Neurol Neurosurg Psychiatry* 1999;**66**:350–6.
23. Mosewich RK, So EL, O'Brien TJ, Cascino GD, Sharbrough FW, Marsh WR, et al. Factors predictive of the outcome of frontal lobe epilepsy surgery. *Epilepsia* 2000;**41**:843–9.
24. Engel Jr J. Outcome with respect to epileptic seizures. In: Engel Jr J, editor. *Surgical Treatment of the Epilepsies*. New York: Raven Press; 1987. p. 553–71.
25. Primrose DC, Ojemann GA. Outcome of resective surgery for temporal lobe epilepsy. In: Lüders H, editor. *Epilepsy Surgery*. New York: Raven Press; 1991. p. 601–11.
26. Ojemann GA, Bourgeosis BF. Early postoperative manage-ment. In: Engel Jr J, editor. *Surgical Treatment of the Epilepsies*. 2nd ed. New York: Raven Press; 1993. p. 539–40.
27. Berkovic SF, McIntosh AM, Kalnins RM, Jackson GD, Fabinyi GC, Brazenor GA, et al. Preoperative MRI predicts outcome of temporal lobectomy: an actuarial analysis. *Neurology* 1995;**45**:1358–63.
28. Wingkun EC, Awad IA, Lüders H, et al. Natural history of recurrent seizures after resective surgery for epilepsy. *Epilepsia* 1991;**32**:851–6.
29. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia* 2010;**51**:676–85.
30. Liava A, Francione S, Tassi L, Lo Russo G, Cossu M, Mai R, et al. Individually tailored extra-temporal epilepsy surgery in children: anatomo-electro-clinical features and outcome predictors in a population of 53 cases. *Epilepsy Behav* 2012;**25**:68–80.
31. Paul F, Veauthier C, Fritz G, Lehmann TN, Aktas O, Zipp F, et al. Perioperative fluctuations of lamotrigine serum levels in patients undergoing epilepsy surgery. *Seizure* 2007;**16**:479–84.
32. Menon R, Rathore C, Sarma SP, Radhakrishnan K. Feasibility of antiepileptic drug withdrawal following extra-temporal resective epilepsy surgery. *Neurology* 2012;**79**:770–6.
33. Salanova V, Andermann F, Rasmussen T, Olivier A, Quesney L. The running down phenomenon in temporal lobe epilepsy. *Brain* 1996;**119**:989–96.