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Safety of video-EEG monitoring and surgical outcome in patients with mesial temporal sclerosis and psychosis of epilepsy

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ABSTRACT

Purpose: Cortico-amygdalohippocampectomy (CAH) has become an important treatment option for patients with refractory temporal lobe epilepsy and mesial temporal sclerosis (TLE-MTS); it has resulted in a 60–70% seizure remission rate and significant quality of life (QOL) improvements. Video-electroencephalography (VEEG) monitoring has been widely used in epilepsy centers for pre-surgical evaluation. A major concern in epilepsy surgery is whether to consider CAH treatment in patients with psychosis of epilepsy (POE). This study analyzed the safety and adverse events (AEs) of VEEG monitoring and the post-surgical outcomes of patients with refractory TLE-MTS and POE who underwent CAH.
Method: Clinical, sociodemographic and VEEG data from 18 patients with TLE-MTS and POE were analyzed. Psychiatric evaluations were performed using DSM-IV and ILAE criteria. The seizure outcome was evaluated using Engel's criteria.
Results: Two patients (11.2%) presented AEs that did not result in increased lengths of hospitalization. Of the 10 patients (55.5%) who underwent CAH, 6 (60%) became free of disabling seizures (Engel I). The psychiatric and QOL evaluations revealed improvements of psychotic symptoms ($p = 0.01$) and in Physical Health ($p = 0.01$) following surgery.
Conclusion: These data reinforce that VEEG monitoring is a safe method to evaluate patients with refractory TLE-MTS and POE in epilepsy centers.

1. Introduction

Epilepsy surgery has become an important treatment option for patients with refractory temporal lobe epilepsy (TLE); current evidence suggests a 60–70% remission rate for long-term epileptic symptoms and significant improvements in quality of life (QOL).[1,2] Data from previous studies have demonstrated that cortico-amygdalohippocampectomy (CAH) is a safe, efficient surgical procedure for patients with refractory TLE and mesial temporal sclerosis (TLE-MTS); the latter condition compromises the primary structures of the limbic system, particularly the hippocampus and amygdala. TLE-MTS is also one of the most common types of surgically remediable epileptic syndromes.[3–5] Prolonged video-electroencephalography (VEEG) monitoring has been widely used in specialized epilepsy centers for pre-surgical evaluation.[6]

One of the major decisions in epilepsy surgery is whether to operate on subjects who have previous histories of psychosis of epilepsy (POE). Many epilepsy centers exclude psychotic patients from their surgical programs due to the possibility of alternative psychosis, postoperative exacerbations of preexisting psychosis and the occurrence of postictal disorders during VEEG, which is facilitated by the reduction of antiepileptic drugs. In addition, few studies have addressed the psychiatric and seizure post-surgical outcomes of patients with refractory epilepsy and pre-surgical psychoses.[7,8] The purpose of this study was to analyze the safety and adverse events (AEs) during VEEG monitoring and the surgical, psychiatric and QOL outcomes of patients with refractory TLE-MTS and a previous history of POE.

2. Methods

2.1. Subjects

One hundred forty-five TLE-MTS patients were followed in the outpatient clinic of a tertiary center (Epilepsy Section of the Universidade Federal de São Paulo, São Paulo, Brazil) from January

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2002 to December 2011. All of the patients had submitted to VEEG monitoring and a psychiatric evaluation. After written informed consent was obtained, 18 TLE-MTS patients with a previous history of POE (12.4%) were included in the study. To be included, the patients required an electroclinical diagnosis of refractory TLE-MTS and POE, which was based on the Diagnostic and Statistical Manual for mental disorders, 4th edition (DSM-IV) and International League Against Epilepsy (ILAE) classifications[9,10] and an age of at least 16 years. All 18 patients were followed for at least two years, and they had clear MRI findings consistent with unilateral or bilateral MTS and concordant interictal and ictal EEG data. Patients were excluded if they suffered from other neurological diseases in addition to epilepsy, cognitive impairments precluding psychiatric and clinical evaluations, or were younger than 16 years old.

2.2. Procedures

The patients were subjected to 2–6 days of continuous video-electroencephalographic (VEEG) monitoring with 32-channel EEG recording. Electrodes were placed on the temporal lobe according to the 10–10 system, including the sphenoidal position. MTS was defined if atrophy, increased T2-weighted signal, decreased T1-weighted signal, and/or a disrupted internal hippocampal structure were present and accompanied by atrophy of the amygdala and/or temporal pole signal alteration upon visual inspection of the MRI pictures. The epileptogenic zone was determined by predominantly ipsilateral interictal epileptiform discharges (80% cutoff) and by seizure onset that was recorded during prolonged VEEG monitoring. Epilepsy was considered to be resistant to medical treatment when the seizures persisted after the utilization of at least two first-line medications for partial seizures at the highest tolerated doses. Initial precipitant injury (IPI) was defined as the occurrence of severe cerebral events in the first year of life before the appearance of epilepsy that required medical intervention and/or hospitalization; such events included febrile seizures, meningoencephalitis, head trauma or severe perinatal hypoxia. The withdrawal of AEDs was made during the first three days at the hospital, and the patients were observed for 24 h each day via monitoring screens that were located outside the monitoring room; the patients were monitored by two EEG-monitoring technicians and a specialized epileptologist who was on call for 24 h. Adverse events (AEs) were defined as falls, fractures, *status epilepticus* (SE), PIP, suicide attempts, and deep venous thrombosis during VEEG monitoring. PIP was considered an adverse event if it occurred within 7 days of the admission date. The Epilepsy Surgery Inventory (ESI-55)[11] was used to evaluate the patients' QOL before and after surgery.

2.3. Psychiatric evaluation

A single psychiatrist (GMAF) conducted the clinical interviews using the DSM-IV axis I and ILAE criteria.[10,12–14] IIP was defined as a chronic psychotic state that often included an insidious onset of paranoid delusions and hallucinations that may be present in clear consciousness and not temporally related to seizures. PIP was defined as episodes of psychosis within 1 week after a seizure(s), psychosis lasting >15 h and <3 months, delusions, hallucinations in clear consciousness, bizarre or disorganized behavior, formal thought disorder, or affective changes, with no evidence of antiepileptic drug (AED) toxicity, non-convulsive *status epilepticus*, recent head trauma, alcohol and/or drug intoxication/withdrawal, or prior chronic psychotic disorder.[13,14] Information regarding the family history of epilepsy and PD was obtained from the patients through broad questions that asked whether any first-degree relative was receiving treatment either for epilepsy or for any PD at the moment of the clinical interview. The psychiatric evaluations occurred pre-surgically and were then held every three months by the same psychiatrist (GMAF). The Brazilian version of the Brief Psychiatric Rating Scale anchored (BPRS-A)[15] was also used to measure the severity of psychotic symptoms before and after surgery, and the scores that were used for the statistical analysis were obtained at one and two years after surgery.

2.4. Surgery and post-surgical evaluation

After the VEEG evaluation, the patients without a surgical indication were followed at three-month intervals by the same neurologist, and the patients with a surgical indication underwent CAH within 2 months of the initial evaluation. The surgical procedure consisted of en block resectioning of the superior, middle, inferior temporal and fusiform gyri, with a posterior limit of 4.5 cm from the tip of the temporal lobe. After opening the temporal horn, the mesial temporal structures (hippocampus, amygdala and parahippocampal gyrus) were also resected.[3] The patients were evaluated one, three, six and 12 months after surgery and then every six months by two neurosurgeons. Engel's classification system was utilized to measure the patients' seizure outcomes one and two years after the surgery.[16] The QOL of all of the patients submitted to CAH was also evaluated after the first and second years after surgery.

2.5. Statistical analysis

The statistical analyses were performed using the version 10.0 of Statistical Package for Social Sciences (SPSS 10.0, Chicago, Illinois). Some socio-demographic characteristics were presented as one-sample proportions that included confidence intervals. The McNemar and Wilcoxon tests were used to analyze the clinical and socio-demographic data, and corrections were used for the multiple statistical comparisons. p values of <0.05 were considered to be statistically significant.

3. Results

The data from 18 patients (12 women, 6 men, mean age of 40.4 years, standard deviation [SD] = 8.97, range of 26–65 years, mean of duration of epilepsy of 29.7 years, SD = 11.13) were analyzed. The mean length of the VEEG monitoring was 94 h. Nine patients (50%) presented with left-sided MTS, eight (44.4%) were right-sided and one (5.6%) had bilateral MTS. Three patients (16.8%) had a positive psychiatric family history, while four (22.2%) had a positive psychic aura history, and eight (44.4%) had an IPI in their epilepsy history. The patients' clinical and sociodemographic characteristics are summarized in Table 1.

Regarding the psychiatric evaluations, according to the ILAE criteria,[10] ten patients (55.5%) had a diagnosis of IIP, and eight patients (45.5%) had a diagnosis of PIP. All of the patients with IIP also presented with the diagnosis of paranoid schizophrenia according to the DSM-IV criteria.[12] All of the patients were taking one antipsychotic drug; Risperidone (RIS) was the most common drug (ten patients), which was followed by Haloperidol (HAL) (five patients) and Olanzapine (OLZ) (three patients). The mean pre-surgical doses of RIS, HAL and OLZ were 3 mg/day, 7.5 mg/day and 10 mg/day, respectively, and the doses did not differ significantly between the PIP and IIP patients ($p = 0.89$).

During the VEEG monitoring process, none of the patients had a cluster of seizures. Two patients (11.2%) presented with one episode of PIP as an AE, and these AEs were associated with more than 100 tonic–clonic seizures during the patients' lives and with the patients' previous PIP histories. No other AEs were recorded. The age of epilepsy onset, duration of epilepsy, mean length of

Table 1
Clinical and sociodemographic characteristics of in psychotic patients with refractory temporal lobe epilepsy and mesial temporal sclerosis.

Patient no./gender	POE	Age of epilepsy onset (y)	Age at VEEG (y)	IPI	Psychiatric family history	Psychic aura	TCS during life	Dominant side	MTS side	Interictal foci	% of laterality at VEEG	Secondary generalization at VEEG	Stay at the hospital (h)	AEs	Engel 1	Engel 2
1/F	IIP	6	39	FS	–	–	<20	R	R	R	100	+	91	–	IB	IB
2/F	IIP	6	44	–	+	–	>20	R	L	B	50	–	58	–	*	*
3/F	PIP	13	35	–	–	–	<5	R	R	A	0	–	96	–	*	*
4/F	IIP	4	44	FS	+	+	50–100	R	B	L	80	–	92	–	*	*
5/F	PIP	1	26	–	–	–	>100	R	R	R	37.4	–	97	–	*	*
6/F	IIP	1	39	T	–	–	>100	R	L	R	96.5	–	86	–	IIB	IIB
7/F	IIP	6	31	FS	–	–	10–20	R	R	L	86	–	110	–	IA	IA
8/M	IIP	12	44	FS	–	–	>100	R	L	L	85	–	124	–	*	*
9/M	PIP	0.7	45	–	–	–	20–50	R	L	L	56.6	–	93	–	IID	IID
10/M	PIP	27	49	–	–	–	>100	R	R	R	62	–	94	+	IA	IID
11/F	PIP	10	38	NFS	–	+	>100	R	L	L	100	–	79	–	IB	IB
12/M	PIP	14	32	FS	–	–	50–100	R	L	L	81.5	–	55	–	IA	IA
13/M	PIP	3	33	–	–	+	50–100	R	L	L	100	–	78	–	IID	III
14/F	IIP	9	65	–	–	–	>100	R	R	R	100	–	115	–	IA	IA
15/F	IIP	32	54	–	+	–	0	R	R	B	50	–	120	–	*	*
16/F	IIP	3	37	FS	–	+	50–100	L	L	L	100	–	96	–	*	*
17/M	PIP	14	40	–	–	–	>100	R	R	L	54	–	108	+	*	*
18/F	IIP	20	33	–	–	–	>100	R	L	L	90.1	–	102	–	IA	IA

A, absence of interictal discharges; AEs, adverse events; B, bilateral; Engel 1, Engel's classification one year after surgery; Engel 2, Engel's classification two years after surgery; F, female; FS, febrile seizures; h, hours; IIP, interictal psychosis; IPI, initial precipitating injury; L, left; M, male; MTS, mesial temporal sclerosis; NFS, non-febrile seizures; PIP, postictal psychosis; POE, psychosis of epilepsy; R, right; T, trauma; TCS, tonic–clonic seizure; y, years; VEEG, video-electroencephalography.
* Patients that did not undergo to surgery.

VEEG monitoring, and lateralized EEG or MRI asymmetries were not associated with the AEs.

Ten patients (55.5%) underwent CAH; five patients had PIP and five had IIP. After two years of post-surgical follow-up, six of the patients (60%) were free of disabling seizures (Engel Class I), three (30%) had rare disabling seizures (Engel Class II), and one presented with a worthwhile seizure improvement (Engel Class III) (Fig. 1). The differences in the post-surgical outcomes between the first and second year were not significant ($p = 1.00$). Antipsychotic drugs were discontinued in all five CAH patients with PIP because they presented with a complete remission of psychotic symptoms after surgery and lacked any recurrence within two years of follow-up. A reduction of the mean antipsychotic doses was observed in the IIP patients after surgery (2 mg/day for RIS and 5 mg/day for HAL), but performing statistical comparisons of the patients who did not undergo surgery was unfeasible due to the reduced number of subjects involved. Among the patients who underwent CAH, a mean BPRS-A score of 39.9 ± 5.36 (range 26–44) was observed pre-surgically; this score was reduced to 26.7 ± 6.21 (range 18–36) in the first year and to 22.3 ± 4.47 (range 18–32) in the second year after surgery. A significant difference was observed between the pre-surgical and first-year scores ($p = 0.012$), but no differences were observed between the PIP and IIP patients ($p = 0.87$).

The ESI-55 was used to measure the patients' QOL before and after surgery. Although QOL improvements were observed in all of the patients' domains after surgery (Fig. 2), significant differences were observed only in the physical health sphere ($p = 0.01$). The p-value was approximately 0.05 in the overall quality of life ($p = 0.07$) and psychosocial health ($p = 0.12$) spheres, and it was not significant in the cognitive and functional sphere ($p = 0.23$).

4. Discussion

The data from previous studies have demonstrated that 30–40% of patients with epilepsy present with a medically intractable disease with available AEDs. CAH is a safe, efficient surgical procedure for patients with refractory TLE-MTS, which is one of the most common types of surgically remediable epileptic syndromes; it confers an approximately 70% chance of long-term seizure freedom.[3–5] However, one of the most important decisions in epilepsy surgery is whether to operate on patients with a previous history of POE. The prevalence of psychoses in hospital-based

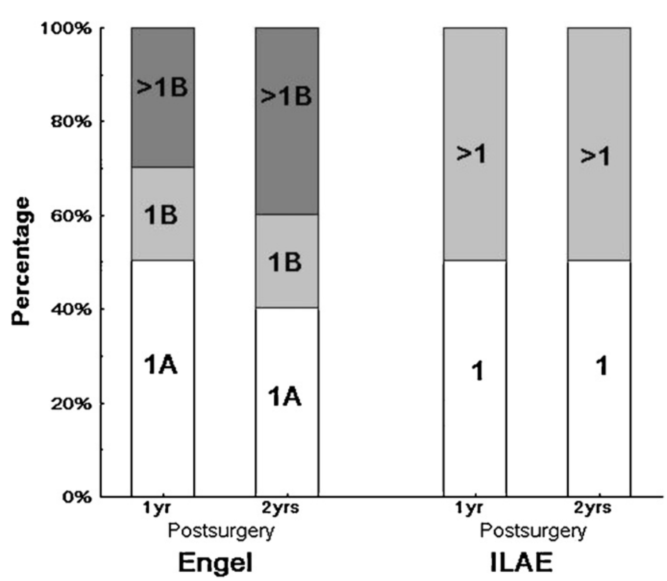

Fig. 1. Engel and ILAE classifications one and two years after epilepsy surgery of patients with mesial temporal sclerosis and psychoses of epilepsy.

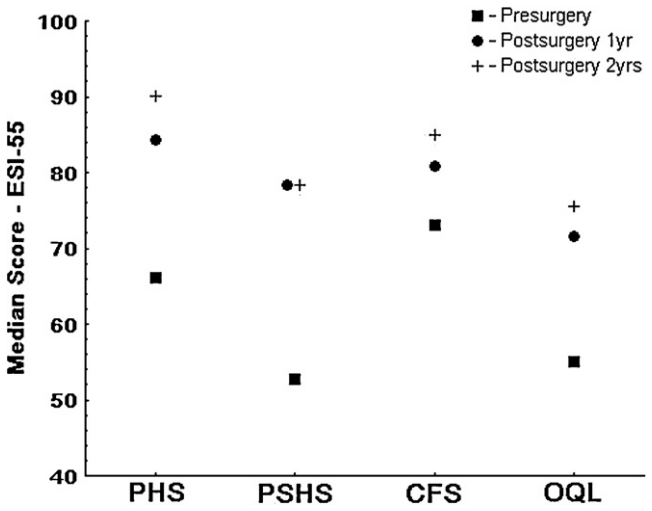

Fig. 2. Median scores of ESI-55 spheres before, after one and two years of epilepsy surgery in patients with mesial temporal sclerosis and psychoses of epilepsy. PHS, physical health sphere; PSHS, psychosocial health sphere; CFS, cognitive and functional sphere; OQL, overall quality of life.

epilepsy services is estimated to be approximately 9%,[17] and the prevalence rates are even higher (19–27%) in specialized centers.[18] Despite this high prevalence, patients with this condition have frequently been excluded (for psychiatric reasons) from a complete evaluation of their epilepsy syndromes. Some reasons to justify this attitude are the occurrence of postictal disorders during VEEG, the possibility of alternative psychosis and postoperative exacerbations of preexisting psychosis.[6,19,20]

Previous studies have suggested that POE recurrence may be closely linked to seizure exacerbation during VEEG.[6,19] The yearly incidence of postictal psychiatric disorders has been reported as 7.9% among patients with partial epilepsy who undergo VEEG monitoring, and episodes of PIP represent the majority of these disorders (6.4%).[20] PIP was the only AE observed in the present study, and it occurred in a slightly higher proportion than had been reported in previous studies.[6,19,20] However, these events did not alter the length of hospitalization for the two patients who presented this AE, and neither AE negatively influenced the post-surgical outcome of the patients who underwent CAH.

Few studies, however, have adequately addressed the psychiatric and seizure post-surgical outcomes of patients with preoperative POE.[7,8] Although some studies have reported a post-surgical remission of psychotic symptoms,[20,21] others have concluded that IIP does not change after surgery, while PIP symptoms may be diminished and even remitted after patients become free of disabling seizures.[22,23] The possible significance of behavioral AEs during VEEG monitoring and post-surgical psychiatric outcome has also been a matter of interest in past studies. Kanemoto et al.[23] reported preoperative episodes of PIP, left-sided surgeries and auras of ictal fear as psychopathological risk factors of postoperative mood disorders. In the present study, all of the PIP patients who underwent CAH displayed a complete remission of their psychotic symptoms after surgery. AEs were more likely to be associated with more than 100 tonic–clonic seizures during the patients' lives and with the patients' previous PIP histories. Although a small number of patients enrolled, the presence of IPI, psychiatric family history, psychic aura, MTS laterality, interictal foci side and generalization during VEEG monitoring did not influence either the occurrence of AEs or the post-surgical outcomes. In addition, alternative psychoses did not occur in the psychiatric follow-up evaluations.

Patients with epilepsy have a lower QOL and higher rates of comorbidities compared with the general population.[11] Therefore, seizure improvement or cessation is of great clinical significance for patients' QOL even in the presence of persisting psychosis.[7,24] Surgery is a better treatment option than prolonged medical therapy for patients with refractory TLE-MTS.[25] In addition, seizure control can be associated with improvements in the psychiatric condition of PIP patients.[7,8,14] Although significant differences were observed only in the physical health sphere domain, the patients presented important QOL improvements in most of the ESI-55 domains at the post-surgical follow-up; such non-significant differences could be caused by the small number of enrolled patients.

To conclude, the present data confirm that VEEG monitoring can be considered to be a safe procedure for evaluating the possibility of surgical intervention in patients with refractory TLE-MTS and POE. Despite the possible occurrence of AEs and the small number of patients enrolled, we did not observe substantial morbidity or an increased length of hospitalization in our sample. In addition, the post-surgical outcome data revealed an overall improvement of psychotic symptoms and QOL among these patients.

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