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Auras in temporal lobe epilepsy with hippocampal sclerosis: Relation to seizure focus laterality and post surgical outcome

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ABSTRACT

We examined the relationship between presence and frequency of different types of auras and side of lesion and post surgical outcomes in 205 patients with medically intractable mesial temporal lobe epilepsy (MTLE) with unilateral hippocampal sclerosis (HS). With respect to the number of auras, multiple auras were not associated with side of lesion ($p = 0.551$). The side of HS was not associated with the type of auras reported. One hundred fifty-seven patients were operated. The occurrence of multiple auras was not associated with post-surgical outcome ($p = 0.740$). The presence of extratemporal auras was significantly higher in patients with poor outcome. In conclusion, this study suggests that the presence of extratemporal auras in patients with MTLE-HS possibly reflects extratemporal epileptogenicity in these patients, who otherwise showed features suggestive of TLE. Therefore, TLE-HS patients undergoing pre-surgical evaluation and presenting clinical symptoms suggestive of extratemporal involvement should be more extensively evaluated to avoid incomplete resection of the epileptogenic zone.

1. Introduction

Temporal lobe epilepsy (TLE) is the most common type of focal epilepsy syndrome in adults [1], and hippocampal sclerosis (HS) its most frequent underlying pathology [2].

Temporal lobe epilepsy with HS is a distinct epileptic syndrome, with characteristic clinical, neurophysiological, and neuroimaging features [3]. Although for most patients with MTLE-HS the hippocampus is the primary epileptogenic area, the epileptogenic network may extend beyond the hippocampus. There is extensive evidence supporting this statement, including neuroimaging [3–9], neuropsychological [10,11], and clinical data [12,13].

Surgery is superior to clinical treatment in patients with TLE with drug-resistant seizures [14]. However, despite the improvement in the evaluation of potential surgical candidates, the short- and long-term success of epilepsy surgery performed for intractable TLE with HS has not remarkably changed in recent decades. In long-term outcome studies, the rate of seizure freedom is 41 to 47% at 10 years [15–18].

Auras – defined as a subjective sensation experienced by the patient during a seizure – constitute a cardinal feature of this syndrome. Since they are usually the first symptom to appear in the course of a seizure, auras are still the best available clinical indicator of the possible location of an epileptogenic zone, and the localizing value of auras may be as accurate as EEG and modern imaging procedures [19].

Typical auras in TLE-HS patients are epigastric sensations and psychic symptoms, which include fear, dysmnestic (such as *déjà vu* and *jamais vu*), and olfactory and gustatory sensations [20–22]. Extratemporal auras, such as visual and somatosensory symptoms, can be reported by patients with TLE [12,19–21,23,24].

Recollection of auras by TLE patients is quite variable, ranging from 20 to 96% [21,25–27]. The patients may report single or multiple auras or occasionally, no aura at all. Auras may be absent either if the ictal discharge originates in a silent cortex or if the patient has lost consciousness too fast to remember the symptom [28]. Amnesia of the aura is associated with bitemporal dysfunction [29], severity of seizure, or spread of the ictal discharge during the aura [30]. There is some evidence supporting the claim that multiple auras are associated with non-dominant TLE [31]. Seizure focus laterality may also influence the type of aura presented by TLE patients [32–34], although this was not confirmed in other studies [19,20].

We have performed a retrospective study aiming to analyze the clinical data of a homogeneous group of patients with TLE and unilateral HS, with emphasis on characteristics of the auras presented by these patients. We assessed the possible correlation between presence of

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multiple auras and side of the HS and post-surgical outcome with respect to seizures. Also, we investigated if the presence of extratemporal auras in this population is associated with post-surgical outcome.

2. Patients and methods

Patients with medically refractory unilateral TLE with HS, followed at the Epilepsy Clinic of the Universidade Federal de São Paulo, São Paulo, Brazil, between July 2000 and May 2011, were included in this study. Diagnosis was established according to the previously reported clinical and electrographic characteristics [35]. All patients were interviewed for detailed clinical data including occurrence of initial precipitant insult (IPI) and febrile seizures (FS), onset of epilepsy, development, presence of aura (both currently and within past years), and frequency of seizures. They also underwent an extensive evaluation consisting of neurological examination, high-resolution brain MRI, neuropsychological and psychiatric evaluations, and psychosocial assessment. All patients had unilateral hippocampal atrophy diagnosed on imaging. The exams were performed in 1.5-T equipment (Siemens Somaton or Phillips Gyroscan) and were blindly analyzed by a single neuroradiologist with expertise in epilepsy (HC, Jr.). Patients with bilateral HS and/or additional abnormalities (except for parenchymal calcifications) detected by visual inspection were excluded.

Selected patients had prolonged noninvasive video–EEG monitoring with scalp-sphenoidal electrodes. After complete pre-surgical evaluation, a subgroup of patients was submitted to surgical treatment (anterior temporal lobectomy). Post surgical outcome was classified according to Engel's scale [36]. Patients were further divided into two groups: good outcome (Engel Class I) and poor outcome (Classes II–IV), for means of statistical analysis.

Auras were grouped following the Classification of Epileptic Seizures of the International League Against Epilepsy [37] and according to their most frequent anatomical localization [22] were divided into four groups: (1) mesial temporal lobe auras, which included psychic symptoms such as dysmnestic, cognitive and affective auras, autonomic auras such as epigastric sensation with or without other autonomic signs or symptoms, olfactory and gustatory sensations; (2) lateral temporal lobe auras, including vertiginous and auditory auras; (3) extratemporal auras, which included somatosensory, visual and dysphasic auras; and (4) unspecific auras, including vague feeling of discomfort, whole body auras, and cephalic sensation. We also classified patients regarding the presence and number of auras in two groups: (1) absent or single aura and (2) multiple auras. The number of auras reported by each patient (absent/single or multiple) refers to those auras reported currently by these patients, while the division in groups according to the type of aura was based on all auras reported during life.

Data were analyzed by either χ^2-test or Mann–Whitney test (U). Multiple logistic regressions were used to investigate the relation between aura types and surgical outcome. Values of $p<0.05$ were considered statistically significant. SPSS 11.5.1 for Windows was employed for statistical analysis.

The Ethics Committee of our institution approved the study.

3. Results

3.1. Clinical characteristics

Two hundred and five consecutive patients (122 women) were included in the study. Age varied from 15 to 64 years (mean 38.9 years, SD 10.5). Sixty percent (122 patients) had past history of IPI; 49 of them (43%) had febrile seizures occurring from three months to seven years (mean 2.06 years). Age of onset of epilepsy ranged from the first year of life to 47 years (mean 12.3), while mean duration of epilepsy from onset of habitual seizures to surgery or to the time of MRI procedure was 26.6 years (SD 12.5, range 3–58). One hundred nine (58%) patients had left HS and 86 (42%) had right HS. Patients had from 0.08 to 30 seizures per month (mean of four per month).

Table 1
Number of auras: clinical and demographical data (n = 205).

	Groups		Statistic	p
	Absent/single	Multiple		
Female[a]	52	65	$\chi^2(1)=3.35$	0.067
IPI[a]	58	61	$\chi^2(1)=0.24$	0.625
FS[a]	24	25	$\chi^2(1)=0.03$	0.867
Age at IPI[b]	1.75	1.66	U = 1706.5	0.920
Age at onset[b]	12	9	U = 4447.5	0.095
Epilepsy duration[b]	25	26	U = 4968.5	0.669
Monthly n of seizure[b]	3	4	U = 4666.0	0.304

IPI: initial precipitant insult; FS: febrile seizure; HS: hippocampal sclerosis.
$p<0.05$ was considered statistically significant.
[a] Percentage.
[b] Median.

3.2. Auras: absent/single or multiple

Eighty-eight patients (43%) had absent (n = 17) or a single aura (n = 71), and 117 (57%) had multiple auras. The auras reported were epigastric (52%), autonomic (30%), fear (19%), dysmnestic (16%), cephalic sensation (15%), visual (14%), vertiginous (12%), somatosensory (9%), affective (except fear — 6%), auditory (6%), vague feeling of discomfort (6%), cognitive (5%), gustatory (4%), whole body (4%), psychic (2%), olfactory (2%), and dysphasic (2%).

No significant differences among the groups absent/single and multiple auras were found regarding general clinical characteristics (Table 1).

With respect to the number of auras and side of lesion, right HS was found in 40% (47/117) of patients with multiple auras and in 44% (29/88) of patients with absent/single auras, which was not significantly different ($p=0.551$).

One hundred fifty-seven patients were operated. Seventy percent was free of disabling seizures (Engel 1). The occurrence of multiple auras was not associated with post surgical outcome: multiple auras were reported by 64 patients with good outcome (58%) and 26 (55%) with poor outcome ($p=0.740$).

3.3. Type of aura and surgical outcome

One hundred sixty-two patients (80%) had mesial temporal auras, and 31 (16%) had lateral temporal auras. Extratemporal auras were reported by 45 patients (22%). Eighteen (9%) patients reported somatosensory auras as part of their habitual seizures. Somatosensory auras were contralateral to the epileptogenic temporal lobe in five patients, non-lateralized in eight, and ipsilateral to the focus in five patients. Twenty-seven (14%) patients reported visual auras during life: eight had simple visual auras, 18 had complex visual hallucination or illusion, and one reported both. Unspecific auras were reported by 48 patients (24%).

The presence of extratemporal auras was significantly higher in patients with poor outcome (Table 2).

Table 2
Aura types and post surgical outcome.

	Outcome (%)		$\chi^2(1)$	p
	Engel 1	Engel 2–4		
Mesial temporal	80	79	0.03	0.856
Lateral temporal	13	19	1.09	0.297
Extratemporal	16	34	6.07	0.014*
Unspecific	24	19	0.38	0.536

* $p<0.05$ was considered statistically significant.

Fifteen patients with somatosensory auras were operated. Three of four who had symptoms contralateral to the epileptogenic temporal lobe had poor outcome, while four of five patients with symptoms ipsilateral to the focus had good outcome. When analyzed separately, somatosensory auras did not predict a poor surgical outcome while visual auras did (Table 3).

3.4. Type of aura and lesion side

Aura semiology was not associated with lateralization of hippocampal sclerosis (Table 4).

4. Discussion

In this study, we failed to confirm an association of multiple auras either with seizure focus laterality or with surgical outcome in TLE patients with unilateral HS. Aura semiology was not associated with the side of the HS. However, the presence of extratemporal auras did predict a poor surgical outcome.

4.1. Prevalence of multiple auras

The prevalence of multiple auras in patients with focal epilepsies is quite variable, ranging from 0.4 to 61% [30,31,38–40]. This wide variability reflects methodological differences in inclusion criteria, aura definition and classification, and heterogeneities of the series with respect to etiology.

Widdess-Walsh et al. [31] found a very low prevalence of 0.4%. The authors only studied auras recorded during prolonged video–EEG monitoring in an epilepsy unit, which explains this low figure encountered. In the epilepsy monitoring units, probably, less than 50% of the recorded seizures are accompanied by subjective manifestations [41]. Reduced levels of medication lead to seizures that quickly and widely spread, which may cause a higher frequency of secondary generalized convulsive seizures, making the report of auras more rare [19].

Reporting of aura depends on gender and IQ of the patient [24,38,42–44] and also on the experience of the interviewer. The importance of obtaining a detailed description of the aura is often overlooked, and the interviewer must have a belief in its importance in order to succeed in this difficult task [38].

In our series, 57% of the patients reported multiple auras. Our sample comprised a homogeneous group of patients with TLE and HS, in contrast with Widdess-Walsh et al. [31], who included patients with temporal or posterior quadrant foci of variable etiology, such as HS, brain tumor, infarct, cortical dysplasia, and vascular malformations. Schulz et al. [30] studied 108 seizures with aura from 23 patients with different types of focal epilepsies, including 13 with temporal focus, four with parieto-occipital focus, two with frontal focus, and four with focal non-localized focus. Fourteen (61%) of these patients had two to three symptoms during their aura. Taylor and Lochery [38] compared two groups of patients with refractory TLE, 41 with HS, and 47 with "alien tissue". Among the 88 patients, the authors found multiple auras in 42 (48%). Kanemoto and Janz [39] analyzed 142 patients with complex focal seizures with both temporal and extratemporal foci; 31 (22%) of them reported multiple auras.

Table 3
Extratemporal auras and post surgical outcome.

	Outcome (%)		$\chi^2(1)$	p
	Good	Poor		
Visual	9	21	4.40	0.036*
Somatosensory	7	17	–	0.084

* $p<0.05$ was considered statistically significant.

Table 4
Type of aura and lesion side (n = 205).

	Hippocampal sclerosis		
Aura type	Left	Right	p value
Somatosensory			
Absent (n)	89.9% (107)	93% (80)	0.618
Present (n)	10.1% (12)	7% (6)	
Visual			
Absent (n)	87.4% (104)	86% (74)	0.836
Present (n)	12.6% (15)	14% (12)	
Auditory			
Absent (n)	95% (113)	94.2% (81)	1.000
Present (n)	5% (6)	5.8% (5)	
Vertiginous			
Absent (n)	85.7% (102)	93% (80)	0.12
Present (n)	14.3% (17)	7% (6)	
Olfactory			
Absent (n)	100% (119)	95.3% (82)	0.03
Present (n)	0% (0)	4.7% (4)	
Gustatory			
Absent (n)	96.6% (115)	95.3% (82)	0.723
Present (n)	3.4% (4)	4.7% (4)	
Whole body auras			
Absent (n)	97.5% (116)	94.2% (81)	0.284
Present (n)	2.5% (3)	5.8% (5)	
Vague feeling of discomfort			
Absent (n)	95% (113)	93% (80)	0.563
Present (n)	5% (6)	7% (6)	
Cephalic sensation			
Absent (n)	82.4% (98)	90.7% (78)	0.106
Present (n)	17.6% (21)	9.3% (8)	
Cognitive			
Absent (n)	95% (113)	96.5% (83)	0.737
Present (n)	5% (6)	3.5% (3)	
Epigastric sensation			
Absent (n)	50.4% (60)	46.5% (40)	0.671
Present (n)	49.6% (59)	53.5% (46)	
Autonomic (no epigastric)			
Absent (n)	66.4% (79)	75.6% (65)	0.167
Present (n)	33.6% (40)	24.4% (21)	
Autonomic			
Absent (n)	31.1% (37)	40.7% (35)	0.183
Present (n)	68.9% (82)	59.3% (51)	
Affective (no fear)			
Absent (n)	95.8% (114)	91.9% (79)	0.247
Present (n)	4.2% (5)	8.1% (7)	
Fear			
Absent (n)	80.7% (96)	82.6% (71)	0.856
Present (n)	19.3% (23)	17.4% (15)	
Affective			
Absent (n)	77.3% (92)	77.9% (67)	1.000
Present (n)	22.7% (27)	22.1% (19)	
Dysphasic			
Absent (n)	97.5% (116)	100% (86)	0.266
Present (n)	2.5% (3)	0% (0)	
Psychic			
Absent (n)	85.7% (102)	77.9% (67)	0.193
Present (n)	14.3% (17)	22.1% (19)	
Psychic other			
Absent (n)	97.5% (116)	98.8% (85)	0.641
Present (n)	2.5% (3)	1.2% (1)	
Psychic dysmnestic			
Absent (n)	88.2% (105)	79.1% (68)	0.082
Present (n)	11.8% (14)	20.9% (18)	

$p<0.05$ was considered statistically significant.

4.2. Different types of auras are not associated with lesion side

The lateralizing value of auras is still controversial in the literature. There is some evidence that experiential phenomena are more common on right temporal lobe stimulation [32,33]. Gupta et al. [21]

reported that right EEG abnormalities occurred more frequently in patients with psychic and autonomic auras. Taylor and Lochery [38] suggested an association of visceral auras with right TLE. Some findings suggest that orgasmic aura originates from the right hemisphere [34]. Other studies failed in correlating semiology of auras with side of pathology of the brain [19,20]. In our study, we found no significant correlation between semiology of auras and side of HS. The exception was olfactory auras, which were reported only by patients with right HS. However, the small number of patients reporting this aura and the fact that no patients with left HS had this type of aura limit the analysis. Dysphasic auras were reported only by patients with left HS, as expected, although statistical analysis failed to confirm this association. There was some predominance of dysmnestic auras in seizures of right temporal lobe origin, though without statistical significance.

4.3. Multiple auras are not associated with lesion side

There are few data supporting that multiple auras are associated with non-dominant hemisphere epilepsy. Epileptic activity originating in the dominant hemisphere may more often result in impairment of consciousness, which affects the ability to report the aura [28].

Widdess-Walsh et al. [31] reported a higher prevalence of multiple auras in patients with right hemisphere epilepsy. The authors studied 31 patients with multiple auras, among 7618 who underwent video–EEG monitoring in their center. Among them, 27 had lesions in the right hemisphere, while only three had a left-sided lesion and one had lesions in both hemispheres. In their series, the seizures of patients who recalled more auras had ictal discharges restricted to the right hemisphere. In a study comparing TLE patients with HS and other lesions, a slight preponderance of right-sided seizures was observed among patients with a higher number of reported auras [38].

On the other hand, amnesia of the aura and lack of aura experience are associated with dominant hemisphere seizures, bitemporal epilepsy and severity of seizures. Schulz et al. [30] analyzed 108 seizures from a heterogeneous group of 23 patients, 13 of whom had TLE. Among these patients, a more widespread distribution of the ictal discharges and more severe seizures were more frequently observed in patients who did not recollect the aura. Inoue et al. [28] reported that temporal lobe seizures without preceding auras tend to originate in the language-dominant temporal lobe. In another study of 58 patients with TLE, lesional or non-lesional in MRI, the authors found that lack of aura was significantly correlated with bitemporal interictal epileptiform discharges, absence of lateralized MRI sclerosis and propagation of the the electrographic seizure to the contralateral temporal lobe. However, the authors found no association between side of TLE and memory of the aura [29].

In our series of 205 patients with TLE with HS, left and right sides well represented, after thorough review of the semiology of auras, we did not find an association of multiple auras and lesion side. It is possible that the recollection of multiple auras is in fact associated with the ictal discharge being restricted to one temporal lobe, whether the right or the left. Seizures involving both temporal lobes would render the patient unable to recall the aura. As Taylor and Lochery [38] remarked, the "aura must occur when there is still functioning, remembering, brain".

4.4. Multiple auras are not predictive of post-surgical outcome

The mechanism responsible for the occurrence of multiple auras is still unknown. One hypothesis is that if the seizure remains restricted to the region of origin, not involving deep and contralateral areas, consciousness is preserved, and therefore, recollection of auras is possible [29]. We hypothesized that multiple auras could reflect a more widespread epileptogenic network and hence a worse outcome after the standard surgical treatment, which consists of resection of mesial temporal structures and limited temporal neocortical tissue. However, in our series, occurrence of multiple auras was not predictive of post-surgical outcome.

The association of multiple auras and surgical outcome has not been previously investigated, except for the work of Widdess-Walsh et al. [31], who studied multiple auras occurring in the same seizure. In their series, in all patients except one, a single epileptogenic zone was usually responsible for these phenomena, and the presence of multiple auras was not a negative prognostic indicator for epilepsy surgery. However, the authors did not address the situation of multiple auras occurring in different seizures. We studied the occurrence of multiple auras during life, which were not predictive of a poor outcome.

4.5. Extratemporal auras correlate with worse post-surgical outcome

Some findings suggest that, in TLE patients, more extensive lesions are associated with poorer outcomes [45]. At the moment, there are no biomarkers that predict the extent of the seizure onset zone in these patients. Current imaging technologies are good at demonstrating hippocampal abnormalities but may miss extrahippocampal subtle pathology. Extratemporal auras, in patients with TLE-HS, may correspond to propagation of the ictal discharge to extratemporal structures or may alternatively reflect an extratemporal epileptogenic area. Auras pointing to extratemporal symptomatogenic zones may be a strong predictor of extratemporal epileptogenicity and, in operated patients, may predict a worse outcome.

Depth recordings have shown that in patients with TLE and HS, most of the seizures arise from the hippocampus. However, electrical stimulation studies suggest that the symptomatogenic area for most of the symptoms associated with mesial temporal lobe seizures corresponds to spread of the epileptiform activity to adjacent structures [46]. Most of the cortex is silent, as electrical stimulation studies have shown. Therefore, clinical signs and symptoms appear only when epileptic discharges begin or spread to eloquent area [24].

Though multiple auras did not correlate with surgical outcome, reporting of extratemporal auras was predictive of a worse outcome in our patients.

Tuxhorn [23] described 10 patients with TLE who presented somatosensory auras. Eight patients had HS, and two had neocortical TLE. The auras were axial in six and in a distal extremity in four. Four had ipsilateral auras and the remaining patients had contralateral face and arm auras, reported in association with epigastric aura.

Erickson et al. [12] studied 81 patients with refractory TLE and found that nine (11%), four of them with mesial temporal sclerosis, had somatosensory auras. Five patients had strictly unilateral somatosensory symptoms during somatosensory auras; in four of them, seizure origin was in the contralateral temporal lobe, with spread to the centrotemporal region. Three patients had bilateral somatosensory symptoms, and surface EEG recordings demonstrated bilateral seizure activity in all these cases. After surgical treatment, 77% of these patients were seizure free after 2 years of follow-up. The authors concluded that the occurrence of somatosensory auras, whether unilateral or bilateral, should not contraindicate temporal lobe resection in patients with refractory TLE in whom semiological, electrophysiological and imaging data clearly support a unilateral temporal seizure focus. However, when analyzing separately the four patients with contralateral symptoms, half of them remained having seizures after the surgery.

In our series, we found a prevalence of somatosensory auras of 9%, which was similar to the literature. The symptoms were contralateral to the epileptogenic temporal lobe in five patients, which is highly suggestive of spread to symptomatogenic regions outside the temporal lobe [23,47], non-lateralized in eight and ipsilateral to the focus in five, suggesting spread to the secondary sensory area. These data suggest that the occurrence of somatosensory auras contralateral to HS

may predict a worse surgical outcome and may be reflecting that in some patients with TLE-HS, the epileptogenic network might extend beyond the hippocampus [4–6,8,11–13,48]. Distinct epileptogenic networks are involved in the generation of seizures in TLE [49], and the detection of patients with extended networks may help to improve of surgical outcomes.

Visual auras – simple or complex hallucinations – typically occur in occipital lobe epilepsy [50]. Bien et al. [51] found elementary hallucinations, illusions, and visual loss reported in all patients with occipital lobe epilepsy and also in patients with occipitotemporal and anteromedial temporal seizure onset. Complex visual hallucinations occurred only in occipitotemporal and anteromedial temporal epilepsy patients [51,52]. In our series, 27 of 205 (14%) patients reported visual auras during life. Visual auras were more frequent in patients with poor outcome.

In the last proposal for a classification of epileptic seizures and syndromes [53], TLE with HS was categorized as a constellation, since it presents clinically distinctive characteristics on the basis of a specific lesion. In this sense, it is expected that clinical presentation may vary among patients that share the common finding of HS in neuroimaging, anterior temporal interictal spikes and seizure onset zone localized over the temporal lobes in the EEG. There is plenty of evidence suggesting that TLE is a disease that affects not only the hippocampus but also other brain structures [4–6,8,11–13,48]. Patients with these characteristics may nevertheless have features of extratemporal involvement [3,8,12], such as extratemporal auras, which could predict a poor post surgical outcome. Seizure semiology may help identify patients with TLE-HS, in whom the extratemporal cortex plays an important epileptogenic role, thus rendering them inappropriate candidates for standard surgical procedure.

In conclusion, in this series consisting of patients with TLE and unilateral HS, occurrence of multiple auras was associated neither with seizure focus laterality nor with post-surgical outcome. In operated patients, reporting of extratemporal auras was predictive of worse surgical outcome, possibly reflecting extratemporal epileptogenicity in these patients, who otherwise showed features suggestive of TLE. Therefore, patients with TLE-HS undergoing pre-surgical evaluation and presenting clinical symptoms suggestive of extratemporal involvement should be more extensively evaluated to avoid incomplete resection of the epileptogenic zone.

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