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Are auras a reliable clinical indicator in medial temporal lobe epilepsy with hippocampal sclerosis ?

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Abstract

Background and purpose: Medial temporal lobe epilepsy with unilateral hippocampal sclerosis (MTLE-HS) is the most frequent form of surgical temporal lobe epilepsy. In this study, we wished to determine whether different types of aura represent a cardinal and characteristic feature of MTLE-HS and might provide a diagnostic complement to help identify patients who will be seizure free after surgery

Methods: We retrospectively collected all types of auras and associations of auras reported by 400 MTLE-HS patients referred for surgery and examined their statistical correlation with the postoperative outcome in a subgroup of 305 patients who underwent surgery.

Results: A total of 876 auras was collected, classified into 12 categories. Globally, MTLE-HS patients reported widely variable auras and groupings of auras. Most common were autonomic and abdominal visceral auras, followed by psychoaffective and experiential auras; less common, but seen in 10- 15% of patients, were non-specific auras, somatosensory auras, and visual auras, and least common, reported by less than 10% of patients, were auditory, gustatory, vestibular, olfactory and intellectual auras. No auras were reported in 10% of patients. 65% of patients experienced more than one (2-7) type of aura. No specific groupings of aura type were apparent. We found no evidence for correlation between postoperative outcome and i) any category of aura, ii) the number of categories of aura per patient and iii) any association of categories of auras.

Conclusion: Auras and association of auras vary widely in MTLE-HS and provide no useful insight into surgical outcome.

Introduction

Medial temporal lobe epilepsy associated with unilateral hippocampal sclerosis (MTLE-HS) is the most frequent form of temporal lobe epilepsy [1]. Surgery is usually associated to a favourable but variable postoperative outcome [2,3]. It remains unclear whether MTLE-HS should be considered a subtype of a broader syndrome of MTLE or whether it represents a unique syndrome. Pathological criteria suggest MTLE-HS may be unique and differ from other focal temporal lobe epilepsies [4]. However the multiple types of MTLE-HS, which include primary, secondary, familial, benign and severe forms, may argue against a single syndrome [5-7]. If MTLE-HS is a distinct syndrome then, regardless of the cause, a cluster of signs should define a single diagnostic entity. In first line, this cluster of signs characterizing MTLE-HS as a single syndrome should include auras and combination of auras, as suggested by initial studies on small populations of patients [8-12]. Typical auras in MTLE-HS patients are described as abdominal visceral sensations, autonomic and psychoaffective symptoms and olfactory or gustatory sensations [13]. At the opposite there are only very few data about the proportion of MTLE-HS who present with less typical aura features: no aura or auras that are not usually associated to MTLE such as somatosensory, visual, or vestibular symptoms, and about their signification in terms of postoperative outcome. We asked here whether auras really represent a cardinal feature of MTLE-HS and might provide a useful additional diagnostic framework. For this purpose we precisely described all types of auras and associations of aura types in 400 well-defined MTLE-HS patients. We then asked whether auras or associations of auras could help to identify those MTLE-HS patients who would be seizure free after surgery in a subgroup of 305 patients who underwent surgery with reliable determination of the postoperative seizure outcome.

Material and methods

Patients

The group of patients studied was identified from the Epilepsy Data Base of the Epilepsy Unit of the Pitié-Salpêtrière Hospital in Paris. It consisted of all patients suffering from refractory medial temporal lobe epilepsy (MTLE) associated with hippocampal sclerosis (HS) who underwent video-EEG examinations between 1991 and 2013.

Criteria for inclusion were: 1) a well defined refractory MTLE with at least one video-EEG record of a seizure, 2) a unilateral hippocampal sclerosis visualized with structural MRI, 3) a well documented description of auras. All patients gave their informed written consent at the time of the video-EEG exam for further publication of data related to their epilepsy.

Collection of data

We retrospectively reviewed all medical records of 400 patients who fulfilled these criteria, to gather the following data:

- demographic data: sex, age
- anamnestic data related to epilepsy: age at onset, early events such as febrile convulsions, head trauma, side of the hippocampal sclerosis, number of antiepileptic drugs at the time of video-EEG recording, median number of seizures per month
- aura characteristics: report and description of each aura; in this study, we considered that an aura was present if associated with at least one, but not necessarily all, of the patient's seizures. All medical records and all charts of the seizures recorded during video-EEG were retrospectively reviewed but we did not determine at the time of the reviewing in how many seizures a specific aura or a specific association of auras occurred for each individual patient exhibiting multiple auras.
- surgery occurrence. If surgery took place the postoperative outcome was defined with a simplified Engel's classification (Engel's class Ia: completely seizure free patients,

Engel's class I: seizure free patients and those who experienced only simple partial seizures, or drug withdrawal seizures, Engel's class II-III-IV patients: those where complex seizures were not abolished and surgery outcome was judged as truly unsatisfactory). Postoperative outcome was assessed at least one year after surgery.

Statistical analysis

We made a monovariate analysis of correlations between postoperative outcome groups (Ia, I, II-IV) and each category of auras or association of categories of auras (MedCalc software). This first analysis was made only for aura categories reported by at least 10 patients. A second analysis consisted of a multiple regression that examined correlations between categories of auras, number of categories of auras, associations of aura category, side of HS and post-operative outcome groups.

Since we did not determine at the time of the reviewing in how many seizures a specific association of auras occurred for each individual patient exhibiting multiple auras, variation between seizures in a patient was not accounted for.

Results

Global population description

There were 185 men and 215 women. 46% suffered from right MTLE-HS and 54% from left MTLE-HS. 80% of patients had a history of early events, mainly febrile convulsions (59%). The median age at onset was 10 ± 9 years, the median duration of epilepsy was 24 ± 12 years (table 1).

324 of the 400 patients underwent surgery (81%) and 76 (19%) did not. Among the 76 patients who did not undergo surgery, 18 (24%) finally declined surgery, 41 (54%) were rejected mainly for psychiatric ($n=24$) or neuropsychological ($n=10$) reasons, 17 were lost to follow up, 9 had accepted surgery and are still waiting for operation, and one patient deceased.

Postoperative outcome could not be determined in 19 patients (14 were lost to one year postoperative follow up, and the 5 remaining patients had a too short postoperative follow up period).

Postoperative outcome was finally reliably determined for 305 patients.

262 of the patients who underwent surgery (86%) were Engel's class I and 43 belonged to Engel's class II - III-IV (15%). Of the class I patients 217 (71%) were Engel's class Ia,

Classification of auras

359 patients (90%) experienced at least one aura. Table 2 provides details of 876 auras, including 37 distinct auras which were described. In order of frequency, auras involved: rising epigastric sensations (44% of patients), feelings of fear or anxiety (29% of patients), rising warm sensations (19% of patients), a thoracic constriction (16% of patients), a déjà vu-déjà/vécu (16% of patients), tachycardia (14% of patients) or tingling, typically bilateral, non ascending and diffuse (10% of patients).

We grouped together auras presumed to originate in similar brain regions, resulting in twelve distinct categories of aura. Thus rising epigastric sensation and nausea were included in the "abdominal-visceral" category. As shown in table 2, about 50% of patients had autonomic and abdominal-visceral, 30% psychoaffective, 20% experiential auras and auras experienced by about 15% of patients were attributed to other categories including somatosensory, visual, auditory, gustatory, vestibular, olfactory, intellectual and non specific auras. Patients could experience different aura categories simultaneously (Figure 1). 65% of patients experienced multiple aura categories (2-7), 25% only one and 10% of patients never experienced an aura.

Each category of auras could be isolated or associated with other categories. Some categories of auras, such as gustatory and intellectual auras, never occurred alone. Other categories including auditory, visual, psychoaffective, olfactory, experiential and vestibular auras were rarely isolated - less than 10%. In contrast, autonomic, abdominal visceral, non specific and somatosensory auras occurred in isolation more frequently (11% to 37% of isolated auras).

Our data revealed no tendency for specific associations between different types of aura. The most frequent grouping was that of abdominal-visceral aura + autonomic aura (in 7% of patients). Autonomic + psychoaffective auras and autonomic + abdominal-visceral + psychoaffective auras both occurred in 4% of patients. No other association was detected in more than 3% of patients.

Type of aura and lesion side

Aura semiology was not associated with lateralization of hippocampal sclerosis.

Correlations with postoperative outcome

We detected no significant correlation between postoperative outcome, defined according to Engels classification, and:

- any category of aura (Figure 2).
- the number of categories of aura per patient
- any association of categories of auras

Specifically, neither monovariate or multivariate analyses provided evidence for prognostic differences between patients with no aura, with non-specific, somatosensory, visual, auditory, gustatory, vestibular or olfactory auras or other patients.

Discussion

This study, of a large population of MTLE-HS patients, reports widely variable auras and groupings of auras, including some types of aura less frequently associated with the syndrome. It finds no correlation between specific aura types or groupings and postoperative outcome. Thus analysis of auras does not help identify patients for whom surgery may be ineffective.

Wide variability of auras and associations of auras in MTLE-HS

This study reports 37 distinct auras, 12 categories of auras and numerous associations of auras experienced by MTLE-HS patients. As expected autonomic and abdominal visceral auras (49% of patients), psychoaffective auras (32%) and experiential auras (21%) were the most frequently reported categories of auras. A second group of auras included some categories less obviously indicative of a medial temporal lobe localization: visual, somatosensory and non specific auras, or no aura at all. The relative high frequency (10-15%) of this latter group of auras and the lack of association with a poorer postoperative outcome strongly suggest that they are linked to MTLE-HS and not to seizures originating outside the medial temporal lobe. Tingling, typically diffuse and bilateral, occurred in auras of 10% of patients. Somatosensory auras are typically described in patients with parietal, insular or opercular epilepsies [12,14] but differed in these MTLE-HS patients in that they tended to begin in the hand, ascend and involve contralateral regions. In agreement with our findings a recent study [15] has reported somatosensory auras in patients with refractory temporal lobe seizures (11%). Similarly, visual auras that occurred in 10% of our sample, have been reported previously in MTLE-HS [16]. We found that 10% of MTLE-HS patients never experienced an aura, a similar level to that from previous work on the significance of the absence of an aura in patients with temporal lobe epilepsy [17]. We note though that an inability of MTLE-HS patients to remember an aura may not argue for an extra hippocampal

seizure focus but rather result from distinct ictal propagation patterns: 1) consciousness may be lost too quickly for patients to retain subjective experience [18] and 2) amnesia may be associated with bitemporal involvement in the seizure [19,20]. Non specific (“difficult to describe”) auras were reported by 14% of our patients. Such auras have been specifically associated with MTLE-HS by the Istanbul workshop [4]. Less frequent categories of aura included auditory, gustatory, vestibular, olfactory and intellectual auras. These auras presumably all involve medial temporal cortex activity, but also frontal orbitary cortex for olfactory auras, the opercular region for gustative auras, neocortical regions around the Heschl gyrus [21] for auditory auras and posterior temporal neocortex [22] for vestibular auras. Such auras do not compromise the diagnosis of MTLE-HS and their presence was not associated with a poorer postoperative outcome.

Localizing value of the auras in MTLE-HS

Multiple arguments suggest that MTLE-HS involves wide areas of structural and functional disturbances beyond the sclerotic hippocampus [4]. Three types of argument favour a distributed symptomatogenic brain network:

- i) categories of aura most frequently associated with MTLE-HS may originate outside the hippocampus (for example, abdominal visceral auras such as rising epigastric sensation and other autonomic auras are linked to the spread of epileptic discharges to the insular cortex [23], and experiential auras could occur when epileptic discharges spread to both lateral and medial temporal cortices [24]).
- ii) categories of auras that are usually attributed to extralimbic regions (somatosensory sensations, visual complex or auditory hallucinations) may be elicited by hippocampal stimulation [25-27].
- iii) the high variability of auras and associations of auras depicted in this study regardless of the postoperative outcome

Auras are not a clinical warning of unsuccessful surgery

Surgery is a highly effective treatment for patients with refractory MTLE-HS. However, only two-thirds of patients are seizure-free in the 2 to 3 years after surgery [2,3,28,29]. Multiple studies have attempted to define variables that influence postoperative outcome [30, 31-34]. Variables tested were typically related to the hippocampal sclerosis (unilateral HS, HS side concordant to the interictal EEG focus, circumscribed FDG-PET hypometabolism) or to the volume of tissue removed during surgery [31]. However little data is available on clinical variables. Studying relations between presence and frequency of auras and post surgical outcomes in 205 patients with MTLE-HS [35], Ferrari-Marinho et al. found that extratemporal auras were associated with a poor surgical outcome. However in that study, extratemporal auras which included somatosensory, visual and dysphasic auras were arbitrarily grouped together and were reported for only 45 patients. In our work, we detected no correlation between any category or any association of categories of auras and postoperative outcome. This absence of correlation between subjective ictal semiology and postoperative outcome may certainly be explained by the variability of the auras and the low frequency of poor outcomes.

Limitation of the study

Our analyses were retrospective, based on medical and seizure charts and we acknowledge the limitations of a retrospective study.

Conclusion

This study shows that auras and associations of auras experienced by MTLE-HS patients are highly variable and do not influence the postoperative outcome. Presumably the wide variability of auras and associations of auras experienced by this group of MTLE-HS patients is linked to a rapid recruitment of diverse and distributed brain regions. However a fast involvement of brain networks that may be both close and distant to the HS may not

necessarily predict a bad postoperative outcome, but rather that epileptic discharges arising from the MTL structures spread quickly to distant circuits. The wide variability of types of aura may represent a hallmark of MTLE-HS, providing support for the notion of a network disease rather than one centered on a single lesion. Implications for patient management are that aura symptoms should not overcome concordant data on seizure initiation site from objective clinical signs, interictal and ictal surface EEG recordings and structural imaging.

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Figure Titles

Figure 1: Number of categories of auras per patient

Figure 2 : Frequency of categories of auras according to the postoperative outcome group

Tables Titles

Table 1 : Patients characteristics

Table 2 : Frequency and types of auras

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Figure 1 Number of categories of auras per patient

Figure 2 Frequency of categories of auras according to the postoperative outcome group

Table 1 Patients characteristics

		<u>Global n (%)</u>
<u>Total</u>		<u>400 (100%)</u>
<u>Demographic data</u>	<u>male</u>	<u>185 (46%)</u>
	<u>female</u>	<u>215 (54%)</u>
<u>Anamnestic data</u>	<u>Total</u>	<u>318 (80%)</u>
	<u>Febrile convulsions</u>	<u>234 (59%)</u>
	<u>Head trauma</u>	<u>55 (14%)</u>
	<u>Meningitis</u>	<u>33 (8%)</u>
<u>Epilepsy data</u>	<u>Age at onset (years)/(median $\pm$ CI)</u>	<u>10 $\pm$ 9</u>
<u>CI=confidence interval</u>	<u>Duration (years)/(median $\pm$ CI)</u>	<u>24 $\pm$ 12</u>
	<u>Right- sided hippocampal sclerosis</u>	<u>185 (46%)</u>
	<u>Left-sided hippocampal sclerosis</u>	<u>215 (54%)</u>
	<u>Seizure frequency/month ((median $\pm$ CI)</u>	<u>6 $\pm$ 9</u>
	<u>Number of AEDs (median $\pm$ CI)</u>	<u>2 $\pm$ 1</u>
<u>Surgery data</u>	<u>Surgery</u>	<u>324 (81%)</u>
	<u>Engel's classification</u>	<u>305</u>
	<u>Seizure free (Engel's class Ia)</u>	<u>217 (71%)</u>
	<u>Engel's class I</u>	<u>262 (86%)</u>
	<u>Engel's class II-IV</u>	<u>43 (15%)</u>

Table 2 Frequency and types of auras

classification of aura	%	n
autonomic	49%	197
rising feeling of warmth	19%	76
thoracic constriction	16%	64
tachycardia	14%	57
thrill-feeling of cold	9%	34
breathless	6%	25
pallor-rubror	5%	18
urge to urinate	2%	9
sweating	2%	7
thirst-hunger	1%	5
abdominal visceral	49%	194
rising epigastric sensation	44%	177
nausea	8%	32
abdominal pain	2%	6
dysphagia	1%	3
psychoaffective	32%	127
fear-anxiety	29%	117
hapiness-well being-sadness	3%	11
near death sensation	1%	2
experiential	21%	83
déjàvu-vécu	16%	63
reviviscence	5%	18
dreamy state	3%	13
premonition	1%	3
non specific	14%	56
undescribable	6%	23
numbness-faintness	3%	12
headache	3%	11
feeling of shaking, stiffness	2%	9
somatosensory	12%	46
tingling	10%	38
pain	2%	9
no aura	10%	41
visual	10%	40
complex hallucinations	6%	25
light variation-blurring-illusion	3%	12
micopsia-macropsia	0,5%	2
elementary hallucinations	0,3%	1
auditory	7%	28
complex hallucinations	4%	17
sound modification	2%	6
tinnitus	1%	4
gustatory	7%	26
(hallucinations/illusions)		
vestibular	6%	22
(vertigo/floating,unsteadiness)		
olfactory	3%	13
(hallucinations/illusions)		
intellectual	1%	3
(depersionalisation/mental diplopia, forced idea)		