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Postsurgical outcome in patients with auditory auras and drug-resistant epilepsy

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ABSTRACT

Purpose: We assessed whether patients with auditory auras have similar outcomes after epilepsy surgery as patients without auditory auras, and hypothesized that patients with non-dominant hemisphere foci might fare better after temporal lobe surgery than patients with dominant resections.
Methods: In this retrospective study, outcome after temporal resection was assessed for patients with drug-resistant epilepsy. Preoperative demographic data, clinical data, and surgical outcome were prospectively registered in a database from 1986 through 2016. Seizure outcome was classified as either seizure-free or relapsed.
Results: Data were available in 1186 patients. Forty five patients (3.8%) reported auditory auras; 42 patients (93%) had temporal lobe epilepsy (TLE), and three patients (7%) had extratemporal epilepsy. Since most patients with auditory auras had TLE and in order to have comparable groups, we selected 41 patients with auditory auras and compared them with patients without auditory auras who had temporal lobe resections (767 patients). There were no significant demographic or clinical differences between TLE patients with auditory auras and those without. Patients who had auditory auras were more likely to relapse after temporal lobe surgery than those without ($p = 0.03$). Among patients who had auditory auras and temporal lobe surgery, side of surgery was not related to postoperative outcome ($p = 0.3$).
Conclusion: Auditory auras are rare among patients with drug-resistant TLE. The presence of an auditory aura in a patient with drug-resistant TLE carries a worse prognosis for a postoperative seizure free outcome and this is not related to the side of surgery.

1. Introduction

An aura is a subjective phenomenon that is the initial symptom of a seizure [1]. Auras are a common feature of temporal lobe epilepsy (TLE), and may have localizing or lateralizing value [2,3]. Some common auras, such as epigastric sensations, predict a favorable outcome after anterior temporal lobectomy (ATL) for drug-resistant TLE [4]. In contrast, auditory auras are relatively uncommon, though a striking clinical symptom when reported. Simple auditory auras, such as ringing and buzzing sounds, probably arise in the primary auditory cortex. Complex auditory auras, such as voices and music are probably produced by activation of auditory association areas in posterior temporal cortex [3].

In drug-resistant TLE, resective brain surgery is superior to prolonged medical therapy [5]. In addition to resection of mesial temporal limbic structures, lateral neocortex is also resected to a varying extent. Lateral resection in the dominant hemisphere, particularly in the superior temporal gyrus, must be smaller in extent than in the nondominant hemisphere [6] (see methods) because of the risk of producing Wernicke's aphasia. In this study, we hypothesized that the ability to perform a more extensive resection of the superior temporal gyrus in the nondominant hemisphere in patients with auditory auras would lead to better seizure outcome than that in patients who had surgery in the dominant hemisphere. In addition, we hypothesized that patients with auditory auras might have worse prognosis than patients without these auras, since defining the appropriate extent of resection is inherently more difficult when auditory auras are present.

2. Methods

In this retrospective analysis, data from all patients with drug-resistant epilepsy who underwent epilepsy surgery were reviewed. Patients were prospectively registered in a database from 1986 through 2016. The diagnosis of epilepsy was made by the epileptologists. There was no age restriction to be included in the analysis. All patients had a comprehensive presurgical evaluation including a brain MRI, video-EEG monitoring, neuropsychological testing, Wada or fMRI for language and memory assessment (selected patients), intracranial EEG (selected patients), and intraoperative electrocorticography (selected patients) [7].

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All patients included in the analysis had surgery for epilepsy. For those who had a temporal lobe resection and an auditory aura, surgery was typically modified to include more superior temporal gyrus and auditory cortex when feasible, unless intracranial EEG demonstrated seizure onset elsewhere (e.g., hippocampal seizure origin) or eloquent cortex was involved. Interim review of patient outcome led us to stop doing routine intracranial EEG monitoring prior to resection in many patients with auditory auras as the yield and outcome after intracranial EEG monitoring did not appear to warrant the procedure; we continued to perform intracranial EEG monitoring in selected patients when warranted based on clinical judgment. However, we performed intraoperative electrocorticography in most of the patients to tailor the resection. We assessed outcome in the first 5 years after surgery. Post-surgical outcome was classified into two groups; 1) seizure-free, with or without auras; or 2) relapse of complex partial or secondarily generalized seizures.

Age, gender, age at afebrile seizure onset, seizure type(s), EEG and MRI findings, date of surgery, date of the first relapse (if any), and date of the last contact with all patients were registered routinely. Demographic variables and relevant clinical variables were summarized descriptively to characterize the study population. To have comparable groups, we selected the patients who had temporal lobe resections, with or without auditory auras. We performed Pearson Chi-square, Kolmogorov-Smirnov, and *t*-test, depending upon the circumstance. To investigate any potential association between auditory auras and outcome after surgery, time-to-event analysis was used to produce a Kaplan-Meier estimate of seizure recurrence. The Cox-Mantel test was used to compare the cumulative time-dependent probability of occurrence of the first seizure after resective temporal lobe surgery in patients with and without auditory auras. This study was conducted with the approval of the Thomas Jefferson University Review Board.

3. Results

From 1986 until 2016, 1261 patients were registered in our database. Data regarding type of aura was available for 1186 patients. Forty-five patients (3.8%) (20 men and 25 women) reported auditory auras with their seizures. Forty-one patients had temporal lobe resections; pathology included gliosis (17 patients), hippocampal sclerosis (13 patients), cortical dysplasia (3 patients), cavernous hemangioma (1 patient), heterotopia (1 patient), hamartoma (1 patient), and normal results (2 patients), and data were missing in one patient. One patient had mesial temporal sclerosis and thermal ablation; he was excluded from the analyses as his procedure differed from all other patients. One patient had a parietal lobe resection (with a left parietal lesion on his brain MRI; deemed gliosis on pathology examination); one had ipsilateral temporal and parietal resections (with dual pathology on his brain MRI; left hippocampal sclerosis and left posterior quadrant atrophy and encephalomalacia by MRI report); and one patient had vagus nerve stimulation surgery (with an unspecified left posterior frontal lesion in the brain MRI report; pathology was not available). Therefore, 42 patients (93%) were diagnosed with TLE and three patients (7%) were diagnosed with extratemporal epilepsy.

Intracranial video-EEG recording was performed in 12 patients. The seizure onset zone was in lateral temporal neocortex in four patients (two patients were seizure-free postoperatively), hippocampus in four (two were seizure-free postoperatively), hippocampus and temporal neocortex simultaneously in one patient (seizure-free), parietal and temporal neocortex simultaneously in one patient (had temporo-parietal resection and is not seizure-free), and temporal neocortical and frontal simultaneously in two patients (both had temporal lobe surgery and one is seizure-free after surgery). Among patients who had auditory aura and temporal lobe resective surgery (41 patients), 11 patients had invasive intracranial EEG recordings. The postoperative seizure outcome was not different in patients with intracranial EEG recordings compared to those without this procedure (6 out of 11 were seizure-free in patients with intracranial EEG recordings and 9 out of 30 were seizure-free in patients without intracranial EEG recordings; $p = 0.2$).

Since most patients with auditory auras had TLE and in order to have comparable groups for the purpose of statistical analyses, we selected those 41 patients with auditory auras and temporal lobe resections (cases) and compared them with patients without auditory auras who had temporal lobe resections (767 patients as a comparison group). Table 1 shows the clinical features of patients with temporal lobe epilepsy and auditory aura, who had temporal lobe resection (41 patients), compared with those without auditory aura (767 patients). There were no significant demographic or clinical differences between these two groups. The prevalence of mesial temporal sclerosis on MRI was not significantly different between these two groups (Table 1).

In patients who had temporal lobe resective surgery, 41 had auditory auras, 767 did not. Mean duration of post-surgery follow-up was not different between these two groups (3.8 ± 1.6 years in patients with auditory aura and 4.1 ± 1.5 years in others; $p = 0.2$). Those with preoperative auditory auras were more likely to experience seizure relapse after surgery ($p = 0.03$; Cox-Mantel test) (Fig. 1). Seizure outcome at year 2 of follow-up was available for 34 patients with preoperative auditory auras and 663 patients without auditory auras. We classified the outcome as seizure-free if the patients did not have any seizures for at least one year before their last visit. Among the patients with auditory auras, 19 patients (56%) were seizure-free; among those without auditory auras, 466 patients (70%) were seizure-free ($p = 0.07$; Chi square test).

For patients who had auditory auras and resective temporal lobe surgery (41 patients), side of surgery was not related to postoperative outcome. Among these 41 patients, 35 were right-handed and therefore the left hemisphere was considered as the dominant side. Six patients were either left-handed (four patients) or ambidextrous (two patients). Among left-handed patients, two had Wada results available showing left-hemisphere dominance and two others had fMRI results showing the same. For ambidextrous patients, one was left-hemisphere dominant according to fMRI results and results were not available in one patient to verify the dominant hemisphere. Excluding the patient with unknown hemisphere dominance, patients with non-dominant hemisphere resection (18 patients) fared similarly with respect to post-operative seizure outcome as those with dominant hemisphere surgery (22 patients) ($p = 0.3$).

4. Discussion

Auditory auras are uncommon among patients with epilepsy [8], and while typically arising from a temporal lobe, they indicate a less favorable outcome after surgery in patients who require resection for drug-resistant seizures. It is believed that simple auditory auras localize to the primary auditory cortex (the transverse temporal gyrus of Heschl) and complex auditory phenomena localize to auditory association areas (temporo-occipital cortex) [3]. This may be the case, although seizure origin elsewhere seems quite likely in many patients as many did not attain seizure freedom after surgery with removal of the presumed epileptogenic cortex. In four patients, hippocampal origin of seizures with auditory auras was demonstrated; two of them were seizure-free after surgery. This might be interpreted as the aura being produced by activation of the memory of sound during a seizure. There are also reports of frontal operculum/perisylvian epilepsy producing auditory auras [9] and this could reflect secondary spread of the ictal discharge from the area of seizure generation to auditory cortex. We must conclude that auditory auras have modest localizing value and do not necessarily indicate that primary or auditory association cortex is responsible for generating seizures.

As patients who had preoperative auditory aura were more likely to experience seizure relapse after temporal lobe surgery, further question can be raised about how reliably these symptoms denote the presence