Epilepsy & Behavior 35 (2014) 34–41

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Different localizations underlying cortical gelastic epilepsy: Case series and review of literature ☆

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ARTICLE INFO

Article history:
Received 7 February 2014
Revised 25 March 2014
Accepted 27 March 2014
Available online 3 May 2014

Keywords:
Gelastic seizures
Gelastic epilepsy
Laughter
Epilepsy surgery

ABSTRACT

Background: Gelastic seizures (GS) are classically observed with hypothalamic hamartomas but they can also be associated with cortical epileptogenic foci.
Objective: To study the different cortical localizations associated with GS.
Methods: We reviewed the data from all patients with cortical GS investigated in our epilepsy unit from 1974 to 2012 and in the literature from 1956 to 2013.
Results: Sixteen cases were identified in our database and 77 in the literature. Investigations provided confident focus localization in 9 and 18, respectively. In our series, the identified foci were located in the mesial temporal structures (2 left, 1 right), lateral temporal cortex (1 right), superior frontal gyrus (1 left), and operculoinsular region [3 right (orbitofrontal or frontal operculum extending into the anterior insula) and 1 left (frontal operculum extending into the anterior insula)]. In the literature, the identified foci (13 right/5 left) were located in the temporal lobe of 4 (1 right inferior, 1 right medial and inferior, 1 right posterior middle, inferior extending posteriorly to the lingual gyrus, and 1 left middle, inferior, and medial), in the frontal lobe of 12 [10 (6 right/4 left) medial (i.e., superior, medial frontal, and/or anterior cingulate gyri), 1 lateral (right anterior inferior frontal gyrus), and 1 right medioposterior orbitofrontal cortex] and in the parietal lobe of 2 (1 left superior parietal lobule and 1 right parietal operculum) patients.
Conclusion: Ictal laughter is a poorly lateralizing and localizing feature as it may be encountered in patients with a focus in the left or right frontal, temporal, parietal, or insular lobe.

1. Introduction

Gelastic seizures (GS) are characterized by recurrent bouts of paroxysmal stereotyped laughter [1]. Since the first description of epileptic laughter by Trousseau in 1873 [2], several case reports and small case series have been published. Gelastic seizures have mostly been observed in association with hypothalamic hamartomas and are thought to be one of the hallmark features of this condition [3]. However, they have also been associated with focal cortical foci, mainly in the inferior temporal [4–8] and the mesial frontal areas [9–11]. A critical review of the literature reveals that more than half of the cases were reported before the era of magnetic resonance imaging and that localization was frequently approximated based on techniques of low spatial and/or temporal resolution such as surface electroencephalography (EEG) or single-photon emission computed tomography (SPECT). Fortunately, some patients had focal epileptogenic lesions [12–16], were studied with intracranial electroencephalography (icEEG) [9,10,17–20], and became seizure-free after epilepsy surgery, providing a more precise and confident localization.

In this study, our objective was to establish the different cortical foci capable of generating gelastic seizures. We will first analyze the data from our center and then review all cases reported in the literature with confident localization.

2. Methods

Video-EEG monitoring reports from all patients admitted to the epilepsy monitoring unit of the Centre Hospitalier Université de Montréal (CHUM — Hôpital Notre-Dame, Canada) from 1974 to 2012 were reviewed to identify potential patients with GS. When it was mentioned in these reports that the patient's ictal semiology incorporated laughter, their video-EEG study was reviewed to confirm the presence of gelastic seizures. Furthermore, the patients' clinical charts were carefully reviewed to collect information on demographic characteristics, seizure semiology, video-EEG data (both scalp and intracranial EEG) (Stellate Harmony, Montreal), MRI findings (Siemens 1.5T Avanto, Germany or Phillips 3T Achieva, Netherlands), magnetoencephalographic electrical current dipole source analysis (CTF 275-sensor MEG system, Canada),

☆ This work was not supported by a grant or otherwise. It has been presented as a poster at the American Epilepsy Society 2013 annual meeting.
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http://dx.doi.org/10.1016/j.yebeh.2014.03.024
1525-5050/

surgical treatment, pathology of the resected specimen, and surgical outcome (ILAE classification) [21] when available. Patients with GS associated with hypothalamic hamartomas were excluded.

We then performed an online search of the Medline database (since inception until April 2013) using the keywords 'gelastic seizures' and 'gelastic epilepsy' limited to publications in English or French. Articles in other languages were not considered as authors have limited ability to read and understand them. The titles and abstracts of all search results were screened for studies which reported cases of gelastic seizures. Potentially relevant studies were revised in full text to identify cases of gelastic seizures unrelated to hypothalamic hamartomas. We also searched bibliographies of reviews, original articles, and book chapters to identify additional cases which might have been missed. All available information for each of these cases was assessed by two reviewers in order to determine the probable localization of their epileptic focus. For final analysis, only patients with confident localization were considered. Confident localization was assumed in the presence of a clear epileptogenic lesion (congruent with other complementary tests) or seizure freedom after surgery resection of the suspected area (whether the patient had an epileptogenic lesion or not).

The study was approved by the Research Ethics Committee of the CHUM. All patients signed an approved written informed consent.

3. Results

3.1. Our case series

We identified 16 patients (0.82%) who met our inclusion criteria and constituted our study population (mean age: 41 years old; range: 20–63) (Table 1) from the 1945 patients evaluated at the epilepsy monitoring unit in our center between 1974 and 2012. The onset of seizures usually occurred at a young age (mean age: 13.3 years; range: 1.4–41). Ictal laughter was not always present during each of the patients' seizures with the exception of one case. When it was present, it was always associated with other ictal manifestations (e.g., altered consciousness, complex motor behaviors). The location of the epileptic focus was based on multimodal analysis of brain MRI (n = 16), video-EEG (n = 16), positron emission tomography (n = 10), ictal SPECT (n = 12), MEG (n = 7), and intracranial EEG (n = 10) findings along with the location of epilepsy surgery and outcome (n = 10) as well as pathological analysis of resected tissue (n = 7) when available. The most likely focus identified for each patient was in the temporal lobe of 8 (1 right temporal, 2 left medial, 2 right medial, 1 left lateral, and 2 right lateral), parietal lobe of 1 (right medial) and frontal lobe of 6 (1 left medial, 1 left superior frontal gyrus, 2 right inferior frontal gyrus, 1 left inferior frontal gyrus, and 1 right posterior orbitofrontal cortex) patients. The 4 foci in the inferior frontal gyrus or posterior orbitofrontal cortex extended to the anterior insula. The last patient had 2 foci, one in the left frontal lobe and the other in the right insula. In this patient, it is unclear which focus was responsible for the GS.

Out of these 16 patients, accurate localization could be assumed with confidence in 9 subjects (patients 4 and 7–14) because they had a clear epileptogenic lesion (congruent with other complementary tests) or became seizure-free after surgery. These foci (5 right/4 left) were located in the mesial temporal structures (2 left, 1 right), lateral temporal cortex (1 right), superior frontal gyrus (1 left), and operculoinsular region [3 right (orbitofrontal or frontal operculum extending into the anterior insula), 1 left (frontal operculum extending into the anterior insula)].

3.2. Cases from the literature

In our literature search, we identified 77 patients with gelastic epilepsy without hypothalamic hamartomas reported in 46 papers published until April 2013 (Supplementary table). Of these 77 patients, we retained only 18 patients (10 males and 8 females) for whom focus localization could be assumed with confidence based on the presence of a clear epileptogenic lesion (congruent with other tests) or control of seizures following epilepsy surgery (whether the patient had a lesion or not) (Table 2). These 18 foci (13 right/5 left) were located in the temporal lobe of 4 (1 right inferior, 1 right medial and inferior, 1 right posterior middle, inferior extending posteriorly to the lingual gyrus, and 1 left middle, inferior and medial) and the frontal lobe of 12 [10 (6 right/4 left) medial (i.e., superior, medial frontal, and/or anterior cingulate gyri), 1 lateral (right anterior inferior frontal gyrus), and 1 right medioposterior orbitofrontal cortex] patients. For the last two patients, the focus was said to be in the parietal lobe (1 left superior parietal lobule and 1 right parietal operculum), although for the last patient, the MR axial cut shown in the article clearly shows extension of the right parietal opercular cortical dysplasia into the midsuperior portion of the insula.

4. Discussion

In this study, we report our experience with 16 cases of GS among which we established confident localization for 9. Combining these 9 subjects with 18 additional cases extracted from the literature with confident localization, we show that ictal laughter is neither a good lateralizing nor localizing feature on its own. Indeed, while there were more cases lateralized to the right hemisphere, a third of patients had a focus on the left. While the majority of foci were concentrated in the medial aspect of the frontal lobe (superior frontal gyrus, medial frontal gyrus, anterior cingulate gyrus, medial posterior orbitofrontal cortex) and basal temporal areas, several other areas could generate GS. These include the superior parietal lobule and the inferior lateral aspect of the frontal and parietal lobes (parietal operculum, lateral posterior orbitofrontal cortex, and inferior frontal gyrus), not uncommonly extending into the insula.

Although several studies have examined gelastic seizures in the past, the majority consisted of case reports or small series [1,4,13,26,28–30]. Many studies have made assumptions on probable localization based on tests with poor spatial and/or temporal resolution (e.g., scalp EEG, SPECT). This raises the possibility of false localization (e.g., an orbitofrontal or operculoinsular focus mistaken for a temporal focus). By relying on anecdotal cases or on small numbers of patients and/or on less accurate localization techniques, some studies have prioritized the involvement of particular areas (e.g., mesial frontal structures) when GS are encountered [5–7,29,31–33], creating bias in the interpretation of some presurgical tests (e.g., ictal SPECT) and bias in planning of intracerebral EEG coverage over the years. It is plausible that this could have led to some surgical failures. Strikingly, there was a disproportionate number of cases with operculoinsular involvement given that these structures are not frequently sampled or resected. In the present study, we attempted to depict a more global and accurate picture of GS by sampling a larger number of cases retaining only those with confident localization (Fig. 1).

This comprehensive portrait of areas associated with GS based on presurgical evaluations and surgical outcome is in line with observations from cortical stimulation studies in patients with epilepsy undergoing an invasive EEG study (Table 3). Despite being carried out in a limited number of patients, electrical stimulation of the following areas has elicited laughter or gelastic seizures: the left basal temporal area [9,34], the right anterior cingulate gyrus [35], the left [36] or right [37] anterior part of supplementary motor area, the left lateral premotor cortex near the falx cerebri (superior frontal gyrus) [37], and the left inferior frontal gyrus [38] (Fig. 1). In addition, the foci listed above are congruent with what is currently known about the pathophysiology of pathological laughing and crying. In a recent comprehensive review of disorders associated with involuntary emotional expression disorder (which includes the syndromes of pathological laughing and crying and emotional lability), Lauterbach et al. [39] concluded that a volitional system involving the frontoparietal (primary motor, premotor, supplementary motor, posterior insular, dorsal anterior cingulate gyrus, primary sensory, and related parietal) corticopontine projections