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Original Article

Auditory aura in nocturnal frontal lobe epilepsy: a red flag to suspect an extra-frontal epileptogenic zone

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ABSTRACT

Objective: To describe the anatomo-electro-clinical findings of patients with nocturnal hypermotor seizures (NHS) preceded by auditory symptoms, to evaluate the localizing value of auditory aura.
Methods: Our database of 165 patients with nocturnal frontal lobe epilepsy (NFLE) diagnosis confirmed by videopolysomnography (VPSG) was reviewed, selecting those who reported an auditory aura as the initial ictal symptom in at least two NHS during their lifetime.
Results: Eleven patients were selected (seven males, four females). According to the anatomo-electro-clinical data, three groups were identified. Group 1 [defined epileptogenic zone (EZ)]: three subjects were studied with stereo-EEG. The EZ lay in the left superior temporal gyrus in two cases, whereas in the third case seizures arose from a dysplastic lesion located in the left temporal lobe. One of these three patients underwent left Heschl's gyrus resection, and is currently seizure-free. Group 2 (presumed EZ): three cases in which a presumed EZ was identified; in the left temporal lobe in two cases and in the left temporal lobe extending to the insula in one subject. Group 3 (uncertain EZ): five cases had anatomo-electro-clinical correlations discordant.
Conclusions: This work suggests that auditory aura may be a helpful anamnestic feature suggesting an extra-frontal seizure origin. This finding could guide secondary investigations to improve diagnostic definition and selection of candidates for surgical treatment.

1. Introduction

The term nocturnal frontal lobe epilepsy (NFLE) has been used to describe a rare form of focal epilepsy characterized by bizarre motor seizures occurring almost exclusively during sleep [1], in which frontal lobe involvement has been postulated since the early 1970s [2,3]. The clinical characteristics of NFLE vary widely among different patients ranging from brief, simple motor phenomena (i.e. paroxysmal arousal, PA [4]) to major manifestations, including complex motor behavior such as epileptic nocturnal wandering (ENW) [5]. Different seizure patterns may coexist in the same patient, representing a continuum in the same epileptic condition [1,6,7]. In recent decades stereo-electroencephalography (sEEG) studies on patients operated for drug-resistant NFLE provided evidence of frontal lobe involvement during ictal motor phenomena with different clinical patterns depending on the specific regions involved [8,9].

In a study of five patients with asymmetric tonic posturing, Rheims et al. have shown a relatively early activation of the supplementary motor area, with a different degree of involvement of the intermediate mesial frontal cortex and frontal cingulate gyrus [10]. Patients with hyperkinetic [11] ictal behavior showed the involvement of mesial-dorso-lateral, orbito-polar, opercular or larger lobar cortical regions [10]. All these seizure types could be included under the general term of hypermotor seizures [10] according to Lüders' classification of seizure semeiology [12].

Moreover, the complexity of motor manifestations and the identified dystonic features may reflect the involvement of subcortical structures, such as the basal ganglia and other cortical areas constituting a functional motor network responsible for ictal symptomatology [7,9,13,14]. Whereas complex motor manifestations appear when the epileptic discharge involves the frontal lobe, the epileptogenic zone may lie in different cortical areas [15]. In particular it has been shown that nocturnal hypermotor seizures (NHS) may originate from the temporal and insular cortex and, recently,

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from the parietal and occipital lobe [9,15–19]. Clinically, no semeiological markers differentiate between seizures of frontal and extra-frontal origin; the only objective symptoms suggestive of an extra-frontal focus are a lower seizure frequency and a major asymmetry in complex motor behavior prevailing ipsilaterally to the epileptic discharge [9,15]. These findings emphasized the importance of anamnestic features, especially subjective symptoms, which are rare in frontal epilepsy and can point to an extra-frontal origin of the epileptic discharge [20]. These manifestations seem to better correlate with an extra-frontal origin of NHS. Subjective symptoms, such as laryngeal and throat discomfort, unpleasant or electrical paresthesia suggest an insular origin of NHS, whereas auditory aura may indicate a temporal origin [9,17,21], but these features have not been studied in depth.

Auditory auras associated with NFLE have been reported [22,23] but these studies did not specifically address this symptom nor its correlation with NFLE. We describe the anatomo-electro-clinical data of a population of patients with NHS associated with auditory aura, diagnosed as NFLE patients.

2. Methods

The study was conducted at the IRCCS Institute of Neurological Sciences of Bologna, Department of Biomedical and NeuroMotor Sciences, University of Bologna (DiBiNeM) after approval by the local ethics committee obtained on September 16, 2010 (no. 10077). The records of all patients from our database of NFLE cases were reviewed, and those who reported an auditory aura as the initial ictal symptom in at least two NHS during their lifetime were selected. NFLE was ascertained when patients with a clinical history of NHS had a video-polysomnographic (VPSG) recording of at least one major attack (bilateral asymmetric tonic/dystonic posturing or other choreo-athetoid and ballistic movements of the limbs, i.e. hyperkinetic seizures) or at least two minor stereotyped episodes (i.e. PA) [24].

Anamnestic and clinical data were collected including: sex, age, handedness, family and personal history, age at seizure onset, seizure semeiology, anti-epileptic drugs (AEDs), therapeutic response (according to Perucca [25]), ictal and interictal EEG, neuroradiological findings, video-EEG, stereo-EEG (sEEG) findings, and surgical details when available.

The features of auditory aura, the side of origin (lateralization) and its relationship with nocturnal and diurnal seizures were described. Auditory symptoms were classified into: (1) simple auditory auras characterized by sounds such as buzzing, ringing, or whistling; (2) complex auditory auras characterized by organized sounds such as voices, music, or meaningful sounds. Three expert neurophysiologists (P.T., F.B., F.P.) reviewed all patients' VPSG data to characterize the semeiological features and classify the patterns of seizures [10, 26], into PA, hyperkinetic seizure (HK), tonic/dystonic (TD), and ENW.

The epileptogenic zone (EZ) was defined by the anatomo-electro-clinical correlation, considering ictal semeiology (including lateralization of auditory aura and language impairment), the side of interictal and ictal EEG abnormalities, VPSG data, the neuroradiological lesion when visible, sEEG findings, and surgical outcome if available. On these bases, patients were divided into three groups: (1) defined EZ, when pre-surgical and surgical information clearly identified the zone from which seizures arose; (2) presumed EZ, when surgical or pre-surgical data were not conclusive but some anatomo-electro-clinical data pointed to a specific zone; and (3) uncertain EZ, when definition of the epileptogenic zone was not possible.

Five patients, who gave their informed consent, were screened for known mutations of CHRNA4, CHRNA2, CHRNB2, KCNT1, DEPDC5, and LG1.

3. Results

3.1. Clinical and surgical data

Eleven out of 165 patients were selected based on the inclusion criteria; seven males and four females were studied (clinical data are shown in Table 1). Mean age of patients was 39.8 years (median 42 years); all but one were right-handed, and patient 4 was ambidextrous. Three patients reported a family history of epilepsy; of these, one (patient 8) had a familial form of NFLE. Two patients had had perinatal distress, another two had suffered from febrile seizures during childhood, and one patient reported head trauma. The mean age at the onset of epilepsy was 7.55 years (median 6 years). Nine out of 11 patients experienced both nocturnal and diurnal seizures: five patients had an onset of diurnal epilepsy (mean delay between nocturnal and diurnal onset of seizures was 1.8 years, range 0.5–4), two patients had an onset of nocturnal epilepsy (mean delay between nocturnal and diurnal onset of seizures was 8.75 years, range 5–12.5) whereas in two patients nocturnal and diurnal seizures began at the same time. All patients had experienced, at least once in their lifetime, very frequent NHS that occurred one or more times per night.

Auditory aura was the first subjective symptom described by eight out of 11 patients; three patients reported a sensory aura that preceded the auditory symptoms. Auditory auras occurred both during the diurnal and nocturnal episodes in five patients, it was only nocturnal in five patients, whereas patient 6 reported an auditory aura only in diurnal hypermotor seizures. Usually, the auditory aura occurred while patients were falling asleep or in the early morning, and could awake the patient from sleep. Two patients could hear the same sound preceding nocturnal episodes during daytime, without motor manifestations. Five patients reported additional auras associated with auditory symptoms: four experienced sensory and one experienced visual aura. Seven patients reported simple auditory auras and only four patients reported complex auditory auras. The auditory symptoms were unilateral or prevalent in one ear in five patients, whereas they were contralateral to the presumed epileptogenic zone in three. Interictal EEG showed epileptiform anomalies in four patients (in the fronto-temporal region in two and in the temporal region in two) and non-specific anomalies in six patients. Ictal EEG recorded epileptic discharges in five patients (frontal origin in two cases, fronto-central in one subject, fronto-temporal in one and temporal in one patient) whereas two patients had non-specific modifications during seizures (flattening of background activity and bilateral desynchronization), in some cases autonomic modification (tachycardia/tachypnea) accompanied the seizure episodes. Neuroradiological examination showed abnormalities in four patients, which were highly suggestive of focal cortical dysplasia (FCD). Patients had a positive response to low doses of carbamazepine or oxcarbazepine, showing a consistent reduction of seizure frequency. Three patients are seizure-free whereas eight have drug-resistant epilepsy. According to the grade classification of drug resistance proposed by Perucca [25], six patients were classified as IIIB and two patients as IIIA.

On the basis of VPSG recording, seizure semeiology was classified as follows: six patients presented tonic/dystonic (TD) seizures, associated with PA in three cases; three patients had hyperkinetic (HK) seizures associated with PA in one; two patients presented both hypermotor manifestations (TD and HK).

The main anatomo-electro-surgical data are reported in Table 2.

3.2. Group 1 (three patients)

Pre-surgical evaluation with sEEG was performed in three patients presenting with drug-resistant epilepsy, demonstrating an extra-frontal origin of the seizures in all three. The ictal discharge