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Bitemporal epilepsy: A specific anatomo-electro-clinical phenotype in the temporal lobe epilepsy spectrum

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ABSTRACT

Purpose: Temporal lobe epilepsy (TLE) with bilateral ictal involvement (bitemporal epilepsy, BTLE) is an intriguing form of TLE whose characteristics need to be carefully identified as BTLE patients are not good surgical candidates. The purpose of this study was to define the anatomo-electro-clinical features differentiating BTLE from unilateral TLE (UTLE).
Methods: Forty-eight BTLE patients underwent long-term video-EEG monitoring (VEEG) and experienced seizures with bilateral temporal lobe involvement. Their main electro-clinical (demographics, interictal and ictal EEG, ictal signs) and neuro-imaging [brain magnetic resonance imaging (MRI)] data were compared with those of a group of 38 UTLE patients.
Results: In comparison with the UTLE patients, the BTLE cohort was significantly older at the time of epilepsy onset ($p = 0.023$), more frequently experienced bilateral asynchronous interictal epileptiform discharges during wakefulness ($p = 0.001$) and sleep ($p < 0.001$), bilateral upper limb dystonia ($p = 0.005$), and auditory auras ($p = 0.027$), and less frequently showed a recognisable initial ictal EEG pattern of focal flattening or low-voltage fast activity ($p < 0.001$), post-ictal memory of seizures ($p = 0.001$), staring ($p < 0.001$), head deviation ($p = 0.004$), oro-alimentary automatisms ($p = 0.006$), and positive brain MRI ($p < 0.001$). MRI revealed neoplastic lesions ($p = 0.007$) or alterations other than hippocampal sclerosis ($p = 0.028$) only in the UTLE patients.
Conclusion: The possibility of recognising BTLE patients during pre-surgical evaluation or being able to suspect bitemporal seizures before VEEG by identifying particular anatomo-electro-clinical patterns is diagnostically important for epileptologists and can help to prevent possible surgical failures.

1. Introduction

Temporal lobe epilepsy (TLE) is the most frequently observed drug-resistant localisation-related epilepsy, especially in epilepsy surgery case series,[1–3] and is usually characterised by an excellent prognosis after tailored resection [3,4]. Before proceeding to epilepsy surgery, it is essential to evaluate the localisation of the epileptogenic zone (EZ), which can be assessed by collecting a careful history and undertaking detailed anatomo-electro-clinical investigations [5,6]. If a patient's history, seizure semiology, interictal and ictal

Abbreviations: TLE, temporal lobe epilepsy; BTLE, bitemporal epilepsy; UTLE, unitemporal epilepsy; EZ, epileptogenic zone; EEG, electroencephalogram; MRI, magnetic resonance imaging; PET, positron emission tomography; FDG-PET, fluorodeoxyglucose PET; FS, febrile seizures; VEEG, long-term scalp video-EEG; SEEG, long-term intracerebral electrode stereo-EEG; AED, anti-epileptic drug; NL, non-lateralisable; IND, independent; ISA, interictal slow activity; IEDs, interictal epileptiform discharges; LVFA, low-voltage fast activity; PiMS, post-ictal memory of seizures; HD, head deviation; OAs, oro-alimentary automatisms; LOC, loss of consciousness; BD, bilateral dystonia; HS, hippocampal sclerosis; FCD, focal cortical dysplasia.

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electroencephalographic (EEG) findings, and magnetic resonance imaging (MRI) and positron emission tomography (PET) neuroimaging data are consistent with a diagnosis of unilateral TLE (UTLE), he or she can be considered a good candidate for surgery [1,7].

TLE patients showing bilateral temporal lobe involvement during seizures may not be optimal surgical candidates. The existence of bitemporal epilepsy (BTLE) is well known and many studies have considered the possible use of surgical therapeutic strategies, albeit with conflicting results [8–12]. However, BTLE has not yet been clearly defined and relatively little is known about the anatomo-electro-clinical data characterising BTLE patients. Hirsch et al. [13] failed to find any significant clinical or neuroradiological differences between BTLE and UTLE patients, although the former had a less frequent history of febrile seizures (FS). Schulz et al. [14] found an association between BTLE and the absence of auras, and it has been recently reported that BTLE is associated with bilateral lateralising ictal signs [15]. It has also been found that BTLE patients less frequently show ictal motor signs than those with UTLE, and experience longer periods of post-ictal unresponsiveness [16].

On the basis of the assumption that pathophysiological mechanisms and epileptic networks are different in BTLE and UTLE, it is possible that the two forms have different anatomo-electro-clinical features. The aim of this study was to investigate the electro-clinical and neuro-imaging characteristics of a cohort of BTLE patients in an attempt to differentiate them from UTLE patients because the identification of an anatomo-electro-clinical phenotype of BTLE would help clinical epileptologists to recognise or at least suspect BTLE when evaluating TLE patients, especially in the case of a pre-surgical assessment.

2. Materials and methods

2.1. Data collection

This multicentre study involved three tertiary referral centres for epilepsy and epilepsy surgery in Milan, Italy: the Claudio Munari Epilepsy Surgery Centre of Niguarda Hospital, the Clinical Epileptology Unit of Carlo Besta Neurological Institute, and the Epilepsy Centre of San Paolo Hospital. Although belonging to different hospitals, these centres cooperate in the context of a multidisciplinary Inter-Hospital Department for Pre-surgical Epilepsy Evaluation (DDEP).

We retrospectively reviewed the electronic charts of 2152 epilepsy patients admitted to the three centres for pre-surgical evaluations between January 1995 and March 2013: 1548 underwent epilepsy surgery, and 48 (2.2%) were identified as having drug-resistant BTLE. The control group consisted of 38 consecutive patients with recorded seizures who underwent surgery because of refractory UTLE between 2005 and 2011 and had been seizure-free for at least 24 months.

Each of the patients in the two cohorts had undergone long-term scalp video-EEG (VEEG) using a digital VEEG recording device (Nihon-Kohden Neurofax or Micromed System Plus Evolution) and electrodes placed according to the international 10-20 system. A total of 223 seizures were recorded in the BTLE group and 86 in the UTLE group. Four BTLE patients also underwent long-term intracerebral electrode stereo-EEG (SEEG) monitoring (Nihon-Kohden Neurofax). The patients' anti-epileptic drug (AED) doses were usually reduced by at least 50% in order to facilitate the recording of seizures.

All of the patients underwent high-resolution MRI performed using a 1.5 T (Siemens Avanto or Philips ACS-NT & Achieva) or 3 T (Philips Achieva TX) scanner. The MRI protocol included transverse spin-echo double-echo images of the entire brain, coronal fast spin-echo T2-weighted and spin-echo FLAIR images, and coronal fast spin-echo inversion recovery T1-weighted images. The transversal and coronal sections were respectively acquired in parallel with or perpendicularly to the axis of the hippocampal formation.

BTLE was diagnosed on the basis of two ictal electro-clinical inclusion criteria: a VEEG and/or SEEG recording of at least one seizure simultaneously or sequentially involving the two temporal lobes, without the possibility of lateralising its onset and subsequent development [defined as a non-lateralisable (NL) bitemporal seizure], and/or the recording of at least two different seizures alternately arising from the two temporal lobes [defined as an independent (IND) bitemporal seizure]. More precisely, a bitemporal seizure was considered NL in the presence of a discharge simultaneously involving the two temporal lobes ('synchronous') or spreading from one temporal lobe to the opposite side and back ('asynchronous'), or ending on the opposite side ('side-switching') (Figs. 1 and 2A and B).

The BTLE patients were divided into two groups (NL or IND BTLE) on the basis of a blinded review of each seizure. In the case of disagreement, or when more than one seizure type was recorded in the same patient, the main seizure pattern was agreed after a collegial re-evaluation during which the epileptologists not only assessed the ictal EEG traces of each patient, but also interictal activity by visually analysing at least ten 20-second wakeful and sleeping interictal traces samples.

After distinguishing the BTLE and UTLE patients, we collected all of their available clinical, neurophysiological and neuroimaging data, concentrating on the main historical information, the results of a neurological examination, ictal semiology, ictal and interictal EEG findings, and MRI and, when available, fluorodeoxyglucose PET (FDG-PET) data.

2.2. Statistical analysis

Contingency table analysis was used to evaluate the associations between the different types of epilepsy and the nominal or dichotomous variables, with the independence of the rows and columns being tested by means of Fisher's exact test. Age at the time of epilepsy onset, age at the time of evaluation/surgery, disease duration and monthly seizure frequency were compared in the UTLE and two BTLE subgroups using the Kruskal–Wallis test. A p-value of <0.05 was considered significant.

The significant variables in the three groups underwent *post hoc* analysis using a Bonferroni correction for multiple comparisons, with a p-value of <0.017 being considered significant.

The data were analysed using SPSS software (version 22).

3. Results

3.1. General patient characteristics

A total of 48 BTLE patients were identified between January 1995 and March 2013; the control group consisted of 38 consecutive seizure-free patients who underwent surgery for UTLE between 2005 and 2011. Table 1 shows their general characteristics.

The difference in the proportion of BTLE and UTLE patients with positive family history of epilepsy (8.3% *vs* 28.9%) was of borderline significance ($p = 0.051$). There were no significant differences in personal antecedents or the presence of FS between the two groups except in the case of central nervous system (CNS) infections, which were reported in only five BTLE patients (10.4%) ($p = 0.018$). The UTLE patients were younger at the time of epilepsy onset ($p = 0.023$).

There were no significant between-group differences in terms of gender distribution, age at the time of evaluation/surgery, disease duration, monthly seizure frequency, the circadian rhythm