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Dysembryoplastic neuroepithelial tumors: Epileptogenicity related to histologic subtypes

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HIGHLIGHTS

- Dysembryoplastic neuroepithelial tumors (DNTs) are benign tumors, predominantly located in the temporal lobe, revealed in young subjects by drug resistant partial epilepsy that is curable by surgery.
- Electroclinical features are similar in the three histologic DNT subtypes (simple, complex and non-specific forms) and consist of late childhood epilepsy onset, partial seizures and EEG abnormalities concordant with the tumor location.
- Intrinsic epileptogenicity characterizes all DNT subtypes but the epileptogenic zone varies according to the histologic features (concordant in simple and complex forms, more extended in most non-specific forms).

ABSTRACT

Objective: To analyze the electroclinical features and the relationship between the epileptogenic zone (EZ), the tumor and focal cortical dysplasia (FCD) in the three histologic subtypes of dysembryoplastic neuroepithelial tumors (DNTs) (“simple”, “complex” and “non-specific forms”).
Methods: We analyzed electroclinical data from 78 patients (50 males; 3–54 years) operated for intractable epilepsy due to a DNT. We compared EZ extent, defined by stereo-electroencephalography ($n = 33$), with the tumor and FCD areas, in each DNT subtype.
Results: Non-specific forms (68%) and temporal location were predominant (73%). The main characteristics consisted of late childhood epilepsy onset (median 12 years), drug-resistant partial seizures and EEG abnormalities concordant with tumor location. In all DNT subtypes, intrinsic epileptogenicity was demonstrated by intralesional recordings ($n = 30$), displaying a depressed background activity interrupted by rapid spikes or polyspikes. EZ co-localized with the tumor in all simple and complex DNTs, but in only 1/3 of non-specific DNTs. The main discordance between the EZ and tumor extent was found in temporal non-specific DNTs associated with extensive FCD.
Conclusion: These results are helpful when planning surgery for DNTs.
Significance: Intrinsic epileptogenicity characterizes all DNTs; however, the EZ differs according to histologic subtypes and is particularly widespread in non-specific temporal forms.

Abbreviations: DNT, dysembryoplastic neuroepithelial tumors; SGNE, specific glioneuronal element; EZ, epileptogenic zone; IZ, irritative zone; LZ, lesional zone; FCD, focal cortical dysplasia; Hz, Hertz; IQ, intelligence quotient; RSD, rhythmic spike discharges; SEEG, stereo-electroencephalography.

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1. Introduction

Dysembryoplastic neuroepithelial tumors (DNTs) are benign tumors, typically located in the supratentorial cortex, usually revealed by drug-resistant partial epilepsy in young subjects. According to the World Health Organization (WHO) classification, DNTs belong to the category of glioneuronal tumors (Kleihues et al., 1993; Louis et al., 2007). However, because of their frequent association with focal cortical dysplasias (FCDs), they are also included among malformations of cortical development (Raymond et al., 1995; Barkovich et al., 2001; Palmini et al., 2004; Blümcke et al., 2011). Three DNT histologic subtypes have successively been described: the "complex form" characterized by a specific glioneuronal element (SGNE) associated with glial nodules (oligodendroglial, astrocytic, or both) and FCD (Daumas-Duport et al., 1988), the "simple form" in which only an SGNE is present (Daumas-Duport, 1993), and the "non-specific forms" in which the glial and dysplastic component are similar to the one observed in the complex forms but the SGNE is absent (Daumas-Duport et al., 1999). Neurons included in DNTs may exhibit an atypical appearance but, by definition, these tumors do not contain ganglion-like neurons. Since their first description from specimens provided by epilepsy surgery, DNTs have been increasingly recognized in epilepsy patients. They account for 18–27% of histologic diagnoses in epilepsy surgery series (Honavar et al., 1999; Pasquier et al., 2002; Daumas-Duport and Varlet, 2003), a lower rate (3.4–9.3%) being reported when non-specific forms are not individualized (Luyken et al., 2003; Sharma et al., 2009). All supratentorial locations may be observed, but the temporal lobe is predominantly involved (Kirkpatrick et al., 1993; Raymond et al., 1994; Honavar et al., 1999; Daumas-Duport and Varlet, 2003; Campos et al., 2009; Thom et al., 2011). The architectural polymorphism of DNTs accounts for the variety of their imaging features, but common characteristics consist of cortical location, absence of mass effect (even in voluminous tumors), and absence of perilesional edema (Daumas-Duport et al., 1988; Stanescu Cosson et al., 2001).

Mechanisms of epileptogenicity are likely multiple. It has been suggested that the presence of neurons within the tumor and an association with FCD may play a role in the epileptogenicity of DNTs (Daumas-Duport et al., 1988). Excitatory glutaminergic neuron receptors are expressed in the tumor tissue (Adamek et al., 2001; Aronica et al., 2001). PET studies demonstrated decreased benzodiazepin binding within the tumor (Richardson et al., 2001) and multidrug resistance proteins are reported to be over-expressed in DNTs (Sisodiya et al., 2002; Vogelgesang et al., 2004). Intractability of epilepsy is well established (Semah et al., 1998); however, electroclinical features are rarely detailed in large series. In addition, the relationship between the epileptogenic zone (EZ) and the lesional tissue, and especially the role of FCD associated with the tumor, are incompletely understood to date. Furthermore, there are no data indicating if EZ organization is similar in different histologic DNT subtypes. In a previous study, we demonstrated that the architecture of the three histologic DNT subtypes may be recognized on MRI, and we described three main structural MRI types that enabled us to distinguish between simple, complex and non-specific histologic forms (Chassoux et al., 2012). The aim of the present study was to analyze the electroclinical data and EZ organization according to the DNT location and the histologic subtypes.

2. Patients and methods

We retrospectively studied the records of all patients operated in our institution for drug resistant partial epilepsy due to a DNT during the last two decades. The study was approved by the local ethics committee. The population consisted of 78 patients (50 males) and accounted for 13% of a series of 585 consecutive patients who underwent corticectomy at Sainte-Anne Hospital between 1990 and 2010. Age at the time of surgery ranged from 3 to 54 years (median 25); 16 patients (20%) were children. Presurgical evaluation consisted of an anatomical and electroclinical correlation study, based on epilepsy history, neurological and neuropsychological examination, interictal and ictal video-EEG recordings and MRI (performed on a 1.5-Tesla magnet since 1995 and 0.5 Tesla before this date, in 16 cases), including 3DT1-weighted, 1.2-mm-thick contiguous slices, axial and coronal T2-weighted and FLAIR (fluid attenuation inversion recovery) sequences. MRI structures were classified into three main types according to the signal abnormalities and delineation (Chassoux et al., 2012): type1 (cystic/polycystic-like, well-delineated, strongly hypointense on T1 sequences), type2 (nodular-like, hypo-hyper heterogeneous signal, partially delineated), and type3 (dysplastic-like, characterized by iso/hyposignal on T1 sequences, poor delineation, gray-white matter blurring). Stereo-electroencephalography (SEEG) was performed in 33 cases (28 before and five after 1996) according to the methodology described by Talairach and Bancaud (Talairach et al., 1992; Bancaud, 1980). Depth multicontact electrodes (stainless steel; diameter: 0.8 mm; contact length: 2 mm; interspace: 1.5 mm; Dixi Micromecanique, Besançon, France) were implanted under general anesthesia, after stereotactic MRI and angiography. Intracranial recordings were obtained using a BMSI 64 channel video-EEG monitor (Nicolet Biomedical, Madison, WI). Bipolar recordings were acquired with a mean amplitude of 200 μV/cm, speed 15 mm/s, low frequency filters set at 1.6 Hz and high frequency filters at 70 Hz. After examination of all electrode contacts, the most informative sites were selected for monitoring. Bipolar and monophasic stimulations were performed using a WPI Ampulse Stimulator (WPI, New Haven, CT) at low frequency (1 Hz, 1–3 ms, 1–3 mA, during 40 s) and high frequency (50-Hz trains, 1 ms, 0.5–3 mA during 5 s). Antiepileptic drugs were progressively reduced during the procedure in all patients. Based on SEEG data, the "lesional" zone (LZ) was defined by the presence of slow waves or depression of activity, the irritative zone (IZ) by interictal spiking and the epileptogenic zone (EZ) as the site of onset of clinical or subclinical spontaneous or electrically induced seizures. It should be noted that, for the purposes of our study, the "lesional" zone corresponds to neurophysiologic criteria independently from imaging data or pathological process. Moreover, seizures elicited by stimulation were considered as valid for the definition of the EZ if the clinical semiology was identical to that of spontaneous seizures.

The whole corticectomy specimens were histologically examined in all cases after fixation in zinc-formalin, paraffin sections (4 μ thick) and staining by Hemalun-Phloxin and Nissl-Luxol (Klüver-Barrera). Complementary immunohistochemistry was done using antibodies directed against glial fibrillary acid protein (GFAP), microtubule-associated proteins (MAP_2) and neuronal nuclei (NeuN). Dysplastic cortex was defined as abnormal cortical organization in correctly oriented cortical specimens and/or presence of neurons with atypical cytologic appearance. Ectopic neurons in white matter adjacent to the tumor were considered abnormal when their number and extent exceeded those normally present in the sub-cortical white matter and/or in presence of grouping or cytological abnormalities. All specimens were reviewed in order to confirm the diagnosis of DNT and to determine the histologic subtype according to the criteria mentioned above. Pathological specimens including histologic features consistent with the diagnosis of ganglioglioma were excluded of the study. As previously described (Chassoux et al., 2000, 2010), histologic findings were compared to SEEG and imaging data. EZ was considered to be co-localized with the tumor when it was confined to