Original article

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Multifocal dysembryoplastic neuroepithelial tumours associated with refractory epilepsy

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ABSTRACT – Dysembryoplastic neuroepithelial tumours (DNET) are a common cause of tumour-associated epilepsy, and are usually located in the temporal lobes. We present a case of multifocal DNETs in both infra- and supra-tentorial locations, in a 23-year-old man with a coincident Type I Chiari malformation, presenting with medically refractory focal seizures. The extensive anatomical distribution of the lesions suggests a genetic component in their tumourigenesis.

Key words: multi-focal tumor, tumor-associated epilepsy, Chiari malformation

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Since its identification as a distinct tumour type in 1988, dysembryoplastic neuroepithelial tumours (DNET) have been increasingly implicated in refractory focal seizures of the paediatric population. Typically located in the temporal lobes, DNETs have also been reported within the periventricular white matter, basal ganglia, thalamus, brainstem, and cerebellum. Those with multifocal involvement are rare, with only four cases reported in which DNETs occurred in infra- and supra-tentorial locations (Leung *et al*., 1994; Krossnes *et al*., 2005; Schittenhelm *et al*., 2007; White *et al*., 2011). Here, we present a patient with multi-focal DNETs of greater spatial extent than previously reported.

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Case study

The patient is a 23-year-old African American man with refractory focal seizures, clinically recognized at age 20, but likely experienced since early childhood, as suggested by reports of staring spells and memory lapses. His typical seizures occurred every two to three weeks, lasted one minute, and were associated with: restlessness, oral and hand automatisms, drooling, guttural sounds, and postictal confusion. Seizures were occasionally preceded by right upper extremity tingling, and had progressed to secondarily generalised tonic-clonic seizures on eight to nine occasions. The patient's seizures were not well controlled on medications, and had been increasing in frequency over the year prior to surgery.

The patient received imaging at age 17 after sustaining an assault with loss of consciousness. MRI revealed several lesions, including those in the right cerebellum, left caudate head, left frontal subcortical white matter, hypothalamus, and bilateral thalami. The largest lesion was in the left medial temporal lobe, measuring $6\times9\times9$ mm^3 without mass effect (*figure 1A*). The patient also had a previous diagnosis of refractory ADHD, unspecified learning disabilities, and labile mood.

The patient underwent video-EEG monitoring for seizure localisation and presurgical evaluation. He experienced seven typical seizures that consistently originated from the left temporal region.

Repeat MRI revealed several non-enhancing focal lesions that were hypointense on T1- and hyperintense on T2-weighted sequences. The left temporal lobe lesion demonstrated interval growth in the preceding six years, measuring $20\times15\times19$ mm^3 and involving the amygdala (*figures 1B, 2B, 2D*). The lateral solid-appearing portion indented the temporal horn of the left lateral ventricle. Other lesions identified on the weighted and FLAIR sequences included three in the corpus callosum (<11 mm), five in the right cerebellum (<8 mm), in addition to lesions in the right middle cerebellar peduncle, left caudate head (4 mm), left frontal subcortical white matter, hypothalamus (5 mm), and bilateral thalami (2 mm) (*figure 2*).

There were no calcifications or haemorrhage. MRI also revealed downward displacement of the cerebellar tonsils, measuring 7.62 mm, constituting an asymptomatic Type 1 Chiari malformation (*figure 2F*). There was no evidence of restricted diffusion, increased blood volume, or abnormal metabolic activity upon further imaging. Evaluation for inflammatory or granulomatous disease was negative.

Based on these findings, gross total resection of the left medial temporal lobe lesion was undertaken *via* a trans-sylvian approach. The anterior head of the hippocampus was also resected to maximise chances of seizure freedom (*figure 1C*).

The surgical specimen appeared grossly as a grey-red soft-tissue mass. Its histological appearance was well circumscribed, and haematoxylin and eosin (H&E) staining revealed oligodendrocyte-like cells (OLC) surrounding cytologically-normal neurons, floating in a minimal myxoid matrix (*figures 1D-F*). The tumour was cortically based and, although the specimen was fragmented, there was vague nodularity (*figure 1G*). OLCs were identified as glial fibrillary acidic protein (GFAP)-positive cells. Synaptophysin and neuronal nuclei (NeuN) were used to highlight neurons and their processes. Cellular atypia, vascular proliferation, mitosis, and necrosis were not present. p53 expression and Ki-67/MIB-1 labelling index were negative and 1%, respectively. Targeted PCR assay did not reveal isocitrate dehydrogenase-1 (IDH-1; codon 132) or IDH-2 mutations (codon 172). There was no mutant $BRAF^{V600E}$ protein detected by immunohistochemistry (VE1 clone, Spring Bioscience, Pleasanton, CA), no tumour immunoreactivity to CD34 (QBEnd 10 clone, DAKO, High Wycombe, UK), and no 1p19q deletions based on fluorescence *in situ* hybridisation. These findings were consistent with a diagnosis of simple DNET (Blumcke *et al*., 2014).

The patient recovered without neurological deficits, and remained seizure-free with noted improvement in mood stability at the six-month evaluation. Six months subsequent to follow-up, however, he was found deceased by family members in the morning. As the patient had been in reasonable health without recurrence of seizures, his death was unexpected. The family members denied bitten tongue, urinary incontinence, or a disturbed environment. An autopsy was not performed in accordance with their wishes.

Discussion

We report a patient with multiple infra- and supratentorial DNETs, presenting with refractory focal seizures. Although only the resected left temporal lesion was diagnosed by histopathological investigation, the imaging features and anatomical distribution of the remaining lesions were highly suggestive of DNETs, making the lesions reported here of greater spatial extent than all other reported cases of multifocal DNET. A potential differential diagnosis includes ganglioglioma, diffuse astrocytoma, and oligodendroglioma based on histological findings, and spongiform gliosis, multicentric astrocytoma, cerebral hamartoma, and mesial temporal sclerosis based on imaging features.

DNETs are thought to represent a disorder in neuronal migration. Cortical DNETs have been suggested

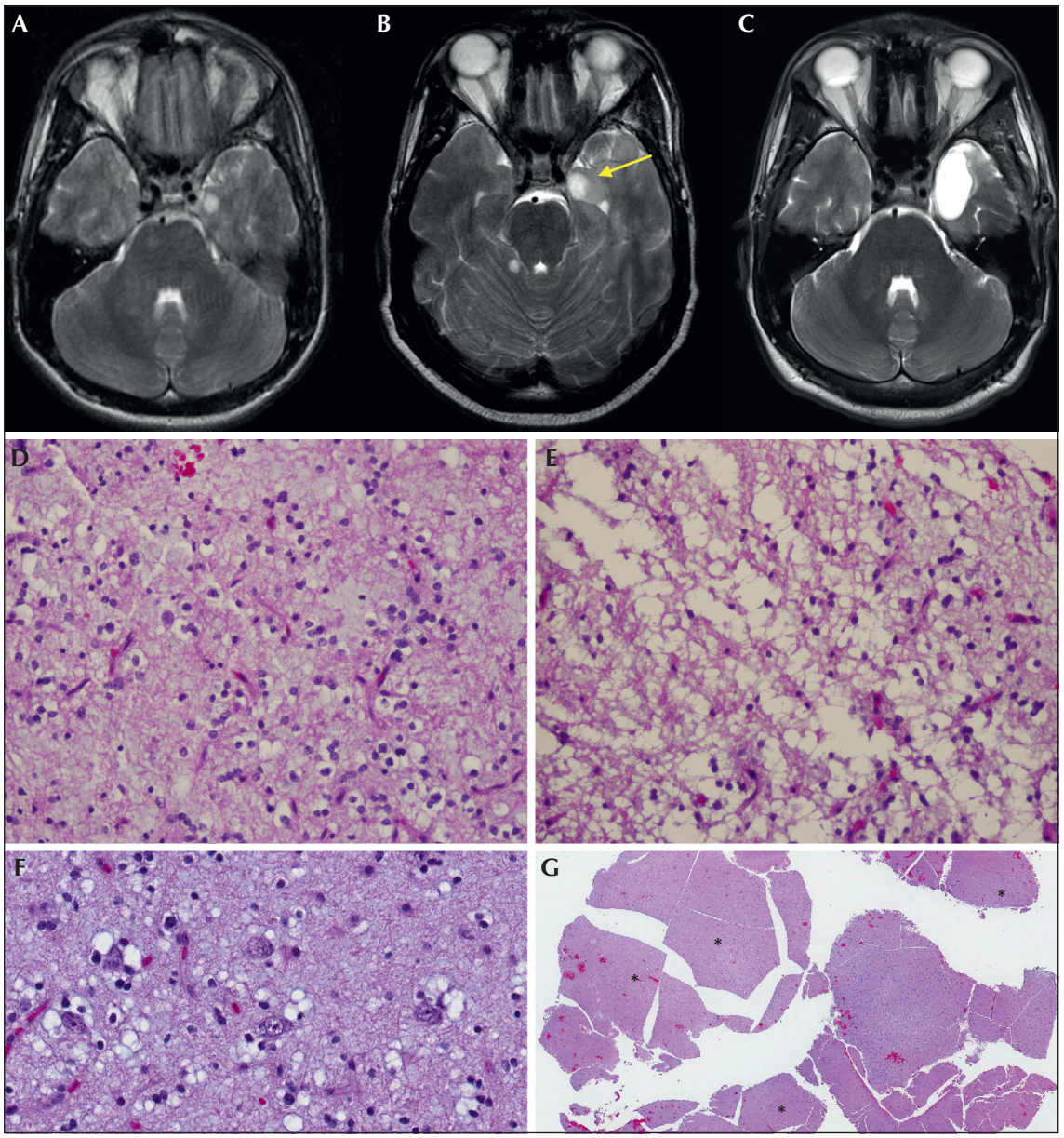

Figure 1. T2-weighted MR images in the axial plane at age 20 (A) and pre-operatively at age 23 (B) demonstrate interval growth of the left medial temporal DNET, and subsequent gross total resection along with the amygdala and hippocampus (C). H&E staining of the left temporal lesion reveals myxoid areas with neurons, surrounded by small OLCs (D-F). Lower power demonstrates nodular hypercellular tumour areas (asterisks) and adjacent normal cortical brain parenchyma (G). (D, E: 200×; F: 400×; G: 10×).

to originate from the subpial granular or subependymal germinal layers (Leung *et al.*, 1994), supported by bilateral nodular lesions extending from the periventricular regions to the cortical surface, such as in the pattern of lesions in our patient. Similarly, cerebellar DNETs are thought to originate from the external granular layer (Yasha *et al.*, 1998).

As cerebellar and cortical development are distinct processes, the existence of infra- and supratentorial DNETs suggest a genetic component to their tumourigenesis. Familial cases have been reported (Hasselblatt *et al.*, 2004), consistent with a germline mutation, but genetic analyses have failed to yield specific associated mutations. Alternatively, the infra-tentorial lesions may be rosette-forming glioneuronal tumours (RGNT), originally considered DNETs of the cerebellum. RGNTs now represent a distinct entity, distinguished in part by intraventricular or vermian involvement (Shah *et al.*, 2010), which do not characterise the

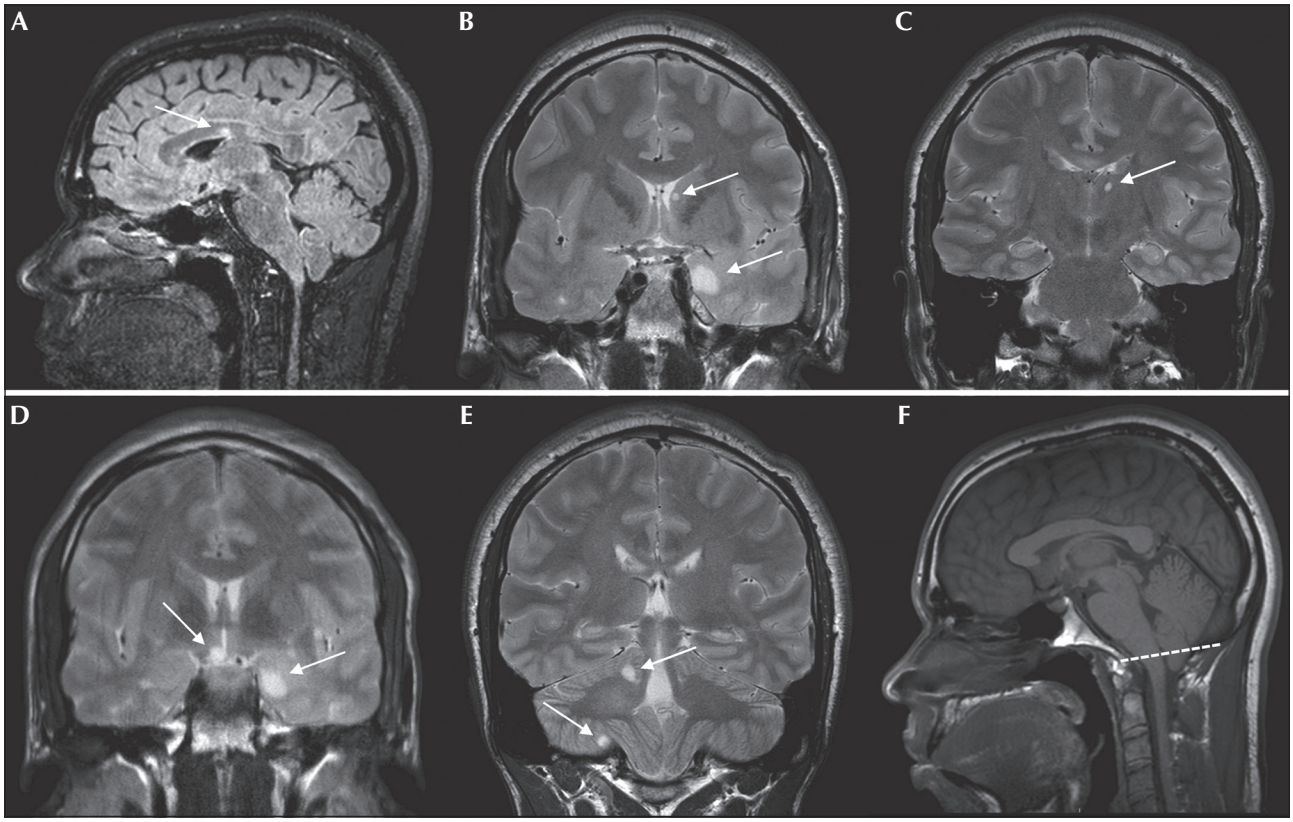

Figure 2. FLAIR MR image in the sagittal plane (A) and T2-weighted MR images in the coronal plane (B-E) show multiple DNETs in the corpus callosum (A), left caudate head (B), left medial temporal lobe (B, D), left thalamus (C), right hypothalamus (D), and right cerebellum (E).
T1-weighted MR image in the sagittal plane demonstrates tonsillar herniation of a Type 1 Chiari malformation (F).

posterior fossa lesions in our patient. Furthermore, reports of isolated cerebellar DNETs demonstrating typical histology (Yasha *et al*., 1998), and the growing number of multifocal DNETs with both infra- and supra-tentorial involvement, make it less likely that such patients harbour two distinct tumour types.

This is only the second reported case of concomitant DNET and Chiari I malformation (Yasha *et al*., 1998). It is not known whether tonsillar herniation is secondary to mass effect of the cerebellar DNET or there exists an aetiological association between the two diseases, although co-existing obstructive hydrocephalus and size of the lesion can be suggestive of the former. The largest cerebellar lesion in our patient only measured 8 mm, and mass effect cannot be assumed.

DNETs are a subtype of glioneural tumours, histologically distinguished by the presence of a neuronal component, and lead to refractory epilepsy in 90-100% of patients. Surgical considerations are complicated by focal peritumoural regions of cortical dysplasia (Leung *et al*., 1994), which may be epileptogenic as in other neoplasms. Furthermore, DNETs are known to alter expression patterns in surrounding tissue, possibly increasing neuronal hyperexcitability and leading to seizures. Hence, the complete epileptogenic focus may need to be outlined by electrocorticography to guide adequate surgical resection. Importantly, excellent seizure control has been reported after resection.

DNETs were originally thought of as benign, quasi-hamartomatous lesions. However, tumour growth and changes in imaging appearance do occur. While this does not necessarily imply malignant degeneration, DNETs rarely do undergo malignant progression (Mano *et al*., 2013). In all such reported cases, the Ki-67/MIB-1 index on recurrence was elevated (>8.5%), whereas the original specimens had significantly lower proliferative indices (Mano *et al*., 2013). For our patient, there was definite growth of the medial temporal lobe DNET, but upon resection, the Ki-67/MIB-1 index was only 1%. Although multiple lesions theoretically increase probability of progression, prognostic factors remain unknown, and in all reported cases of multifocal DNETs, the primary reason for resection was refractory epilepsy.

In the present case, the patient died in his sleep one year postoperatively, ruling out the possibility of death secondary to acute surgical complications. There have been reports of sudden, unexpected deaths in patients

with DNETs. In one case, the patient had poorly-controlled generalised seizures for over ten years (Sirbu, 2011), placing her at increased risk for sudden unexplained death in epilepsy (SUDEP). Our patient's seizures were eliminated by the surgery, however, reducing his all-cause mortality risk to that of the general population. Furthermore, there was no known sleep disorder or cardiac abnormality that may have predisposed him to SUDEP. Another potential cause of death is status epilepticus, although the circumstances of his death were not indicative of recent seizure activity. In the other reported case, the patient did not have a history of seizures but died within 24 hours of acutely developing nausea, headache, and vomiting (Raghavendra *et al*., 2010). Autopsy revealed bilateral tonsillar herniation secondary to cystic swelling of a supratentorial DNET, which measured 5×6 cm^2. Progressive enlargement of DNETs from spontaneous intralesional haemorrhage and formation of cystic cavities has also been observed elsewhere (Thom *et al*., 1999). Although none of our patient's lesions were of substantial dimensions at the time of surgery, progressive enlargement of any of his lesions could have led to a similar scenario, particularly given the coincident Chiari malformation.

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TEST YOURSELF

Q1: What is the common presentation of patients with DNETs?
Q2: What is the treatment for DNETs?
Q3: What are the most common locations of DNETs?
Note: Reading the manuscript provides an answer to all questions. You can check for the correct answer by visiting the Educational Centre section of www.epilepticdisorders.com