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Large Epileptogenic Type IIIb Dysplasia: A Radiological and Anatomopathological Challenge

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Key words
- IIIb dysplasia
- Differential diagnosis
- Drug-resistant epilepsy

Abbreviations and Acronyms
DNET: Dysembryoplastic neuroepithelial tumor
FCD: Focal cortical dysplasia
FDG: Fluorodeoxyglucose
GG: Ganglioglioma
ILAE: International League Against Epilepsy
MET: Methionine
MRI: Magnetic resonance imaging
PET: Positron emission tomography

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BACKGROUND: **Type IIIb dysplasia is a subtype of focal cortical dysplasia associated with a tumor, most frequently with gangliogliomas then with dysembryoplastic neuroepithelial tumors (DNETs). Their preoperative diagnosis often remains equivocal since specific features are missing. The functional results (i.e., seizure free) is good with 81%–87% of Engel Ia at 5-year follow-up.**

CASE DESCRIPTION: **A 4-year-old boy presented with a 1-year history of severe, invalidating, drug-resistant epilepsy. Imaging workup demonstrated a huge left limbic lesion, of which diagnosis remained speculative. Because of worsening neurological status, resective surgery was recommended after multidisciplinary discussion. The resection was performed through left transtemporal approach under neuronavigation (C.R.). Postoperative magnetic resonance imaging assessed uncomplicated near-total resection. Histopathological analysis showed combined features of a DNET of nonspecific type and a focal cortical dysplasia.**

CONCLUSION: **We describe a rare condition of type IIIb dysplasia combining a focal cortical dysplasia with a DNET. Preoperative diagnosis of the lesion was of utmost difficultly, thereby rendering mandatory a thorough histopathological examination of resected specimen in the vast majority of cases. Increased recognition of the condition brings up the hypothesis of a genetic continuum or linkage between the 2 conditions. Functional results on seizure activity after ablative surgery are good and maximal safe resection should be the goal.**

INTRODUCTION

Focal cortical dysplasias (FCDs) are developmental abnormalities of the gray matter architecture. Their incidence ranges from 3% to 20%.[1] In children younger than 18 years of age, FCDs are the most frequent lesion found at histopathological examination after epilepsy surgery. The second most common are neoplasm. In rare cases, FCDs can be associated with other lesions, resulting in lower presurgical diagnostic accuracy.

CASE REPORT

A young boy of 3 years and 11 months presented with drug-resistant epilepsy that had begun 16 months earlier. The mother's pregnancy and the child's first years of life were uneventful with a normal psychomotor development. His parents and siblings had no medical history. Only a maternal cousin also suffered from epilepsy, but that was controlled with 1 antiepileptic drug. The beginning of his epilepsy was subacute. Initial seizures were absence-type seizures, lasting for 10–30 seconds, a few times per week. The neurological examination was normal. The epilepsy worsened rapidly, with seizures occurring several times a day. A first treatment with valproate was initiated with good control (disappearance of seizures) for 6 weeks. Unfortunately, the seizures recurred; levetiracetam was introduced with, again, good control but with onset of behavioral dysfunctions (aggressiveness, language regression, agitation). The treatment was switched to 4 drugs: levetiracetam, carbamazepine, risperidone, and clobazam. Despite this heavy treatment, the patient still suffered from several seizures a day.

A complete workup was done. Electroencephalogram showed an important lateralization of the basic rhythm that seemed almost absent in the left hemisphere. The interictal rhythm showed epileptiform activity in the left temporo-occipital area. The cerebrospinal fluid was unremarkable: no white cells, no anti-NMDA receptor autoantibodies, and no oligoclonal bands. A magnetic resonance imaging (MRI) scan performed at the age of 3 revealed a large lesion of the left limbic lobe disclosing hyper T2 signal intensity and hypo T1 signal intensity without contrast-enhancement nor mass effect. The lesion measured 7.5 × 2.55 × 2.5 cm and encompassed the amygdala, hippocampus, parahippocampal gyrus, and posterior cingular gyrus with occipital extension (Figure 1). Positron emission tomography (PET) using the methionine as tracer (MET-PET) failed to reveal enhanced uptake within the lesion,

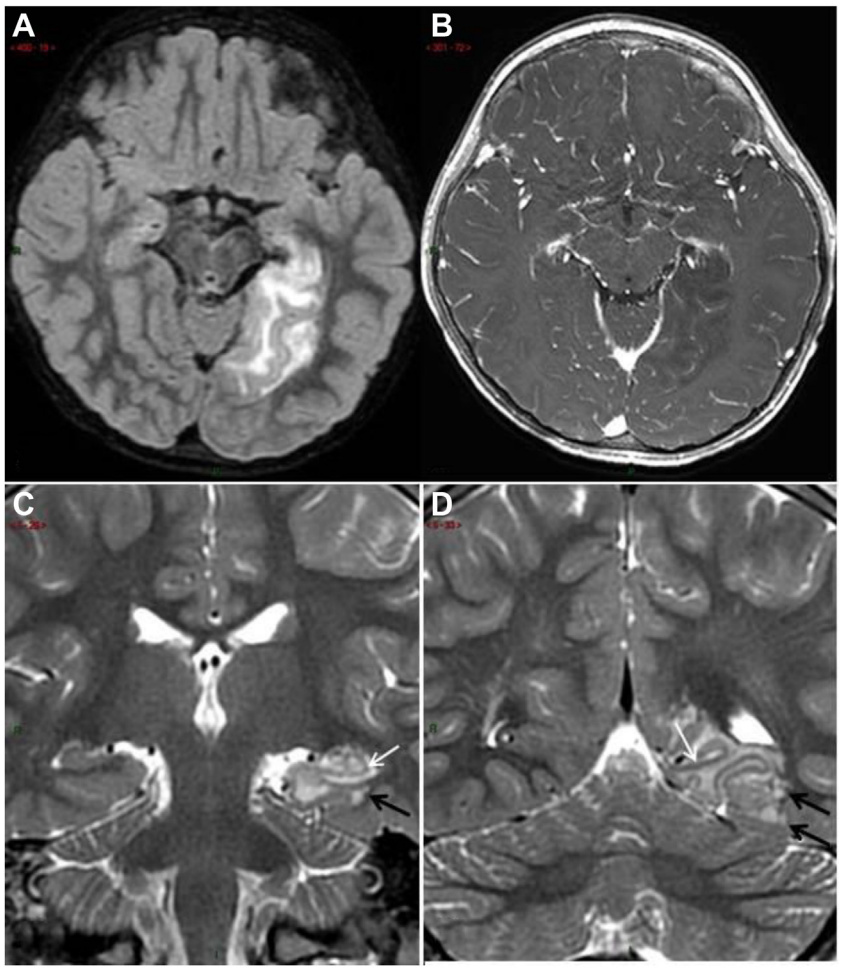

Figure 1. Magnetic resonance imaging workup. (**A**) Unenhanced axial transverse fluid-attenuated inversion recovery view showing strong hypersignal intensity of subcortical white matter together with apparently preserved overlying cortex within left-sided temporal lesion. (**B**) Contrast-enhanced axial transverse T1-weighted view in a similar slice location disclosing hypo signal intensity and absence of blood-brain barrier disruption within diseased left temporal parenchyma. (**C**) Magnified T2-weighted coronal view showing hyperintense process infiltrating the hippocampus and para-hippocampus with preservation of normal thickness and signal intensity of paleo-cortical (*white arrow*) and neocortical ribbon. A subtle bubble-like appearance at few small places was present (*black arrow*). (**D**) Magnified T2-weighted coronal view at a more posterior slice location as in (**C**) showing similar imaging features with preserved cortical appearance (*white arrow*) and subtle bubble-like areas (*black arrows*).

thereby suggesting a low-grade process. PET using the fluoro-deoxy-glucose (FDG) as a tracer demonstrated decreased metabolism within left temporal and mesiotemporal areas (Figure 2). Brain MRI examination was repeated 1 year later, but failed to reveal any change in intrinsic signal intensity characteristics nor appearance of a brain-blood barrier disruption.

The differential diagnosis was broad. The findings were considered compatible with a low-grade tumor or a large FCD. A gliotic scar of postinflammatory process was not excluded because of the integrity of the adjacent cortical gray matter and the subtle shrinkage of the diseased area when compared with a contralateral mirror area, but normal cerebrospinal analysis almost ruled out this hypothesis. A mesiotemporal sclerosis was also suggested based on the PET features, but the MRI findings were not consistent with this diagnosis.

After debate, the multidisciplinary team of our reference Center for Chronic Refractory Epilepsy recommended large surgical resection. The procedure was done by a transtemporal approach under neuronavigation through 3 small cortectomies on T2 and T3 to prevent venous drainage impairment (C.R.). The lesion had a gelatinous appearance but was more solid than normal, surrounding parenchyma. The resection was uncomplicated, and the patient woke up without any new deficit. Visual fields were not evaluable preoperatively and postoperatively. One week after surgery, the patient was still seizure free and was discharged to a revalidation center for neuropsychological reeducation. Six months postoperatively, he is still seizure free (International League Against Epilepsy 1). The postoperative MRI showed an uncomplicated, near-total resection of 99.7% (Figure 3). The histopathological analysis of resected specimens highlighted combined features of dysplasia and dysembryoplastic neuroepithelial tumor (DNET), nonspecific type, with BRAF V600E mutation (World Health Organization grade 1), thereby resulting in a final diagnosis of type IIIb FCD (Figure 4). This diagnosis was reviewed and confirmed by an external pathologist in a specialized center (C.A. Maurage, CHU Lille, France).

DISCUSSION

Cortical dysplasias are a group of developmental malformations mainly featuring abnormalities in neuronal differentiation and migration resulting in subsequent cortical gray matter disruption. It is a common cause for chronic refractory epilepsy. In 2011, Blümcke et al.,[2] from the ILAE task force, proposed a revised classification of FCDs in which the type III is characterized by an FCD associated with another lesion, type IIIb, which is the combination of FCD and glial or glioneuronal tumor. The true incidence of such lesions remains unclear because the coexistence of the tumor frequently biases anatomopathological reports. In a vast cohort of 60 FCD patients in which type IIb was the most frequent (48.8%), no patient was reported with a type IIIb.[1] The most frequently associated tumors in type IIIb FCD are gangliogliomas (GGs) and DNETs with, respectively, 45%–58% and 20%–33% of type IIIb FCDs.[3-5] Functional prognosis after surgical treatment is good, with 81%–87% of Engel Ia (i.e.,

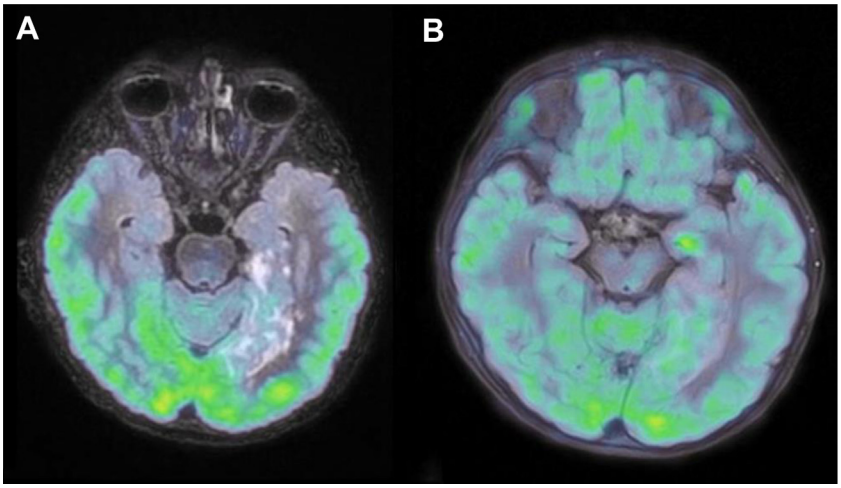

Figure 2. Positron emission tomography workup. (**A**) Fluoro-deoxy-glucose tracer showing hypometabolism in the diseased area but no abnormal uptake. (**B**) Methionine tracer which showed the absence of abnormal uptake.

completely seizure free since surgery) at 5-year follow-up.[3,6]

The preoperative differential diagnosis of such lesions mainly remains probabilistic. At MRI examination, FCD is revealed by the concomitant presence of focal cortical thickening, poorly defined transition between cortical gray and underlying white matter, and hyperintensity of the subcortical white matter on T2/fluid attenuation inversion recovery images with decreased signal intensity on heavily T1-weighted images.[7] Transmantle subcortical signal changes and localized loss of cortical volume are additional features.[3]

DNETs usually shows grape-like cyst formation (80%) with subcortical involvement, but some may harbor a more infiltrative pattern without cyst. As with any hyperhydrated process, it appears hyperintense on T2-weighted images and hypointense on T1-weighted ones. Enhancement after contrast agent perfusion is inconstant. Calcifications may be seen on susceptibility-weighted images (GRE-T2 or SWI-BOLD), but are better depicted on computed tomography scanner images.[3] They are usually located in the temporal lobe but might affect other areas.[6,8] In our patient, there was no enhancement, no calcifications, and no cyst that could have suggested the diagnosis of DNET.

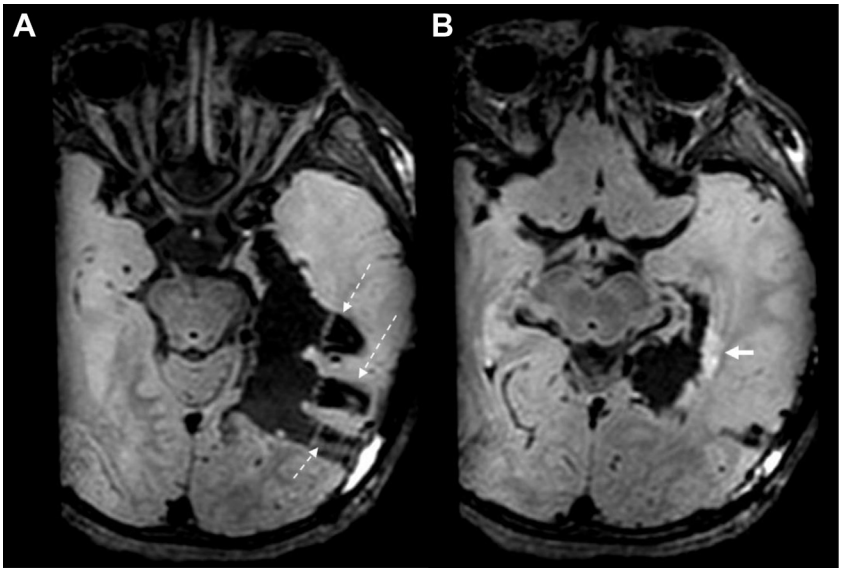

Figure 3. Postoperative magnetic resonance imaging. (**A**) Fluid attenuation inversion recovery view on the biggest part of the lesion showing a large uncomplicated resection through 3 small cortectomies (*dotted white arrow*). (**B**) Fluid attenuation inversion recovery view a few slices higher than (**A**) showing a small residue evaluated at 0.3% of the lesion (*plain white arrow*).

FDG-PET fails to allow differentiation between the 2 lesions. MET-PET noteworthily but inconclusively demonstrates higher tracer uptake in DNET and GG.[9] In our case, no increased uptake of the 2 tracers was observed.

The genetic factors predisposing to DNET and/or FCD are not well known. There is a more precocious mean age of onset of epilepsy in FCD patients (8 years) than in DNET patients (19 years), and a more frequent familial history of seizure in patients with FCD,[10] consistent with different pathogenesis. Yet, DNET is a rare neoplastic condition accounting for 0.6%–0.8% of all brain tumors in children,[11] but cortical disorganization in the vicinity of tumors is found in 80% of glioneuronal tumors (GGs and DNETs).[4] This strong concomitance of the 2 kinds of lesions suggests a common pathway of development. This recent hypothesis has been reinforced by immunohistochemical and molecular studies showing common mutation especially between GG and FCD but also fewer between DNET and FCD. The expression of CD34, a stem cell marker present in early neurulation, is clearly present in both GG and FCD[12] but not always in DNET.[13,14] The same has been shown for the mutation of BCL-2,[12] an apoptotic receptor that could cause failure of tumor suppression and for activation components of Pi3K-mTOR pathways, which are also present in both GG and FCD.[15] Only 1 case of a mixed lesion associating DNET and a rosette-forming glioneuronal tumors presenting a mutation of the mTOR pathway has been described.[16] Furthermore, BRAF mutation, associated with the activation of MAP-ERK pathway and proposed as linked to the

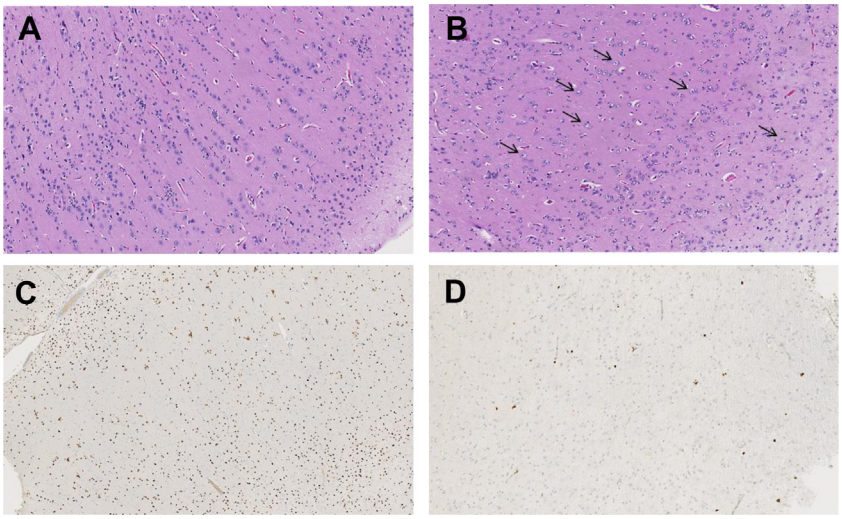

Figure 4. Histopathological workup. (**A**) Dysplastic part of lesion shows cortical disorganization with columnar aspect (hemoxylin and eosin ×100). (**B**) Tumoral dysembryoplastic neuroepithelial tumors part of lesion also shows cortical disorganization with abnormal neurons (*black arrows*) (hemoxylin and eosin ×100) and (**C**) glial reaction but without specific glioneuronal element (Olig2 ×50). (**D**) Ki67 is slightly increased in glioneuronal tumor, corresponding to grade I according to the World Health Organization classification (Ki67 ×100).

epileptogenesis of different lesion,[17] has been described frequently in GG and associated FCD[17] but less frequently in DNET.[14,17,18] Mutation in FGFR1, also related to an activation of the MAPK/ERK pathway, has been widely found in DNET.[18]

All of these findings suggest similar, yet slightly different, mechanisms and pathogenesis between those lesions that could represent different aspect of the same spectrum and are sometimes referred to as "focal malformations of cortical development."

CONCLUSION

We describe a rare condition of type IIIb dysplasia combining a focal cortical dysplasia with a DNET. Preoperative diagnosis of such a lesion is difficult, thereby rendering mandatory a thorough histopathological examination of resected specimens in the vast majority of cases. Increased recognition of the condition suggests the hypothesis of a genetic continuum or linkage between the 2 conditions. Functional results on seizure activity after ablative surgery are good and maximal safe resection should therefore be the goal.

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