Epilepsy surgery in the first months of life: a large type IIb focal cortical dysplasia causing neonatal drug-resistant epilepsy


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ABSTRACT – Focal cortical dysplasia is a common cause of medically refractory epilepsy in infancy and childhood. We report a neonate with seizures occurring within the first day of life. Continuous video-EEG monitoring led to detection of left motor seizures and a right frontal EEG seizure pattern. Brain MRI revealed a lesion within the right frontal lobe without contrast enhancement. The patient was referred for epilepsy surgery due to drug resistance to vitamin B6 and four antiepileptic drugs. Lesionectomy was performed at the age of two and a half months, and histopathological evaluation confirmed the diagnosis of focal cortical dysplasia type IIb (FCD IIb). The patient is free of unprovoked seizures without medication (Engel Class I) and is normally developed at 36 months after surgery. The case study demonstrates that FCD IIb may cause seizures within the first day of life and that epilepsy surgery can be successfully performed in medically intractable patients with a clearly identifiable seizure onset zone within the first three months of life. Although radical surgery such as hemispherectomy and multi-lobar resections are over-represented in early infancy, this case also illustrates a favourable outcome with a more limited resection in this age group.

Key words: neonate, seizure, focal cortical dysplasia, type IIb, surgery
Focal cortical dysplasia type IIb (FCD IIb) is a major cause of drug-resistant focal epilepsy (Palmini and Holtathausen, 2013). The pathogenesis has not yet been completely unravelled, but dysregulation of the mTOR pathway appears to play a role in the formation of dysplastic neurons (Crino, 2015). The histopathological hallmark of FCD IIb is the presence of dysmorphic neurons and balloon cells (Blümcke et al., 2009, 2011). Typical magnetic resonance imaging (MRI) findings consist of an increased subcortical signal on T2-weighted (w) and FLAIR sequences, often in a wedge-shape configuration with a blurring of the grey-white matter interface. FCD IIb arises during foetal brain development. However, seizures rarely occur within the neonatal period but typically in infancy and childhood. Here, we report a patient with seizure manifestation as early as within the first 24 hours of life due to right frontal FCD IIb.

Case study

Patient history and clinical findings

The patient was a female newborn with a history of an uneventful pregnancy and vaginal delivery at 39 weeks of gestational age. After normal postnatal adaptation (APGAR: 10/10; umbilical cord: pH 7.35), seizures started 16 hours after birth. Seizure semiology comprised left motor seizures of the arm and leg evolving to generalized tonic-clonic seizures. There was no family history of epilepsy, stillbirths, or neurodegenerative disorders of early infancy. An extensive work-up for neurometabolic diseases revealed no abnormalities. Seizures were refractory to age-appropriate dosages of vitamin B6, phenobarbitone, levetiracetam, topiramate, and oxcarbazepine. None of the criteria for tuberous sclerosis complex were met.

Routine EEG, continuous video-EEG monitoring, and brain MRI

Routine and continuous video-EEG monitoring using Xitek hard- and software equipment (Natus DBA, Excel-Tech Corp., Oakville, Canada) were performed using standard adjustments (0.5-Hz low-frequency filter, 70-Hz high-frequency filter; resistance <10 kΩ). Routine EEG revealed subclinical seizure patterns, intermittent slow activity, and sharp waves over the right frontal region. Continuous video-EEG monitoring detected right frontal seizure patterns, 13 to 30 seconds prior to clinical seizure onset (figure 1A, B). Seizure semiology comprised clonic seizures of the left extremities and bilateral clonic seizures. Brain MRI was obtained using a 1.5-Tesla scanner (3D sequences with an isotropic resolution of 1.0 to 1.5 mm: T1w sequences before and after the administration of a gadolinium-based contrast agent and T2w and fluid attenuated inversion recovery (FLAIR) sequences, with axial, sagittal, and coronal reformations; Siemens Magnetom Aera, Munich, Germany). A well delineated lesion of the right frontal lobe was observed, measuring 2.0 × 2.5 × 2.6 cm (figures 2A, B). The MRI signal intensity was hyperintense on T1w imaging and hypointense on T2w imaging compared to the surrounding unmyelinated white matter. There was neither contrast enhancement nor perifocal oedema. As a reference, the MRI of an eight-year-old boy with histologically proven FCD IIb is shown (figures 2C, D). This reference patient was operated due to medically refractory epilepsy at the age of eight years and is seizure-free after an observation period of five years (Engel Class I). The boundaries of the FCD IIb of the reference patient appear much less sharp and reveal hypointensity on T1w imaging and hyperintensity on T2w imaging.

Epilepsy surgery, genetics, and outcome

The patient was referred for epilepsy surgery based on concordant results from presurgical evaluation ([1] seizure semiology: left motor seizure; [2] EEG seizure onset zone: right frontal; and [3] MRI lesion: right frontal). Lesionectomy was performed at the age of two and a half months and histopathological investigation of the surgical specimen revealed FCD with balloon cells fulfilling criteria for FCD type IIb (Blümcke, Thom et al., 2011). The specimen revealed higher cellularity (figures 3A-D) compared to the specimen of the reference patient mentioned above who was operated on at the age of eight years (figures 3E-G). Trio exome sequencing on a HighSeq2500 (Illumina Inc., San Diego, USA) after SureSelect v6 enrichment (Agilent Technologies Inc., Santa Clara, USA) for the index patient and both parents revealed no pathogenic mutations of proteins involved in mTOR pathway regulation. The antiepileptic medication was tapered six months after surgery. During a post-surgical observational period of 36 months, the patient suffered from a fever-associated seizure at the age of two years. She reached age-appropriate milestones for infant development (i.e. motor skills and speech) and revealed no functional deficits.

Discussion

We report a patient with type IIb FCD and seizure onset on Day 1 of life who successfully underwent resective epilepsy surgery at two and a half months of life. The epileptogenic zone may significantly extend beyond the visible lesion on brain imaging (Bouet et
Invasive studies are therefore often necessary for epilepsy surgery candidates to further map the epileptogenic zone and to delineate eloquent cortex (Noachtar and Borggraefe, 2009). We did not perform invasive studies in our patient due to the following:

- an appropriate distance of the lesion to eloquent areas such as the primary motor cortex;
- concordant results for EEG seizure onset, seizure semiology, and location of the lesion;
- and a clearly delineated lesion.

Given these three findings, we weighted the risks and benefits and decided against an invasive study which, in general, can be performed even in this age group (Duchowny et al., 1998). Although reports on epilepsy surgery within the first years of life are less common than in older patients, the results of surgery with respect to seizure freedom or seizure reduction are at least comparable. In a recent Canadian survey, 66% and 100% of patients reached seizure freedom (Engel Class 1) after lesionectomy within the first three years of life due to FCD and low-grade tumours, respectively (Steinbok et al., 2009). The need for contemporary epilepsy surgery for appropriate candidates is further supported as patients with

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**Figure 1.** (A, B) Right frontal EEG seizure pattern (maximum lead: F8) recorded at six weeks of age.
Figure 2. MRI at the age of six weeks shows a 2.0 × 2.5 × 2.6-cm lesion with hyperintense signal on T1-weighted (w) imaging (A) and hypointense signal on T2w imaging (B) with moderate non-homogeneity primarily seen within the centre of the lesion on T1w images. The opposite pattern could be detected in a reference patient with proven FCD IIb in a similar location to that of the index patient, whose MRI at the age of eight years is depicted in panels (C) and (D), showing a less well delineated hypointense signal on T1w imaging (C) and hyperintense signal on T2w imaging (D).

eyear-onset epilepsy (< one year of age) show a better developmental outcome when surgery is performed within the first year of life, compared to patients in whom surgery was scheduled later (Loddenkemper et al., 2007). Epilepsy surgery within the first year of life tends to comprise disconnection procedures, such as functional hemispherotomy for large dysplastic unilateral malformations (such as hemimegalencephaly), structural brain damage due to neonatal stroke, and vascular malformations such as cerebral angiomatosis (Sturge Weber Syndrome), rather than tailored resections of well delineated lesions, as reported in this case (Steinbok et al., 2009). This is most likely due to the fact that patients with large unilateral lesions manifest earlier with medically refractory seizures and cognitive deterioration than patients with smaller lesions (Fauser et al., 2006; Honda et al., 2013; Wu et al., 2014).

Gross cerebral lesions are rarely encountered within the neonatal period. The most frequent entities with supratentorial location are teratomas, low-grade astrocytomas, and primitive neuroectodermal tumours (PNETs) (Buetow et al., 1990). These lesions should be distinguished from FCDs based on distinct neuroimaging findings such as non-homogeneous signals (i.e. teratoma), cystic components (i.e. astrocytoma), and contrast enhancement (i.e. PNETs) (Borja et al., 2013). However, histological evaluation of the surgical specimen is warranted to ascertain the diagnosis which is essential for further prognosis and management.

The imaging findings in our patient contrast the common MRI findings of FCD IIb. Commonly, FCD IIb appears on brain MRI as a blurry, wedged-shaped lesion. In addition, lesions typically exhibit a hyperintense signal on T2w imaging.
Figure 3. (A-D) Index patient; (E-H) reference patient. (A) H&E-staining of the index patient with neonatal FCD IIb showing increased cellularity with numerous balloon cells and dysmorphic neurons, as well as focal calcifications (black arrows). (B) Higher magnification of (A) showing balloon cells with homogeneous eosinophilic cytoplasm (white arrows) and dysmorphic neurons with prominent nissl substance (black arrows). In contrast, H&E staining of specimens from the reference patient (who received MRI and surgery due to medically refractory epilepsy, performed at the age of eight years) (E, F) shows similar cytological abnormalities with balloon cells (white arrows in [F]) and dysmorphic neurons (black arrows in [F]), although with a lower cellularity/density compared to the index patient with neonatal FCD IIb (A, B). These differences are highlighted by the accumulation of neurofilament protein (NF SMI32) in dysmorphic neurons (C, G) and vimentin expression in balloon cells (D, H) based on immunohistochemical staining. Scale bar: (A, C, D, E, G, H) 100 μm; (B, F) 50 μm.

We hypothesize that the signal appearance of FCD IIb in our case was most likely due to increased cellularity and myelination in the affected area, as demonstrated in the histopathological specimen of the index patient at two months of life compared to a reference patient aged eight years. These observations are supported by recent findings that myelin loss in combination with a reduced number of oligodendroglia cells occurs over time in FCD IIb specimens compared to normal neuronal tissue, and this is probably due to activation of the mTOR pathway (Scholl et al., 2016). The authors also identified a correlation between the duration of epilepsy and loss of myelin. These findings might support that FCD IIb is not a stable disease on a molecular level but rather undergoes changes over time with mTOR activation and subsequent myelin loss. In addition, the contrast with the surrounding physiologically unmyelinated white matter may have also contributed to the well delineated borders of the neonatal FCD IIb on MRI in the presented case.

In summary, FCD IIb may manifest as early as the first day of life and may show a different pattern on neuroimaging in the neonatal period compared to older age groups. Epilepsy surgery should be performed as early as possible in order to reduce seizure burden and secondary complications such as cognitive impairment, behavioural problems, and social sequelae (Elliott et al., 2008; Berg et al., 2016).

Key points

• Seizures due to focal cortical dysplasia type IIb (FCD IIb) may manifest within the first days of life.
• Imaging features of FCD IIb may be atypical in neonates.
• Epilepsy surgery can be successfully performed within the first three months of life.

Disclosures.
None of the authors have any conflict of interest to declare.

References

Neonatal drug-resistant epilepsy due to type IIb FCD


