

Genetic generalized epilepsies with frontal lesions mimicking migratory disorders on the epilepsy monitoring unit

Susanne Fauser  | Thomas Cloppenburg | Tilman Polster | Ulrich Specht | Friedrich G. Woermann | Christian G. Bien

Epilepsy Center Bethel, Krankenhaus Mara, Bielefeld, Germany

Correspondence

Susanne Fauser, Epilepsy Center Bethel, Mara I Hospital, Maraweg 21, 33619 Bielefeld, Germany.
Email: Susanne.fauser@mara.de

Abstract

Objective: Some patients with genetic generalized epilepsy (GGE) may present with ambiguous and atypical findings and even focal brain abnormalities. Correct diagnosis may therefore be difficult.

Methods: We retrospectively collected six patients investigated on the epilepsy monitoring unit with MRI abnormalities mimicking focal cortical dysplasia (FCD-like) or heterotopias, but with semiology and EEG features of GGE. We compared them to four additional patients with GGE and nonmigratory abnormalities.

Results: All six patients presented with frontal MRI lesions: radial (“transmantle,” $n = 4$), cortical-subcortical ($n = 1$), and periventricular heterotopia ($n = 1$). Five had positive family histories. Semiologic lateralizing signs compatible with the lesion were seen in four. Five patients had 3/s spike-wave complexes, with an asymmetric appearance in three. Regional EEG changes matched with the side of the abnormality in three patients. Invasive EEG ($n = 2$) or postoperative outcomes ($n = 3$) argued against an ictogenic role of the MRI abnormalities. Histology showed mild malformation of cortical development, but no focal cortical dysplasia. The six patients were finally diagnosed with juvenile myoclonic epilepsy ($n = 2$), juvenile absence epilepsy ($n = 2$), or GGE not further specified (nfs, $n = 2$). Compared to these patients, the other four (final diagnoses: childhood absence epilepsy, $n = 1$; perioral myoclonia with absences, $n = 1$; and GGE nfs, $n = 2$) had no lateralizing EEG findings.

Significance: Patients with GGE may have coincidental MRI abnormalities. These cases are challenging as frontal epilepsy and GGE can present with similar semiologies. GGE with coincidental FCD-like lesions/heterotopias is in particular difficult to diagnose as patients have more lateralizing features (in semiology and EEG) than those with tumors. A detailed noninvasive presurgical evaluation may be justified. We point out red flags that may help to distinguish GGE from frontal epilepsy, even in the presence of brain abnormalities: 3/s spike waves (even if asymmetric), changing lateralizing signs at different times, and a positive family history hinting at GGE.

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KEYWORDS

3/s spike-wave complexes, genetic generalized epilepsy, MRI, neuronal migratory lesion, neuropathology, tumor

1 | INTRODUCTION

Amidst the euphoria about the successful reintroduction of epilepsy surgery in some European countries in the late 1980s, “traditional” epileptologists warned about equating brain lesions in epilepsy patients with epilepsy cause in every single case.¹ “Modern” surgically oriented epileptologists, however, could claim a major step ahead for epileptology in most operated cases: removal of a part of the brain resulting in seizure freedom in a patient with previously pharmacoresistant seizures proved that the resected brain region contained the focal origin of this epilepsy.

For genuine generalized epilepsy syndromes, on the contrary, there has never been a gold standard proving their “generalized” nature. Even generalized EEG abnormalities, the hallmark of generalized epilepsies, are not unequivocal. In fact, they can appear in patients who are eventually successfully operated on.² At the beginning of the 21st century, “generalized epilepsies” were increasingly conceptualized as rapidly originating from focal cortical origins within an extended interhemispheric, corticosubcortical network.^{3,4} This moved the generalized epilepsies closer toward the focal epilepsies. In parallel to this, presurgical epileptology made a major step forward by increasingly recognizing subtle epileptogenic malformations of cortical development by means of high-resolution MRI and morphometric MRI analysis.⁵ As a result, some extratemporal (mainly frontal) epilepsies and the generalized epilepsy syndromes could appear to be no longer categorically different. In fact, there are striking similarities between some frontal lobe seizures and absences.⁶

Even though the concept of generalized seizures and generalized epilepsy has never formally been abandoned,⁷ all the abovementioned trends may have led to a blurring of the border between “focal” and “generalized.” To the best of our knowledge, only few focal epilepsy cases with features of generalized epilepsies were indeed described (in part even with 3/s spike waves).^{8,9} However, the patients reported in these case reports were not operated on. Therefore, they did not clarify the conceptually important borderline between focal and generalized. Vice versa, it would not come as a surprise if patients with generalized epilepsies occasionally had been studied for suspected focal epilepsy and even had undergone focal resective surgery. A description of these patients would be helpful to avoid erroneous surgical suggestions.

In this paper, we report on our experience with such cases. We paid special attention to patients with frontal MRI

Key Points

- Patients with genetic generalized epilepsy (GGE) may have coincidental MRI abnormalities
- These cases are challenging as frontal epilepsy and GGE can present with similar semiology
- GGE with FCD-like lesions of the brain or heterotopias is in particular difficult as patients have more lateralizing features than those with tumors
- We point out red flags that may help to distinguish GGE from frontal epilepsy, even in the presence of a brain irregularity
- Positive family history, 3/s spike waves (even if asymmetric), and alternating lateralizing signs at different times hint at GGE

abnormalities appearing as migratory disorders or malformations of cortical development (FCD-like lesions or heterotopias) and features of genetic generalized epilepsy (GGE) because they seem to be a subgroup of patients with “irregular” EEG findings and lateralizing signs. We intended to support the distinction of focal vs generalized epilepsies, and we aimed to point out “red flags” that may help in identifying patients at risk of being misclassified in a presurgical setting.

2 | METHODS

We retrospectively assessed patients only after admission to the epilepsy monitoring unit of the Epilepsy Center Bethel^{10,11}; in some patients, a diagnosis of generalized epilepsy was made only after epilepsy surgery. All ten reported cases fulfilled the ILAE criteria of refractory epilepsy. They had failed adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules regarded as effective for focal and generalized epilepsies (whether as monotherapy or in combination) to achieve sustained seizure freedom such as lamotrigine, valproate, levetiracetam, or topiramate (Table 1). We focused on six patients with FCD-like lesions of the brain/heterotopias and EEG features reminiscent of GGE. We compared them to four additional patients with GGE and non-migratory-like MRI abnormalities. MRI imaging and reading followed a standardized epilepsy-dedicated protocol,¹² including the use of automated texture analysis to highlight MR features of focal cortical

TABLE 1 Summary of relevant findings in patients 1-10

Patient number, gender	Epilepsy syndrome	MRI findings	Age at disease onset	Age at preoperative VEEG	Interictal EEG	Seizure type/ictal EEG	Lateraling semiologic signs	Photosensitivity	Family history	Medical history	Epilepsy surgery/long-term outcome
Lesions mimicking malformations of cortical development											
1, m	JME	Right frontal lesion initiating FCD IIb (FCD-like) Histo: mMCD II VBM results (maps): Junction + Thickness – Extension –	12 y	26 y 30 y	gen. SW, with right frontal maximum; right frontal SW; 3/sec SW (often with right frontal onset)	Absence seizures: 3/s SW with right-sided preponderance of amplitudes Myoclonic jerks: gen. polyspikes GTCS; gen. polyspikes	Yes Myoclonic jerks mainly bilat., sometimes isolated in the left upper extremity	Yes (but only initially)	Positive: cousin and uncle with JME	VPA, LTG, LEV, CLB, OXC, BRIV	Right frontal extended lesionectomy, last follow-up 2.5 y after epilepsy surgery: unchanged seizures (frequency, semiology), unchanged normal cognitive abilities, continues education
2, f	No syndrome	Right frontal lesion initiating FCD IIb Histo: mMCD II VBM results (maps): Junction + Thickness – Extension –	2.5 y	3.5 y	Not lateralized SW; alternating right and left frontal poly-SW	Tonic seizures, myoclonic seizures, and GTCS: not lateralized	Yes Infrequent left-sided myoclonic jerks, however, no lateralizing sign in most seizures	No	Positive: father with prolonged febrile seizures until the age of 6 y	CLB, LEV, VPA, ESM, OXC	Right frontal extended lesionectomy, last follow-up 3 y after epilepsy surgery: reduced seizure frequency, unchanged semiology, unchanged normal cognitive abilities, attends kindergarten
3, f	JAE	Left frontal lesion initiating FCD II or tumor Histo: oligodendroglial hyperplasia VBM results (maps): Junction + Thickness + Extension +	10 y	18 y	Surface EEG: frontal SW and poly-SW right > left; 3/s SW Invasive EEG: SW (3/s) und lafa in the premotor area	Surface EEG: absence seizures: 3/s SW Invasive EEG: absence seizures (→ GTCS); 3/s SW in SMA adjacent to lesion Cave: patient had no electrodes far from lesion	No	No	Negative	LTG, ESM, MSM	Invasive EEG (grid electrode): left frontal extended lesionectomy in 2012, last follow-up 6.5 y after operation: unchanged seizures (frequency, semiology), unchanged cognitive abilities below average, no data for social outcome available

(Continues)

TABLE 1 (Continued)

Patient number, gender	Epilepsy syndrome	MRI findings	Age at disease onset	Age at preoperative VEEG	Interictal EEG	Seizure type/ictal EEG	Lateralizing semiologic signs	Photosensitivity	Family history	Medical history	Epilepsy surgery/long-term outcome
4, f	JAE	Right frontal lesion imitating FCD IIb VBM results (maps): Junction + Thickness – Extension –	15 y	23J y	Surface EEG: SW, poly-SW, 3/sec SW left and right frontally; during presurgical monitoring right» left, in routine EEGs left» right Invasive EEG: SW, poly-SW, 3/s SW left > right frontally	Surface EEG: absence seizures: 3/secGTCS; 3/sec SW > gen. poly-SW Invasive EEG: GTCS:right frontal 3/s SW but far away from lesion	Yes, but not consistent Head version to the left and right, alternating with different seizures	No	Positive:aunt with epilepsy (according to patient; however, this occurred after traumatic brain injury)	LEV, VPA, LTG	Invasive EEG (depth electrodes), no surgery,normal cognitive abilities, shop assistant in a supermarket, no follow-up after VEM in our clinic
5, f	JME	Right insular lesion, imitating FCD VBM results (maps): Junction – Thickness – Extension –	17 y	24 y	Not lateralized poly-SW; short bursts with 3/s SW with maximum right» left frontally	Myoclonic jerks-> GTCS: gen. poly-SW with right frontal onset	No (bilateral myoclonic jerks-> GTCS)	No	Positive: brother has JME	LTG, VPA, ZNS, LEV	No epilepsy surgery, last follow-up 0.5 y after VEM: unchanged seizures (frequency, semiology), unchanged normal cognitive abilities, continues education
6, m	No syndrome	Right periventricular heterotopia VBM results (maps): Junction – Thickness – Extension +	15 y	23 y	3/s SW, gen polyspikes -> 3/s SW	Versive -> myoclonic-> GTCS:bifrontal 3/s poly-SW -> short interruption -> bilateral diffuse seizure pattern	Yes Head version to the left, left-sided myoclonic jerks	No	Positive: mother and brother had febrile seizures	LTG, TPM, LEV	No epilepsy surgery,normal cognitive abilities, works as coachbuilder,no follow-up after VEM in our clinic
Patients with tumors											
7, f	No syndrome	Left temporal meningioma	Infancy until age 6 y, again at 47 y	54 y	gen. 3/s poly-SW	Absences with bilateral myoclonic jerks; gen. 3/sec poly-SW;GTCS: not captured	No	No	Data not available	LEV, LTG	No epilepsy surgery,normal cognitive abilities, shop assistant in a supermarket, no follow-up after VEM (Continues)

TABLE 1 (Continued)

Patient number, gender	Epilepsy syndrome	MRI findings	Histo	Age at disease onset	Age at preoperative VEEG	Interictal EEG	Seizure type/ ictal EEG	Lateraling semiologic signs	Photosensitivity	Family history	Medical history	Epilepsy surgery/ long-term outcome
8, m	No syndrome	Right frontal tumor, astrocytoma WHO II	Histo: astrocytoma WHO II	15 y	29 y	gen. 3/s SW, frontal SW right > left (postoperatively)	Myoclonic jerks: gen. spikes and poly-SW GTSC: not captured	No	No	Negative	VPA, CBZ, LTG, TPM	Tumor resection in 2005, last follow-up 2.5 y after surgery, unchanged seizures (frequency, semiology), unchanged cognitive abilities slightly below average, seeking work
Patients with other lesions												
9, m	Perioral myoclonia with absences	Left temporal injury		17 y	25 y	gen. 3/s SW; gen. poly-SW	Myoclonic head and perioral jerks: in the rhythm with gen. 3/s SW; polytypic myoclonic jerks: gen. poly-SW GTSC: not captured	Myoclonia in the right m. depressor anguli oris	No	Positive: mother with generalized epilepsy	LTG, LEV, VPA, lorazepam	No epilepsy surgery, last follow-up 1 y after VEM, unchanged seizures (frequency, semiology), unchanged normal cognitive abilities, finished his studies in sociology, seeking work
10, m	CAE	Left frontal cystic lesion		2 y	27 y	3/s SW and poly-SW	Absences: 3/s SW and poly-SW GTSC: not captured	No	No	Negative	VPA, LTG	No epilepsy surgery, last follow-up 2.5 y after VEM, unchanged seizures (frequency, semiology), unchanged normal cognitive abilities, seeking work

Abbreviations: BRIV, brivaracetam; CAE, childhood absence epilepsy; CBZ, carbamazepine; CLB, clobazam; ESM, ethosuximide; FCD; focal cortical dysplasia; f, female; gen., generalized; GTCS, generalized tonic-clonic seizure; Histo, histology; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; Jafa, low amplitude fast activity; LEV, levetiracetam; LTG, lamotrigine; m, male; mMCD, mild malformation of cortical development; MSM, mesuximide; OXC, oxcarbazepine; SMA, supplementary motor area; SW, spike wave; TPM, topiramate; VPA, valproic acid; VBM, voxel-based morphology; VEM, video-EEG monitoring; y, years; ZNS, zonisamide.

dysplasia.¹³ All ten patients underwent VEM for several days. Invasive VEM was added in three cases. In the operated patients, the postoperative seizure outcome was classified according to the classification by Engel.¹⁴ Moreover, the postoperative semiology of seizures was considered.

We identified these patients from the memory of neurologists at this center or during case discussions of problematic cases in clinical conferences. This paper is not meant to estimate the frequency of this constellation because neither the numerators nor denominators for such calculations are clear.

3 | RESULTS

We assembled ten cases from the time period 2005 to 2016. Patient histories, clinical manifestations, and MRI and EEG findings are summarized in Table 1 and in Figures 1-5 and Figures S1-S5.

3.1 | Patients with MRI abnormalities mimicking or appearing as migratory lesions (FCD-like lesions/heterotopia) (n = 6)

MRI revealed the following abnormalities: transmantle-like signal abnormalities (suggesting focal cortical dysplasia [FCD] type IIb¹⁵) (patient nos. 1, 4, 5; Figures 1-5, Figure S1; Figures 1, 4 and 5A), small periventricular areas of cortical signal suggesting nodular heterotopias (patient no. 6) (Figure S1A), and a mixture of both (patient no. 2) (Figure 2A). In retrospect, different from classical transmantle dysplasia as seen in FCD type II, the “lesions” appeared not funnel-shaped but rhomboid (patient nos. 1, 4, 5; Figures 1, 4 and 5A) and “fluffy.” In patient no. 3, cortical-subcortical blurring was seen (Figure 3A).

All patients had *seizure semiology* principally compatible with genetic generalized epilepsy (absences, myoclonic and generalized tonic-clonic seizures, one child with tonic

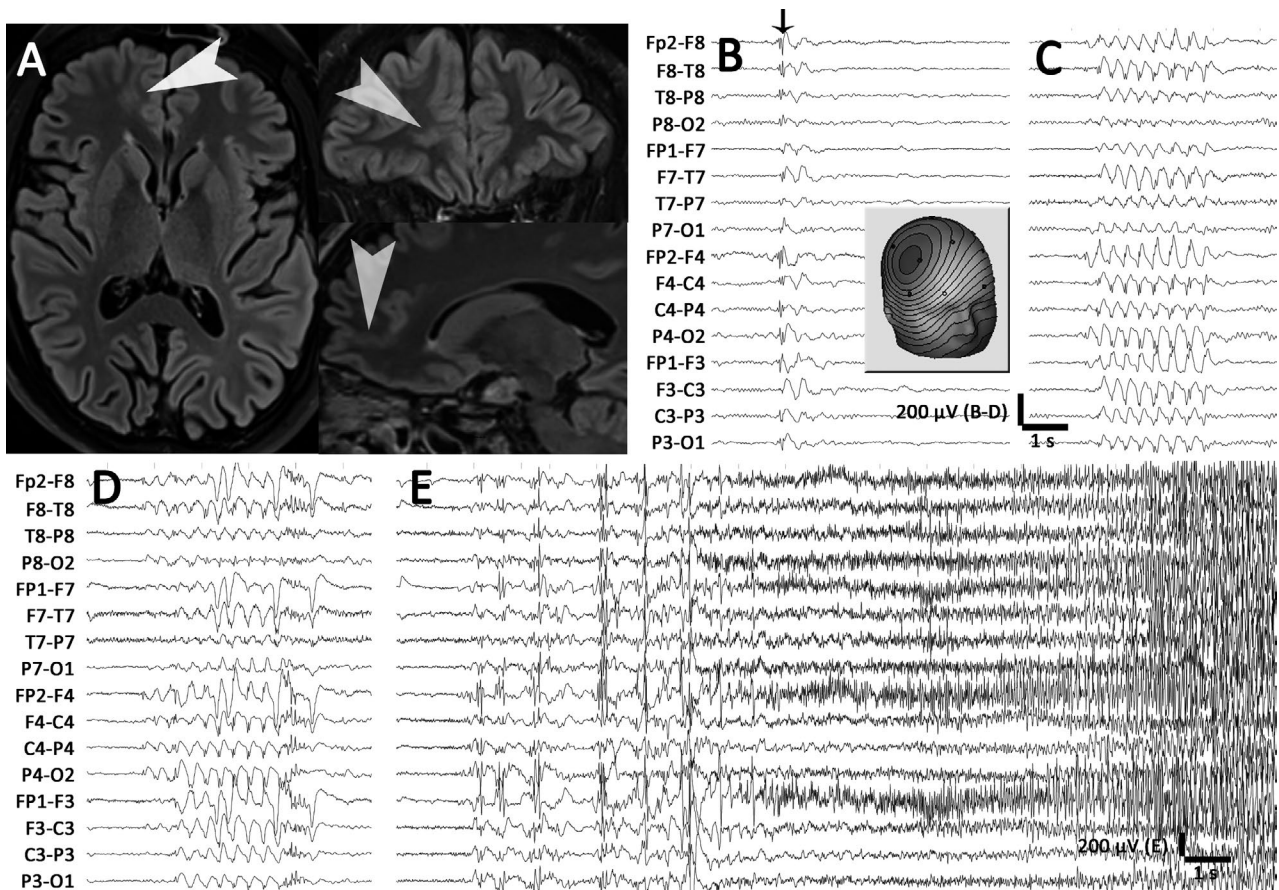


FIGURE 1 Patient 1 (juvenile myoclonic epilepsy). (A) MRI showed a lesion in the right frontal lobe mimicking a transmantle dysplasia (arrows). (B-D): Interictal EEG consistently lateralized to the right hemisphere. Polyspikes had a right frontal maximum (B), and 3/s spike waves had either a right frontal preponderance of amplitudes (C) or a right-hemispheric onset (D). The epilepsy was pharmacoresistant. Thus, video-EEG monitoring was performed and reproduced the lateralized interictal findings. (E) The only preoperatively captured generalized tonic-clonic seizure began with bilateral myoclonic jerks of the upper extremity and was without semiologic or electroencephalographic lateralizing signs. Myoclonic seizures, however, were sometimes asymmetric and then always manifested in the left body part (not shown). With knowledge of the MRI lesion, focal right frontal epilepsy was diagnosed. After extended lesionectomy seizure semiology, seizure frequency and EEG findings were unchanged. Histology revealed mMCD type II

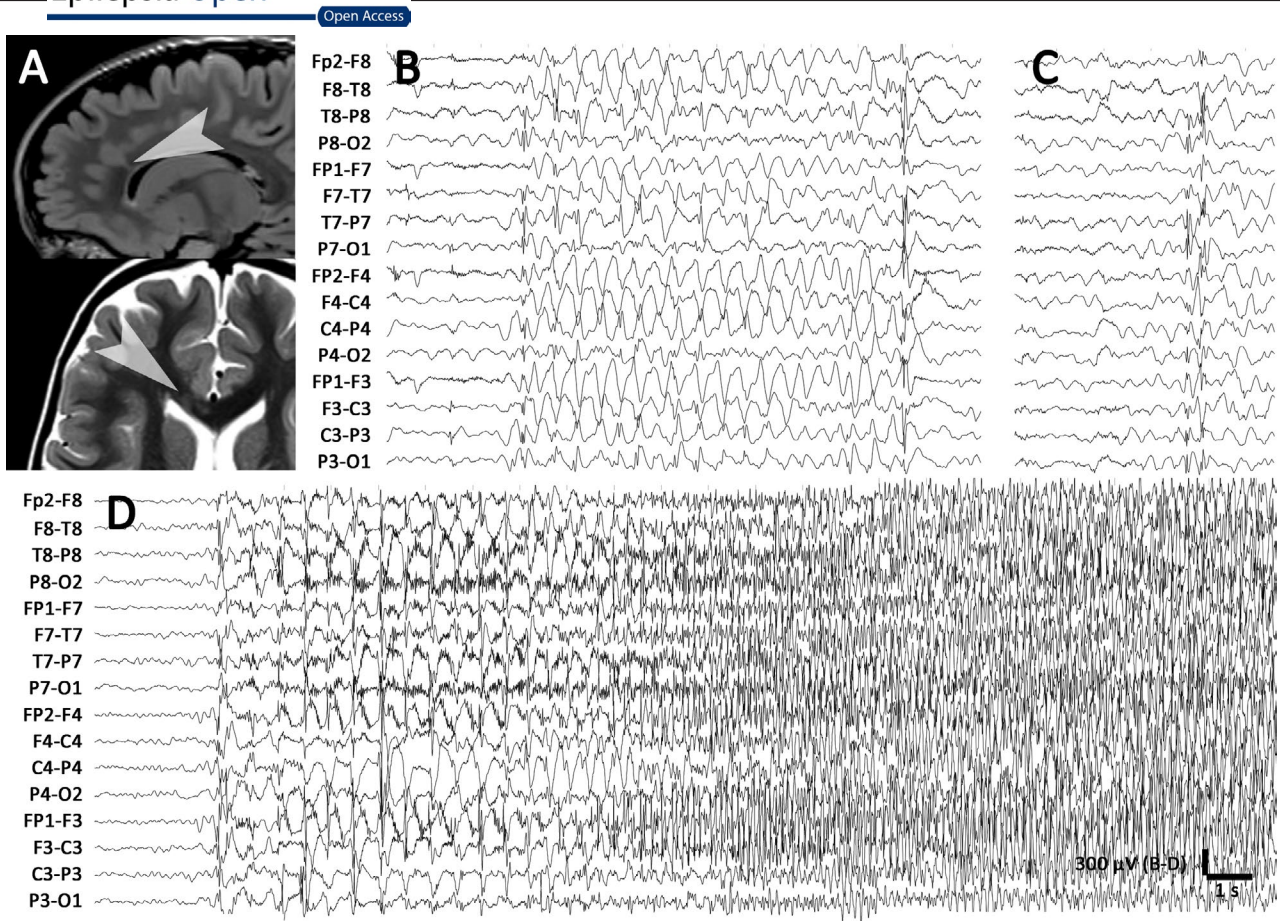


FIGURE 2 Patient 2 (no syndrome). (A) MRI revealed a lesion in the right cingulate gyrus with features of a transmantle dysplasia and of periventricular heterotopia. The epilepsy was pharmacoresistant. (B,C,D): Ictal EEG patterns of different seizure types: (B) absence-like seizure followed by repetitive bilateral myoclonic jerks without semiologic or electroencephalographic lateralizing signs, (C) myoclonic jerk of the left upper extremity (contralateral to the lesion) with bilateral polyspikes, and (D) a generalized tonic-clonic seizure with initial tonic posturing of the left upper extremity and a generalized seizure pattern in EEG. Focal right frontal epilepsy was supposed. After extended lesionectomy seizure semiology, seizure frequency and EEG findings were unchanged. Histology revealed mMCD type II

seizures as well). No patient had clonic, hyperkinetic, or focal seizures with automatisms. Three patients (patient nos. 1, 2, and 6) had *semiologic lateralizing signs* consistently compatible with the abnormality. *Family history* was positive for epilepsy or febrile seizures in five patients. Photosensitivity was seen in one patient (patient no. 1) in EEGs at an early stage of the epilepsy (Table 1). In the *surface video-EEG monitoring (VEM)*, five patients (patient nos. 1 and 3-6) had 3/s spike-wave complexes (Figures 1C,D, 3D, 4C,D and 5B; Figure S1B,D); however, in two of them, this was clearly asymmetric in appearance (Figures 1 and 4C,D). Moreover, (poly-)spike waves were asymmetric in four patients during presurgical VEM (Figures 1, 3B,C, 4E and 5C,D). The predominant regional EEG changes matched with the side of MRI abnormality in three patients (patient nos. 1, 4, and 5) during VEM. In two patients (patient nos. 2 and 3), regional interictal epileptic discharges were alternating between the left and right sides without side preference. In one patient (patient no. 4), earlier EEGs

were available showing (in contrast to the VEM) regional epileptic discharges contralateral to the imaging abnormality (Figure 4B-D).

In two patients with *invasive VEM*, there was evidence for a frontal premotor rather than a generalized onset zone of 3/s spike waves (patients no. 3 and 4) in spontaneous habitual seizures. In patient 3, seizure onset was close to the lesion, but obviously by chance as the patient did not benefit from epilepsy surgery (Figure 3E). In patient 4, the seizure onset zone was clearly away from the frontopolar lesion (Figure 4G-I). None of the three *operated patients* (n = 3) experienced a postoperative change in seizure frequency or seizure semiology. *Histology* revealed mild malformation of cortical development (mMCD type II)¹⁶ (patient nos. 1 and 2) and oligodendroglial hyperplasia (no. 3)¹⁷.

Final diagnoses of epilepsy syndromes: juvenile myoclonic epilepsy, n = 2; juvenile absence epilepsy, n = 2; GGE not further specified (nfs, n = 2).

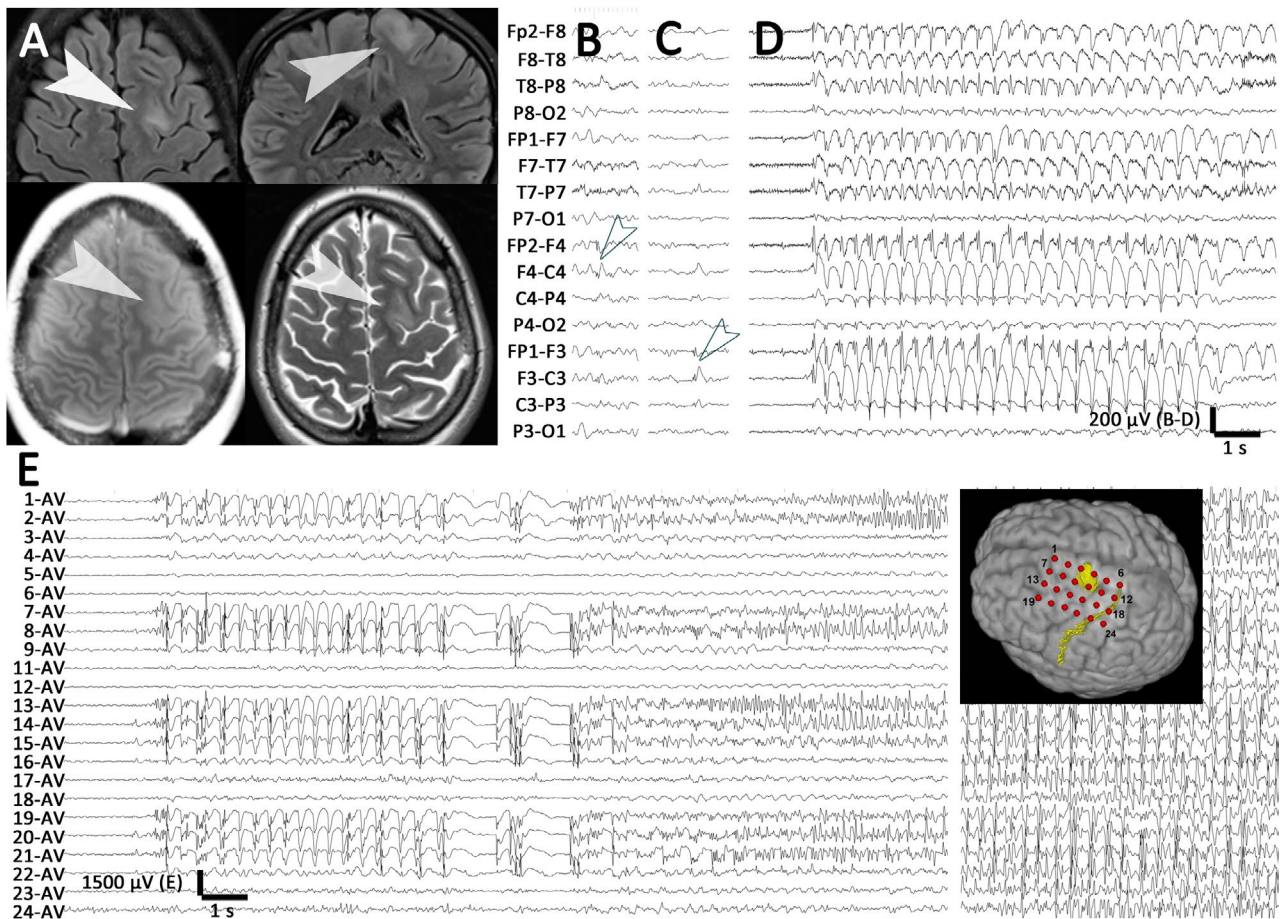


FIGURE 3 A: MRI showed a left frontal (premotor) lesion reminiscent to a tumor or focal cortical dysplasia. Surface EEG (B-D) revealed alternating right (B) and left (C) frontal spikes and generalized 3/s SW paroxysms with and without clinical signs of an absence seizure (D). (E) The invasive EEG is shown in a referential montage to a common average (AV) electrode comprising all electrode contacts. The implanted grid electrode gave evidence of an initial seizure pattern in the premotor area (absence) with gradual spread to the precentral and postcentral gyrus (then evolving to generalized tonic-clonic seizure without lateralizing semiologic signs). The grid electrode suggested a perilesional seizure onset, alternative hypothesis: bilateral premotor seizure onset in a typical absence seizure (not detected in the left hemisphere for lack of a contralateral electrode). The lesion was operated on for tumor-surgical reasons, but also because at least a relevant influence on ictogenesis was suspected. Unchanged seizure semiology after lesionectomy pointed, however, to the alternative hypothesis. The lesion (histology: oligodendroglial hyperplasia) was not causally related to the absence epilepsy. [Correction added on May 21, 2020, after first online publication: Figure 3 legend has been revised.]

3.2 | Patients with other lesions (n = 4)

3.2.1 | MRI diagnoses were as follows

(a) Tumors: One patient fulfilled MRI criteria of a meningioma in the left temporal lobe (patient 7, Figure S2A; Figures S2-S5). This patient was not operated on. One had a histologically proven astrocytoma WHO II in the right frontal lobe (patient 8, Figure S3A). (b) Other lesions: Patient 9 presented with a posttraumatic lesion in the left temporal pole, probably as a consequence of frequent falls during generalized tonic-clonic seizures (Figure S4A). In patient 10 with unusual pharmacoresistant absence seizures, a cystic lesion was found in the left frontal lobe (Figure S5A).

Seizure semiology was in all patients compatible with GGE (absences, myoclonic and generalized tonic-clonic seizures).

Family history was positive for epilepsy in two patients. No patient was photosensitive. In the *surface VEM*, all had symmetric 3/s spike-wave complexes (Figure S2B,D; Figure S3B; Figure S4B,C; Figure S5B). In patient 8, polyspike waves alternated between the right and left sides (Figure S3D,E) without a side preference. One patient (patient no. 10) had the syndrome of “perioral myoclonia and absences with myoclonia” in the right musculus depressor anguli oris,¹⁸ which must not be confused with focal epilepsy. The others had no lateralizing semiology (Table 1). In none of the patients was *invasive video-EEG monitoring* performed, obviously, because the diagnosis of GGE was not questioned further after presurgical surface monitoring despite the brain lesions. One patient (patient no. 8) was finally, after a diagnosis of GGE had been made, *operated on* for purely tumor-surgical reasons. As expected, seizure frequency and semiology did

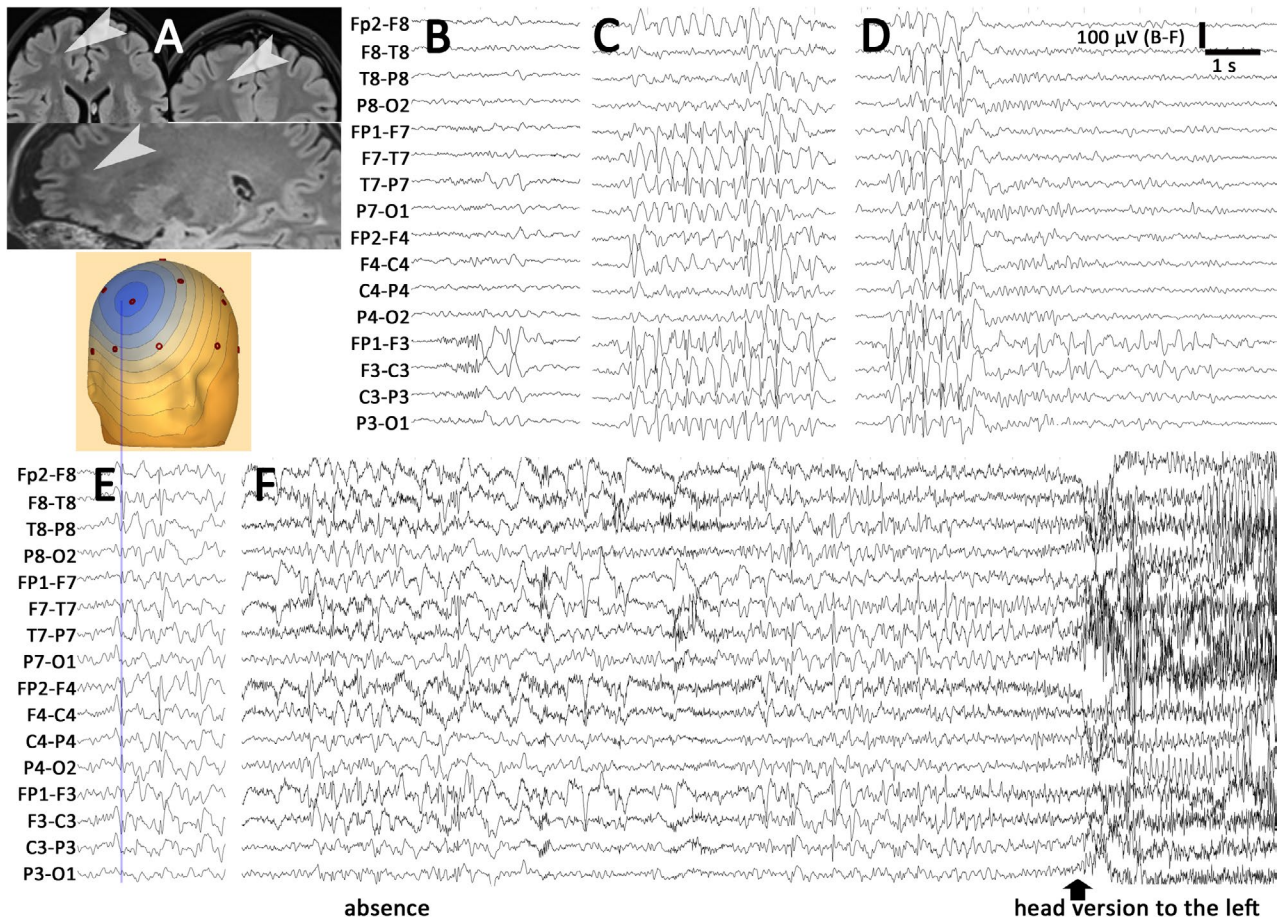


FIGURE 4 Patient 4 (juvenile absence epilepsy). (A) MRI revealed a lesion in the right frontal lobe very similar to patient 1, reminiscent of a transmantle dysplasia. Interictal routine EEGs at different times (B–D), however, showed left frontal regional epileptiform discharges (contralateral to the lesion). (B) Left frontal polyspikes, (C) 3/s SW with left hemispheric preponderance, (D) 3/s SW with a left frontal decay. In contrast, during video-EEG monitoring with surface electrodes (E, F) (which was performed because of pharmacoresistance) interictal polyspikes consistently had a right frontal maximum (E). Absence seizures had bilateral frontally accentuated 3/s SW (not shown). The only captured generalized tonic-clonic seizure (F) began with an absence seizure, and then evolved to an eye and head version to the left (contralateral to the lesion) compatible with seizure onset from the right frontal lobe. Invasive video-EEG monitoring was performed. (G) Electrode position of depth electrodes in the invasive video-EEG monitoring. (H–I) Invasive EEG results are shown in a bipolar montage, and H and I are shown in the same montage. (H) Most 3/s SW bursts had a maximum or onset left in the red depth electrode, more pronounced in the distal frontoparasagittal than in the proximal frontomesial contacts. The blue box indicates the electrode contacts within the “migratory lesion” which were not maximally involved in the EEG onset. (I) Ictal onset of the only GTCS had (similar to the absences) a maximum in the left frontoparasagittal contacts. During course of seizure, there was an eye and head version to the right side. Taken together, interictal and ictal EEG gave no consistent evidence for seizure onset from the lesion. The patient was not operated on

not change postoperatively. The postoperative EEG showed an ipsilateral amplitude preponderance of the epileptic discharges (breach rhythm).

Final diagnoses of epilepsy syndromes: childhood absence epilepsy, $n = 1$; perioral myoclonia with absences, $n = 1$; GGE nfs, $n = 2$.

4 | DISCUSSION

In ten presurgically studied and in four instance operated cases, the diagnosis of generalized epilepsies was made only after admission to the epilepsy monitoring unit. All patients

had received at least two AEDs that are usually effective in GGE in adequate doses without seizure control. The cases with MRI abnormalities appearing as migratory disturbances were particularly misleading. The others were unequivocally identified as GGE after surface VEM. However, even in the difficult cases with migratory disorder–like imaging, the data suggest the unambiguous diagnosis of GGE supporting the conceptual distinction between focal and generalized epilepsies, even in these seemingly “borderline” cases. The reasons are that even these cases had typical generalized seizure types, 3/s spike-wave EEG, in some a positive family history or photosensitivity, and no improvement upon focal resection.

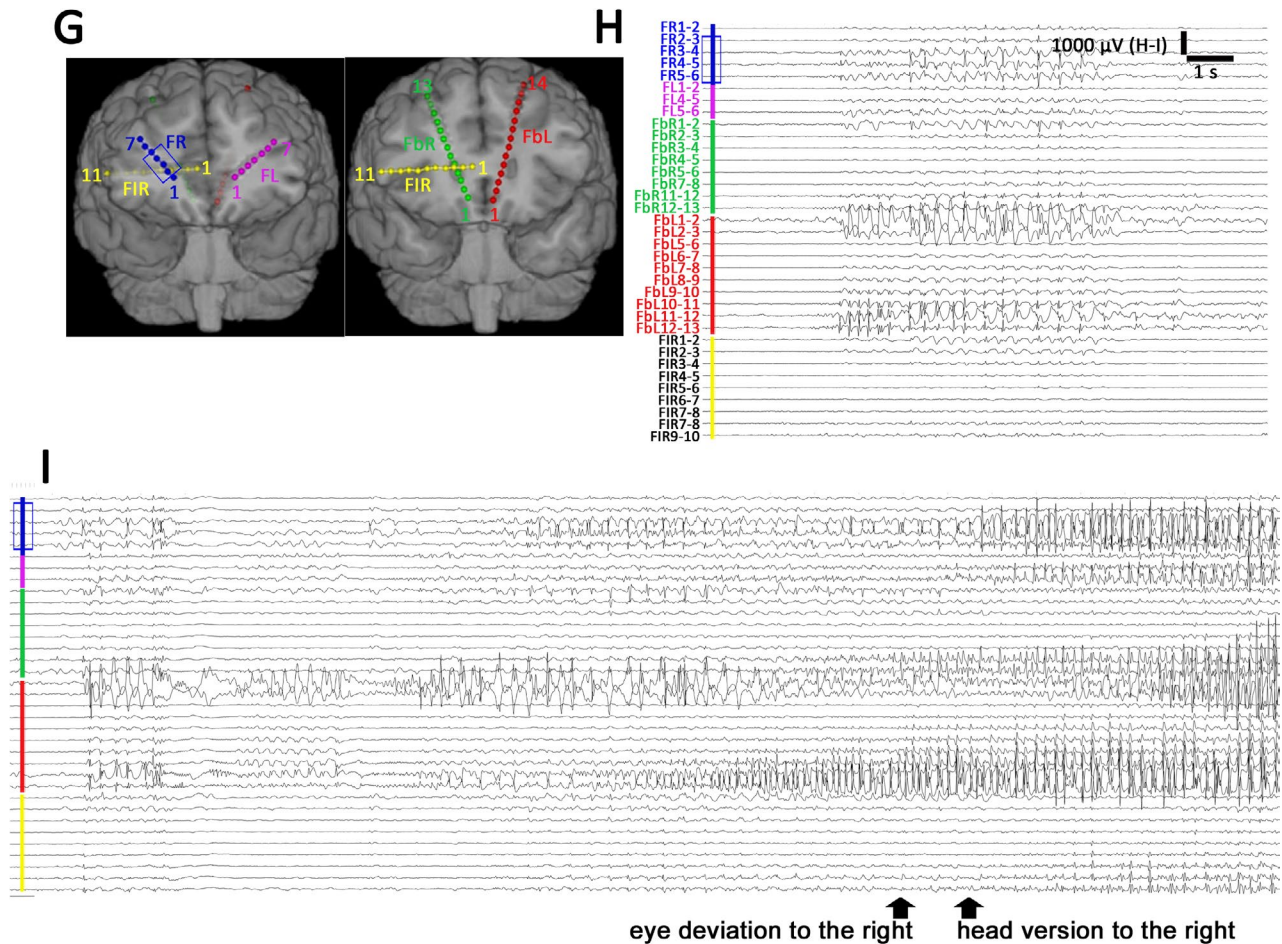


FIGURE 4 Continued

There are “red flags” that can help the epileptologist to identify patients with generalized epilepsies even in the presence of a frontal MRI abnormality: no clearly focal seizure semiology (such as unilateral clonic or hyperkinetic seizures or focal seizures with automatisms), alternating (or inconsistent) electrographic regional discharges, alternating (or inconsistent) semiologic lateralizing findings, 3/s (poly-)spike waves as the leading seizure pattern (even when asymmetric), a positive family history, and photosensitivity.

Another “red flag” is dysplasia-like radial lesions different from FCD type II or periventricular heterotopias, as they are probably not specific and thus play no crucial role in ictogenesis, but often present with obviously atypical semiologic or EEG features (see results).

Thus, some of these cases with dysplasia-like MRI abnormalities may bias toward focal epilepsy. One may be reminded of several tendencies and suggestions from the period covered here that might have contributed to the tendency to consider some of these cases as focal rather than generalized:

- There is a growing literature reporting on patients with a coincidence of focal (mainly temporal lobe) epilepsy and

genetic generalized epilepsies showing a worthwhile improvement of epilepsy after resection of the lesion.^{19–23}

- “Mixed” ictal EEG patterns have been described in patients with the coexistence of generalized and focal epilepsy, where focal seizures either evolved from generalized spike waves or focal seizures recruited a generalized network.^{23,24}
- Symptomatic epilepsies may imitate genetic (“idiopathic”) generalized epilepsies.²⁵
- It has been suggested that one should not overinterpret “generalized” EEG abnormalities (such as hypsarrhythmia, slow spike-wave complexes, (poly-)spike-wave complexes, polyspikes, and electrodecrement) as arguments against surgical epilepsy treatment in lesional patients.² Classical 3/s spike waves, however, were not explicitly mentioned in this study.
- The hypothesis that even classical 3/s spike-wave complexes may emanate from focal epileptogenic lesions and can be cured by epilepsy surgery was postulated by Kakisaka et al (2011).²⁶ However, evidence for that hypothesis was based on only one patient with a temporomesial ganglioglioma in whom 3/s spike waves disappeared after epilepsy surgery.

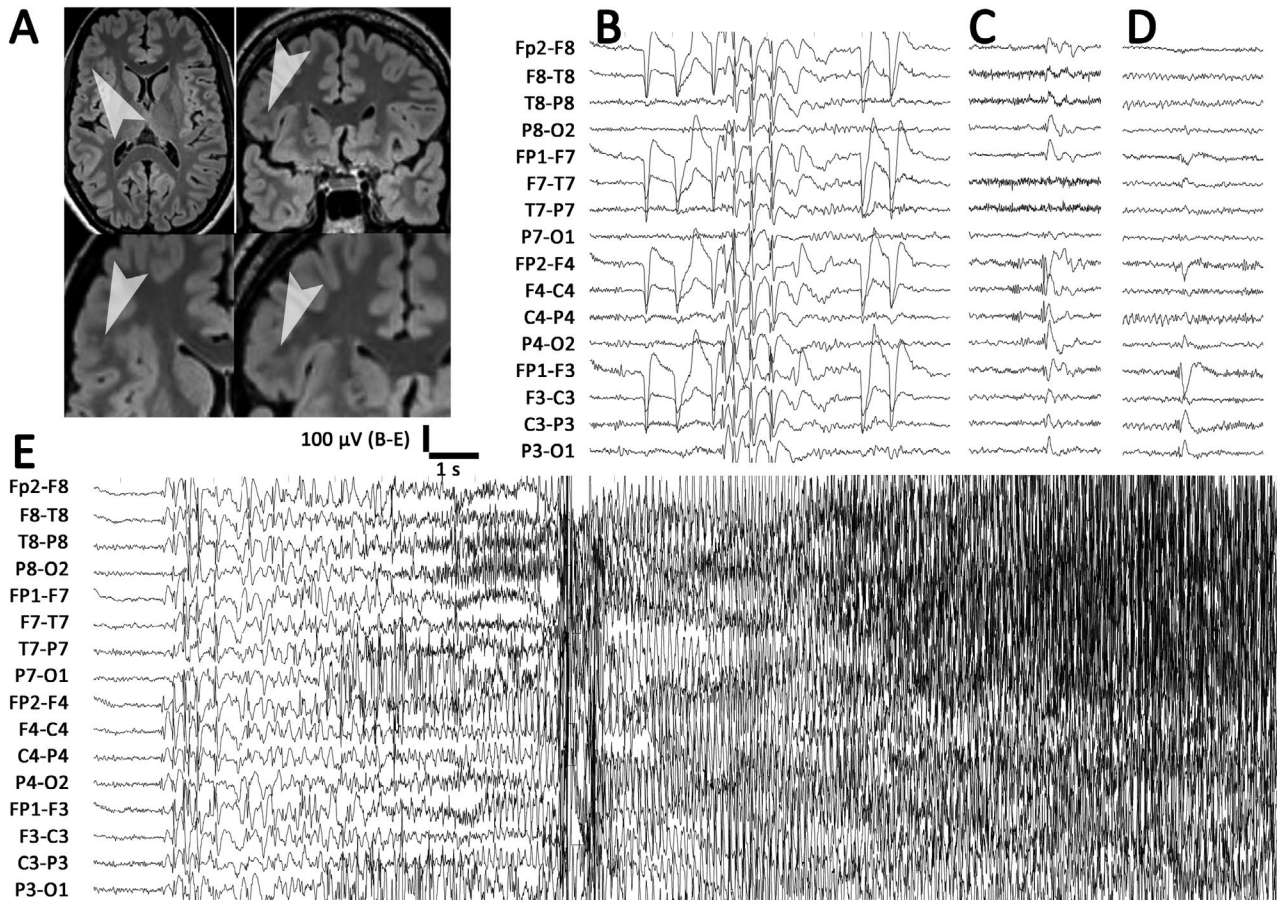


FIGURE 5 Patient 5 (juvenile myoclonic epilepsy). (A) MRI showed a lesion in the right frontoopercular area mimicking a focal cortical dysplasia with blurred gray-white matter junction (arrow). The epilepsy was pharmacoresistant. Interictal EEG (B-D) showed short bursts of 3/s SW (B), and generalized irregular polyspike waves, more often with a right (C) than with a left (D) frontal accentuation. The only captured GTCS (E) was without clinically or electroencephalographically lateralizing signs (bilateral myoclonic jerks followed by a GTCS) after sleep deprivation. The patients were not operated on because a diagnosis of genetic generalized epilepsy was made

- Although there are clinical and EEG diagnostic criteria for the diagnosis of generalized genetic epilepsies by ILAE, in cases with more irregular findings, the diagnosis remains difficult. Sometimes, only epilepsy surgery permits a final decision on whether the hypothesis of focal epilepsy is supported.
- Absence epilepsies are generally known to respond well to medication. More recent literature, however, reports patients with juvenile absence epilepsy who do not become seizure-free.²⁷
- The good predictive value of FCD type II lesions on MRI regarding postoperative seizure freedom^{28,29} may have made the VEM team overoptimistic in cases such as patients 1-5 with mimics of this lesion type.

Some of the dysplasia-like MRI abnormalities had a quite uniform appearance (patient no. 1, 2, 4, 5) in that they reached from the cortex to the ventricle, were “fluffy,” and had not a funnel but rather rhomboid shape. Such lesions have not yet been reported, in particular not in patients with GGE. Although we cannot exclude a random coincidence of

these lesions with GGE, their surprising uniformity may hint to a specific relationship between them. Similar lesions with a transmantle aspect were not seen in our patients with focal epilepsies. A few earlier case reports presented patients with absence epilepsies and small periventricular nodular heterotopias.³⁰⁻³² Carney et al (2013)³² depicted the MRIs of two such patients who were similar to our patient nos. 2 and 6.

In the 1980s, histological cortical microdysgenesis was described in patients with genetic generalized epilepsies: an increase in partially dystopic neurons in the stratum moleculare, the white matter, the hippocampus, and the cerebellar cortex, an indistinct boundary between the cortex and subcortical white matter and lamina 1 and lamina 2, as well as a columnar arrangement of cortical neurons.^{33,34} The tissue for histologic examination was obtained during the autopsy of patients who had mostly lived independently; however, some of them were in the Bethel residential area (assisted living care). Since that time, the concept of microdysgenesis has been questioned.³⁵ Before conceptualizing GGE as a thalamocortical network disease,³⁶ quantitative neuroimaging found not only diffuse cortical abnormalities, but also

frontal abnormalities, for example, in juvenile myoclonic epilepsy.³⁷ These findings were replicated in more recent MRI studies.³⁸ Moreover, mutations in the EFHC1 gene were identified in JME patients that may lead to radial migrational disturbances.^{39,40} Genetic studies were not conducted on the subjects considered in the present case study. Taken together, mild migrational (radial) disorders, even though not reflected upon standard histopathological workup in our cases, might not mandatorily be an independent second entity, but are possibly compatible with and potentially even related to GGE.

An important question is whether these abnormalities contribute to ictogenesis. In our small patient series, the removal of the FCD-like radial lesions did not have any effect on the epilepsy (semiology and seizure frequency), despite the preoperative asymmetric EEG findings and lateralizing semiologic signs. Possibly, these lesions were integrated in a larger, “generalized” epileptic network and had some influence on the surface EEG and semiology, as has been postulated for small periventricular heterotopias.³² The disappointing postoperative results, however, argue against a crucial role in ictogenesis. Moreover, we conclude that these abnormalities are different from FCD type II with its high intrinsic epileptogenicity that results in focal epilepsy with a good chance for postoperative seizure freedom.

An alternative interpretation of the asymmetric EEG findings and lateralizing semiologic signs may be a “partially focal” generation of GGE independent from the visible abnormalities. Functional MRI-EEG and magnetoencephalogram (MEG) studies analyzed sources of interictal and ictal activity in absence epilepsy.^{41–43} They provided evidence for circumscribed brain areas (most commonly frontal, more infrequently also temporal, parietal, and occipital) responsible for absence seizures appearing bilaterally symmetrically and generalized with conventional scalp EEG. Results from invasive VEM in two of our patients support the notion (as discussed before)^{44,45} that absence seizures are not immediately generalized but, before spreading, involve premotor (parasagittal) frontal areas. In our patient sample with unusually focal accentuation of interictal and ictal discharges, the initially focal epileptic activity may have spread less rapidly and more asymmetrically than otherwise.

It should be considered that brain lesions can be an incidental finding without any relationship to GGE, as was obviously the case in our patients 7–10.¹ In such cases, the evaluation of patient history, semiology, and the performance of VEM are the crucial diagnostic steps. In juvenile myoclonic epilepsy, and also in other types of GGE without MRI lesions, significant asymmetries in EEG and clinical seizures were described in a considerable number of patients.^{46–48} Moreover, concerning semiology, it is important to know that there are some special syndromes or subsyndromes within the group of GGE (eg, juvenile myoclonic epilepsy with orofacial reflex myocloni or perioral myoclonia with absences)

that may manifest with myoclonic jerks restricted to circumscribed muscle groups. They can occur unilaterally and even sometimes do not change side in individual patients.¹⁷ These cases should not be misinterpreted as focal epilepsies, as initially in case 9. The analysis of an earlier case series of patients with generalized epilepsies suggested that asymmetry in EEG or seizure semiology, the eagerness to enroll patients in drug studies or surgical programs, and the lack of team thinking involving several epileptologists may lead to the misdiagnosis of generalized epilepsy as focal epilepsy.⁴⁹

We conclude that, in doubtful patients, in particular those with FCD-like MRI abnormalities or small periventricular heterotopias whose seizures cannot be adequately treated with AEDs usually effective in GGE and with equivocal findings, a thorough presurgical video-EEG evaluation is recommended. Only in selected “difficult” cases with lesions and lateralizing signs congruent to the lesion should implantation of invasive electrodes be considered. The abovementioned “red flags” should be considered. Our results provide evidence that, before becoming invasive, a thorough analysis of earlier EEGs and maybe another surface VEM must be considered. If these investigations show variable lateralizing signs, invasive VEM is not indicated. After all, the fundamental distinction between generalized and focal epilepsies is still justified.

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CONFLICT OF INTERESTS

CGB obtained honoraria for speaking engagements from UCB (Monheim, Germany), Desitin (Hamburg, Germany), and Euroimmun (Lübeck, Germany). He receives research support from Deutsche Forschungsgemeinschaft (German Research Council, Bonn, Germany) and Gerd-Altenhof-Stiftung (Deutsches Stiftungszentrum, Essen, Germany). US received financial support from Desitin (Hamburg, Germany) for serving on scientific advisory boards and obtained honoraria for speaking engagements from Desitin, UCB (Monheim, Germany), and Eisai (Frankfurt, Germany). He received research support from Desitin. TP received personal fees from Desitin, Novartis, Shire, UCB, and Zogenix outside the submitted work. The remaining authors have no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. The study has been approved by the Ethics Committee in Münster (2019-576-f-S).

ORCID

Susanne Fauser  <https://orcid.org/0000-0003-3063-1586>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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