



Genetic generalized epilepsy and generalized onset seizures with focal evolution (GOFE)



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ABSTRACT

"Generalized Onset with Focal Evolution" (GOFE) is an underrecognized seizure type defined by an evolution from generalized onset to focal activity during the same ictal event. We aimed to discuss electro-clinical aspects of GOFE and to emphasize its link with Genetic Generalized Epilepsy (GGE).

Patients were identified retrospectively over 10 years, using the video-EEG data base from the Epilepsy Unit of Strasbourg University Hospital. GOFE was defined, as previously reported, from an EEG point of view with an evolution from generalized onset to focal activity during the same ictal event.

Three male patients with GOFE were identified among 51 patients with recorded tonic-clonic seizures. Ages at onset of seizures were 13, 20 and 22 years. Focal clinical features (motor asymmetric phenomenon) could be identified. EEG showed generalized interictal discharges with focal evolution of various localization. Four seizures were recorded characterized by 2–3 s of generalized abnormalities followed by focal (parieto-occipital or frontal) discharges. There were initially uncontrolled seizures with lamotrigine, but all patients reported a good outcome with valproate monotherapy.

We emphasize that GOFE presents many similarities with GGE. Recognition of the GOFE entity could bring a therapeutic interest avoiding misdiagnosis of focal epilepsy and consequently inappropriate use of narrow spectrum anti-seizure medicine.

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Introduction

Genetic Generalized Epilepsy (GGE) corresponds to a subgroup of Generalized Epilepsies with generalized seizure types, generalized spike-wave and a presumed genetic etiology. This group of GGEs is broad and includes a variety of common (polygenic with "complex" inheritance) and rare (polygenic or monogenic) syndromes. Idiopathic Generalized Epilepsies (IGEs) is a distinct and more limited subgroup of GGE which carries prognostic and therapeutic implications. IGEs include Childhood Absence Epilepsy (CAE), Juvenile Absence Epilepsy (JAE), Juvenile Myoclonic Epilepsy (JME) and Epilepsy with Generalized Tonic-Clonic Seizures Alone (GTCA) [1]. Classification of seizure and epilepsy types is crucial: it provides a common language which allows better communication between caregivers, facilitates diagnosis, treatment and prog-

nosis. The 2017 International League Against Epilepsy (ILAE) Classification of the Epilepsies [1–3] is currently used.

The "unknown" category of the ILAE 2017 classification emphasizes the fact that focal or generalized seizures can be difficult to evaluate, with some patients who do not match either the focal or generalized group. Generalized Onset with Focal Evolution seizures" (GOFE) is a recent and underrecognized entity [4–6]. It is an electroencephalographic evolution from generalized onset to focal activity during the same ictal event which refers to generalized epilepsy. It may be associated with semiology suggestive of focal seizures, leading to a misdiagnosis and sometimes to inappropriate treatment especially when no crisis could be registered.

Here we report three cases of GOFE that could be classified as GGE following the ILAE 2017 classification.

Methods

Patients were identified retrospectively over 10 years from the video-EEG database of the Epilepsy Unit of Strasbourg University

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Hospital. Inclusion criteria were: (1) adolescent and adult-age onset epilepsy (2) with at least one tonic-clonic seizure (TCSZ) recorded in long term video-EEG monitoring (VEM). GOFE was defined, as previously reported, from an EEG standpoint with an evolution from generalized onset to focal activity during the same ictal event.

Detailed family and personal medical history, imaging data and VEM were analyzed. VEM consisted of continuous EEG and video recording during 24 h, waking and sleeping, including scalp fronto-temporal basal and polygraphic and deltoid electrodes. Interictal activity was analyzed, as well in-detail ictal events, in order to differentiate between focal or generalized entities. Next-generation sequencing was performed for patients 1 and 2, using a panel targeting 204 epilepsy-associated genes. Informed consent for study inclusion was obtained from patients and parents or legal guardians, in compliance with the Declaration of Helsinki.

Results

Among 51 patients with adult or adolescent-onset epilepsy and recorded TCSZ in our tertiary center between 2011 and 2021, 45 (88 %) patients presented with focal epilepsy (structural and/or genetic), 3 (6 %) with GGE (two IGE including one JME and one GEFS + with SCN1A mutation), and 3 (6 %) with seizures of unknown etiology corresponding to the GOFE entity definition. No patient was identified with both focal and generalized epilepsy. 85 TCSZ were recorded.

These three patients with GOFE were initially referred for video-EEG because of persistent or worsening seizures. Electroclinical phenotypes of these patients are summarized in Table 1. The mean age of seizure onset was 18 years (range, 13 to 22 years). There was no personal history of epilepsy or risk factors for epilepsy. Mother of patient 1 had a history of familial seizure. Neurological exam and cerebral MRI were normal.

Four GOFE seizures were recorded during VEM (2 for patient 1; 1 for patients 2 and 3). They all presented with generalized interictal discharges when awake and during sleep, without focal interictal abnormalities. GOFE seizures were characterized by 2 to 3 s of generalized abnormalities followed by focal (left parieto-occipital, left frontal or right frontal) evolution of discharge (Fig. 1). The semiology at generalized EEG onset consisted of behavioral arrest in the three patients, and they all presented focal clinical features during focal ictal phase with head and ocular version, or with figure 4 sign. Genetic screening in 2 patients (patient 1 and 2) was negative. All had normal intellectual development. Despite initial uncontrolled seizures, the three patients became seizure-free: patient 1 and 2 after discontinuation of lamotrigine (LTG) and addition of valproate (VPA), and patient 3 following increased dose of VPA.

Discussion

We report three additional cases of GOFE seizures, that serves to expand clinical, EEG and therapeutic description of patients with this rare type of GGE. This entity has been recently described and is still undergoing precise characterization in patients with GOFE [4–9].

In previously reported patients with GOFE, seizure onset often occurs during childhood or adolescence, with onset ages ranging between 10 months to 15 years [4,6] whereas our described patients started later, between 13 years and 22 years. All patients described in the literature first presented with diverse types of initially-suspected seizures and syndromes. Most of them were initially suspected of generalized tonic-clonic seizures as were the

three patients reported here, but some patients were misdiagnosed with focal seizures and treated according to this diagnosis.

Indeed, clinical semiology of GOFE seizure alone could incorrectly suggest focal epilepsy, especially during the phase of focal evolution. Seizure onset could consist of behavioral arrest, staring or generalized myoclonic seizure. In our reported patients the episodes usually start with behavioral arrest, without any manifestation that could suggest generalized or focal initiation. This clinical part was associated with 2 to 6 Hz generalized spike-waves or polyspike-waves. During focal evolution, clinical semiology is variable, depending on the topography of the ictal recruiting pattern, with in our cases unilateral versive events or figure-4 sign. Most of the focal ictal EEG anomalies are anteriorly localized in frontal or temporal regions; occipital regions are rarely involved. In our report, all seizures became bilateral tonic-clonic after focal evolution, which is different from prior reports. All of the patients usually present brief generalized interictal discharges, particularly during sleep. Typical generalized seizures (generalized absence, generalized tonic-clonic, myoclonic and tonic seizures) can also be recorded [6].

Differentiation between focal and generalized seizures could be challenging, and clinical and/or EEG focal features can often be found in IGE [10]: from 35 to 46 % in GTCA (forced head and eye version, “figure-4 sign”, focal motor tonic-clonic, unilateral tonic/dystonic posturing etc.), 14 to 61 % in JME with focal and asymmetric jerks, or oral and manual automatisms reported in 40 % to 76 % of absence epilepsy (CAE, JAE). Focal interictal EEG abnormalities seem to be present among one-third of the patients with IGE [10]. However, this type of anomaly could be distinct from GOFE.

It is common to see widespread changes at the beginning of a focal seizure, and it may be difficult to exclude the possibility that GOFE reflects secondary bilateral synchrony in focal epilepsy. However, as previously explained [6], there are several arguments for generalized epilepsy in patients with GOFE as the absence of lateralization of the generalized discharges seen at seizure onset, the systematic presence of generalized interictal epileptiform discharges, the absence of focal interictal abnormalities, and the good outcome with broad-spectrum anti-seizure medication (ASM).

The pathophysiology of GOFE is unclear. Several authors [4–6] hypothesize that focal structural abnormalities support self-sustained hyperexcitability of low-threshold cortical structures. These focal cortical abnormalities could correspond to acquired neurological injuries [6] or microdysgenesis [10,11], invisible using current MRI techniques. Even if these focal abnormal areas are unable to generate *de novo* seizures, they could be a cause of focal cerebral dysfunctions that lead to predominance of seizure activity in one area, or focal weakness of seizure termination mechanisms leading to longer seizure duration in the affected area [9].

Most of the patients presented with a normal MRI, and only a few had non-specific abnormalities (Chiari malformation, arachnoid cyst [6,7]). A patient reported by Linane et al. [6] with right mesial temporal sclerosis also presented with abnormal neurological exam (gait ataxia, dysarthric speech), moderate intellectual impairment and a family history of epilepsy in a 1st degree relative, suggesting a possible genetic-structural etiology associated with GOFE. Although this was not found in our patients, it was reported that the localization of the focal discharge could move between different seizures in the same patient [6], emphasizing the “nonstructural” origin of so-called “focal EEG pattern”. Monogenic etiologies of GOFE seem exceptional. In the literature, one patient bearing a *SCN1A* mutation is described as presenting with GOFE in a peculiar GEFS + phenotype [12]. Two patients from our cohort had a specific clinical epilepsy gene sequencing panel, with no pathogenic variant found. Even if in half of the cases a positive family history of epilepsy with IGE “spectrum” is found, GOFE

Table 1

Clinical data from our cohort compared to available literature. CBZ, carbamazepine; CLB, clobazam; CZP, Clonazepam; EEG, electroencephalography; FeS, febrile seizure; FIA, focal impaired awareness; FS, focal seizure; GOFE, Generalized onset seizure with focal evolution; GPSW, Generalized Poly Spike and Waves; GSW, Generalized Spike and Waves; GTCS, generalized tonic-clonic seizure; Hz, hertz; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; MRI, magnetic resonance imaging; Nb, number; NS, non-specified; PHT, phenytoin; OXC, oxcarbazepine; RFM, Rufinamide; SGTCS, secondary generalized spike-and-wave; TPM, topiramate; VPA, valproic acid; ZNS, zonisamid.

	Patient 1	Patient 2	Patient 3	Williamson et al. 6 cases	Linane et al. 10 cases
(Mean) age of onset (m: month; y: year)	13 y	20 y	22 y	4,8 y [10 m-14y]	9 y [3y-15y]
Familial history	FeS	No	No	3/6	6/10 (3 FeS)
Neuroimaging	Normal MRI	Normal MRI	Normal MRI	4/4 normal MRI	6/8 normal MRI, 1 right mesial temporal sclerosis, 1 left anterior middle cranial fossa arachnoid cyst
Initial					
Suspected seizure type	GTCS	GTCS	GTCS	GTCS, absences, FS, FIA, SGTCS	GTCS, focal, myoclonic
1st treatment	LTG	LTG	VPA	CBZ, PHT	8/10 with ≥ 2 treatments; LEV (7/10), TPM (5/10), LTG (5/10), OXC or CBZ (3/10), LCM (1/10), ZNS (1/10)
Onset of GOFE					
Clinical onset	Behavior arrest	Behavior arrest	Behavior arrest	Absence (4/6) Myoclonic (2/6)	Behavior arrest, staring, brief myoclonic jerk
EEG onset	GPSW (2 s)	GPSW (2 s)	GPSW (2 s)	2 to 6 Hz GSW or GPSW activity	3 to 5 Hz GSW or GPSW activity
Evolution of GOFE					
Clinical evolution	Blinking, right clonic ocular version, unconsciousness → bilateral tonic-clonic	Left head version, figure 4 sign → bilateral tonic-clonic	Left head version → bilateral tonic-clonic	Clonic activity, focal motor features, automatisms or immobility	Versive head turning, automatism (oral, verbal, manual)
EEG evolution (focal)	Left parieto-occipital (for both seizures)	Right frontal	Left frontal	Left posterior quadrant (3/6), left frontotemporal (1/6), left hemisphere (1/6), right hemisphere (1/6)	Frontal region (10) temporal region (6), occipital (1) parietal (1)
Interictal epileptiform discharges	3–5 Hz GSW or GPSW	3–5 Hz GSW or GPSW	3–5 Hz GSW	GSW and GPSW 2,5–6 Hz	GSW and GPSW 2 to 9 Hz
Long-term effective treatment/Nb of prior treatment	VPA/2	VPA/2	VPA/1	NS	LEV (8), LTG (6), TPM (4), CLB (3), VPA (2), CZP (1), RFM (1)

probably involves many genes (multigenic origin) and current clinical panel sequencing does not seem informative.

GOFE patients could be generally considered as presenting drug-resistant epilepsy (with some patients being treated with several ASM [4,6]), but probably due to a misdiagnosis of focal seizures leading to inappropriate treatment by narrow spectrum ASM [13]. The previously described patients usually reported good outcome after the discontinuation of ASM specific for focal epilepsy (i.e. sodium channel blockers like oxcarbazepine, carbamazepine) or after posology adjustments or addition of broad-spectrum treatments (such as VPA, LVT, topiramate, clobazam). It is now well recognized that broad-spectrum ASM are preferred in cases of IGE [13,14]. However, it has also been reported that LTG was associated with a risk of paradoxical seizure aggravation in IGE, especially in JME, while levetiracetam (LVT) and VPA appear to be lower risk [14]. We reported aggravation in patient 1 and 2 with LTG, and a seizure-free evolution for the three patients with tailored doses of VPA. We do not argue against the use of LTG in GOFE, but we hypothesize, as in JME, that LTG may aggravate epilepsy in patients with GOFE and we call for special attention in such cases. Instead, we recommend other broad-spectrum ASM as VPA or LVT.

According to the current 2017 ILAE Classification of the Epilepsies, it may be difficult to classify patients presenting this

particular pattern. Indeed, GOFE cannot be classified into the focal seizure type because it corresponds to a generalized onset seizure without a limited initial network, suggesting classification into the generalized seizure type or into the unknown seizure type due to association of focal and generalized ictal electroclinical patterns. Logically, GOFE should be classified as one of the generalized epilepsies. Indeed, there are several features in patients with GOFE corresponding to IGE, as previously suggested: ictal and interictal generalized epileptiform activity; positive familial history of seizures; unremarkable MRI; aggravation by specific ASM (sodium channel blockers); and no known genetic etiologies. Despite the presence of some common features in patients with GOFE, it seems not possible to define a new syndrome due to the limited data currently available.

The main limitation of our work is the small number of patients. This is explained by a monocentric study, but also and especially by the fact that GOFE is a very rare entity, which is highlighted by the few cases reported to date. However, this entity is probably underdiagnosed. Indeed, patients with GGE are rarely referred for VEM except for those with drug resistance or doubt about the epilepsy type, as in our patients. This generally leads to brief VEM that rarely allows seizure recording.

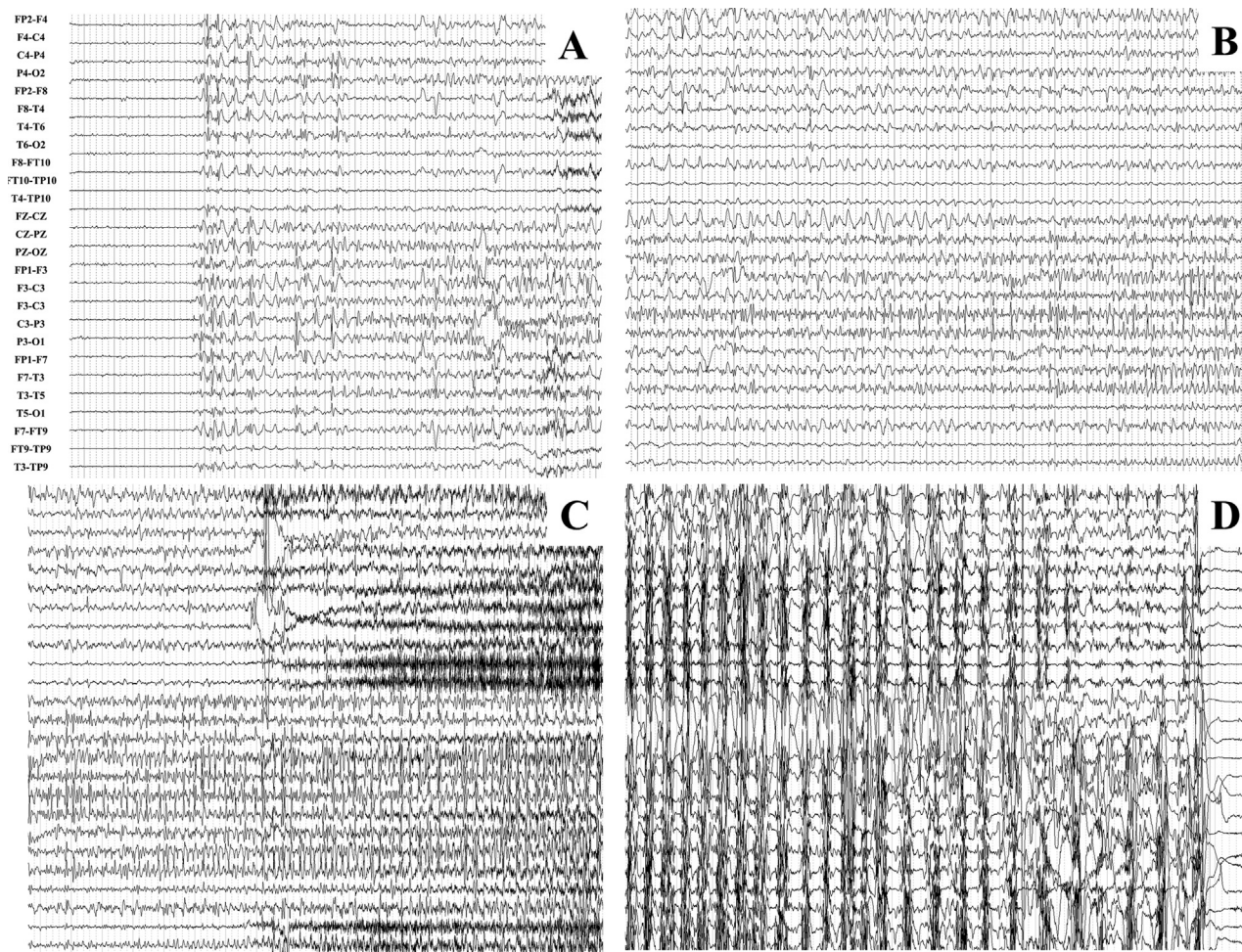


Fig. 1. Patient 1. Bipolar longitudinal montage, Scale 250uV/2 s, Total Seizure duration 1'40". **A)** ictal onset, with asymptomatic 2.5 Hz Generalized Spike and Waves discharge. **B-C)** focal evolution with widespread left discharges. **D)** seizure end.

Conclusion

We reported three additional cases of GOFE that illustrate the limits of classification systems sometimes blurring distinction between generalized and focal epilepsies. It is important to keep in mind GOFE in patients with suspected generalized epilepsy especially when focal clinical signs and/or persistence or worsening of seizures occur with certain ASM, which does not exclude the diagnosis of IGE. Recognition of this entity would avoid misdiagnosis and lead to an appropriate management. Finally, this pattern may suggest a new subgroup of GGE (especially into IGE) in the ILAE Classification of the Epilepsies, but further reports are required to strengthen these findings.

Ethical publication statement

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.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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