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Can emotional stress trigger the onset of epilepsy?

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ABSTRACT

Objective: The aim of this study was to investigate the potential role of an acute adverse stress as "trigger" for the onset of epilepsy.
Methods: Among 4618 consecutive patients, twenty-two reported a major life event within three months before the onset of epilepsy.
Results: All patients had focal epilepsy except one with idiopathic generalized epilepsy. The temporal lobe was involved in 90% of patients with focal epilepsy. More precisely, 13 patients (62% of patients with focal epilepsy) had medial temporal lobe epilepsy (MTLE), two had lateral temporal lobe epilepsy, four had temporo-parietooccipital junction epilepsy, and two patients had central lobe epilepsy. The mean age and the median age at onset of epilepsy for patients with MTLE were both 38 years (range: 9.5–65 years). Ten patients had right and three had left MTLE. Among patients with focal epilepsy, MRI was abnormal in 7 (33%) with hippocampal sclerosis in four, periventricular nodular heterotopia in two, and complex cortical dysgenesis in one. The mean age at onset of epilepsy for patients with brain lesions was 26 years (range: 9.5–49). Twelve patients (54%) reported a death as a triggering factor for the onset of their epilepsy. Seven patients (32%) reported that a relationship of trust had been broken. Three patients (14%) had been subjects of violence. No patient reported sexual abuse as a triggering factor.
Conclusion: This study provides evidence that some patients (5/1000 patients) began their seizures in the wake of significant life events. The average age at onset of epilepsy is quite late, around age 30, even in the presence of brain lesions. These patients are emotionally and affectively more prone to have consequences of a stressful life event. The recognition and management of such situations may bring significant relief with improvement of the control of epilepsy.

1. Introduction

Several studies have reported an association between stressful life events and exacerbation of epilepsy [1–4], but few studies implicated acute stress in the onset of the disease. Koutsogiannopoulos et al. used a phenomenological approach and interviewed 19 patients on the occurrence of significant life events in the year prior to the diagnosis of generalized or focal epilepsy [5]. They underlined the possible role of life stressors as triggers for the onset of epilepsy. We performed a longitudinal study over 11 years to investigate the potential role of acute adverse stress in precipitating epilepsy. All patients included in this study have spontaneously linked a prior emotional shock with the onset of their epilepsy.

2. Patients and methods

The study was undertaken among 4618 patients with epilepsy who were evaluated at least once between January 1, 2004 and December 31, 2014 at the epilepsy unit of Montpellier, which is a tertiary center for adolescents and adults. The diagnosis of epilepsy was ascertained by two senior epileptologists (PhG, AC). Patients who reported an emotional shock within three months before the onset of epilepsy were included in this study. They were interviewed during the following consultations to assess the time relationship between the emotional shock and the onset of the epilepsy, the type and severity of the emotional shock, and their opinion about the responsibility of the event for their epilepsy. We never looked actively into the occurrence of such events before the onset of seizures, which might have led to overestimation, and all events had been reported spontaneously by the patients. All patients had at least one video-EEG according to the international 10/20 system and one brain MRI (1.5 or 3 T).

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3. Results

A total of 22 patients (10 males, 12 females) (4,7/1000) reported a major life event preceding the onset of the epilepsy. Table 1 summarizes the demographic data, the epilepsy syndrome, the type of life event, and the response to drugs. Mean age of the patients at the time of inclusion in the study was 42 years (range: 15–7). The mean age and the median age at onset of epilepsy were 32 years (range: 9.5–65) and 29 years, respectively. Two patients (cases 13, 22) only had an awake video-EEG and six patients a nap video-EEG (cases 7, 8, 14, 20–22), five had a recording lasting 24 to 48 h (cases 11, 15, 17–19), and ten had presurgical assessment with EEG during 5 days (cases 1–6, 9, 10, 12, 16). Patient 6

Table 1
Demographic and clinical characteristics of the patients.

Patient	Sex	Onset of epilepsy (years)	Lat.	Age at referral (years)	Febrile seizures	MRI	Type of epilepsy	Circumstance	Evolution/severity of the epilepsy
1	M	16	R	36	No	Normal	L lateral temporal lobe	First seizure (focal evolving to GTCS) on the day his father was buried	Drug resistance then seizure-free after psychotherapy; low dose of CBZ
2	F	33	R	33	No	Normal	R temporoparietooccipital junction	One week after the murder of her sister by husband	Drug resistance
3	F	27	R	33	No	Cortical dysgenesis of the left parietal lobe	L centroparietal lobe	One week after the death of her brother (brain tumor); this patient still visits her brother's grave every week 10 years later	Drug resistance
4	F	21	R	33	No	Left nodular periventricular heterotopia (occipital horn)	L temporoparietooccipital junction	Three months after the death of her mother (breast cancer)	Drug resistance
5	F	16	R	35	No	3 T normal	R temporoparietooccipital junction	Two months after the death of her father	Drug resistance
6	M	45	R	48	No	3 T normal	L mesial temporal lobe	Two months after he found his brother-in-law dead due to suicide (head exploded by firearm)	Seizures only in condition of stress; no surgery was proposed for this patient because right-handed man with a normal hippocampus
7	F	52	R	62	No	Normal	R mesial temporal lobe	Two months after the death of her brother (cycling accident)	Spontaneous amelioration of the frequency of seizures when the psychological trauma was taken into account
8	F	65	R	71	No	Normal	R mesial temporal lobe	One month after the death of her husband	Drug sensitive; low dose of CBZ
9	F	16	R	33	No	R hippocampal sclerosis	R mesial temporal lobe	One month after the death of her father	Drug resistance; seizure-free since surgery; follow-up after surgery: 10 months
10	F	28	R	29	No	R nodular periventricular heterotopia (occipital horn)	R temporoparietooccipital junction	One week after the death of her father in her arms (massive myocardial infarction)	Drug resistance
11	M	18	R	29	No	Normal	R mesial temporal lobe	One month after the death of a good friend in a car accident; he should have been in the car but decided to drive home with someone else	Drug sensitive
12	F	11	L	24	No	Normal	L central lobe	Few days after witnessing a catastrophe (several deaths and panic provoked by fireworks)	Drug resistance
13	M	38	R	49	No	Normal	L mesial temporal lobe	One month after learning that his wife was having an affair (it ended up in divorce)	Drug sensitive
14	M	17	R	25	No	Normal	R mesial temporal lobe	One week after breaking off a sentimental relationship	Drug resistance
15	M	36	L	34	No	Normal	R mesial temporal lobe	One month after his divorce	Drug resistance
16	M	30	D	34	No	R hippocampal sclerosis	R mesial temporal lobe	Few days after his wife left suddenly with no explanation; frequent seizures in stressful condition	Seizures precipitant: emotion; seizure-free after surgery; follow-up of 3 years
17	M	49	R	65	No	R hippocampal sclerosis	R mesial temporal lobe	Two months after separation (it ended up in divorce), and his daughter does not want to speak to him	Drug sensitive
18	M	55	R	57	No	Normal	R mesial temporal lobe	Two months after his exclusion from the municipal team, which he resented as a great injustice	Drug sensitive
19	F	47	R	62	No	Normal	L lateral temporal lobe	Two days after being molested by her husband for the first time; no head trauma	Drug sensitive
20	F	59	R	63	No	Normal	R mesial temporal lobe	Three months after being molested by her husband for the first time; no head trauma	Drug sensitive; seizures precipitant: emotion
21	F	9.5	R	59	Yes	L hippocampal sclerosis	L mesial temporal lobe	One week after seeing her father with his mistress in the family home, as a child	Drug resistance
22	M	15	R	15	No	Normal	Idiopathic generalized epilepsy	One day after a severe aggression without help from bystanders; no head trauma	Died by drowning

Lat.: lateralization; CBZ: carbamazepine; R: right; L: left, T: tesla.

also had an intracranial recording. All patients had interictal abnormalities. Seizures were recorded in ten patients (cases 1–6, 9, 10, 12, 16). Two patients with right hippocampal sclerosis (HS) and mesial temporal lobe epilepsy (MTLE) (cases 9, 16) were operated and have remained seizure-free since surgery (follow-up of 8 months and 36 months, respectively).

All patients, except patient 22 who had idiopathic generalized epilepsy, had focal epilepsy. Temporal lobe was involved in 19 patients (90% of patients with focal epilepsy). More precisely, 13 patients (62% of patients with focal epilepsy) had MTLE (cases 6–9, 11, 13–18, 20, 21), two had lateral temporal lobe epilepsy (cases 1, 19), and four had temporoparietooccipital junction epilepsy (cases 2, 4, 5, 10). Two patients (cases 3, 12) had central lobe epilepsy, with patient 3 showing a propagation of seizures toward the parietal lobe. The mean age and the median age at onset of epilepsy for patients with MTLE were both 38 years (range: 9.5–65 years). Ten patients had right and three had left MTLE. Among the 21 patients with focal epilepsy, MRI was abnormal in 7 (33%) with HS in four (cases 9, 16, 17, 21), and periventricular nodular heterotopia along the occipital horn in two (cases 4, 10). Patient 3 had a complex cortical dysgenesis over the left parietal lobe (Fig. 1), but the seizure onset was central. The mean age at onset of epilepsy for patients with brain lesions was 26 years (range: 9.5–49).

Twelve patients (54%) reported a death as a triggering factor for the onset of their epilepsy: the person had been close to them in 11 cases (cases 1–11; three men, eight women), and the death was witnessed in a crowd for patient 12. Seven patients (32%) reported that a relationship of trust had been broken. More precisely, five patients (18%) reported a divorce or a sentimental separation (cases 13–17; five men) and two another cause (cases 18, 21; one man, one woman). Three patients (14%) had been subjects of violence (cases 19, 20, 22; two women, one man). No patient reported sexual abuse as a triggering factor. Three cases are illustrated below.

4. Selected observations

4.1. Patient 1

A 36-year-old right-handed man was referred for presurgical assessment of drug-resistant focal epilepsy. Seizures begin with a loss of contact preceded by an aura, the patient freezes, without automatisms, and the post-ictal phase is characterized by dysphasia, confusion, and amnesia. Secondary generalization was fairly common. He had his first secondary generalized tonic–clonic seizure at age 16 on the day his father was buried. Some persons told him at the time that the devil had jumped from the burial coffin onto him. Interictal EEG was characterized by spike–waves over the right temporal leads and fast activities on T3–T5 in deep nREM sleep. Ictal EEG demonstrated onset over T3–T5 (Fig. 2). The interictal and ictal EEG was very suggestive of a cortical dysplasia, but brain MRI was normal. Surgery was contraindicated in this right-handed patient because of the lateral temporal lobe onset of the seizures and the normality of the MRI. Several drugs were used in this patient in combination, and he was also included in a clinical trial with no success and premature discontinuation. Stress and emotion were, for this patient, the most common seizure triggers. Psychotherapy helped him look at things with more detachment. The patient became seizure-free with a follow-up of 18 months. Antiepileptic drugs were progressively reduced to carbamazepine (600 mg/day) monotherapy.

4.2. Patient 2

A 33-year-old right-handed woman was referred for assessment of drug resistant focal epilepsy. She had her first seizures at age 16, one week after the murder of her sister by her husband. Her MRI was normal. She had benefited from psychiatric care but never got over her sister's death. At referral, she had at least two seizures per week despite carbamazepine (400 mg bid) and clonazepam (1 mg/day). Previously, she had received valproate, levetiracetam, pregabalin, and lamotrigine with incomplete seizure control. Physical and neurological examinations were normal. Long-term video-EEG was performed for 48 h: the interictal activity was characterized by sharp waves and theta activities in the right posterior region. The patient had 5 seizures during the first long-term EEG monitoring. Clinically, they were all brief episodes of loss of consciousness without automatisms and without language disturbance in the postictal phase. Seizure duration was about 30–60 s. All five ictal activities were characterized by discharges on the right temporoparietooccipital junction (Fig. 3).

4.3. Patient 3

A 32-year-old right-handed woman was referred for assessment of drug resistant focal epilepsy. She had her first seizure at age 27, one week after the death of one of her brothers from a brain tumor. She had been very close to him. She resented this event as a great injustice. Before, she had had a normal life and had worked and, also, had had a very active social life, going out with friends with consumption of alcohol and recreative drugs and numerous episodes of sleep deprivation. Seizures were characterized by an aura (sensation in the right hand or dizziness) followed by loss of consciousness. Her MRI showed a complex cortical dysgenesis of the left parietal lobe (Fig. 1). In order to propose surgery, to be sure of the origin of the seizures, an intracranial recording was performed. Unfortunately, the onsets of seizures were central with propagation toward the parietal lobe, and surgery was contraindicated. The patient had proper psychiatric management in our center, but only a slight improvement of her mental status was obtained. She still visits her brother's grave every week 10 years after his death.

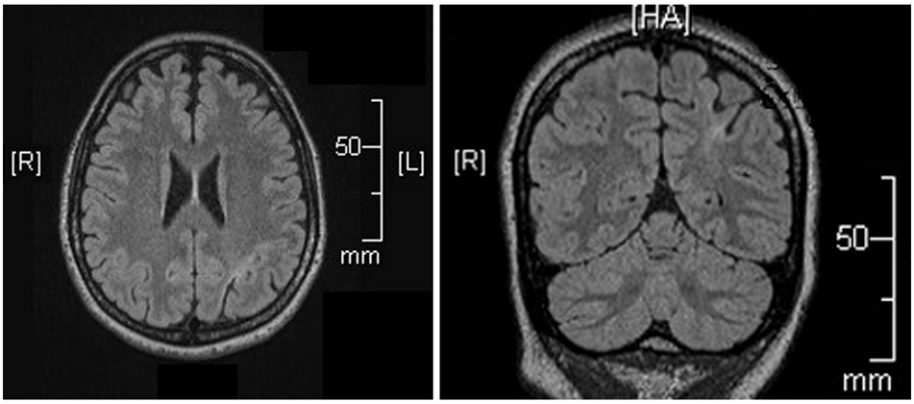

Fig. 1. MRI (FLAIR) showed a complex cortical dysgenesis of the left parietal lobe.

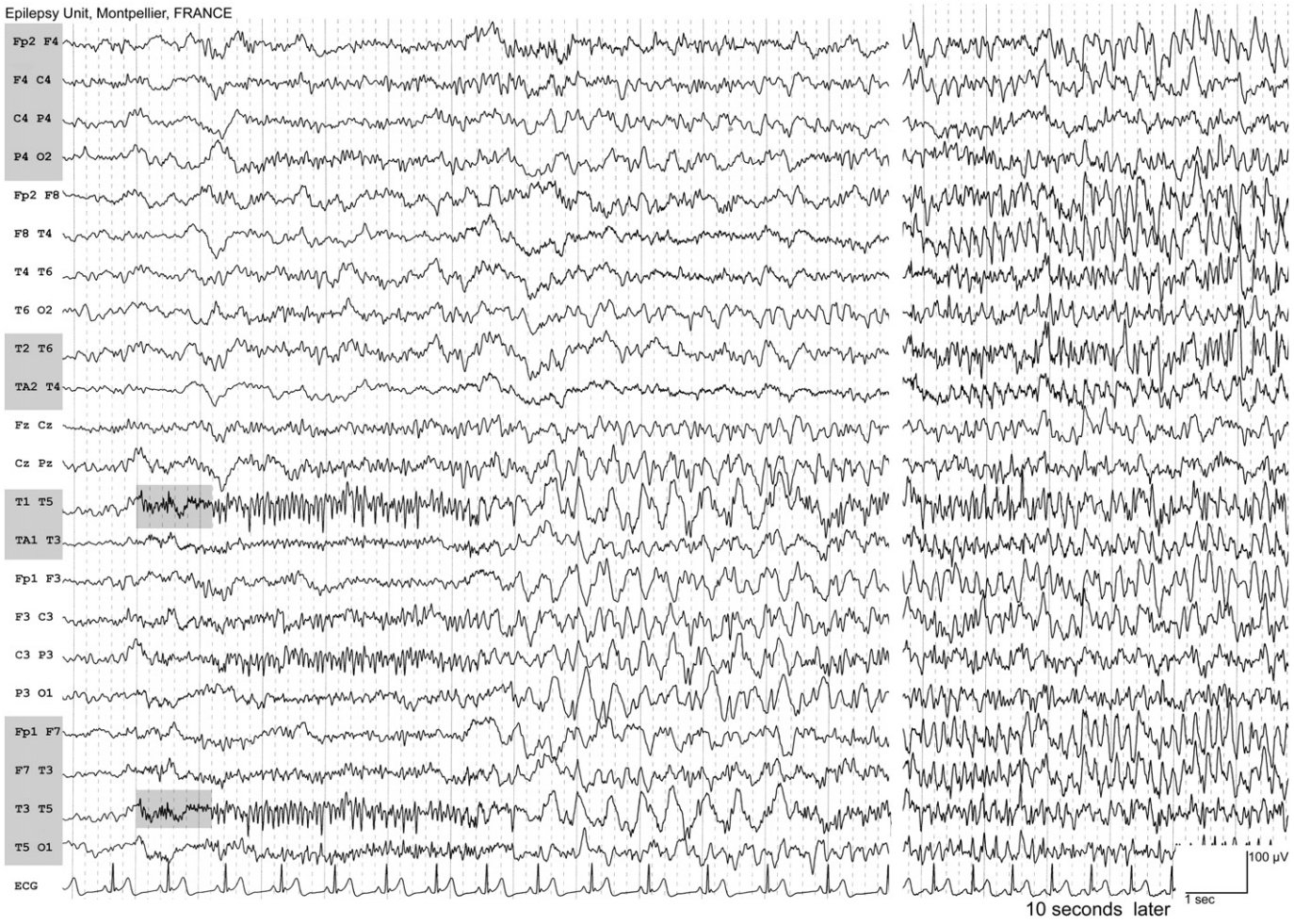

Fig. 2. EEG with international 10-20 electrode system with supplementary anterior/inferior temporal electrodes (TA1, T1, TA2, T2), electrocardiogram. Seizure during nREM sleep. There are fast rhythms on the left posterior temporal region (gray area) that build up a recruiting discharge with increasing amplitude and decreasing frequency, with a "comb-like" aspect, with 13 Hz fast spikes, followed by rhythmic slow spike–waves at 2 Hz over the left parietooccipitotemporal junction. Ten seconds later, the ictal changes spread to the left anterior temporal lobe as well as to the right temporal lobe.

5. Discussion

The role of important, traumatizing life events in the appearance of chronic diseases such as diabetes mellitus or cardiovascular disorders is an old concept. In the field of neurology, chronic stress has been implicated in Parkinson's [6] and Alzheimer's diseases [7]. Patients with chronic stress have a higher risk of developing dementia with a more rapid progression. Rotman and Mattson hypothesize that both Alzheimer's disease and chronic adverse stress affect hippocampal neural networks in a similar fashion [7]. In their extensive review of the effect of chronic stress in Parkinson's disease, Djamshidian and Lees quoted Gowers who wrote more than a century ago that anxiety and emotional shock are the most common antecedents of Parkinson's disease. These authors speculate that chronic emotional stress may cause dopaminergic cell loss [6].

The role of an acute stressor is recognized in psychiatric disorders (acute anxiety, post stress traumatism, depression), in sleep disorders (insomnia nightmares, nREM parasomnias), and before the onset of narcolepsy. In some patients, the onset is insidious, but in others, it is abrupt. A severe psychological stress such as divorce, mourning, and even stressors such as head trauma, infection, and a bee sting, often precedes the appearance of narcolepsy by a few weeks [8]. Guiraud et al. investigated 247 consecutive cases of ischemic stroke, using the Interview for Recent Life Events, and found that these were associated with an increased risk of ischemic stroke [9].

In this study, we found that stressful life events may contribute to the onset of epilepsy, although this remains an uncommon finding. Contrary to patients with psychogenic nonepileptic seizures [10,11], no sexual abuse was reported by these patients. The most common factor was the death of someone close (half of the cases). Because we never looked actively into the occurrence of a stressful life event before the onset of seizures, there is a possibility that this phenomenon was underestimated. Except for the patient with idiopathic generalized epilepsy, all had focal epilepsy with an implication of the temporal lobe in 90% and MTLE in about 60%. Patients with MTLE were more likely to have nondominant hemisphere TLE (nine vs three). The role of the limbic system in emotions is well known. McLaughlin et al. investigated the consequence of the terrorist attack at the 2013 Boston Marathon and found a significant correlation between the activation of the amygdala when exposed to negative images and the development of the symptoms of posttraumatic stress disorder [12]. The more the amygdala reacted to the negative images, the more probable was the predisposition to the symptoms of posttraumatic stress disorder. Of particular interest is the fact that the amygdala projects to the hypothalamus as well as to the hippocampal formation [13]. Chronic stress causes a prolonged activation of the hypothalamic–pituitary–adrenal axis [6]. In the amygdala kindling model of epilepsy, Jones et al. demonstrated that repeated exposure to restraint stress promotes a vulnerability to the development of experimental limbic epileptogenesis, and this effect could be related to elevated corticosterone level [14]. The same team studied the

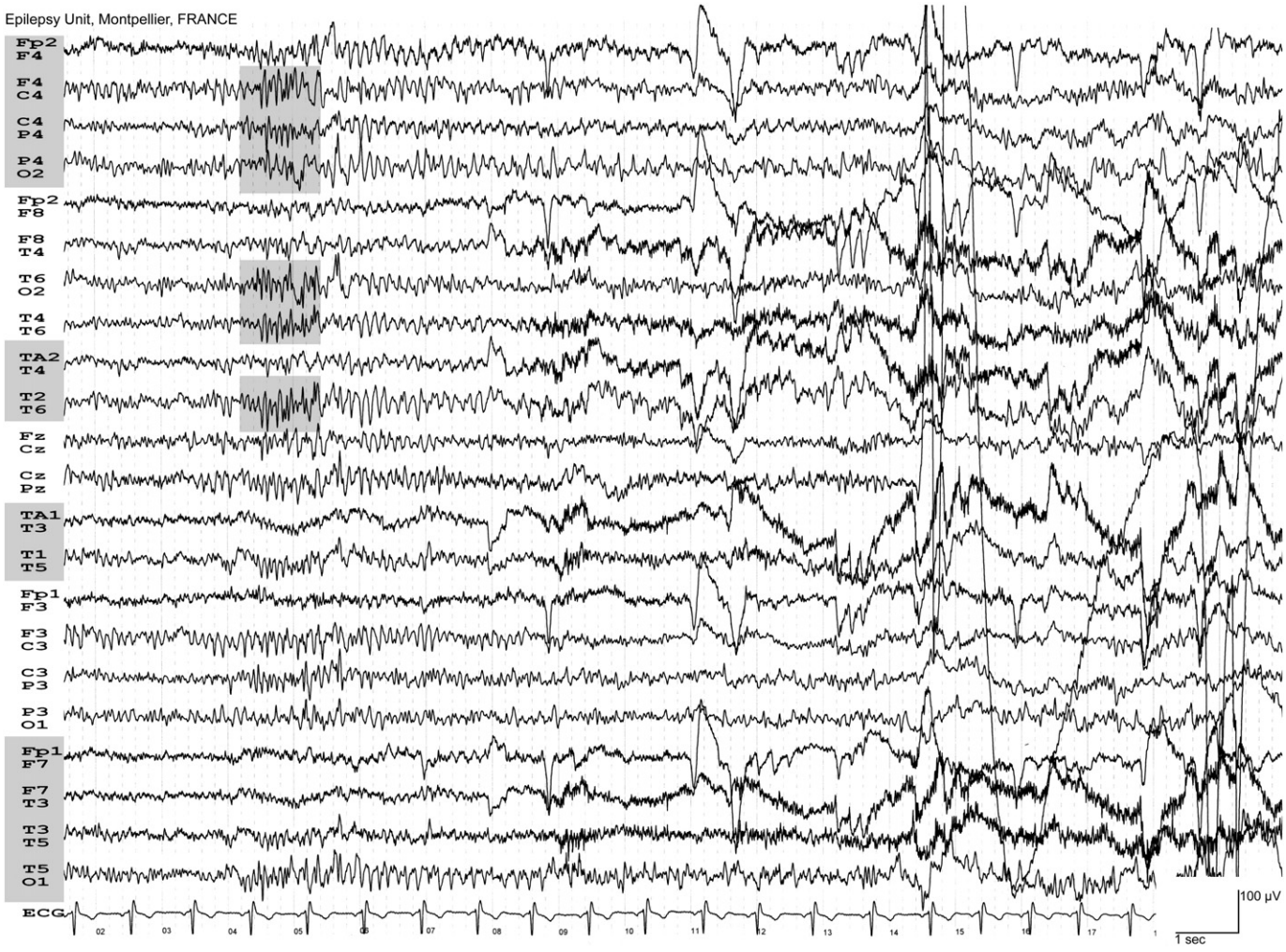

Fig. 3. EEG with international 10–20-electrode system with supplementary anterior/inferior temporal electrodes (TA1, T1, TA2, T2), electrocardiogram. Seizure onset at the 3rd second of the plate with polyspikes (gray area) on the right parietooccipitotemporal junction followed by rhythmic activity over the right parietal lobe.

effects of maternal separation in rats, a model of early life stress, to amygdala kindling limbic epileptogenesis [15]. They found that early life stress leads to a dysregulation of the hypothalamic–pituitary–adrenal axis resulting in excessive corticosterone release following seizures. Preseizure treatment with a corticosterone synthesis inhibitor reversed the effects of maternal separation on both seizure threshold and duration; the authors concluded that corticosterone may have an aggravating role in kindling epileptogenesis.

Mesial temporal lobe epilepsy represents more than half of the focal epilepsies in our series, but there were also four patients with parietooccipitotemporal junction epilepsy, two patients with lateral TLE, two patients with central lobe epilepsy, and one with idiopathic generalized epilepsy. The development of MTLE in humans may follow a pattern. In most cases, an early event, usually a complicated febrile seizure, takes place in early childhood followed by a latent period of several years, after which spontaneous recurrent seizures appear leading to the chronic epileptic condition. Only patient 21 had a typical history with febrile seizures and onset of epilepsy around age 10. For the others, there was no history of febrile seizure, and the onset of epilepsy was later than usual, around age 40. Indeed, the average age at onset of epilepsy in our population of 22 patients is quite late, around age 30, even in the presence of brain lesions.

In about two-thirds of the population, brain MRI was negative, but one-third had lesions. Patients 3, 4, and 9 had congenital malformations, and the question is: why did epilepsy not start earlier? For patient 3 with a complex malformation of the parietal lobe (Fig. 1), a drug-resistant epilepsy started one week after the death of her brother despite accumulated risk factors when she was younger. At every consultation, patient 10 with periventricular heterotopia tirelessly repeated the same question: why did my epilepsy start at age 28? Only patients 1 and 3 had received intensive psychological help. For the others, the psychological care was performed during the epilepsy clinics. Nevertheless, taking into account the possibility that the acute stressful life event was responsible for the epilepsy led to improvement of epilepsy. It was a huge relief for the patients to have this relationship acknowledged.

Patient 1 with left lateral temporal lobe epilepsy became seizure-free after psychotherapy, and his treatment was reduced to carbamazepine monotherapy, which would have been considered an Engel Class 1a result after surgery! The effects of behavioral treatment in epilepsy are only beginning to be recognized, even if there are classic studies using biofeedback in epilepsy [16]. Martinović evaluated the effects of antistress programs or individual cognitive therapy in two groups of seven patients with drug-resistant juvenile myoclonic epilepsy; seizure freedom was obtained in three and four patients, respectively (50% of the population) [17]. Lundgren et al. reported that Acceptance and Commitment Therapy and yoga decreased seizure index and increased quality of life in patients with drug-resistant epilepsy [18].

In conclusion, there is a small subgroup of patients with epilepsy (5/1000) who spontaneously report a stressful life event prior to the onset of epilepsy and who consider this event to be the essential cause of their epilepsy. The actual occurrence of significant life events prior to the onset of a chronic condition like epilepsy is most probably much higher,

since many subjects will be unlikely to state such a relationship, as they may think that this most private matter will not be accepted by their rational doctor. There are many mechanisms that may account for the important role played by life stressors in the onset of a chronic epilepsy. Clearly, a "post-stressor epilepsy" is not a syndrome, but several epilepsy types (involving the nondominant temporal lobe in many) may occur in persons who are emotionally and affectively more prone to have consequences of a stressful life event. What is really important is the fact that recognition of such a relationship may help patients and may decrease the level of refractoriness of epilepsy in selected cases. Another implication of this study regarding seizures that begin after a significant psychological trauma, they should not automatically be suspected of being psychogenic. We, thus, suggest that stressful life events should be systematically evaluated in patients with new onset of epilepsy, and that specific help and counseling should be provided whenever applicable or useful.

Individual contribution

Dr Gelisse — Study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; study supervision.

Dr Genton — Critical revision of the manuscript for important intellectual content.

Pr Coubes — Critical revision of the manuscript for important intellectual content.

Dr Tang — Acquisition of data.

Dr. Crespel — Study concept and design; acquisition of data; critical revision of the manuscript for important intellectual content.

Disclosure or conflict of interest

Dr. Crespel received support for teaching programs from Sanofi-Aventis, UCB, and GSK and served as an advisory board member for Eisai.

Dr. Genton received speaker honoraria from Sanofi-Aventis, Novartis, GSK, Pfizer, Janssen-Cilag, UCB, and Eisai and received support for teaching programs from Sanofi-Aventis and UCB.

Dr. Gelisse received support for teaching programs from Sanofi-Aventis, UCB, and Psicofarma. He received a research grant from the French League Against Epilepsy and Janssen-Cilag. He worked as consultant for Eisai.

The remaining authors have no conflicts of interest.

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