Clinical Neurophysiology 132 (2021) 1757–1769

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Review

Stimulus-Induced Rhythmic or Periodic Intermittent Discharges (SIRPIDs) in patients with triphasic waves and Creutzfeldt-Jakob disease

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ARTICLE INFO

Article history:
Accepted 8 May 2021
Available online 20 May 2021

Keywords:
SIRPIDs
Triphasic Waves
Creutzfeldt-Jakob disease
Sleep-wake cycle
Sleep-to-wake transition
Cyclic alternating pattern

HIGHLIGHTS

- Generalized Periodic Discharges vary according to the sleep-wake cycle.
- SIRPIDs may be seen as a typical pattern of transition from sleep to a waking state in metabolic/toxic encephalopathies with triphasic waves.
- SIRPIDs may be seen as a typical pattern of transition from sleep to a waking state in patients with Creutzfeldt-Jakob disease.

ABSTRACT

Since the term Stimulus-Induced Rhythmic, Periodic, or Ictal Discharges (SIRPIDs) was introduced into the vocabulary of electrophysiologists/neurologists, there has been an ongoing debate about its significance, as well as its correlation with outcomes. SIRPIDs are frequently seen in patients who are critically ill from various causes. The literature reflects the findings of triphasic morphology, with the generalized periodic discharge (GPD) classification in many patients with SIRPIDs: toxic/metabolic encephalopathies, septic, and hypoxemic/hypercapnic encephalopathies, but also sharp periodic complexes in Creutzfeldt-Jakob disease and advanced Alzheimer's disease. In these settings, GPDs disappear when patients fall asleep and reappear when patients spontaneously wake up, or are awoken by an external stimulus, or sometimes because of a respiratory event, with the possibility of the appearance of GPDs with a cyclic alternating pattern. SIRPIDs may be seen as a transitional pattern between sleep and waking states, corresponding to a postarousal/awakening phenomenon. As SIRPIDs are a transient phenomenon and can usually be recorded repeatedly with each stimulation, the word "*Ictal*" could be replaced by "*Intermittent*": Stimulus-Induced Rhythmic or Periodic Intermittent Discharges. However, considering that SIRPIDs may be "*potentially ictal*" or on an *"ictal–interictal continuum"* in some situations, the "*plus*" modifier may be added: SIRPIDs-plus.

Contents

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https://doi.org/10.1016/j.clinph.2021.05.002
1388-2457/

1. Introduction

The appearance of delta waves, in response to external stimuli in comatose patients after cerebral trauma, was initially described as a "paradoxical arousal effect" (Fischgold et al., 1955). Chatrian et al. reported bilaterally synchronous high-voltage delta waves, followed by 6–8 c/s rhythmical activity higher over the posterior head regions in seven comatose patients who had a head injury (Chatrian et al., 1963). Schwartz and Scott studied 55 patients with about half having head injuries, hypotension-hypoxia (9 cases), vascular disorders (7 cases), metabolic disorders (4 cases), encephalitis (5 cases), tumors (2 cases), and fat embolism (1 case). Their EEGs showed prolonged periods of delta activity after various stimuli, an activity that occurred with states ranging from drowsiness to deep coma. In 15 of the 87 recordings with stimulus-related changes, delta episodes *without* stimulation were recorded, similar in the form and distribution, but usually briefer and without clear clinical evidence of increased alertness. These EEG findings resolved within five weeks, and 50% of the subjects had a favorable outcome (Schwartz and Scott, 1978).

To describe this type of reactivity to auditory and/or painful stimulations, Hirsch et al. proposed the term of Stimulus-Induced Rhythmic, Periodic, or Ictal Discharges (SIRPIDs) (Hirsch et al., 2004). The acronym SIRPIDs enjoyed widespread use in the EEG literature, and the American Clinical Neurophysiology Society (ACNS) suggested adding "Stimulus-Induced" to various EEG patterns (Hirsch et al., 2021). As SIRPIDs include all SI-patterns, we will continue to use the acronym SIRPIDs.

SIRPIDs are frequently seen in critically ill patients from various causes (Braksick et al., 2016). In this article, we will take a clinical approach to demonstrate that SIRPIDs may be seen as a typical and expected pattern of transition from sleep to wakefulness in patients having Generalized Periodic Discharges (GPDs) with triphasic morphology previously referred to as triphasic waves (TW) and also seen in patients with Creutzfeldt-Jakob disease (CJD). A thorough review of the literature on SIRPIDs can be found elsewhere (Johnson et al., 2018).

2. Methods

The present study is a narrative review enriched with reports from personal cases. All cases presented in this article were hospitalized at the University Hospital of Montpellier, France. The aim is to describe the effect of the sleep-wake transition on the occurrence of some pathological EEG patterns. To understand the effects of arousal reactions, the first step is to recognize the effect of sleep on the EEG patterns commonly seen in critically ill patients. IV benzodiazepine (BZP) injections are often used in clinical practice as a therapeutic test for typical absence status or other forms of status epilepticus. In these situations, both EEG and clinical improvement must occur to consider the test positive (Thomas et al., 2006). Although the effects of IV BZP injections or other hypnotic drugs on GPDs are described in this review, criteria for nonconvulsive status epilepticus (NCSE) are not discussed. IV BZP injections are presented as a model of "sleep-induction".

EEG patterns in post-anoxic encephalopathies (post-cardiac arrest syndrome) are usually not difficult to recognize as they range from GPDs with or without triphasic morphology to burst-suppression patterns, to electro-cerebral inactivity (Bauer et al., 2013). However, their prognostic value is the subject of ongoing investigation (Bongiovanni et al., 2020; Ruijter et al., 2019). Post-anoxic encephalopathy represents a special entity and should be a separate category and analyzed separately. For these reasons, we decided to exclude postanoxic encephalopathies from this review.

3. Definitions

SIRPIDs are rhythmic in 40% of cases and periodic in 60% (Grossman and Foreman, 2018). Periodic activities are characterized by paroxysms separated by periods of non-paroxysmal activity (with or without EEG background activity or periods of flattening after the paroxysms). According to the ACNS, the term "periodic" implies a "*repetition of a waveform with relatively uniform morphology and duration with a clearly discernible interdischarge interval between consecutive waveforms and recurrence of the waveform at nearly regular intervals*" (Hirsch et al., 2021). Rhythmic activities are characterized by a fairly regular succession of paroxysmal waves. As the acronym SIRPIDs includes the terms "*rhythmic*" *or* "*periodic*", there is a need to clarify, and differentiate what these two patterns represent (Kaplan et al., 2021). "Periodic activities" misinterpreted as "rhythmic activities" may lead to an incorrect diagnosis of NCSE (Lapergue et al., 2010).

4. Arousal and cyclic alternating pattern

Arousals, either "spontaneous" or provoked by external stimuli (mainly auditory), may occur during NREM sleep. Arousals are characterized by abrupt changes in the EEG with transitions to faster rhythms (alpha, theta, beta, but not spindles), lasting at least 3 seconds, which briefly interrupt sleep continuity (Berry et al., 2020). However, several other types of phasic events take place throughout all NREM sleep stages, amongst which are: delta bursts, vertex sharp waves, K-complex sequences (with or without spindles), polyphasic bursts, K-alpha, K-delta, intermittent alpha. During the recording, these phasic events rarely appear in isolation, but most commonly tend to group in sequences with periods of phasic activity alternating with periods of more stable EEG, separated by periods of prolonged stability. It is possible to recognize these different patterns in all the stages of NREM sleep (N1, N2, and N3). Terzano et al. recognized a micro-structural cyclicity in NREM sleep, identifying alternating periods of activation (phase A) and deactivation of background (phase B) (Terzano et al., 1985). This cyclic alternating pattern (CAP) is interrupted by periods of sustained EEG stability (non CAP).

5. Difficulties in scoring EEG-vigilance stages in patients with generalized periodic discharges

Publications conflict regarding the presence of TWs in wakefulness. From a behavioral point of view, "fully" awake should be considered as a state of full consciousness, with the person's ability to detect and interact with the environment. From the American Academy of Sleep Medicine (AASM) (epoch of 30 seconds), wakefulness is comprised of more than 50% of an alpha/posterior dominant rhythm (Berry et al., 2020). This rhythm is replaced by a low-amplitude mixed-frequency EEG pattern when eyes are opened. Furthermore, there are often eye-blink artifacts and rapid eye movements when the subject scans his environment. The EMG tone is normal or high with muscle artifacts on the EEG. Both behavioral and EEG criteria are not met in cases of toxic/metabolic encephalopathy with TWs to enable scoring these patients as "fully" awake.

Hepatic encephalopathy may be interpreted as a syndrome of daytime sleepiness (Montagnese et al., 2015). The severity of hepatic encephalopathy is graded using the West Haven Grading System (Vilstrup et al., 2014). Grade 0: minimal, with changes in memory, concentration, and intellectual functioning. Grade 1: mild, with mood changes. Grade 2: moderate, with no energy, inappropriate behavior. Grade 3: severe, with somnolence to semi-stupor. Grade 4: coma. The EEG progresses from a slowing of background to TWs in grade 3. In grade 4, TWs are progressively replaced by low voltage slow waves that progress to cerebral inactivity. Uremic and other encephalopathies with TWs are also characterized by excessive daytime sleepiness that appears at the early stages of the disease, which may progress to coma. Patients with TWs have no reactive alpha rhythm on their EEG and have diminished awareness that qualifies as a persistent drowsy state. Patients are slow and do not interact well with their environment; the eyes are partially closed.

It is known that sleep evolves with age and with different neurological diseases (Li et al., 2018). In patients with TWs, sleep patterns and their changes (both sleep architecture and physiological sleep elements) are strongly influenced by the underlying pathology. Although few studies are available, patients with neurodegenerative brain diseases have alterations in sleep architecture with a progressive reduction of physiological sleep paroxysms (k-complexes and spindles). These elements become less numerous but also change in morphology, amplitude, and frequency. They, therefore, become more difficult to identify (Kang et al., 2016; Peter-Derex et al., 2015; Terzano et al., 1995). Furthermore, in these patients, the physiological distribution of sleep stages is also altered (N3, as well as REM phases, are less represented). The changes often progress with disease progression (Kang et al., 2016). Few data are available about sleep structure in patients with metabolic encephalopathies. In these patients, there is a significant alteration in the normal sleep-wake cycle, and it may be difficult to identify sleep-wake transitions. Moreover, there is an important reduction in sleep duration, resulting in a poorer representation of the physiological sleep paroxysms (Baldy-Moulinier et al., 1981; Boulanger et al., 2006; Liu et al., 2015).

In all of these situations, the identification of wakefulness and sleep patterns on the basis of conventional guidelines can be difficult. It is based on close observation of the patient by the EEG technologist and via video (e.g., eyes closed; the patient is immobile; the patient is snoring, hypopneas or apneas may occur). The EEG shows diffuse theta or delta waves without muscle artifact and when BZPs are used fast pharmacological rhythms. Respiratory

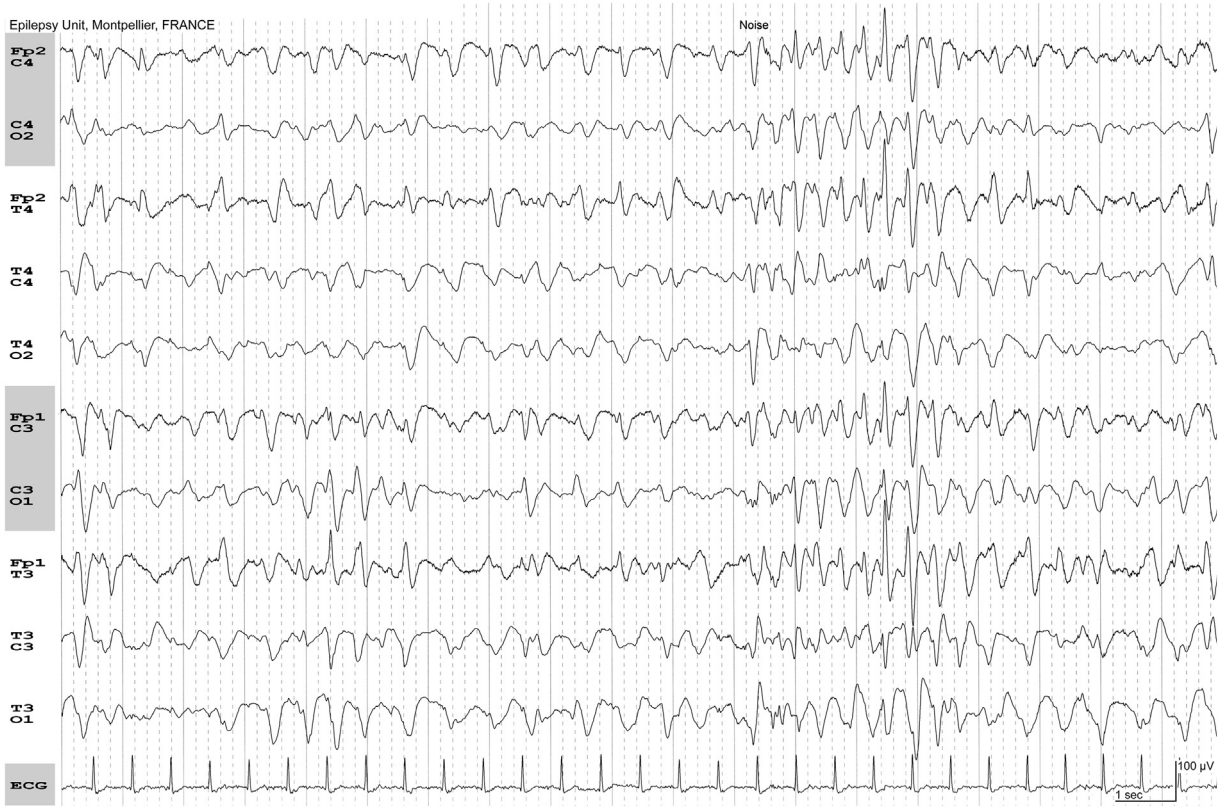

Fig. 1. 81-year-old woman with non-alcoholic cirrhosis. Hyperammonemic encephalopathy (blood ammonia 127 µmol/L; N 11–51) in the context of urinary tract infection. At the beginning of the EEG sample, the patient is drowsy. There are triphasic waves (TW). Some are asymmetric. A noise provokes a transitory immediate increase in TW discharge without muscle artifact. This activation corresponds to a higher degree of mental alertness but without an apparent arousal reaction. The patient remained in a drowsy state.

tracings help to identify respiratory events but can also help to recognize when patients fall asleep. In NREM sleep, breathing becomes more regular, both in frequency and amplitude.

6. SIRPIDs in metabolic/toxic encephalopathies and other encephalopathies with triphasic waves

The effect of sleep on metabolic/toxic or other encephalopathies with TWs is not well known. In hepatic encephalopathy, TWs resolve with sleep (Pang et al., 2011). Kurtz et al. investigated spontaneous night sleep in cirrhotic patients and noted that TWs and delta activity regressed in two severely affected patients when they fell asleep (Kurtz et al., 1972). Baldy-Moulinier et al. investigated 18 cirrhotic patients with hepatic encephalopathy (Baldy-Moulinier et al., 1981). TWs or rhythmic delta waves were mainly present during wakefulness. They decreased or disappeared during sleep without reappearing during REM sleep, but more rarely, their presence in NREM sleep was noted in some patients. Niedermeyer, in his Textbook of Electroencephalography, wrote of hepatic encephalopathy that "*when such patients are allowed to fall asleep, normalization of the record takes place for the duration of sleep*" (Niedermeyer, 1999).

Boulanger et al. studied 71 patients with TWs due to various etiologies (renal failure (15 cases), hepatic failure (11 cases), multifactorial (15 cases), cerebral anoxia (7 cases), sepsis (7 cases), delirium/dementia (4 cases), and other (12 cases) (Boulanger et al., 2006). Auditory and/or noxious stimulation frequently increased TWs (Fig. 1). Sleep occurred in eight cases during which TWs abated. Sleep patterns consisted of diffuse theta activity without spindles. The authors suggested: "*that TWs behave like sleep potentials, appearing when the level of consciousness is slightly increased with a stimulus and decreasing with deepening coma or more profound sleep*".

TWs are present during an intermediate level of consciousness. Patients with TWs are somnolent and lethargic. EEGs show fewer muscle artifacts and few eye movement artifacts. A degree of higher alertness reflected by the presence of muscle artifacts and the opening of the eyes may suppress TWs temporarily (Supplementary Fig. 1A, 2B), but stimulation must be vigorous enough to produce muscle artifacts. TWs disappear when patients fall spontaneously asleep (Fig. 2; Supplementary Fig. 3A, 6B), and after IV BZPs (Figs. 3–5; Supplementary . 1B, 2C, 4C, 5B). In a series of 10 patients with various etiologies, TWs were rapidly abolished by IV BZPs without improvement in mental status, and their abolition was not attributed to a specific antiepileptic effect of the drugs (Fountain and Waldman, 2001). The EEGs show patterns of sleep with diffuse theta or delta waves, faster pharmacologically rhythms but no spindles. This effect of BZPs on the TWs is transient (Husari et al., 2020). We reported a 36-year-old man hospitalized in ICU for coma. The EEG showed continuous GPDs at 1.5 Hz that completely regressed after IV propofol but without improvement in the clinical state. No conventional antiseizure drugs (ASD) were used, and the patient had a rapid and complete recovery with carnitine supplementation (Ornithine TransCarbamylase deficiency) (Gélisse et al., 2019; Kaplan et al., 2021). In metabolic/toxic encephalopathies with TWs, the effect of BZPs or propofol thus appear not to be a response of TWs to the pharmacological effect of the drugs, but rather the result of the sleep induction.

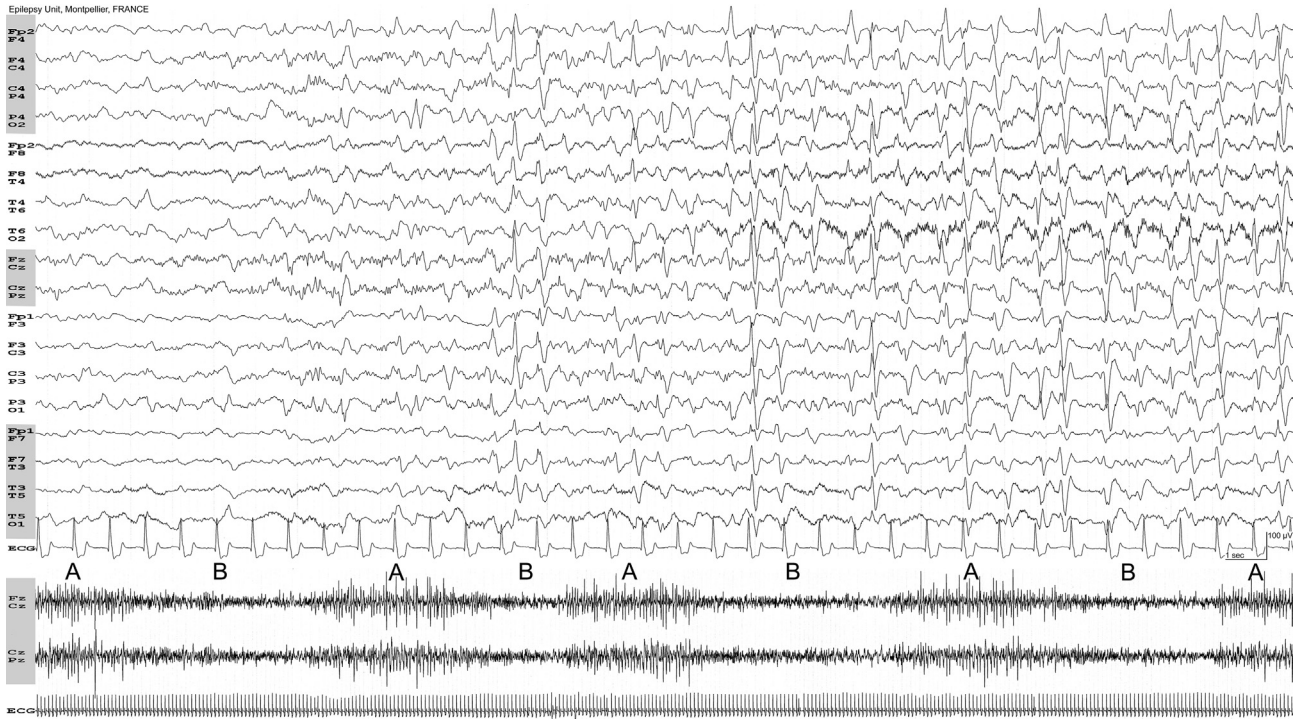

Fig. 2. Multi-factorial encephalopathy in a 75-year-old woman with bilateral pneumonia treated with piperacillin-tazobactam (4 grams every 8 hours). Acute renal failure (estimated creatinine clearance using MDRD formula: 34.7 mL/min). Vascular leukoencephalopathy and brain atrophy on CT scan. Moderate-stage Alzheimer's disease. Malnutrition. Severe impairment of the vigilance. **Top:** The patient is sleeping at the beginning of the sample. An episode of apnea/hypopnea causes arousal with profound inspiration and a loud gasping sound. Generalized periodic discharges with triphasic morphology appear at the same time as the profound inspiration. **Bottom:** 274-second epoch. Cyclic alternating pattern with runs of pseudoperiodic discharges (phase A) with the triphasic waves (TW) alternating with periods of lower voltage with theta and delta waves. Phase A corresponds to an arousal reaction after an episode of apnea/hypopnea. Auditory stimulations during the B-phase pattern bring out the TWs of the A-phase. The causes of TWs appear to be multiple in this patient: cerebral atrophy, infection, renal insufficiency, and antibiotics that may not be cleared with the renal insufficiency. Improvement of the EEG 20 days later. TWs were still present but less abundant.

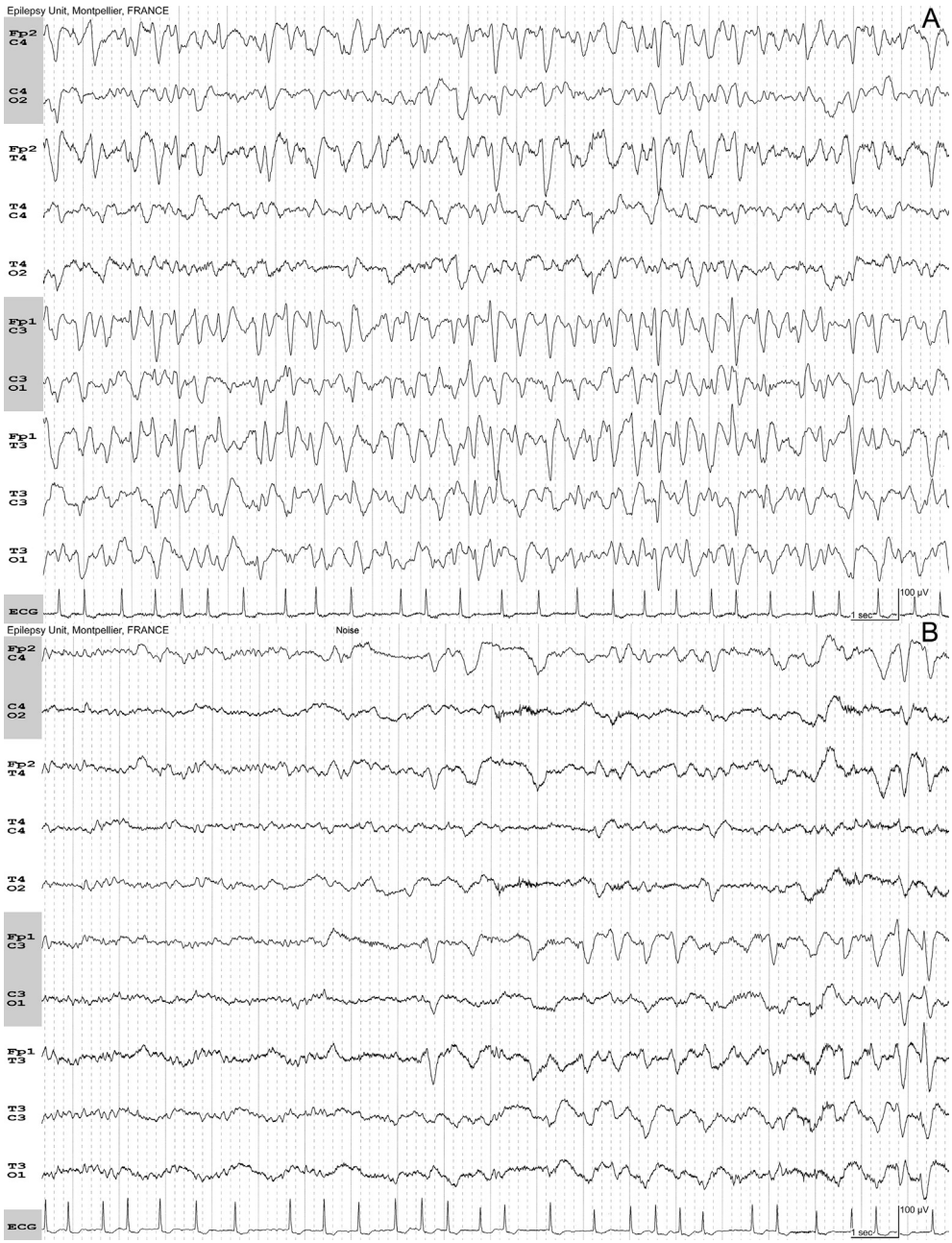

Fig. 3. Contrast-induced encephalopathy in an 87-year-old woman. Post-thrombectomy iodine extravasation into a right Sylvian ischemic stroke. **A:** Impaired vigilance, patient's eyes are closed. Asymmetric triphasic waves (TW) at 2 Hz with a clear predominance over the left hemisphere. Because of this asymmetry, non-convulsive status epilepticus was initially diagnosed, and 0.5 mg clonazepam was administered IV during the EEG. TWs disappeared, but the test was negative as there was no behavioral awakening. The patient fell asleep. **B:** No TW at the beginning of the sample. Loud noise causes arousal with muscle artifacts, and TWs reappear with a clear predominance on the left side. During this continuous EEG monitoring, several stimulations (auditory or painful) were done with the same effect. Follow-up EEG one week later showed marked improvement as did the clinical state (Supplementary Fig. 1A-F).

When patients wake up spontaneously, or because of a respiratory event, a noise, or pain, TWs reappear in an intermediary state (Figs. 2, 3; Supplementary Figs. 1–6) before they eventually disappear when the patient "fully" awakens with better responsiveness. Alternatively, the patient may return to sleep (Supplementary Fig. 1C), with the possibility, in this case, of their appearance with a cyclic alternating pattern (Fig. 2). SIRPIDs may be seen as a typical and expected pattern of transition from sleep into the waking state for patients with TWs. As noted, TWs were initially described in hepatic encephalopathies but can also be seen in uremic, septic, hypoxic, hypercapnic, and toxic encephalopathies (lithium, baclofen, ifosfamide, beta-lactam antibiotics, pregabalin...) (Gélisse et al., 2019; Kaplan et al., 2021; Sutter et al., 2013). Etiologies are often multiple, e.g., uremic plus septic plus third- or fourth-generation cephalosporins. TWs can be seen in basal meningitides (tuberculosis (Konno et al., 2010), borreliosis (Eriksson and Wictor, 2007), neurocysticercosis (Gélisse et al., 2019)). Other bacterial agents for basal meningitides include listeria, syphilis (Beach et al., 2011). TWs can also be observed in carcinomatous meningitis, immunosuppressant drug-induced aseptic meningitis, pneumococcal meningitis with vasculitis (Gélisse et al., 2019), and post-radiation encephalopathies (Supplementary Fig. 6).

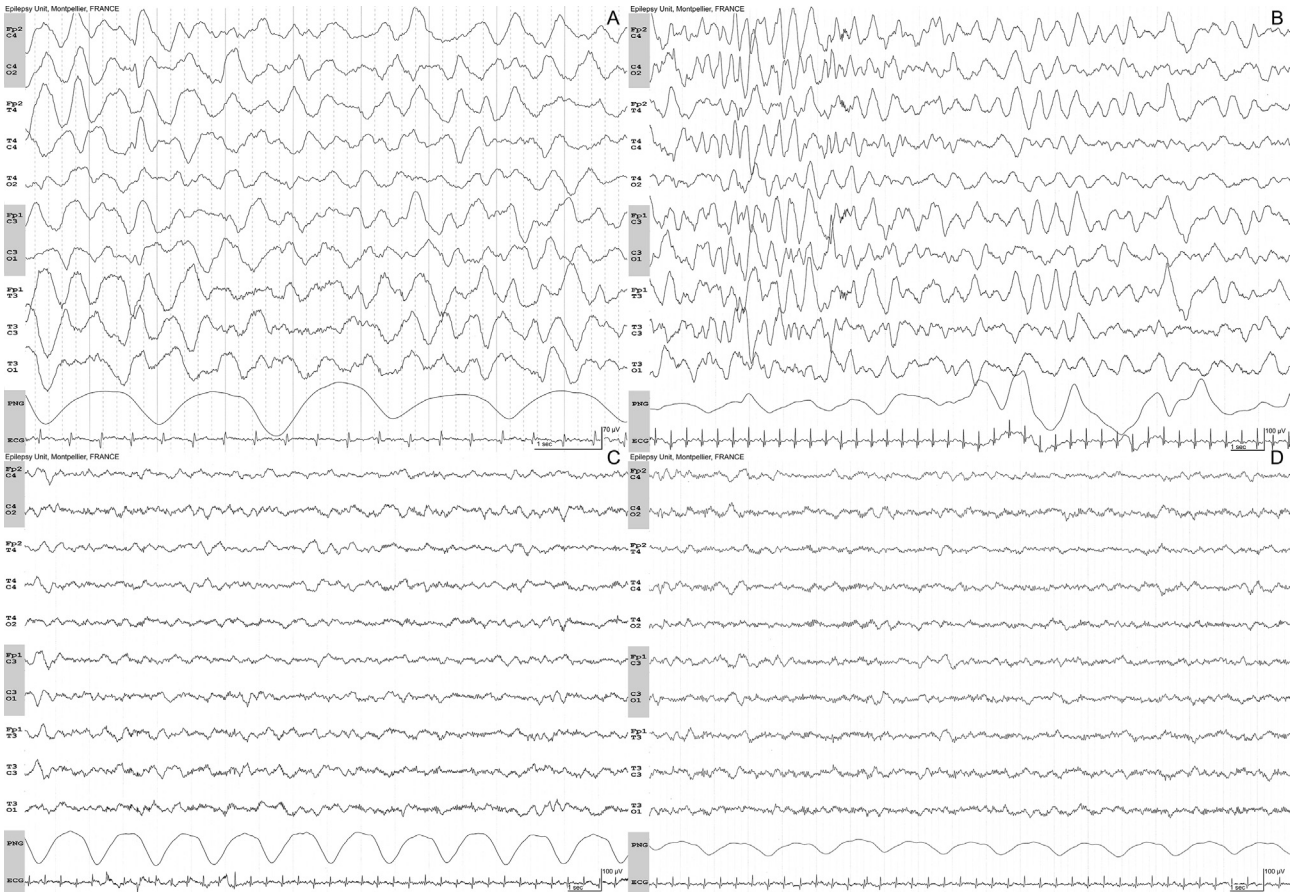

Fig. 4. Influenza B-associated Reye's syndrome in a 32–month-old girl. One hemiclonic seizure. AST 13,212 U/L (N < 60), ALT 6523 U/L (N < 28), creatine kinase 1298 UL (N < 228), LDH 10,256 U/L (N < 305), factor II 21% (N 70–120), factor V 21% (N 60–140), factor VII 9% (N 50–120), factor X 24% (N 50–120). **A and B:** Eyes closed. Abnormal continuous diffuse rhythmic delta waves. The child is not sleeping, note some muscle artifacts and breathing irregularities. **C and D:** After IV-midazolam, the delta waves progressively disappear. There are pharmacological beta rhythms. Regular breathing pattern.

Respiratory-rate abnormalities are an almost invariable development in metabolic encephalopathies (Alpert, 2011). These patients may have periodic breathing while sleeping (Posner et al., 2019). Patients with Cheyne-Stokes respiration have periodic low-voltage irregular activity (phase B) alternating with high-voltage slow-wave activity (phase A) (Bauer, 1999). Heart rate acceleration and hyperventilation coincide with phase A, and patients appear to be more aroused during this phase. Stimuli applied during phase B lead to high-voltage slow-wave activity. Fig. 2 shows a typical example of periodic breathing with runs of GPDs with a triphasic morphology that coincide with hyperventilation following an episode of apnea/hypopnea.

As postulated by Sutter et al. TWs are a marker of structural brain disease coupled with toxic-metabolic perturbations (Sutter et al., 2013). More recent work has highlighted the important role of white matter disease, white matter atrophy, or global cerebral atrophy in facilitating the occurrence of TWs (Kotchetkov et al., 2021). TWs may sometimes be asymmetric, e.g., in the case of a positive history of stroke (Fig. 3), or a breach rhythm (Gélisse et al., 2019). They are numerous causes of GPDs with triphasic morphology. They certainly share the same reactivity despite the different etiologies: present the day with a low state of vigilance when the patients are drowsy, transitory attenuation or suppression with an enhanced level of vigilance reflected by the presence of muscle artifacts, disappearing during sleep, and reappearing on awakening. In their series of 70 patients with chronic lung diseases hospitalized for acute respiratory failure, Laxenaire-Aug et al. presented one comatose woman in whom a nociceptive stimulation-induced bilateral rhythmic delta activity that we would now interpret as SIRPIDs (Laxenaire-Aug et al., 1970). In all of these conditions, the reappearance of TWs immediately after awakening in a low vigilance state must be interpreted with caution and certainly do not represent the continuum between ictal and interictal activity but a post arousal/awakening reaction seen in encephalopathic patients. TWs are not observed in children. The EEG of children with Reye's syndrome is abnormal but without TWs, but rather with generalized continuous delta activity (Garrel et al., 1977). These delta waves disappear during sleep induced by BZP (Fig. 4) and reappear upon awakening (Fig. 5).

There is controversy regarding the effects of BZP on the EEG of patients treated with third- and fourth-generation cephalosporins (Triplett et al., 2019). Husari et al. evaluated patients with cefepime-induced encephalopathy and reported an increase in the TWs in 19 patients with arousals and/or stimulation, and a decrease in one (Husari et al., 2020). TWs were absent during sleep/resting and appeared primarily with stimulation in 11 patients (stimulus-induced). Administration of IV BZP was done in 10 patients with transient abatement of the TWs without immediate clinical improvement in 50%, no effect on the TWs in 50%. ASD intake escalation in 10 patients had no rapid EEG or clinical results. Interestingly, in this series of cefepime-induced encephalopathy, preexisting subcortical white matter disease was observed in the majority of the patients. White matter disease seems to favor TWs (Kotchetkov et al., 2021).

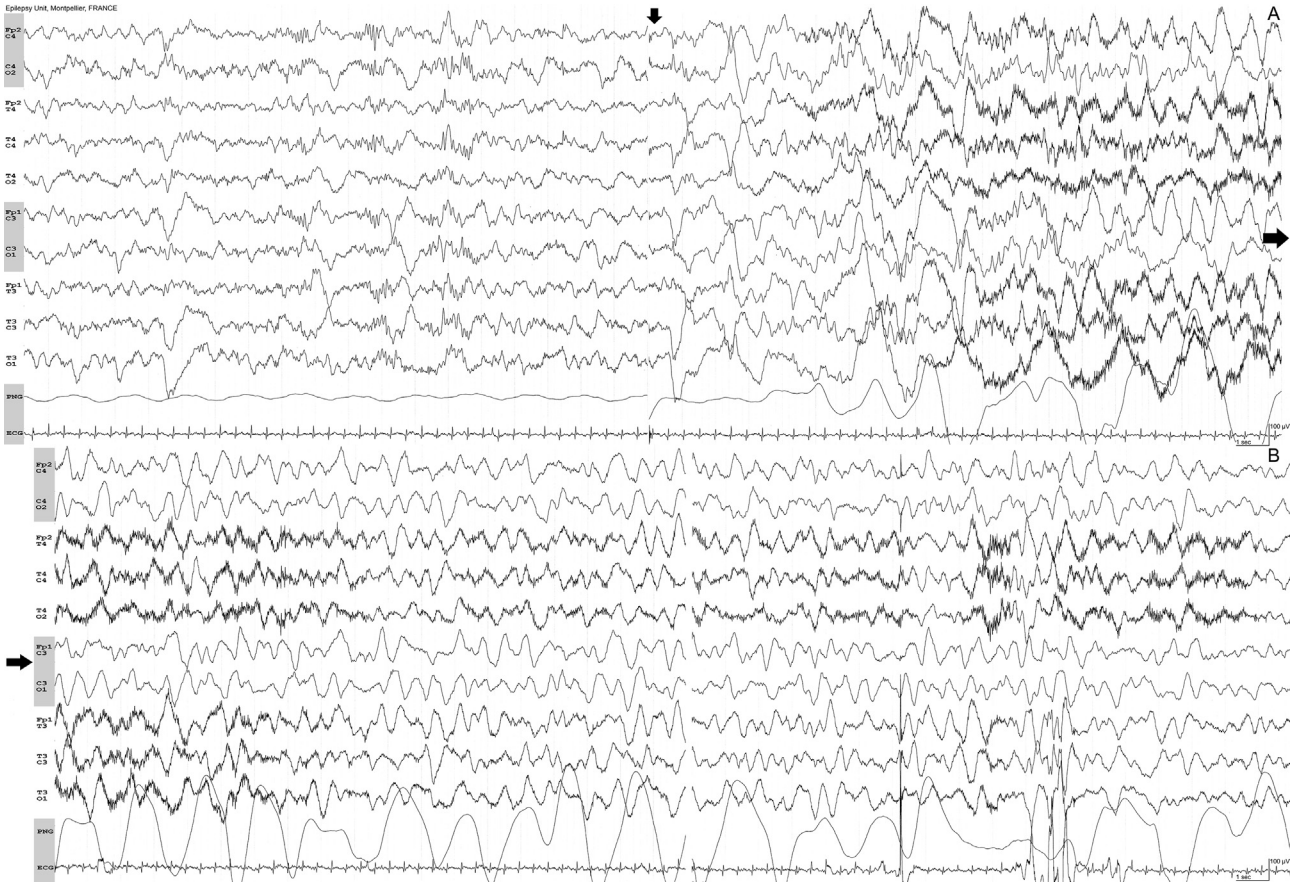

Fig. 5. Same child as Fig. 4. **A:** EEG recorded 18 minutes after IV-midazolam. The child is sleeping. The EEG now shows a mixture of frequencies with slow waves and faster activities at 9 Hz. An auditory stimulus causes arousal with high amplitude delta waves and rhythmical theta waves followed by rhythmical delta waves. There are muscle artifacts. **B:** Awakening. Continuous delta waves, muscle artifacts, irregular, and deep-breathing. This is an example of stimulus-induced Generalized Rhythmic Delta Activity.

7. Creutzfeldt-Jakob disease and Alzheimer's disease

In CJD, waking EEGs evolve as a function of disease progression, from non-specific patterns such as diffuse slowing, frontal intermittent rhythmic delta activity (FIRDA), paroxysmal patterns resembling TWs, and finally, to typical periodic sharp wave complexes (PSWC). These complexes may be lateralized to one hemisphere before becoming generalized (Chiofalo et al., 1980) (Figs. 6 and 7; Supplementary Figs. 7, 8). Sleep dysfunction is common in CJD (Kang et al., 2016) with sleep complaints, sleep-disordered breathing, progressive loss of the normal sleep EEG architecture, and loss of the physiologic sleep EEG patterns that explain the difficulties to identify the sleep stages using standard criteria.

From a historical point of view, the inhibitory effect of hypnotic drugs on the PSWC has been observed many years ago by different authors using IV diazepam (DZP) (Bortone et al., 1994; Brechet et al., 1980; Capon et al., 1975; Elliott et al., 1974; Evans, 1975; Richter, 1968; Rossini et al., 1979, Sundaram and Young, 1989; Szirmai et al., 1976; Terzano et al., 1995) while orally given DZP did not affect the complexes (Szirmai et al., 1976). IV clonazepam (CNZ) (1 mg) led to an incomplete disappearance of PSWC after 45 seconds whereas, up to 6 mg die orally given did not influence (Schlenska and Walter, 1989). More recently, midazolam was reported to suppress PSWC but also the FIRDA patterns (Wieser et al., 2004). Sundaram and Young reported details of a 62-year-old patient whose periodic complexes disappeared during spontaneous and chloral hydrate-induced sleep but that reappeared on arousal. IV DZP produced the same effect (Sundaram and Young, 1989).

Short-acting barbiturates can temporarily suppress PSWC, such as secobarbital (Pallis and Spillane, 1957) and sodium amobarbital (Lee and Blair, 1973). Propanidid, a non-barbiturate IV anesthetic used 40–50 years ago for induction, led to a very transient improvement of the EEG with interparoxysmal intervals five to six times longer than those resting as well as a decrease in the amplitude of the PSWC (Szirmai et al., 1976). PSWC disappear during general anesthesia with a burst-suppression pattern and invariably reappear on decreasing dose (Lapergue et al., 2010) (Fig. 6; Supplementary Fig. 8E-8H).

PSWC disappear during spontaneous sleep or after sedative drugs (Wieser et al., 2006). They tend to disappear after IV methylphenidate, with a transient clear improvement of the clinical state. Patients returned to baseline after 20 minutes (Elliott et al., 1974; Rossini et al., 1979). In contrast with IV DZP, methylphenidate suppressed the PSWC without alteration of background activity (Elliott et al., 1974). BZPs are effective antiseizure drugs but, above all, are anxiolytic and hypnotic agents. The effect of IV BZPs should not be considered as a direct effect of the drug on the PSWC, but the effect of sleep induction. There is no improvement of the mental status, the patient stays immobile, the eyes are closed. Orally given BZPs (Schlenska and Walter, 1989; Szirmai et al., 1976), conventional

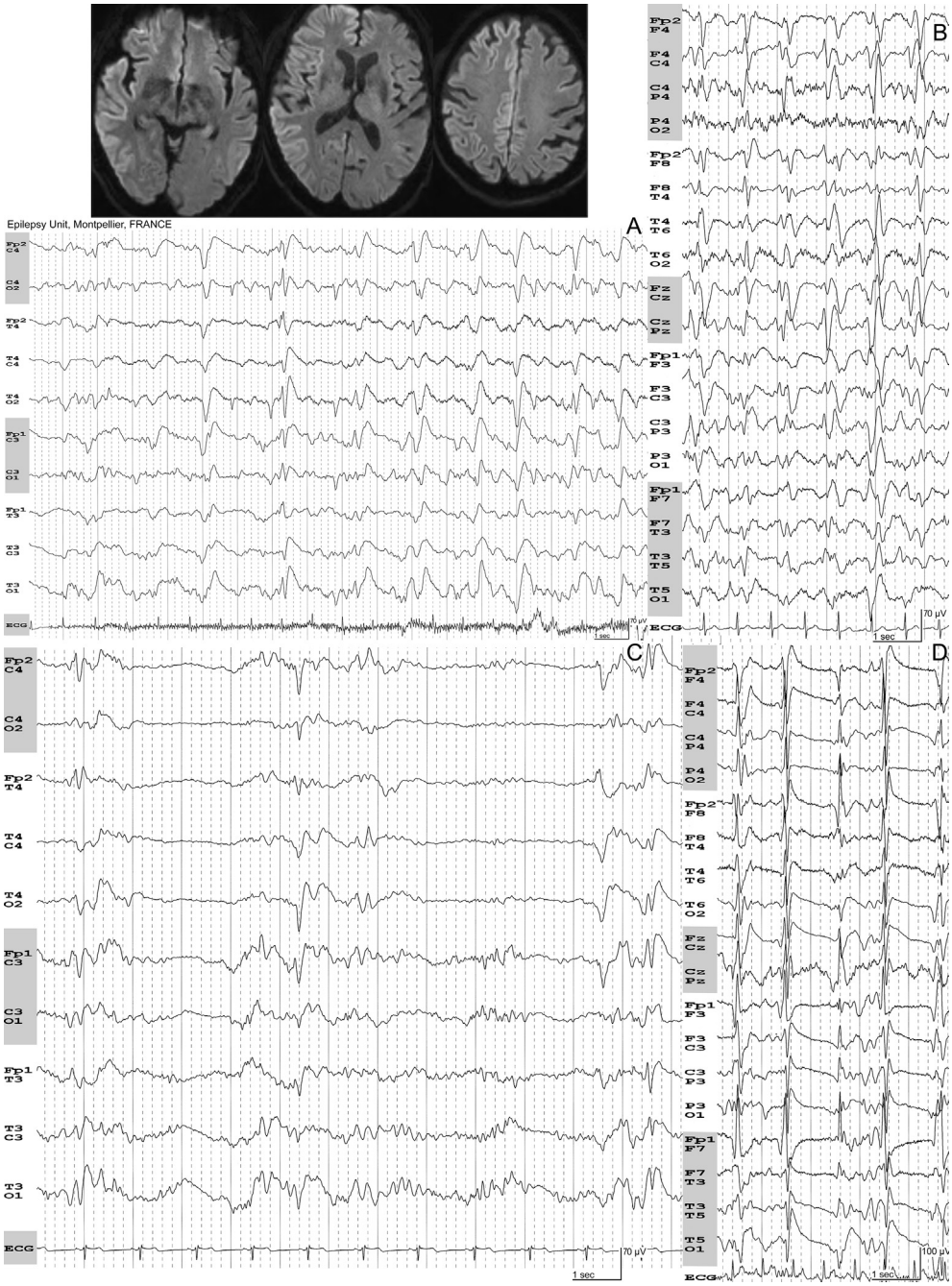

Fig. 6. A 72-year-old woman was hospitalized for depression and behavioral disorders. Diffusion-weighted MRI showed an increased signal in the cortex of the right cerebral hemisphere. **A:** The patient was sleeping (not shown). During spontaneous awakening, she starts moaning. Note the muscle artifact on the ECG derivation. Bilateral periodic complexes appear. This portion of the EEG was interpreted as SIRPIDs with vocalization, and antiseizure drugs (ASD) were started. **B:** Two days later, the patient was treated with phenobarbital and IV levetiracetam but without clinical improvement. Note the diffuse periodic complexes at 1–1.5 Hz but with predominance over the right hemisphere and the vertex region. The EEG was interpreted as showing non-convulsive status epilepticus but with no effect by treatment with ASDs. After this EEG, the patient was admitted to the ICU. **C:** Three days later, burst-suppression pattern. The patient was treated with midazolam, propofol and sufentanil but also carbamazepine and levetiracetam. Note the asymmetry between the two hemispheres with better background over the left hemisphere. There was an apparent improvement of the EEG with a decrease of the periodic complexes. When propofol was stopped, periodic complexes reappeared, and a diagnosis of Creutzfeldt-Jakob disease (CJD) was finally made. **D:** 15 days later, typical pattern of CJD. Protein 14–3-3 positive in the CSF. See Supplementary Fig. 8A-8L for a complete description of this patient.

non-sedative ASDs (Fig. 6B; Supplementary Fig. 8B-8I) do not affect the periodic complexes. The improvement of the EEG after IV BZP and other hypnotic drugs can be easily reversed by stimulations with the reappearance of the PSWC (Supplementary Fig. 7E, 7F). But above all, studies showed that PSWC disappeared when the level of consciousness was reduced and reappeared during stimulations that we would now interpret as SIRPIDs (Brechet et al., 1980; Goto et al., 1976; Sundaram and Young, 1989). The decrease of the level of consciousness was associated with slow waves, during which myoclonic jerks disappeared, the heartbeats and breathing rate were reduced with the possibility of apnea (Bortone et al., 1994; Goto et al., 1976). Terzano et al. recognized two-phase alternating patterns in CJD (Lechi et al., 1983; Terzano et al., 1981, 1995). Phase A was characterized by periodic discharges, whereas phase B showed attenuation or suppression of the discharges. Phase A was associated with increased arousal,

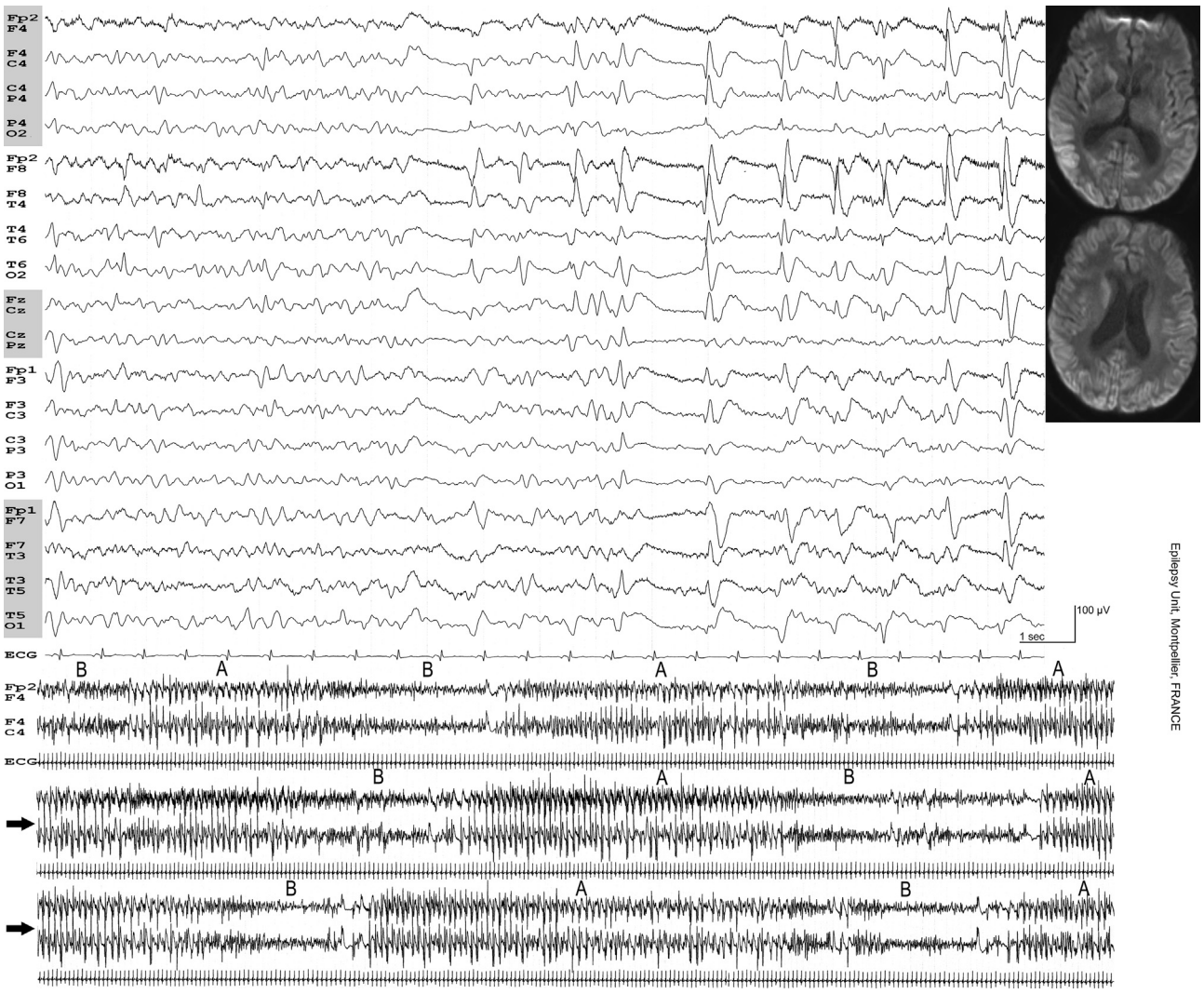

Fig. 7. 67-year-old woman with Creutzfeldt-Jakob disease. Rapid cognitive decline. Mutism. Reflex myoclonic jerks. Protein 14–3-3 positive in the CSF. High-signal intensity on diffusion-weighted MR images in the right caudate nucleus and the cortex, especially the right temporo-occipital region. **Top:** Spontaneous arousal provokes the appearance of periodic sharp wave complexes (PSWC) with a predominance over the right hemisphere. **Bottom:** three continuous 180-second epochs with sequences of PSWC (Phase A: greater arousal) alternating with periods of lower voltage with theta waves (Phase B: lesser arousal). It would have been interesting to have a thoracic pneumogram to determine whether the disruption of sleep was due to respiratory events.

whereas phase B was associated with a reduction in the arousal level and hypotonia. NREM sleep was characterized by 0.5–4-Hz activities, arousal reactions by the reappearance of the periodic discharges (Terzano et al., 1995) corresponding to the current definition of SIRPIDs. Stimuli (sound, touch, or light) applied during phase B rapidly brought out the typical periodic discharges of the A-phase. Before entering the late stages of the disease, if sensory stimulations were intense enough to provoke an awakening, the EEG no longer showed cyclic activity but sustained periodic discharge sequences (Terzano et al., 1981). Garnés Sánchez et al. reported a patient with PSWC during wakefulness and arousals. Sleep apneas were associated with the abrupt reappearance of the PSWC accompanied by increased heartbeats (Garnés Sánchez et al., 2018).

Lapergue et al. reported ten patients who have been hospitalized in an ICU for a presumed refractory NCSE with a final diagnosis of sporadic CJD. Two typical examples of SIRPIDs after an auditory stimulation are shown (Lapergue et al., 2010), but other examples can also be found in older studies (Capon et al., 1975; Evans, 1975; Goto et al., 1976). On spontaneous or provoked awakening, PSWC reappear. This emergence can be misinterpreted as a seizure (Fig. 6A; Supplementary Fig. 8A, 8B). In patients with CJD, SIRPIDs may be seen as a typical and expected transitional patterns seen from sleep to wakefulness.

TWs have been reported in advanced Alzheimer's disease (AD) (Markand and Brenner, 2003; Primavera and Traverso, 1990; Rae-Grant et al., 1987; Sundaram and Blume, 1987). In AD, waking EEG patterns progress with the course of the disease from a slowing of the background to TWs, to periodic sharp complexes (Imazu, 1990). However, as opposed to the patterns seen in CJD, the complexes are less frequent. Only the sleep organization has been extensively studied in AD. The effect of sleep on the TWs and sharp complexes is unknown but these sharp waves probably disappear in sleep and reappear on awakening (cf CJD). SIRPIDs may probably be seen as a typical pattern of transition from sleep to a waking state, but more specific studies are needed. Fig. 8 shows an example of a 90-year-old woman with the same reactivity two years later (Supplementary Fig. 9). Furthermore, as elderly people with preexisting brain atrophy are also more vulnerable to minor metabolic changes or the side effects of drugs, TWs in metabolic/toxic encephalopathies can also be seen in these patients (Fig. 2). These TWs share the same reactivity as non-demented elderly people.

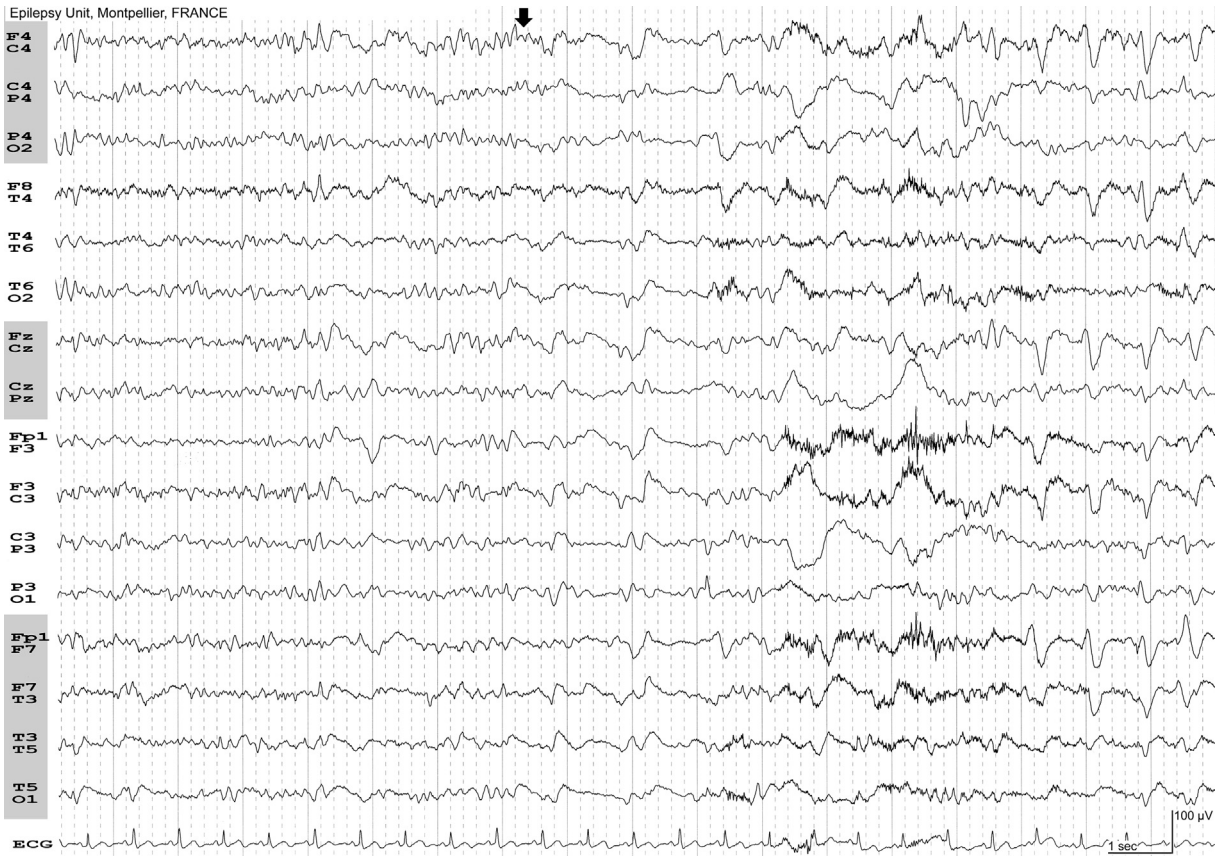

Fig. 8. 90-year-old woman with an advanced form of Alzheimer's disease (AD). Diagnosis of AD, six years earlier. At the beginning of the panel, the patient's eyes are closed. As she has AD, it is not possible to determine if the patient is sleeping or if she is deeply relaxed. An auditory stimulus (arrow) causes arousal (muscle artifacts) with bilateral (predominantly anterior frontal) periodic triphasic waves (TWs). The same reactivity was recorded two years later (Supplementary Fig. 7) but with sharp periodic complexes instead of TWs. The patient died at the age of 94.

8. Anesthesia associated de novo generalized periodic discharges

Delta patterns with sharp components corresponding to TWs have been observed in the recovery phase after self-poisoning with barbiturates (short-acting barbiturates and phenobarbital) and non-barbiturates hypnotic drugs. In mild comas, delta waves were likely to be elicited by acoustic stimuli (Kubicki et al., 1970a, 1970b). Generalized periodic discharges related to anesthetic withdrawal (GRAWs) (Bhatt et al., 2014) can be seen after burst-suppression patterns induced by pentobarbital (Bhatt et al., 2014; Herman, 2007; Husari and Ritzl, 2021; Lancman et al., 1997) and more rarely after propofol (Bhatt et al., 2014; Husari and Ritzl, 2021). GRAWs appear with a less typical triphasic morphology (Fig. 9). This pattern does not represent the recurrence of SE or NCSE in comatose patients but rather a transient and resolving encephalopathy in the following 24–48 hours (Husari and Ritzl, 2021). Husari and Ritzl reported 13 patients in whom the pattern was stimulus-dependent (either activated with stimulation or presenting only as SIRPIDs) (Husari and Ritzl, 2021). Patients with hypoxic/anoxic injury, epileptic encephalopathies, and GPDs prior to burst suppression were excluded from their study. For these authors, the stimulus-dependent nature of the GPDs was an important finding.

9. Conclusion

SIRPIDs are easy to recognize but may be difficult to interpret. The use of the word "Ictal" in the definition is more ambiguous than it sounds. As well as FIRDA, SIRPIDs represent a non-specific EEG pattern. Like FIRDA, SIRPIDs can be seen in a large variety of settings. As SIRPIDs are only transiently seen, occurring with each noxious stimulation of the patient either in the same EEG recording or during subsequent EEGs, the word "Ictal" might best be replaced by "Intermittent": Stimulus-Induced Rhythmic or Periodic Intermittent Discharges retaining the term "SIRPIDs".

However, considering that SIRPIDs may be "*potentially ictal*" or on an *"ictal–interictal continuum"* in some situations, SIRPIDs that contain spikes, polyspikes, spike-waves at 3 Hz or more, fast "epileptic" rhythms could be termed SIRPIDs-plus, while bi- or tri-phasic complexes below 2.5 Hz should not so defined. As the arousal reactions in sleep contain beta rhythms, these beta activities must be clearly differentiated from polyspikes and fast "epileptic" rhythms.

Author contributions

Dr. Gélisse - Acquisition of data - Analysis, and interpretation - Writing- Reviewing and Editing- Study supervision.

Dr. Crespel - Acquisition of data - Critical revision of the manuscript for important intellectual content - Reviewing and Editing.

Pr. Gigli - Critical revision of the manuscript for important intellectual content-Reviewing and Editing

Dr. Kaplan - Critical revision of the manuscript for important intellectual content- Reviewing and Editing.

All co-authors have been substantially involved in the study and preparation of the manuscript. No undisclosed persons have had a primary role in the study or manuscript preparation. All co-authors

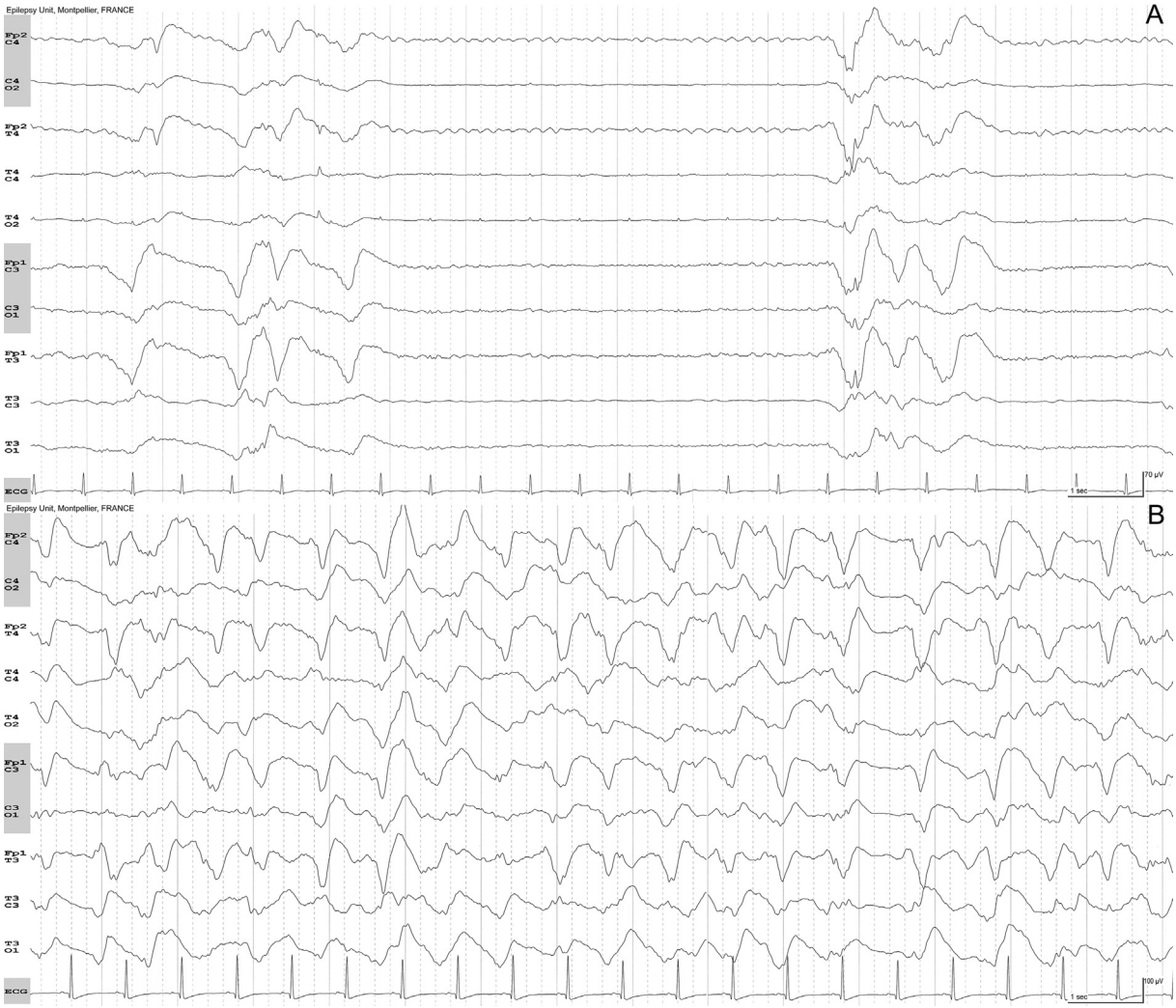

Fig. 9. 19-year-old man with focal epilepsy (right posterior polymicrogyria, and subcortical heterotopia) with poor compliance to his treatment. Refractory generalized convulsive status epilepticus treated with pentobarbital (PTB) (5 mg/kg/h) with a burst-suppression pattern for 48 hours **(A)**. On PTB withdrawal, bilateral triphasic waves (TW) at 2 Hz **(B)** misinterpreted as non-convulsive status epilepticus, were noted. PTB was restarted. Forty-eight hours later, on PTB withdrawal, there was the same pattern of TWs. PTB was restarted, but after discussion, it was decided to interpret the TWs as non-ictal, and PTB was stopped. Four days later, no TWs were seen on the follow-up EEG. There was a full recovery.

have approved the submitted version of the paper and accept responsibility for its content.

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.

Acknowledgments

Dr. Kaplan has been on the board of the American Board of Clinical Neurophysiology, the American Clinical Neurophysiology Society, consulted for Ceribell and lectured on EEG.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2021.05.002.

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