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B. Perin, William Szurhaj

► **To cite this version:**

B. Perin, William Szurhaj. New onset refractory status epilepticus: State of the art. *Revue Neurologique*, 2022, 178 (1-2), pp.74-83. 10.1016/j.neurol.2021.12.005 . hal-03603778

HAL Id: hal-03603778

<https://u-picardie.hal.science/hal-03603778v1>

Submitted on 22 Jul 2024

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New Onset Refractory Status Epilepticus: State of the art

B. Perin¹W. Szurhaj^{1,2}

1: Department of clinical neurophysiology, Amiens University Medical Center, France

2: Equipe CHIMERE EA7516 – Université Picardie Jules Verne

Word count for the paper (without abstract): 3553 words

Title: 39 characters

Abstract: 203 words

References : 82

Table 1

Figures : 4

Correspondence to:

Pr William Szurhaj

Service de Neurophysiologie Clinique

CHU Amiens-Picardie

80054 Amiens Cedex, France

Tél. : +33 3 22 08 77 76

szurhaj.william@chu-amiens.fr

Sponsoring:

This study is not industry-sponsored.

Conflict of interest :

None

Keywords : NORSE, FIRES, autoimmune encephalitis, status epilepticus

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Abstract

NORSE (new onset refractory status epilepticus) has recently been defined as a clinical presentation, not a specific diagnosis, in a patient without active epilepsy or other preexisting relevant neurological disorder, with new onset of refractory status epilepticus without a clear acute or active structural, toxic or metabolic cause. It includes the concept of FIRES described in children with a similar condition but preceded by a 2–14-day febrile illness.

NORSE constitutes the acute phase of an entity preceded by a prodromal phase which may be accompanied by numerous manifestations (febrile episode, behavioural changes, headache, ...), and followed by a chronic phase marked by long-term neurological sequelae, cognitive impairment, epilepsy and functional disability.

There are many causes of NORSE: autoimmune, infectious, genetic, toxic, ... but in half of the cases, despite an exhaustive assessment, the cause remains undetermined. Paraneoplastic and non-paraneoplastic autoimmune encephalitis remains by far the leading cause of NORSE.

For these reasons, immunotherapy should be considered rapidly in parallel with the treatment of the status epilepticus, including in cryptogenic NORSE. Good communication with the family is important because the management of the acute phase is long and difficult.

Although mortality remains high (11-22%), and sequelae can be severe, the majority of survivors can have a good or fair outcome.

Keywords : NORSE; FIRES; autoimmune encephalitis; status epilepticus

Introduction

The term NORSE (new onset refractory status epilepticus) was introduced by Wilder-Smith in 2005 to describe seven cases of adult women (mean age 33 yr), without a history of epilepsy, having presented a prolonged refractory status epilepticus (SE), without an identified cause. Their outcome was poor (five died) [1]. The term febrile infection-related epilepsy syndrome (FIRES) was then proposed in 2010 to describe 22 previously healthy children with prolonged or recurrent seizures occurring 2–14 days after fever onset [2]. Fourteen of them had refractory SE. Two children died, eight remained in a state of impaired consciousness. A few series of patients with similar conditions in adults and children had previously been described [3–5]. Subsequently, other similar series have also been described under different terms, especially in children, such as DESC (devastating epileptic encephalopathy in school-age children) [6], and AERRPS (acute encephalitis with refractory repetitive partial seizures [7]. But despite a different age of onset and the eventual occurrence of a febrile illness preceding the acute episode, the clinical presentation and the course (often poor) were often very similar in the different series reported. Whether these syndromes corresponded to distinct or similar entities was then debated [8,9]. The current position is to consider the two presentations as the same condition.

Recently, a multinational expert panel was convened to propose consensus definitions.

NORSE has been defined as a clinical presentation, not a specific diagnosis, in a patient without active epilepsy or other preexisting relevant neurological disorder, with new onset of refractory SE without a clear acute or active structural, toxic or metabolic cause [10]. Status epilepticus is considered as refractory when persisting despite administration of at least two appropriately selected and dosed parenteral medications including a benzodiazepine. In most of cases, SE persists 24 hours after onset of anaesthesia, either without interruption, or recurs on appropriate anaesthetic treatment or after anaesthesia withdrawal. They are then considered as NOSRSE (new onset super-refractory status epilepticus).

Based on the same consensus definition, FIRES is now considered as a subcategory of NORSE [10]. Its diagnosis requires prior febrile infection starting between two weeks and 24 hours before onset of refractory SE. This definition excludes cases in which the fever occurs at seizure onset, or <24 hours prior to seizure onset.

Both NORSE and FIRES include all ages since there is no strong evidence to separate childhood- and adult-onset forms [11].

Although NORSE is rare, its management is challenging for care teams because the condition is severe. Causes are numerous requiring exhaustive assessment, often compromising appropriate therapeutic management.

Aetiologies

About 50% of NORSE cases remain unexplained.

For half of the cases in a series of 130 patients whose aetiology could be determined, the authors found that the majority resulted from autoimmune encephalitis (37%) including 19% non-paraneoplastic, 18% neoplastic, and 8% infectious encephalitis [12].

In the retrospective series of 26 NORSE patients, the proportion of cryptogenic cases was 73%, confirming the idea of the particularly refractory character of NORSE without a determined cause. An autoimmune cause was identified for 19% (most often an anti-NMDA receptor encephalitis), an infectious cause for 8%. Seven neuropathological examinations were obtained by brain biopsy and or autopsy to establish a diagnosis in three cases : acute disseminated encephalomyelitis, candida and herpes simplex virus encephalitis [13].

More than 180 causes of SE have been identified that can be grouped into four themes: Inflammatory / auto immune encephalitis, infectious, genetic/ congenital, and toxic disorders [14–17].

First of all, a meticulous infectious assessment is to be carried out so as not to ignore atypical infectious encephalitis that would justify specific treatment. The main viruses to look for are herpes simplex virus 1, varicella zoster virus, Epstein-Barr virus, cytomegalovirus, enterovirus, measles, mumps, John Cunningham virus, human immunodeficiency virus. There are also arboviruses, such as the Jamestown canyon encephalitis found in North America [18], Japanese or West Nile virus, and tick-borne virus. *Mycoplasma pneumoniae*, *Bartonella henselae*, *Listeria*, Lyme, *Mycobacterium tuberculosis*, rickettsiosis, neurosyphilis are the main bacteria to look for and we must not forget amoebae, parasites like *Toxoplasma gondii* and fungi especially in immunocompromised patients [14,19].

Four cases of NORSE likely related to SARS COV-2 encephalitis have been reported, three of which were improved by intravenous immunoglobulins, which suggested the autoimmune mechanism of encephalitis [20–22].

Paraneoplastic and non-paraneoplastic autoimmune encephalitis remains by far the leading cause of NORSE. Anti-NMDA receptor and anti-VGKC complex encephalitis (LGI 1 and CAPSR2) are among the most commonly encountered types of autoimmune encephalitis [23–25]. Anti-GABA(B) receptor encephalitis and anti-GABA(A) receptor encephalitis are often complicated by SE [26].

Among 25 cases of anti-GABA_A encephalitis (21 and 15% concerning anti NMDA_R and LGI1 encephalitis), a Dutch national cohort study highlighted that nearly 50% were NORSE [27].

Six cases of steroid-responsive encephalopathy with autoimmune thyroiditis (Hashimoto encephalitis) complicated by NORSE have also been recently reported [28]. Finally, the genetic causes, more rarely identified, are the mutations SCN1A, PCDH19, CADASIL, mitochondrial disorders, DNM1L, MELAS, POLG1 [14]. Uncommon causes have also been reported: a case report of voluntary poisoning with organophosphates [29], some with synthetic cannabinoids use [30], one subacute encephalopathy with seizures in alcoholics (SESA) syndrome and one Creutzfeldt-Jacob disease [12].

The characteristics of cryptogenic NORSE seem similar to those of autoimmune encephalitis. According to some authors, a major proportion would therefore have an autoimmune origin involving an unidentified antibody [14].

Clinical features

Two age peaks are observed in adults, due to different causes: predominance of autoimmune causes in patients under 30 and predominance of paraneoplastic causes in those around 60 years old [31]. The sex-ratio is different according to age: female predominance in adults, and male predominance in children [11]. An underlying autoimmune condition is the most common comorbidity in NORSE, while most FIRES patients are previously healthy.

NORSE most often corresponds to the second phase of a larger entity, which classically consists of three phases: a prodromal phase; an acute phase in which NORSE is integrated; and a chronic phase.

Most patients arrive at the hospital at the acute phase, after the onset of seizures, but in hindsight, prodromal symptoms are found in two-thirds of cases [32], and febrile illness in 30-50% of NORSE cases [31,33]. Prodromal symptoms may consist in confusion, fatigue, minor upper respiratory tract infection or gastroenteritis, minor upper respiratory tract infection, flu-like symptoms, behavioural changes, hallucinations, cognitive impairment [8,11,32,34].

Seizures develop 1-14 days after the prodromal phase. They become rapidly frequent, increasing in intensity, and usually evolving into refractory SE. These are focal seizures, more often temporal, which can become bilateral tonic-clonic seizures [33]. Myoclonic or tonic seizures may be observed.

In the vast majority of cases, the SE becomes super-refractory to treatment [31]. Its duration is variable – lasting from a few days to several months. If the patient survives, this acute phase is

usually followed by a chronic phase with refractory epilepsy and neurological deficit, cognitive deficits, and behavioural abnormalities.

Some symptoms are important to identify because they can point to specific aetiologies. Psychiatric symptoms or behavioural changes, during the prodromal phase, especially in a young female, will point to anti-NMDAr encephalitis. During the acute phase, non-epileptic oro-lingual dyskinesias are prominent and should not be considered as ictal manifestations. Prominent psychiatric symptoms associated with cerebellar ataxia will suggest rather anti-AMPAr encephalitis. In elderly males, limbic encephalitis associated with hyponatraemia (due to a syndrome of inappropriate anti-diuretic hormone) suggests anti-VGKc complex encephalitis; in this context, faciobrachial dystonic seizures are suggestive of anti-LGI1 encephalitis, while cerebellar dysfunction, neuromyotonia, dysautonomia, and insomnia are suggestive of anti-CASPR2 encephalitis. Stiff person syndrome will point to anti-GAD or anti-amphysin encephalitis. Anosmia/ageusia at the prodromal phase will be suggestive of a SARS-Cov-2 origin. Parieto-occipital seizures may suggest posterior reversible encephalopathy syndrome (PRES) or a mitochondrial disorder.

Electroencephalography (EEG)

Even if clinical symptoms are not observed, subclinical seizures are often recorded on EEG. Continuous EEG is therefore essential for managing these patients.

Seizures are essentially partial seizures, most often involving the temporal, or frontotemporal or perisylvian regions. They may evolve into continuous critical activity.

In interictal condition, or after the SE has subsided, the background activity is slowed down, sometimes consisting of a generalised rhythmic delta activity, suggestive of autoimmune encephalitis (Fig. 1) [35]. This aspect should be known and should not be mistaken for SE. Similarly, oro-lingual dyskinesias, frequently observed in NMDAr encephalitis, are not accompanied by ictal discharges on EEG and should not be considered as seizures.

The background slowing may be predominant in the frontotemporal regions.

Periodic or quasi-periodic epileptiform discharges are common on EEG in such conditions. All types of periodic discharges have been described: focal, multi-focal, bilateral, generalised. There is often an alternation between periods with periodic discharges and seizures.

Other specific aspects have been described, especially in autoimmune encephalitis: *i*) excess beta activity (range 14-20 Hertz) (EBA), which does not appear to be solely related to anticonvulsant treatments [35]; *ii*) extreme delta brush (EDB) (Fig. 2). EDB patterns consist in

a paroxysmal beta-delta complex consisting of 15-18 Hz beta activity superimposed over 1-3 Hz delta waves. EBA and EDB are diffuse or predominate in frontocentral areas. EDB pattern has been suggested to be a specific EEG sign of NMDAR encephalitis, and is found in around half of patients. But it has been also described in other causes of FIRES [36].

Neuroimaging

Brain magnetic resonance imaging (MRI) may be normal in the initial phase (around 50% of cases) [11], but imaging abnormalities appear in 70-80% of cases during the acute phase [33,37,38].

In the acute phase, abnormalities are most often visible in FLAIR and T2 sequences. A diffusion restriction is observed in 5-14% of cases [11,37]. A diffuse leptomeningeal enhancement is shown in 25-40% of cases [37,38] and could be associated with poorer outcome and pharmaco-resistant epilepsy [37].

T2/FLAIR changes predominantly involve the mesial temporal lobe (50-60%) unilaterally or bilaterally. They may also involve the neocortex and particularly the perisylvian region. Abnormalities can also be seen in subcortical regions: thalamus, basal ganglia, claustrum (Fig. 3). Signal abnormality in the brainstem, multifocal subcortical infarcts, cerebellar oedema, haemorrhage are other possible findings [39].

It is unclear whether MRI changes represent a specific pathogenic mechanism or are only the consequence of prolonged ictal activity.

Cerebrospinal fluid (CSF) analysis

In two thirds of cases, pleocytosis (<10 cells/l) and slightly increased protein level is observed [32,40]. Pleocytosis can suggest an infectious, autoimmune or paraneoplastic cause since non-infectious SE itself does not commonly cause CSF pleocytosis (6% of cases) [41]. In contrast, elevation of CSF protein content is found frequently in non-infectious SE.

Aetiological assessment

Proposed aetiological assessment is developed in Table 1.

Treatment approaches

The management of NORSE remains challenging due to a lack of randomised or controlled studies and management protocols. Aetiological diagnosis must be a very early priority because, in some cases, the treatment of the cause will allow the treatment of seizures. There is no

specific treatment for NORSE and FIRES. The therapeutic management of NORSE includes two main axes: antiseizure management and immunotherapy [14,15,19, 43-45].

Antiseizure management

Antiseizure medications are often disappointing [46] especially for cryptogenic NORSE [13,47]. The first stage of management, however, remains the conventional active management of SE according to expert recommendations in order to control seizures [48–51]. There is in this context no antiepileptic drug to favour, the approach with this class of drugs is the same as for conventional treatment of SE.

By definition, NORSE is refractory to the first and second lines of treatment [52]. This is why the use of intravenous anaesthetics is predominant (75%) and obtaining a burst-suppression trace is often necessary to resolve the SE [14,53]. The anaesthetics classically used are midazolam, propofol (in adults) and thiopental. In adults the most commonly used anaesthetic is midazolam while in children it is barbiturates [14,15,45]. Ketamine can also be used especially in case of failure of the anaesthetics initially attempted. Cessation of seizures on ketamine was observed in 57% to 63% of cases of refractory SE or super-refractory SE in two retrospective cohort studies [54,55]. However, available data have issued from retrospective single- or multi-centre cohort studies or even from single case reports. We must be mindful of the risks associated with using prolonged, high-dose barbiturates. These factors prolong the stay in the intensive care unit and increase related complications and the duration of mechanical ventilation. In addition, longer duration of the suppression-burst trace is associated with poorer cognitive outcome [49]. Continuous EEG is recommended to monitor treatment effectiveness, to detect the persistence of non-convulsive seizures, and to adapt anaesthetic treatment [56].

Two studies have evaluated the beneficence of the ketogenic diet. The first one conducted in a population of nine children with FIRES, reported cessation of seizures obtained in seven of nine children. A second study in nine children with having a super refractory SE allowed a weaning of the anaesthetics during the start of the ketogenic diet. In addition the ketogenic diet would have a double anti-inflammatory and antiseizure effect [57,58]. A case series of 10 adults with a super refractory SE also showed efficacy [59].

An open label case series found an effectiveness of cannabidiol in six out of seven children with FIRES with a decrease in the frequency and duration of seizures and a decrease in the number of concomitant antiepileptic treatments [60].

These data suggest the effectiveness of the ketogenic diet and cannabidiol in this entity. However, there is no randomised controlled trial available for confirmation.

Hypothermia and vagus nerve stimulation have also been attempted in this indication, but again without a controlled trial. Further studies are needed.

Immunotherapies

There are no guidelines available regarding the use of immunotherapies in NORSE. The effectiveness of these treatments is based largely on single case reports, retrospective cohort studies, and expert opinion [12,15,16,46,61,62]. There is no prospective controlled study available. Experts agree, however, on early and systematic immunomodulatory treatment, even when a definite immune aetiology has not yet been identified. The precocity of treatment would be a prognostic factor of favourable evolution [12,46]. Thirty-seven percent of NORSE cases have an autoimmune cause and most cases of cryptogenic NORSE would have an unidentified autoimmune cause [12]. Therefore, it has been suggested that early immunotherapy should be given in cases of cryptogenic super-refractory SE [49].

Appropriate immunotherapy is similar to that used in autoimmune encephalitis with first and second lines [19,23,63]. The first line classically includes high-dose corticosteroids, intravenous immunoglobulins, and plasma exchange [64]. The need for very early immunomodulatory treatment, once the infectious causes have been eliminated, is emphasised [12,46]. Precocity of immunomodulatory treatment would guarantee better prognosis. However, it may be difficult at the early stage to eliminate viral encephalitis. This is the reason why some authors recommend the use of first-line immunoglobulins since they will not aggravate management of viral encephalitis and may even be beneficial [19,65]. The co-administration of an antiviral treatment should be maintained the time necessary to rule out the infectious origin or confirm the autoimmune origin.

If there is no response to first-line immunomodulatory therapy, a second line may be proposed. Some authors have also pointed to the lack of efficacy of this first line of treatment, especially in the case of cryptogenic NORSE and FIRES [47,66,67].

Twenty to 50% of autoimmune encephalitis cases require a second line of treatment. The compounds conventionally proposed are rituximab and cyclophosphamide [15,19,63,68,69]. There are very few data on tacrolimus: to our knowledge a single case report of acute encephalitis with refractory, repetitive partial seizures [70].

In recent years, anticytokines have also been considered as a potentially effective second- or third-line treatment. Anakinra is a recombinant version of the human interleukin-1 receptor antagonist. The literature on anakinra mainly concerns children with FIRES [71]. The first published case was a 32-month-old child with FIRES without a determined aetiology. Anakinra was started on day 6 after failure of antiepileptic drugs and corticosteroid therapy. It was accompanied by the cessation of seizures, and the recurrence of seizures at the end of the treatment was stopped when it was reintroduced. The main side effect reported was a drug reaction with eosinophilia and systemic symptoms (DRESS). At 12 months of evolution the child had exceeded his previous cognitive abilities [72]. Finally, an international retrospective study of 25 children with FIRES has been published. Anakinra started early significantly reduced the duration of mechanical ventilation and the length of hospitalisation. It reduced seizures by more than 50% in 11 of 15 children for whom these data were available [73]. However, there is no prospective controlled study to evaluate the efficacy and safety of anakinra in this indication and to establish its administration modalities.

Tocilizumab is a humanised antiinterleukin (IL)-6 receptor monoclonal antibody, which blocks IL-6-mediated signal transduction [74]. Its place in the therapeutic strategy of NORSE would be in the third line after failure of rituximab. One prospective cohort study of seven NORSE patients resistant to rituximab found a cessation of seizures for six of them after one or two doses (4–8 mg/kg) of tocilizumab [75]. A few case reports have since been published illustrating the potential efficacy of tocilizumab on NORSE refractory to antiseizure treatments and first- and second-line immunotherapy [76,77]. Its interest in the treatment of rituximab-refractory autoimmune encephalitis had previously been reported in a retrospective study of 185 patients [78]. Potential serious adverse reactions such as cytopenia and infections have been reported although some authors consider this treatment to be better tolerated overall than cyclophosphamide [75]. The use of tocilizumab was in some cases supported by the increase in interleukins and in particular IL6 in the CSF of patients. However it is not recommended given the urgency of the situation to wait for their dosage before treating them [71,76].

Although the level of evidence is still insufficient to establish guidelines, these results are encouraging.

Outcomes

The prognosis for NORSE remains severe. Most cases of NORSE evolve to super-refractory SE, leading to a prolonged stay in the intensive care unit (a median stay of 15 to 40 days [14]).

The mortality rate is around 12% in children [40] and 11-22% in adults [12,79]. In survivors, the majority of patients present with long-term neurological sequelae, cognitive impairment, epilepsy and functional disability.

Predictors of poor outcome include NORSE aetiology, duration of SE and medical complications. Cryptogenic NORSE has a poorer outcome than NORSE of determined cause. Autoimmune aetiologies have lower mortality rates compared to others [80]. Use of barbiturates and a high number of anaesthetics have also been associated with a poorer prognosis. Some even proposed to avoid intravenous anaesthetics unless there were generalised seizures [81]. However, it is unclear whether this is due to an independent effect of prolonged anaesthesia or to the relationship between anaesthetic use and severity of SE. Further studies about this question are needed.

Functional disability is related to neuroimaging findings. Hippocampal atrophy is found in more than 50% of cases [37] (Fig. 4). It is more frequently observed in case of hypersignal at the acute phase, but can also be found without an initially visible hypersignal. This atrophy appears a few weeks after the acute phase [37]. Cortical atrophy is also common, reported in almost 50% of patients. Less commonly, abnormal white matter signal and basal ganglia or thalamus changes are described [39]. Hippocampal atrophy and diffuse cortical atrophy have been significantly associated with reduced cognitive level, poor functional outcome and subsequent epilepsy [37].

Persistence of epilepsy in the chronic phase is frequent, affecting more than 80% of patients [12,38]. This epilepsy is often described as drug-resistant [38]. This contrasts with the fact that unprovoked seizures are relatively rare in patients with anti-NMDAr, anti-LGI1 or anti-GABA(B) encephalitis in remission [27]. This discordance may be explained by the association between duration of SE in NORSE and drug-resistant epilepsy [79].

In the various published cohorts, it is usually said that return to a normal life is rare. However, in a cohort of 31 patients, the authors report that 32% of the 31 patients returned to their clinical baseline condition [79]. In another cohort of NORSE patients, Gaspard et al. report that among the survivors (n=63), 41% had a good outcome (mRS:0-1) and a fair outcome (mRS:2-3; mild or moderate disability) in 38% of patients [12]. The follow-up of the reported cohorts is often relatively short (usually less than 18 months). However, improvements, especially in NMDAr encephalitis, can be long, requiring several years. A longer follow-up of cohorts will be interesting to appreciate the real long-term evolution of these patients.

Conclusion

NORSE and FIRES are uncommon but very serious situations, with high mortality and morbidity. Management of NORSE patients is challenging for healthcare teams. These conditions are also difficult for families, especially since they frequently affect children and young adults, and the length of hospital stay, especially in intensive care, is often long, sometimes several months. Communication between the families and the care teams is essential, especially since many specialties are involved in care (resuscitators, neurologists, neurophysiologists, etc.). It is essential to properly identify a most responsible physician to integrate information from subspecialties [82].

But a better identification of NORSE thanks to a consensual definition, the constitution of cohorts in progress facilitating research, the early use of immunotherapies, the appearance of new molecules targeting interleukin pathways are sources of hope for the management of these patients.

Disclosure of interest

The authors declare that they have no link of interest.

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Legends:

Figure 1 : EEG of a 18-year-old woman with anti-NMDAr encephalitis. Longitudinal montage. See the generalized rhythmic delta activity.

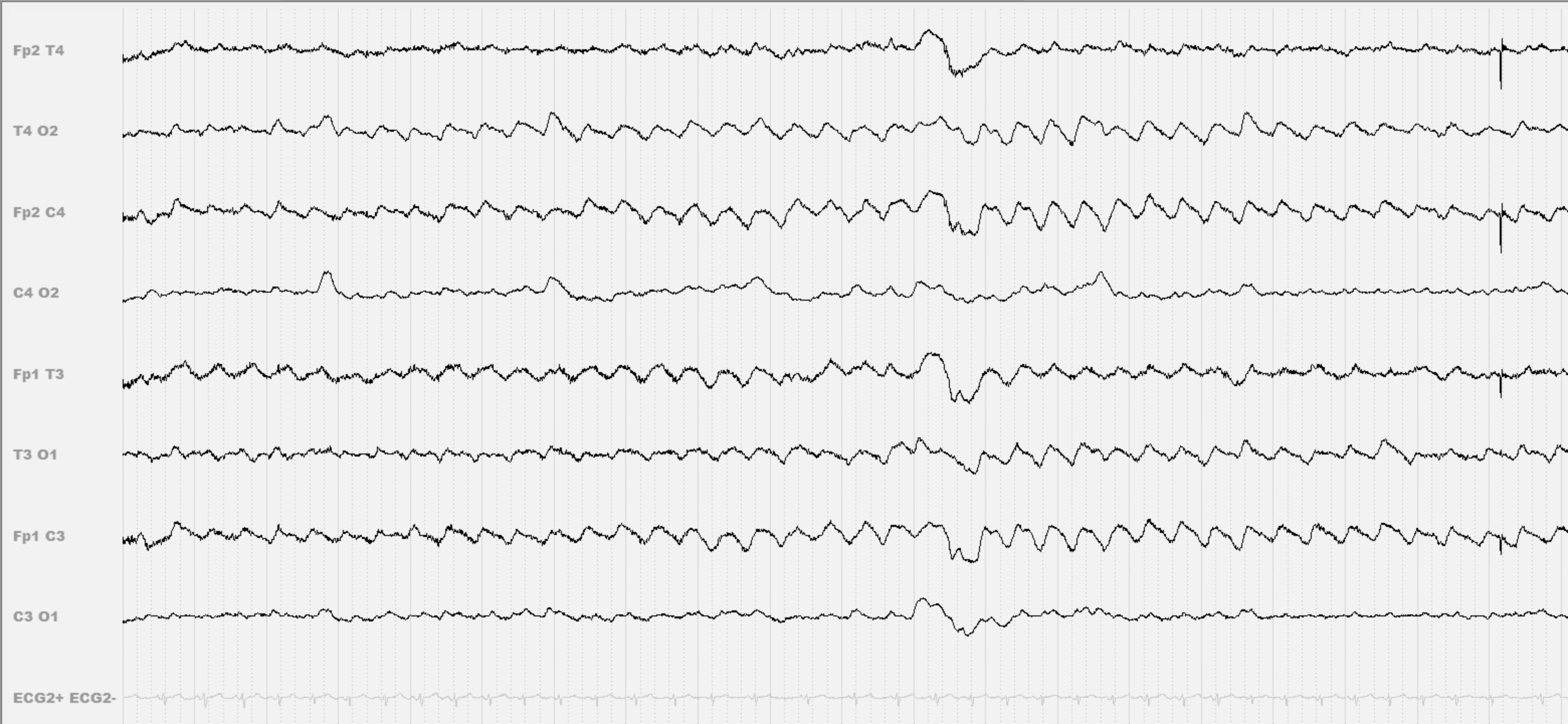
Figure 2 : EEG of a 22-year-old woman with anti-NMDAr encephalitis. Longitudinal montage. See the extreme Delta brush over the fronto-central regions.

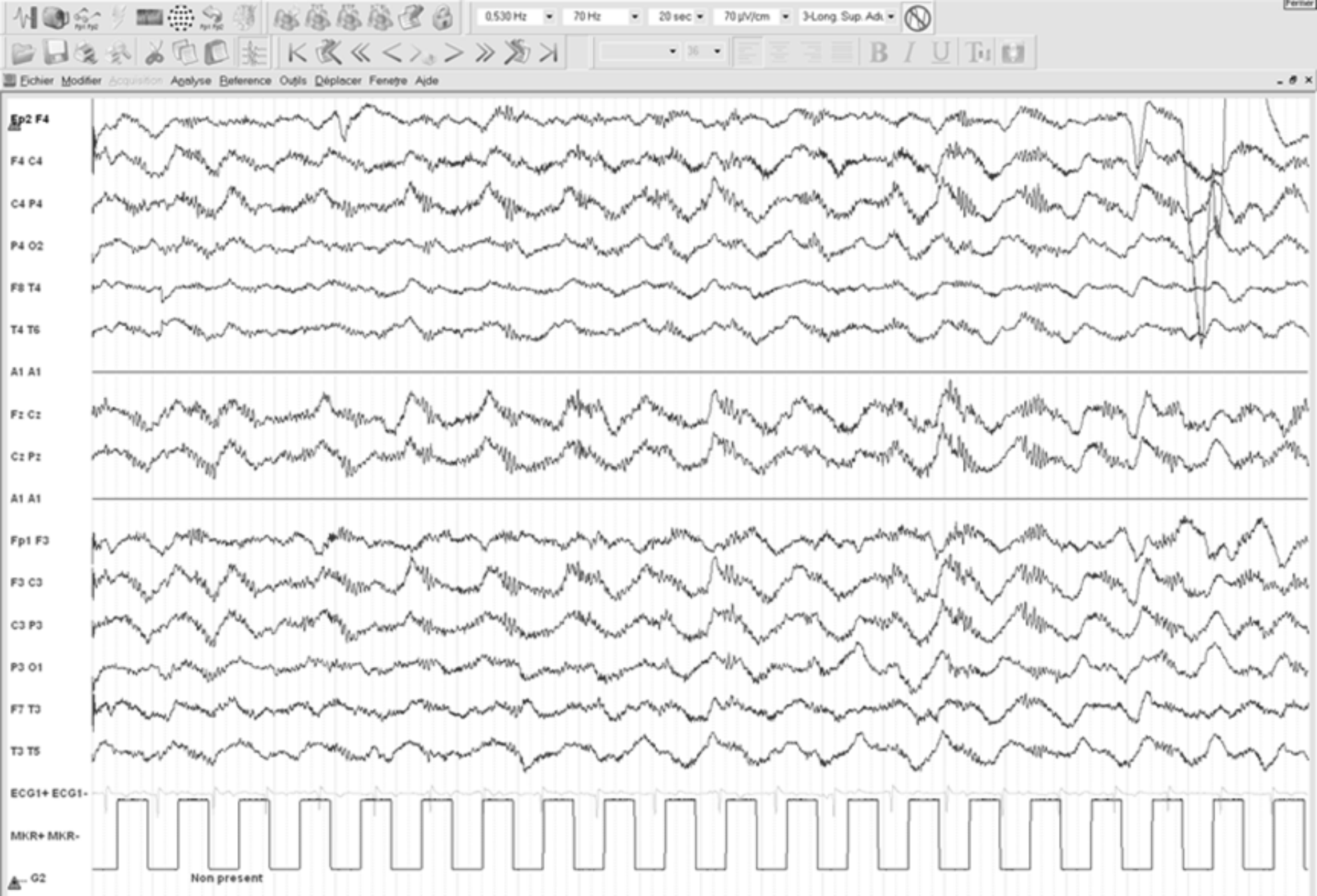
Figure 3 : MRI of a 63-year-old man with anti-LGi1 encephalitis. Axial T2 FLAIR sequence. See the FLAIR hyperintense signal of the left hippocampus, of the anterior part of the right insula, and of the right basal ganglia.

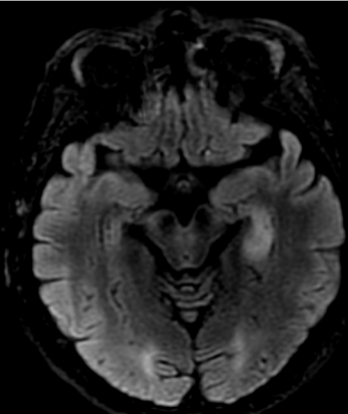
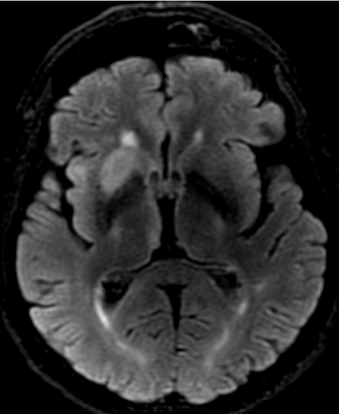
Figure 4 : MRI of a 36-year-old man with anti-Ma2 encephalitis. Coronal T2 sequences. Left: at the acute phase of NORSE: see the hyperintense signal of the bilateral medial temporal regions. Right 1 year after NORSE. See the bilateral hippocampal atrophy.

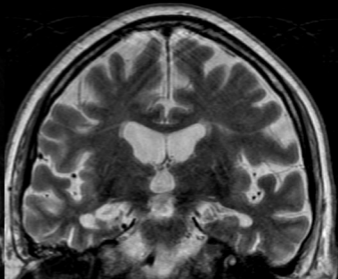
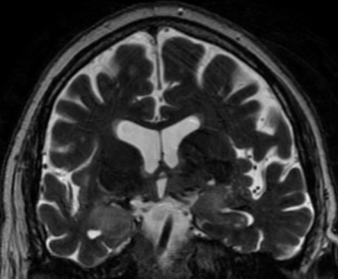
Fichier Modifier Acquisition Analyse Reference Outils Deplacer Fenetre Aide
 0,530 Hz 60 Hz 25 sec 150 μ V/cm 7-LONG9

[Icons: Play, Stop, Sum, Brain, Left Arrow, Clock, Recorder, Fp1 Fp2, Lightning, Grid, Fp1 Fp2, Select, MMN, RR, R/F, Sum, Waveforms, Print]









Recommended in all patients	
MRI brain with contrast angiography and venography	
Blood and serum analysis	Standard biological assessment
	Autoimmune antibody panel: ANA, ANCA, anti-thyroid, anti-neuronal surface antigens, onconeural antibody panel
	VDRL, HIV 1-2, bacterial and fungal cultures, Bacterial serologies: <i>Chlamydia pneumoniae</i> , <i>Bartonella henselae</i> , <i>Mycoplasma pneumonia</i> , <i>Coxiella burnetii</i> , <i>Shigella</i> sp. and <i>Chlamydia psittaci</i> .
Nasopharyngeal swab	Respiratory viral DFA panel; SARS-CoV2 PCR
Gastrointestinal pathogens	multiplex PCR
CSF	Cell counts, protein, and glucose, immunoelectrophoresis
	Bacterial and fungal stains and cultures including <i>Mycobacterium tuberculosis</i>
	RT-PCR for HIV, PCR for HSV1-2, VZV, EBV
	PCR for <i>Chlamydia pneumoniae</i> , <i>Bartonella henselae</i> , <i>Mycoplasma pneumonia</i> , <i>Coxiella burnetii</i> , <i>Shigella</i> sp.
	VDRL, Lyme
	Paraneoplastic and autoimmune epilepsy antibody panel
EEG	
Immunocompromised patients	
Serum analysis	Serology for cryptococcus species, <i>Histoplasma capsulatum</i> , <i>Toxoplasma gondii</i>
CSF	Stain for fungi, PCR for <i>Toxoplasma gondii</i> , JC Virus, CMV, HHV6, parvovirus +/- West Nile Virus
Risk of exposure to specific pathogens	
according to geographical factors	
Oncological screening	
Serum analysis	Cancer serum markers
CSF	CSF cytology and flow cytometry
CT chest-abdomen-pelvis, pelvic or scrotal ultrasound, pelvic MRI, mammogram	
whole body PET CT	

Screening for inborn error of metabolism and mitochondrial disorders
Ammonia, acute porphyria screen, LDH, urine analysis Plasma and CSF lactate, pyruvate, muscle biopsy
Genetic screening
Panel, whole exome, CGH array, mitochondrial genome sequencing
Brain biopsy

Table 1: Aetiological assessment. Adapted from [14,42].

ANA: antinuclear antibodies, ANCA : antineutrophil cytoplasmic antibodies ; CSF : cerebrospinal fluid ; EBV : Epstein- Barr Virus; EEG : electroencephalogram ; HHV6 : human herpesvirus 6, HIV 1-2 : human immunodeficiency virus; LDH : lactate dehydrogenase ; HSV1-2 : Herpes simplex virus 1-2, MRI : magnetic resonance imaging ; PCR : polymerase chain reaction ; SARS-CoV-2 : severe acute respiratory syndrome coronavirus 2; VDRL : venereal disease research laboratory, VZV : varicella-zoster virus.