Universitat de Girona

NONCONVULSIVE STATUS EPILEPTICUS: ASSOCIATION BETWEEN EEG PATTERNS AND ALTERATIONS AND OUTCOME

FINAL DEGREE PROJECT

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ABSTRACT

TITLE

Non-convulsive status epilepticus: association between EEG alterations and patterns and outcome.

BACKGROUND

Status epilepticus (SE) is a common neurological emergence with a high mortality and high range of sequelae in survivor patients. It is classified as convulsive (CSE) and non-convulsive (NCSE) status epilepticus. Both require prompt diagnosis and management, nevertheless there is a lack of information regarding NCSE prognosis and therapeutic decisions. For that reason, nowadays, the main investigations in this field are related to outcome and management of NCSE, mainly with the first one as to know the possible good or bad outcome of the patient, the management and related decisions would be easier.

As the electroencephalogram (EEG) is the main tool in NCSE diagnosis and is a mandatory test in these patients, a growing body of the literature suggests that there is a relationship between EEG alterations or patterns and the NCSE outcome although this association has not been clarified yet.

AIMS

Our main aim is to identify the relationship between the EEG patterns and alterations and the prognosis in NCSE.

Our secondary aims are to determine if the EEG patterns or alterations give information for refractory status epilepticus (RSE) prediction in NCSE and to determinate if the association between EEG patterns and prognosis or evolution in NCSE is the same in paediatric, adult and elderly population.

METHODS

We suggest a retrospective multicentre cohort using a sample of approximately 1492 patients with clinical and electroencephalographic NCSE diagnosis.

KEYWORDS

Status epilepticus, non-convulsive status epilepticus, electroencephalography, EEG pattern, prognosis.

ABBREVIATIONS

ADL	Activities of daily living
AED	Antiepileptic drugs
ASE	Absence status epilepticus
BIPLEDs	Bilateral independent synchronous PLEDs
BM	Blood glucose measurement
BNZ	Benzodiazepines
CBC	Complete blood count
CNS	Central nervous system
Coma-GED	Coma with generalized epileptiform discharges
Coma-LED	Coma with lateralized epileptiform discharges
CPC	Cerebral performance category
CPSE	Complex partial status epilepticus
CSE	Convulsive status epilepticus
EDs	Epileptiform discharges
EEG	Electroencephalogram
EMSE	Epidemiology based mortality score in SE
ESES	Electrical status epilepticus during sleep
GABA	Gamma-aminobutyric acid
GCSE	Generalized convulsive status epilepticus
ICU	Intensive care unit

IEDs	Interictal epileptiform discharges
mRS	Modified Rankin Score
MSW	Multiple spike-and-waves
NMDA	N-methil-D-aspartate
NCSE	Non convulsive status epilepticus
SE	Status epilepticus
SPSE	Simple partial status epilepticus
STESS	Status Epilepticus Severity Scale
SW	Spikes-and-waves
PEDs	Periodic epileptic discharge
PGDs/GPDs	Generalized periodic discharges
PLDs/LPDs	Lateralized periodic discharges
RDA	Rhythmic delta activity

INTRODUCTION

GENERALITIES

Status epilepticus (SE) comprise a range of disparate conditions, often categorised into convulsive and non-convulsive. Despite the fact that every article, book, or source in which is possible to look up information about SE gives you different definitions of the term, all of them agree in two important points. On the one hand SE is a neurological emergency with a high rate of morbidity and mortality. On the other hand, it is said that it is a situation where there are continuous epileptic seizure discharges, with or without motor or convulsive signs that are so prolonged and/or repetitive that they cause neurological dysfunction and alterations in neurochemical and physiological activities of the brain[1] and associated with continuous epileptiform discharges in the electroencephalogram (1,2).

The major discussion lies in determining of how long the seizures can be, some authors say that at least 30 minutes of clinical or electrographic manifestations are needed to diagnose the status (3–7), others say that with even less time we can already consider the disorder as the physiological changes have started (2,4,8–10); but again, all of them agree in one thing, that SE needs to be treated as soon as possible to prevent as much as we can the bad outcomes. We have taken into account the time definition of the last report of the ILAE considering at least 5 minutes of clinical or electroencephalogram (EEG) manifestations to diagnose the status, and 30 minutes as the time of ongoing seizures activity after which there is a risk of long-term consequences (2,11).

Before starting with the SE theoretical framework it is important to know that although some information about convulsive status epilepticus will appear in the text, most of the explanation will be about non-convulsive status epilepticus (NCSE), due to some characteristics are the same in both disorders and it is the main protagonist of this project.

Epidemiology

SE has been demonstrated to have an age-dependence, presenting a bimodal age distribution with a first incidence in young children and another among elderly patients (11,12).

[1] Including the failure of mechanisms responsible for seizure termination leading to prolonged seizures and neuronal death, neuronal injury, and alterations of neuronal networks.

The incidence of all types of SE in Europe is from 17 to 41 per 100.000 per year (8,10,13,14). NCSE incidence is about 2'6 to 7'8 per 100.000 per year but it depends on the definition of "convulsive" and the presence of different age groups in the population, but it is hard to recognise so it could be more frequent (10,13,14). The fraction of NCSE is from 5% to 49%, and complex partial status epilepticus (CPSE) is the most frequent subtype with a 16 to 43% of all cases. Moreover, in patients with controlled generalized convulsive status epilepticus (GCSE) there are persisting NCSE in approximately 14% of them (subtle NCSE) and in comatose patients with no clinical signs of seizure activity the prevalence of NCSE is about 8% (12,15).

Finally, to mention the economic burden of the SE, we have only found one study that talks about it. There are not enough studies to know the direct and indirect costs of status, but a study in USA says that compared with other well-known emergency pathologies (acute myocardial infarction, congestive heart failure, intracranial haemorrhage) SE results in the highest direct inpatient cost (about 4 billion US dollars per year)(16).

Pathophysiology

Seizures are most frequent in the immature brain, yet the structural, functional, behavioural and cognitive sequelae of brief and prolonged seizures are less profound and more subtle at young ages than in mature brains (17).

After a few seconds or minutes, most seizures stop by themselves because the brain has mechanisms to stop neuronal hyperxcitability and synchronous shots. In SE, there is a failure of these mechanisms because of an imbalance between excitatory and inhibitory neuronal networks, and seizures become self-sustaining, longer after the precipitating convulsive stimulus and with a neuronal hypersynchrony as a result (17).

GABA, that is the inhibitory neurotransmitter system of the brain, is one of the main neurotransmitters affected in SE, both before this onset, and during the status. This dysfunction causes a change to the brain's balance towards excessive excitation (11).

At the beginning of SE, GABA receptors are internalized from the neuronal membrane, making them unavailable to mediate synaptic inhibition and antiepileptic drugs (AED) responsiveness (increasing resistance to GABAergic agents) and participating in sustain ongoing seizure activity. Furthermore, during SE, in parallel to other changes, excitatory NMDA receptors are recruited and inserted into the

plasma membrane, which contributes to the persistence of cellular hyperexcitability. Another mechanisms of pharmacoresistence is the upregulation of Mpr2 (multidrug resistance protein 2) (7,8,11,17).

But usually seizures does not happen only in one area of the brain, they may spread to other regions and be generalized. The control over this seizure propagation is due to some subcortical regions like the substantia nigra parts reticulata (SNR) (17).

SE also alters the expression of numerous genes that can predispose the brain to persistent susceptibility to episodes of SE or to compensatory reduction of excitability. These changes may occur within hours or weeks after SE and they involve in part proconvulsant structural changes, like neurogenesis (17).

After prolonged SE, neuronal injury and death may be provoked by the mechanisms explained before and by excessive glutamate release, alterations in calcium influx and excitotoxicity. Neuronal death begins to appear in the hippocampus after 20 minutes of continuous seizure activity and in other brain regions, mild damage is presented after 40 minute (8).

Finally, although basic mechanisms are always very similar, in all types of SE there are not the same processes involved. In absence SE the neuronal population involved is the thalamocortical and its synchronisation depends on GABAergic processes. Furthermore, in simple and CPSE, the hippocampal formation, adjacent limbic and neocortical structures are relevant, and their generation and maintenance involve activation of NMDA and other glutamate receptors (6).

Apart of the neurological disorders, seizures affect other organs and mechanisms, producing an increase in body temperature and in serum glucose, and lactic acidosis for example (11).

To sum up, all these changes support aggressive treatment of seizures at earlier time points, before developing self-sustaining seizures and pharmacoresistance, but the aggressiveness of this treatments may be different depending on the patients and the neurochemical processes involved, and maybe the best tool that we have nowadays to study the seizures mechanisms as close as possible to the origins is the EEG.

Aetiology

The underlying causes of SE are varied, they can differ according to the patient population being studied and are very similar in the different kind of status. It's important to take into account the comorbidities, especially in elderly patients as that may impair the identification of the aetiology of SE. There are so many ways to classify the aetiology and we have separated it in some groups that embrace all the possible causes (2,8,10,18):

1. Known or symptomatic (SE caused by a known disorder, which can be structural, metabolic, inflammatory, infectious, toxic or genetic):

    Acute (stroke, intoxication, encephalitis, metabolic disorders, drugs, head trauma…)

    Remote (posttraumatic, postencephalitis, poststroke…)

    Progressive (brain tumour, dementias, Lafora's disease…)

    Acute on remote

    SE in defined electro clinical syndromes or previous epilepsy with an acute trigger

2. Unknown/ Cryptogenic/idiopathic

*See the criteria used in every subtype in covariables section: aetiologies.

Stroke seems to be the most prevalent cause of status, while infection is the most common triggering factor in adults, and in children approximately half of SE, approximately, are secondary to infections with fever (14,19). Moreover in children the presence of febrile SE should rule out infectious cause (8). In patients with pre-existing epilepsy the main triggers are medication withdrawal or noncompliance, a concurrent infection, alcohol abuse or withdrawal, sleep deprivation, pregnancy and delivery and the own acute processes (8,15,16).

More or less the 10% of SE are cryptogenic or idiopathic without a known diagnosis. And some of them may be the first manifestation of epilepsy (3).

A part of the main cause of the status, there are some risk factors to develop it, like younger age, prior convulsive seizures, structural brain abnormalities, and acute cortical neuroimaging abnormalities (12).

We have attached the ILAE list of the causes of SE. It is from September 2015, and it is supposed to be updated periodically. See it in Annexe 2.

Classification and clinical manifestations

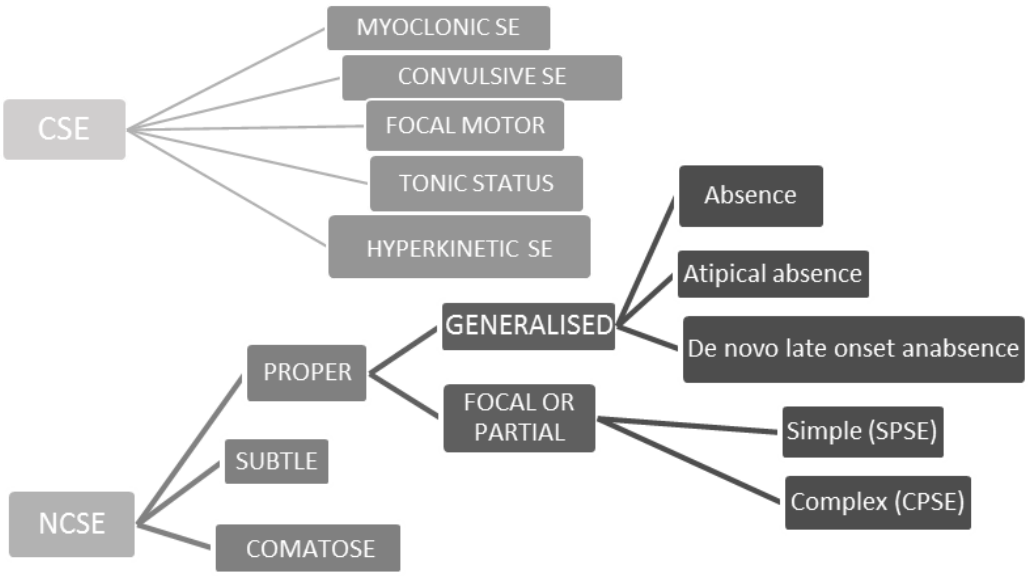

Figure 1. SE classification. Adapted from : (2,13,14,20,21)[2]

Convulsive status epilepticus: subtype of status with excessive and motor convulsive activity. It has different subtypes, and it may be generalised or partial depending on the onset area, and the partial ones can be secondarily generalised (5,10).

Non-convulsive status epilepticus: The clinical aspects in NCSE are so varied, the main one is cognitive impairment or consciousness disorder[3] but we can find others classified in negative symptoms or impairments and positive phenomenology (subtle and often overlooked), autonomic signs, automatisms, and bizarre behaviours including wandering, hallucinations, fear… (22) Every subtype of NCSE has different clinical and EEG characteristics and some particular triggers and aetiologies (ANNEXE 1).

[2] We have made this classification after a deep, systematic review of the actual information about NCSE. Recently we have get access to the last ILAE report about the NCSE classification. There are some difference between our classification and the ILAE's one: they include subtle status epilepticus on the NCSE with coma; in the generalized subgroup they add the myoclonic absence status (we have explained it on the absence status) and they add the aphasic status on the subgroup of focal NCSE. Despite of those little differences, our classification is so similar to the last ILAE report. That demonstrate that out review was extents enough to arrive to the same conclusions.

[3] The loss of consciousness is defined when no or inadequate reaction to external stimuli can be obtained and the patient is amnestic during this episode (21)

Diagnosis

In general terms, only the examination of the patient should allow the subdivision between non-convulsive and convulsive forms, and then with clinical and/or electrophysiological information may allow to make the diagnosis of focal or generalised status, having in mind that status with a focal beginning tends to generalise electrophysiologically and clinically within a short period after onset (20).

Even though it is essential to act quickly, is important to have information about the possible cause and severity of the situation. Some of the diagnosis techniques in the NCSE are done at the same time that the treatment, but we have explained in different points to make it clearer. The diagnosis approach should include:

- Detailed clinical history[4]
- Physical examination including a complete neurological examination (11).
- Laboratory studies[5]
- Electrocardiogram
- Neuroimaging: after patient's stabilization, but not in all patients, only in focal abnormality on neurological examination or focal onset of seizures, malignancy, closed head injury, neurocutaneuos disorder, absence of a history of alcohol abuse, patient aged >65 and seizure duration >15 min (11).
- Lumbar puncture: when there is fever, severe headache, or persistent altered mental status and asymptomatic patients immunocompromised (11).
- EEG: is the definitive test for diagnosing a seizure disorder.

[4] It include: time since the start of the status, personal, medical and familiar antecedents, toxics consumption, sleep alterations, AED, comorbities, history of neurosurgery, history of renal failure, immunosuppression, recent electrolyte abnormality, psychiatric history…(11)

[5] It include: serum glucose, electrolytes, urea nitrogen, creatinine, magnesium, calcium, complete blood count, pregnancy test in women of childbearing age, AED levels, liver functions tests, and drugs-of-abuse screening and alcohol level (11).

Both GCSE and NCSE require prompt diagnosis and intervention but as we know, the clinical features of NCSE are subtle and not specific, so the diagnosis is no way straightforward, usually underdiagnosed and mistaken by other pathologies (11,15,20). So, it is important to do a differential diagnosis to differentiate between normal behaviour or non-epileptic medical disorders and the real NCSE (16,21,22) (Figure 2). Generally, any fluctuation or unexplained alteration in behaviour or mental status warrants an EEG and considerate NCSE diagnosis. The same in patients with convulsive status epilepticus who are expected to be awake gradually after the motor features of seizures disappear (subtle NCSE) and in patients without any other visible signs than coma (13,20,21).

Figure 2. Medical disorders mimicking NCSE (16,21,22)
Cardiac Dysrhythmias
Metabolic encephalopathy
Migraine aura
Posttraumatic amnesia
Prolonged postictal confusion
Psychiatric disorders
Substance de- or intoxication
Transient global amnesia
Transient ischaemic attack

Another important thing to take into account is that although a detailed diagnosis of the underlying cause seems to be one of the best known predictors for prognosis, finding seizure subtypes and epilepsy syndrome or the aetiology or neurologic disease of NCSE is frequently not possible at the time of admission, being the EEG the main tool to make the correct diagnosis and probably to get the first outcome information.

In the annexe 5, there are the EEG criteria for NCSE diagnosis, and a diagnostic algorithm.

Prognostic

Although SE represents only a low percentage of all neurological emergencies, it is one of the major causes of morbidity and mortality in epilepsies. The morbidity-mortality rates varies considerably in different studies depending on different factors, like patients age, presence of base diseases and clinical complications, classification of SE, and the therapeutic conduct adopted.

In general the status epilepticus mortality rate varies from 7’6% to 39% being GCSE associated with a mortality rate as high as 22% and in NCSE it can vary from 7’7% to 52% in different population based studies including all subtypes of NCSE and all ages groups (12,15,17,19,22–24). Elderly population has a higher risk for mortality and morbidity than any other age group, but this could be due to the number and severity of the underlying diseases or aetiologies in that ages (19,25).

Several prognostic factors seems to be important to predict the outcome of status epilepticus, and are very similar as in other pathologies: age, cause, seizure duration, and response to treatment. It is

important to note that the major determinant of outcome or the most important confounding factor seems to be the underlying cause (4,12,14,17,25):

- High mortality: patients with cerebral anoxia, acute symptomatic ethology or multiple medical problems or complications and de novo SE and prolonged SE or refractoriness to treatment.
- Low mortality: patients with known epilepsy and precipitating factors, as low serum concentrations of antiepileptic drugs.

Nowadays there are emerging methods to measure the outcome in SE. Rossetti (26) proposed a prognostic score called Status Epilepticus Severity Score (STESS) based on four outcomes predictors determined before treatment administration: age (65-year cut-off), previous history of seizures, seizure type and extent of consciousness impairment. Although this score has been validated in a cohort study (27) and it is easy to apply and predict bad outcome; it seems that it has a low predictive value for good outcomes (23). Another new score called Epidemiology based Mortality score in SE or EMSE (28) predicts better than STESS bad outcome, it can be adapted to different regions and to advances in medicine, but it is more difficult to perform and it needs validation in prospective cohorts (23).

Comatose NCSE has a poorer prognosis than proper NCSE. The causes of SE may be overlapped with the causes of coma, but the epileptic activity could lead to an additional disturbance of consciousness, a deeper stage of coma, and additional brain damage (20). The NCSE contributes to the burden of dysfunction in addition to the cause of coma, which can be structural, metabolic, toxic or a combination of all of them. Retrospective studies have recognised NCSE as a robust predictor of a poorer outcome in patients with critical illness, irrespective of the cause (20).

The most common complications in SE are respiratory fail, fever, hypotension, infections, hyperthermia, tachycardia, systemic and pulmonary hypertension, pulmonary oedema, cardiac arrhythmias, metabolic acidosis, hypoxia, hyperkalaemia… (10). It is known that systemic complications are related with the seizures by themselves, with the treatment and with prolonged intensive care unit care or prolonged immobility (29). That makes us think that sometimes, the cure may be worse than the cause, and again shows us that we need some method to assess from the beginning which management or treatment is the most appropriate for each patient. See complications related with SE, treatment and ICU care in annexe 4.

There are some neurologic sequelae that may follow NCSE. In a retrospective study that evaluates the outcome in the NCSE they saw that 8'5%, 17% and 6% patients had severe, moderate and mild (transient neurological and/or cognitive sequelae lasting less than one month) sequelae respectively and 61% had no sequelae at all (14). In other study 14% of patients with NCSE had poor outcome (without including deaths)(19). These numbers are very similar to the ones reported in CSE, where poor outcome, excluding deaths, is reported from 15 to 20% in adults (5,19) and about 15% in children (5). Sequels can be: secondary epilepsy in patients without it, with the status as the first epileptic episode, cognitive deterioration, behavioural problems and focal neurologic deficits depending on the zone affected (diplegia, cerebellar syndromes, extrapyramidal syndromes, decorticate rigidity…), etc (5).

To conclude, outcome assessment after NCSE is hampered by the difficulty for separating the effects of continuous seizure activity from those of any underlying cause and from complications occurring in the clinical course, including effects of treatment. A better understanding of SE prognosis factors would assist in making treatment related-decisions (16,17). There is evidence that epileptiform activity in the EEG is associated with poor outcome and EEG may be regarded as the most important prognosis biomarker to evauate the prognosis of a patient with SE (30). So, a better understanding of SE prognostic factors, especially the alterations in EEG, would assist in making treatment related-decisions and to improve the NCSE patient's poor outcome.

Treatment: ***time is brain*** (10)

There is a lot of controversy about NCSE treatment. The main reason is that we don't know yet how aggressively NCSE has to be treated. Some authors consider that the damage caused by an aggressive treatment could be worse than the injuries of the seizures themselves (4,6,13). It is important to have in mind that NCSE is characterized by a significant short-term morbidity and mortality and it is a neurological emergency, so despite the different opinions about the aggressiveness of the treatment, we must be clear that NCSE should be finished quickly to prevent patients from serious injuries, particularly if consciousness is impaired. As in other types of status epilepticus, identify and treat the underlying cause, as long as we can find it, is a basic component for a successful management, but usually is not possible on the first moment.

So, it is reasonable to begin pharmacologic treatment after 5 minutes of continuous seizure, in an attempt to abort the seizure prior to the development of physiologic changes that limit response to treatment or promote neuronal injury (8). Moreover, after the first 15 minutes of status is very

complicated to control it. The main objectives in order to prioritize the management are: to stop the crisis, maintain homeostasis and treat complications(8–11,18).

General measures: they are as important as the pharmacologic treatment, essential for neuronal injury prevention, for maximising the supply of oxygen and glucose to the brain by maintaining cerebral blood flow and blood gases and reducing cerebral metabolic needs (9–11).

- Guedel airway
- O2 saturation control, secretions aspirations and 30% oxygen with ventimask
- Heart rate, blood pressure (above 120mmHg and should not be allowed to fall below 90 mmHg), temperature and ECG monitoring
- BM tests (discard hypoglycaemia) and administer 100mg intravenous thiamine to prevent Wernicke encephalopathy with glucose solution.
- Two venous accesses
- Blood tests (toxics, drugs levels, CBC, hepatic and renal function, "ionogram", calcium, phosphor, magnesium) and urine tests (toxics)
- Urine catheter and diuresis control
- Evaluate the indication of intubation.
- If an infection is suspected, consider early empiric antibiotics since head CT and lumbar puncture may be delayed until patient stabilization.

Pharmacologic treatment:

- Pre- hospital treatment. Only in patients that are not hospitalized in any service, and when it is possible because of most times the NCSE is not suspected at the pre-hospital phase: lorazepam 2mg IV or diazepam 5mg IV or midazolam 5-10MG IM or rectal diazepam (9,10)
- First line: intravenous benzodiazepine such as diazepam or lorazepam (10mg iv during 2-3 minutes) (9–11,18).
- Second line if there is not seizure control: add valproate (30mgkg bolus in 3-5min+ perfusion during 24 hours) or phenytoin 20mg/kg in 50mg/min bolus (9–11,18).
- Alternatives(9–11,18):
    - Phenytoin 20mg/kg in bolus+ valproate 30mg/kg in different venous accesses.
    - Levetiracetam 1500mg in slow bolus and repeat the dosis in 15 minutes.
    - Valproate 30mg/kg + keppra 1500mg in bolus.
    - Levetiracetam: 30 to 50mg/kg intravenous load at 100 mg/min.

- ICU admission when there is an awareness level decrease, systemic complications or structural lesion evidence (9–11,18).

Treatment in paediatric patients is very similar. See a treatment algorithm example for paediatric population and for adults in annexe 3.

REFRACTORI NONCONVULSIVE STATUS EPILEPTICUS

It is the most serious form of status epilepticus, which is understood as SE that cannot be clinically and/or electrographically controlled with first and second line of AEDs (7–9). About 30% of the patients with SE fall in the refractory form, and 15% still have seizure activity after 3 AED. NCSE and focal onset seizures are independent risk factors for RSE (7,8).

The main mechanisms for drug resistance in RSE is the internalization of GABAergic receptors that we have already explained in the pathophysiology point. Apart from that, it has peculiarities related to its duration and severity, like the hypoglycaemia secondary to hyperinsulinism, faulty self-regulation of cerebral flow, excitotoxicity, neuronal damage, brain oedema, body temperature increase related to muscle activity, and throughout a later phase multiple organ and system dysfunction followed by cardiovascular failure (4,7).

Treatment principles are the same as in SE. The first steps are the same, thus is the evolution of the same illness. After general considerations including intensive care unit admission, which is crucial in any emergency situations, and the firsts AED lines. Anaesthesia is recommended to achieve a burst suppression pattern (21). There are three main agents:

- Midazolam (GABA-A agonist agent): 0’2mg/kg IV followed by an IV infusion at 0’1 to 0’4 mg/kg/hr, and titrated until seizure suppression on EEG (7,11).

- Barbiturates like pentobarbital (NMDA antagonist): initial dose of 5mg/kg IV followed by an infusion of 0’5-9mg/kg/hour in that case until burst suppression pattern on EEG. It needs ECG monitoring due to can compromise cardiovascular status (7,11).

- Propofol (direct GABA agonist, NMDA antagonist and Ca+ channel modulation effects): 1-2 mg/kg dose and then infused at 2 to 5 mg/kg/min, until seizure suppression on EEG. In that case it is necessary to have into account the Propofol infusion syndrome (PIS) characterized by severe metabolic acidosis, rhabdomyolysis, and cardiovascular collapse which can be fatal (7,11).

Ketamine and lacosamide are useful in RSE when the other drugs do not work, or are insufficient (7,8). These drugs can induce iatrogenic coma, and respiratory suppression needing intubation and mechanical ventilation (7,11). Knowing that it is easy to understand that continuous monitoring or serial EEG are essential tools in RSE management.

RSE is associated with a poor outcome with a mortality rate from 16% to 50%, 26% of neurological deficits and only a minority of patients (about 35%) return to their premorbid functional baseline (7,8,22,24). So, maybe the best treatment should be the prevention or early prediction of RSE and used it as a tool for planning appropriate therapy instead of trying so many aggressive treatments that could be worse than the disease. Probably the best way to predict that, again, will be the EEG.

ELECTROENCEPHALOGRAM

The EEG is a relatively old technique, but it is still a great assistance's tool for the clinician to diagnose and treat certain neurological pathologies, like SE. Moreover, the EEG is a low cost, non-invasive and painless exploration (31).

It is the registration and evaluation of electrical potentials generated by the brain that explore the CNS function. The normal EEG activity depends on the integrity of cortical neurons, diencephalic structures, brainstem and the connections between the cerebral cortex and deeper structures. The brain electrical charge is originated in the pyramidal cells in the brain cortex. These cells are like little electrical dipoles with positive and negative polarity that create spontaneous inhibitory or excitatory impulses and have synchronous activity. The EEG activity reflects the summation of these synchronous activity of millions of neurons that have similar spatial orientation (31,32).

In clinical contexts, EEG refers to the recording of the brain spontaneous electrical activity, recorded from standard sites on the scalp following the international 10 to 20 system of electrode placement (annexe 6). It shows oscillations at a variety of frequencies, meaning different and characteristic spatial distributions, or different states of the brain function. The different pairs of electrodes are combined constituting the montage. The montages and other parameters can be adjusted digitally during or after recording, in order to obtain more information for the interpretation and analysis of EEG patterns because any montage is perfect to detect all types of abnormalities (31,32). The two main montages are:

- Monopolar or referential: it records the potential difference between an activity area electrode and a reference, placed in a neutral area (31,32).

- Bipolar montage: it register the voltage difference between two electrodes placed in cerebral activity areas (31,32).

It is an important diagnostic test to evaluate patients with SE especially for NCSE because it can provide support for the diagnosis and help to classify the underlying subtype. All authors agree that EEG is essential in NCSE diagnosis because only with clinical features diagnosis can not be done (5,6,8,12,13,16,21). But there are a lot of controversial information about which other roles EEG could have in NCSE. The main controversial point is about using the EEG as an outcome predictor tool (1,4,23,33).

JUSTIFICATION

I would like to start using the expression that Sutter uses in his article: "NCSE became a *Pandora's Box* of unusual clinical features, challenging EEG patterns, and disputed treatments and prognoses" (3). CSE is known to be associated with high mortality and neurologic sequels and there is a general agreement that needs urgent and aggressive management. However, some cases of NCSE require urgent attention as in CSE, but unfortunately it is usually overlooked and consequently not treated properly. Moreover there is a lack of studies or information concerning outcome, and prognosis is almost certainly underestimate.

As we have seen before, there is some controversy concerning predictive indicators of outcome in NCSE and we don't know which role seizures play in the prognosis by it selves. Although some authors agree that the underlying cause of NCSE is often one of the most important factors in determining outcomes, a growing body of literature suggests that electrical seizure in NCSE also contributes to predict outcome (12). And how can we study the seizure behaviour as close as possible to its origins? With the EEG.

Furthermore, the aetiology or other possible prognostic factors of NCSE are frequently not known at the time of admission, being the EEG the main and mandatory tool to approach a correct diagnosis. Probably we can use it to take full advantage and get all the possible information about the patient's state, including an earlier prognostic information. That means to have the diagnosis confirmation at the same time that the information about poor or good outcome of the patient and to have an idea about the aggressiveness needed in the management.

Some studies have tried to find out which role EEG patterns and alterations have in the NCSE, but the biggest part of these articles have so many limitations specially related to very small samples. Moreover, results are controversial in some of them. There is one study that found some EEG patterns (IEDs and PEDs/subtle SE) as an independent risk factor for RSE prediction (1), but they only included patients with GCSE, excluding paediatric patients (<15 years old) and the sample size was only 94 adult patients. Another one shows that the absence of a posterior dominant rhythm and changes in stage II sleep patterns give independent information for mortality and for complete recovery respectively in patients with SE after correction for some knowing predictor (33). This study, on the one hand, has some strengths because they had into account confusion variables and it is a prospective study. In the other hand, there are some limitations too, the sample size is too small,

with only 120 adult patients (excluding again another age population), they include all subtypes of SE (not only NCSE, where we know that EEG is indispensable for diagnosis) and it was made using continuous EEG which is not available in all hospitals.

In brief, our project will be the first study to determinate or analyse which EEG patterns and alterations can give us information about the outcome in NCSE with a sample large enough to find relevant clinical findings. Furthermore, it will be a multicentre study, having into account all the confusion variables and overcoming the limitations found in other similar studies. And maybe this information will open doors to new prospective studies to determine which treatment of NCSE can improve outcomes depending on the prognostic EEG information, how vigorously and aggressively should these treatments be, and also improve the NCSE knowledge and prognosis to leave the *Pandora's Box* tag to the next poorly known disease.

HYPOTESIS

EEG patterns or alterations in patients with clinical and electroencephalographic diagnosis of NCSE, give independent information for prognosis and can predict RSE evolution. Moreover this outcome predictor patterns and alterations are the same in different age groups (children-adults-elderly).

OBJECTIVE(s)

MAIN OBJECTIVE

Determinate which EEG patterns and alterations give independent information for prognosis in patients with clinical and electroencephalographic diagnosis of NCSE after correction for knowing predictors.

SECONDARY OBJECTIVES

Analyse which EEG patterns and alterations give independent information for RSE prediction in patients with clinical and electroencephalographic diagnosis of NCSE.

Determinate if the association between EEG patterns and prognosis or evolution in patients with NCSE is the same in paediatric, adult and elderly population.

METHODOLOGY

STUDY DESIGN

Multicentre study. Retrospective cohort, longitudinal, observational and analytic.

STUDY POPULATION

Inclusion criteria

Patients with NCSE diagnosis (both criteria):

- Clinical: change in behaviour and/or mental processes from baseline. Prolonged awareness or consciousness disorder during at least 5 min (2,18) without major motor symptoms and/or convulsions. Or comatose patients, understanding coma as an unarousable psychologic unresponsiveness in which the subject lies with closed eyes (13,20,21), with NCSE suspicion. Or subtle NCSE, defined as late or end stage of GCSE or the ominous endpoint of difficult-to-treat or advanced untreated convulsive SE (14,21).
    - Consciousness disorder is defined as a state of altered awareness of self and the environment. It may be examined by the patient's response to external stimuli and preserved memory.
    - Coma diagnosis is dependent on neurological examination showing loss of consciousness and signs of disturbed brainstem function. It has to be differentiated from confusional states and impairment of consciousness.
- Electroencephalographic: We will use the modified Salzburg Consensus Criteria for NCSE. See it in annexe 5.

From:

- Hospitalised in any service
- Adult ICU and emergency room
- Paediatric ICU and emergency room (children >/= 1 year)
- Coronary unit.

Exclusion criteria

- Neonatal patients (<1 year). We exclude these patients because of the electrical differences in the EEG patterns with the other patient groups and the variability of electrical alterations in the neonatal group itself.

- Anoxic encephalopathy. Some authors consider severe metabolic or anoxic encephalopathies with continuous epileptiform EEG alterations not as SE (21). One of the main reason is because that pathologies has a high rate of mortality caused by the underlying cause and they can bias the results (33).

- Triphasic waves pattern (or continuous 2-Hz generalized PDs with triphasic morphology). We exclude it because it is specific for metabolic (hepatic) causes.

  We define it as: surface negative, blunted triphasic complexes with a) low-amplitude, blunted, negative first phase (often wide-based); b) dominant, steep positive second phase; and c) slow rising third "slow wave" component. No polyspike component.

  Complex duration: 400-600msec. Amplitude: 100-300 uV on referential montage or smaller on bipolar. Frequency: 1.0-2.5Hz. Persistence: wax and wane, occupy> 10% of a standard recording (20min). Evolution/reactivity: decrease with sleep, drowsiness or after BZPs; increase and reaper with arousal or noxious stimulation (20,34).

SAMPLING

The sampling method will be conveniently a multistage method, with a first step of conglomerates, selecting participating centres by convenience according to our selection criteria (explained in "multicentricity" paragraph). The second step will be a non-probabilistic consecutive sampling including all the patients in each hospital who fulfil the inclusion and exclusion criteria during the established period of time until they fill up the three patterns groups with the estimate number of patients. It is the most convenient method taking into account that NCSE is a low-prevalence disorder and we will make a retrospective study.

SAMPLE SIZE

To calculate the sample size we will use the mortality and poor outcome rates that we have found in the literature. The average rates of mortality and the severe sequelae or poor outcome in NCSE is

about 30% and 11'25% respectively. So, we will assume a 41% as a reference rate for our variable poor or bad outcome. Moreover, we have estimated NCSE distribution for every pattern that we will use (see it in variables section), being about 56% for pattern A, 16% in pattern B and 28% in pattern C according with previous studies (13,33).

With this information, GRANMO application has been used to calculate the sample size of the study (using "two independent proportions" option). The same procedure is needed for each EEG pattern, using in every case the estimated population rate. We assume that the event rate in no-exposed is 0'41. The dropout rates is 0 because it is a retrospective study.

Accepting an alpha risk of 0'05 and a beta risk of 0'2 in a two-side test, 271 subjects are necessary in pattern A, 815 in the pattern B, and 406 in the pattern C, to detect as statistically significantly a proportion difference of 12% between the estimated reference for poor outcome in NCSE and the expected for each pattern. ARCSINUS approximation has been used.

For the two alterations that we have described, as they can occur at the same time as the other patterns, we have not included them to calculate the sample. Once we will have the distribution of patients in these two groups we will calculate the power of the contrasts using the GRANMO application.

Talking about the secondary objective, we can get an idea of the power that would give us our sample size calculated for our main objective. We know that about the 30% of the SE fall in a RSE. So, knowing the estimated number of patients that we will have in each pattern (271 in pattern A, 815 in pattern B, and 406 in pattern C) and accepting an alpha-risk of 0'05 in a bilateral contrast, the power of the hypothesis testing is of 88% for pattern A, 98% for pattern B, and 96% for pattern C, to detect as statistically significantly the difference of 10%.

MULTICENTRICITY

Based on our hospital register, in 1 year in Hospital Universitari Dr. Josep Trueta the number of patients with NCSE is about 20. This numbers can vary depending on the hospital, being more elevated in some of them. We have estimated a needed sample size of 1492 patients with NCSE diagnosis in total. With all these considerations in mind, we propose a multicentre retrospective cohort with 12 different participating hospitals of Spain and a recruitment period of 6 retrospective years in order to ensure the attainment of the sample size.

To establish a good communication we will assign: a principal investigation team who will act as the main director of the trial, a monitor who will be the link between the principal investigation team and each centre, a main investigator in each participating centre in the study (neurophysiologists) and we will guarantee the quality of the members/staff (the tasks for every role are explained in the "work plan" point).

In general, neurology and neurophysiology work teams involved in multicenter trials arise when new topics of interest appear. As far as we know, nowadays there is not any group of hospitals working in epilepsy. For that reason we will create our multicentre selection through the study group of epilepsy of the Spanish Society of Neurology. We will propose our project, and we will chose between the centres who are enrolled in this group.

The principal investigation team and the monitor will have to ensure that the chosen centres are appropriate, so they will visit them and they will meet the staff. The Collaborating centres have to meet the following criteria In order to ensure the appropriateness of their participation:

- Belong to the Spanish Society of Neurology (SEN) work team.
- Belong to the study group of Epilepsy of the Spanish Society of Neurology.
- Previous experience on research.
- Presence of a neurophysiology department.
- Presence of patients hospitalized at adult and paediatric ICU and at neurology department.
- Availability of portable EEG to use it in emergency room, ICU and other hospitalization service.
- Availability of the EEG and clinical diagnosis of NCSE, and other relevant information (variables described in the protocol) in the clinical history of the patients.
- Neurophysiologists experienced in electroencephalographic diagnosis of NCSE.

VARIABLES

INDEPENDENT

Electroencephalography (EEG)

There are different kind of EEG registration, depending on the patient.

- Standard EEG: it works placing superficial electrodes that are attached to the scalp with a conductive gel. The machine works with 18 channels, using bipolar and monopolar montages and at least 20 minutes of recording. The position of the electrodes are applied according to the international 10-20 system (annexe 6)
- Reduced EEG: there are only 11 electrodes. 9 in activity areas, and 2 in neutral areas.
    - With subcutaneous needle electrodes: in comatose and ICU patients. It works placing subcutaneous needle electrodes instead of the superficial ones.
    - Paediatric: in child's patients. It is the same mechanism as the standard EEG, but with less electrodes.

As part of the recording, repeated noxious, tactile, verbal and auditory stimuli are systematically delivered with patient reaction registered (Annexe 7).

Patterns and alterations

PATTERN 1→ Generalized periodic discharges (PDs or GPDs): waves with relatively uniform morphology and duration with a quantifiable interdischarge interval between consecutive waveforms and recurrence of the waveform at nearly regular intervals (between 0,3Hz and several seconds). The discharges have no more than 3 phases or any waveform lasting 0.5s or less, regardless of the number of phases. These include:

- Spike-and-wave or sharp-and-wave (SW) that can be typical (at 3-3,5Hz, rhythmic, generalized, synchronous, and symmetric) or atypical (which lack one or more of these features)
- Multiple spike-and-waves (MSW) that are repetitive complexes of two or more spikes followed by a slow wave.

(Annexe 8, Figure 1)

PATTERN 2→ Rhythmic delta activity (RDA): repetition of a waveform with relatively uniform morphology and duration and without an interval between consecutive waveforms. Is less than 4Hz, and the duration of one cycle of the rhythmic pattern should vary by less 50% from

the duration of the subsequent cycle for the majority of cycle pairs to qualify as rhythmic.
PATTERN 3→ Lateralized periodic discharges (LPD or PLD): are surface-negative bi-, tri-, or polyphasic discharges consisting of spike, sharp, polyspike components, variably with slow-wave complexes lasting 60-600 msec, of 50-150 uV in amplitude, usually occur at 0,5-2Hz. PLED-proper, PLED-plus, BiPLEDs and multifocal PLDs are also included in that group. (Annexe 8, Figure 2)
***References**:* (1,13,20,33,34)
ALTERATION 1→ Absence of a posterior dominant rhythm
ALTERATION 2→ Changes in stage II sleep pattern characteristics (presence-absence)
***Reference**:*(33)

The patterns are the main points that we want to evaluate, and for which the sample size have been calculated. We also add the two alterations because we have found evidence that they are probably related to NCSE prognosis (33). As the alterations can occur at the same time as the other patterns, we have not included this group to calculate the sample, and we will include it in the group of all patients that present the characteristics described to analyse the relationship with prognosis too and we will calculate the power of the contrasts once we have the patients distribution for each group.

DEPENDENTS

Prognosis

We will define it using three different neurologic validated scales, two for adult population and one adapted for paediatric patients: the CPC or cerebral performance categories (annexe 9), the mRS, modified Rankin Scale (annexe 10) and for child, the paediatric cerebral performance category or PCPC (annexe 11).

Talking about adult patients' scores, the first one is originally described to evaluate quality of life after successful resuscitation from a cardiac arrest and the second one to evaluate the degree of disability or dependence in daily activities after stroke or other causes of neurological disability. But both are easy to apply, they have established validity, low interobserver variability and the items that describe can be generalize to assess the level of function in other neurological disorders. So, we will use both of them, firstly because we have found evidence in other SE articles that these scores have been used to SE outcome evaluation (12,30,35). Secondly, because knowing that we will work with different hospitals which may evaluate patients with both scores and we will collect the data in a retrospective mode, to avoid the lack of information, facilitate the process and asses that variable as objectively as possible.

As we include in our described population paediatric patients, we have found an alternative to measure prognosis that will be valid for this population, the paediatric cerebral performance category (PCPC). In an overview of selected studies on NCSE in children, PCPC have been used in several studies (12). This score was developed and validated to quantify short-term cognitive impairment in children. This scale is a modification of the CPC for describing the degree of brain damage in adults, with operational definitions adapted for children (12,36).

Based on recent evidence and previous studies, we will treat this variable as dichotomus as follows:

Good neurologic and vital outcome	**Poor neurologic and vital outcome**
- CPC 1 and CPC 2	- CPC3, CPC4, CPC5
- 0-2 in mRS	- 3-6 in mRS*
- PCPC 1, 2 or 3	- PCPC 4, 5 or 6

*in patients with a previous NCSE mRS of 3 or more, we will accept as a poor neurologic and vital outcome at discharge a difference >/= to 1 points in the scale between the mRS at the discharge and the initial one.

Evolution to refractory status epilepticus: we will consider RSE as seizures that do not respond to first and second line anticonvulsant drug therapy used correctly and with adequate doses or seizures lasting more than 60 minutes (2). We will treat it as a dichotomus variable: evolution to RSE or no evolution to RSE.

COVARIABLES or CONFUSION VARIABLES:

These variables will be collected to be taken into account, to avoid confusion and to be able to obtain interpretable results because they have been demonstrated to be associated with the NCSE prognosis and evolution. We also decided to take information about some other variables that can be useful to describe other characteristics about our study population and could be used to obtain a deeper analysis in our research or to consider them to describe the results.

Status epilepticus severity score (STESS).

It will be conducted retrospectively. It is based on four outcome predictors (age, history of seizures, seizure type and extend of consciousness impairment), determined before treatment institution (26). We will define as a qualitative dichotomic variable, with a score of 0-2 defined as favourable prognosis and indicating low risk of death and a score >/= 3 defined as unfavourable prognosis.
See it in annexe 12.

Epidemiology based Mortality score in SE (EMSE).

It will be conducted retrospectively. It is based on four parameters and 45 items to choose: aetiology, age, comorbidity and EEG.

As STESS we will define it as a qualitative dichotomic variable, with a score high or equal of 64 for bad outcome, and less for good outcome (23,28). See it in annexe 13.

Type of NCSE: clinical classification. We will define it as a qualitative nominal variable. The characteristics of every subtype are in the annexe 1.

- Typical absence status epilepticus
- Atypical absence status epilepticus
- Late onset de novo absence
- Simple partial status epilepticus (SPSE)
- Complex partial status epilepticus (CPSE)
- Subtle status epilepticus
- Comatose status epilepticus

Aetiology/cause: It's seems to be the major determinant of outcome related principally with mortality. We will classify it as follows and we will define it as a qualitative nominal variable with more than 2 groups:

Acute symptomatic. SE occurring during within 7 days of an acute disease, such as CNS infection, cerebrovascular disease like cerebral infarction or acute cerebral haemorrhage, toxic or metabolic insults (alcohol or drug consumption or withdrawal) , or within 4 weeks of a head injury.
Febrile. SE in a previously neurologically healthy child where the only provocative factor was a febrile disease with axillary temperature >/= 38ºC and not related to CNS infection.
Progressive symptomatic. SE related to progressive diseases such as brain neoplasms or neurodegenerative disorders including innate metabolic errors, genetic brain disease…
Remote symptomatic. SE in an individual with prior (>7days) neurological disease, including cerebrovascular disorders (remote cerebral haemorrhage or cerebral infarction), brain trauma (>4 weeks), or other systemic disease in the absence of acute insult.
Acute on remote symptomatic. SE occurring during an acute neurological insult or trigger: fever, systemic infection, brain tumour oedema, acute exacerbation of brain disease, toxic or metabolic insults, alcohol or drug withdrawal or intoxication.
Previous epilepsy with acute triggering. SE occurring in a previously epileptic individual with documented low AED level, AED withdrawal, history of AED noncompliance or change in therapy.
Cryptogenic/unknown/idiopathic. SE occurring in patients with no history of seizures and absence of any other acute problems

References: (14,15,17,19,23,25)

*Anoxic encephalopathies are not included in this classification because they will be excluded (see it in exclusion criteria).

Comorbidity: it will be evaluated with the EMSE score. In EMSE, the score for comorbidity was derived from the Charlsons comorbidity index (CCI-score). In that index various diseases are scored and in EMSE they adapted the punctuations obtained depending of the mortality rates to their score (28). See it in annexe 11.

ICU patients: patients hospitalized in ICU are known to have major morbimortality than patients hospitalized in other services, consequently they usually have poorer outcome than other patients. We will consider at the time of NCSE diagnosis if the patients were or not hospitalized in ICU service. It will be a qualitative dichotomic variable: being or not being in ICU at the diagnosis moment.

Complications: as in other pathologies, some complications have a role in the prognosis of patients. In agree with the consulted bibliography, we will divided in three groups (10,17,29,37), so we will consider it a qualitative nominal variable:

- Treatment related-complications: aesthetic drugs such as phenobarbital and pentobarbital can cause cardiotoxicity, thiopental is associated with sever arterial hypotension and propofol with hepatotoxicity and metabolic acidosis, cardiac failure and rhabdomyolysis.
- Complications related with prolonged ICU stay: infections (respiratory, urinary…), respiratory failure, cardiac dysfunction…
- Complications due to the seizures themselves.

See complications that will belong to each group in annexe 4.

Treatment delay: there are evidence enough to consider that early treatment initiation is important for rapid SE control, and the effect of treatment delay on outcome may be related with worse outcome. We will consider as a continuous dichotomic variable: treatment delay >/= or < of 1 hour.

Prior epilepsy: it seems that the outcome is worse in patients without epilepsy than in patients with epilepsy. We will take that item into account in a qualitative dichotomic variable: having or not having prior history of epilepsy.

Structural CNS lesion: It will be a qualitative dichotomic variable: having or not having structural SNC lesion.

Drugs received before performing the EEG: to consider it to describe the results we want to take this variable into account because some drugs can have effect in the EEG patterns. For that reason the neurophysiologists who will define the EEG patterns for each patient needs to consider if any drug has been taken before the EEG realization and add it to the data collection.

Sociodemographic variables

- Age: this variable has been defined in the third objective. That's because we know that the age is an important factor to control in our study due to the variability in the normal EEG, the different aetiology of the NCSE… in different age groups. We also want to analyse if the association between EEG patterns and prognosis or evolution in patients with NCSE is the same despite the age. So, we will have this variable into account in the statistical analysis point. We will separate it in three groups:
    - Childs: 1-14 years.
    - Adults: 15-64 years.
    - Elderly: >/= 65 years.
- Sex: female or male.

DATA COLLECTION

We will obtain all the variables information and we will perform the different scales or scores retrospectively with the available information for each patient that was prospectively included in the databases of each hospital. To know the presence or absence of prior epilepsy or structural brain lesions, we will investigate the medical history of each subject. We will take the age at the episode of NCSE, not the actual one.

It will be a neurophysiologist who will diagnose the existence of electroencephalographic NCSE, and the pattern classification according to the medical history information of the patients. In order to accomplish the ethical aspects, and avoid investigator bias, the principal investigator will not have access to the personal information and the medical history of the patients. In order to achieve this, we will create an anonymization method to codify patients' information in each participating hospital before it gets to the principal investigator to analyse them.

STATISTICAL ANALYSIS

All the statistical analysis of the variables will be performed using the Statistical Package for the Social Sciences programme version 12.0 (SPSS Inc, Chicago, Illinois).

Statistical significance will be considered at a p value <0.05.

UNIVARIANT DESCRIPTION

Categorical variables will be expressed as relative frequencies and percentages. Quantitative variables will be described by means of standard deviation (when normal distribution) or median and quartiles (if variables without normal distribution).

BIVARIANT DESCRIPTION

Categorical variables will be compared with the Chi-square or Fisher's Exact tests. To compare variables with 2 groups we will use the T-test or Mann-Whitney and ANOVA/Krsukal-Wallis to compare 3 or more group.

In quantitative variables we will use t-Student method when they present normal distribution and for comparison of means between non-normally distributed variables, ANOVA and Man-Whitney tests will be used.

MULTIVARIANT DESCRIPTION

To adjust our variables for co-variables in order to avoid potential confounders and obtain interpretable results from the study, a logistic regression analysis will be performed to analyse both the association between EEG patterns (and alterations) and prognosis and the same EEG patterns and alterations and the evolution to refractory status epilepticus.

To analyse the third objective we will stratify the population for ages and we will make the multivariate analysis that I have mentioned before in every age group.

ETHICAL CONSIDERATIONS

This is an investigation without any risk, since the information will be collected retrospectively. There will be no changes on the biological, psychological, or social individuals of the participant patients.

This study will be conducted in accordance to the human rights and to the ethical tenets defined on the World Medical Association Declaration of Helsinki of “Ethical Principles for Medical Research Involving Human Subjects” of 2013 (38) .

It will comply with “Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal, “BOE” núm. 298”, we will guarantee the confidentiality and the anonymity of all data related to the participants when collecting data and publishing results.

Moreover it will comply with “Real Decreto Legislativo 1/2015, de 24 de julio” por el que se aprueba el texto refundido de la Ley de garantías y uso racional de los medicamentos y productos sanitarios, “BOE” núm. 177”, we will guarantee the rational use of medicines and medical devices.

Before carrying out the study, the research protocol will be sent to the ethic committee (CEIC, “comitè ètic d’investigació clínica”) and has to be evaluated and approved for it and for each hospital before being performed.

Every investigator will have to declare no conflict of interests.

STUDY LIMITATIONS

- Confounding bias: as it is a retrospective cohort, it is difficult to control the possible confounding variables. In order to avoid this problem we will collect data for those variables that we think could influence the results (based also upon those collected in previous studies). Then we will adjust the results with a multivariate analysis.

- For the same reason above mentioned, complete medical data will not be available for all patients. Although the important data to have results should be available.

- Due to NCSE is a relatively low-prevalent disorder, it will take long to achieve the estimated sample size in only our hospital. To minimize this restraint we decided to perform a multicentre study, so this way, it will be easier and faster to collect all patients that are needed.

- Inter-observer variability: as is a multicentre study and there will be an investigator in each hospital, inter-observer variability may appear. For that reason we have designed the different meetings and evaluation reports explained in the “work plan” point, to ensure that all the information is recruited following the described criteria.

- Information bias: to avoid this bias we will create an anonymous method for the central information recruitment. With this method we will guarantee that the principal investigation team that will analyse the data, will not know from whose subject or whose hospital every data comes from.

- An EEG pattern represents a time-frozen part of a permanently changing river of abnormalities. Therefore it may be better to follow the patient’s state and to evaluate it using continuous monitoring or serial EEG instead of only abbreviated or standard EEG, because some information could be missed. But there are a lot of hospitals without serial or continuous EEG monitoring availability. So we have decided to use standard EEG registration, mainly because in our hospital we do not have this source and to extrapolate the results to all the centres in the same situation.

CLINICAL AND HEALTHCARE IMPACT

As we have explained, non-convulsive status epilepticus is a disease with a high clinical relevance due to the high morbi-mortality of the patients, and the elevate range of sequelae, but nowadays, there's still no information enough about how to predict the outcome. The effort to investigate and measure outcome predictors in medicine has as goals: increase the effectiveness of different interventions, establish new management objectives and decisions adapted to the needs of each patient, and develop standards to guide professionals in optimizing utilization of resources. That would be used to improve our patients' life quality, whether that means to save them alive or minimize their poor outcomes and sequels.

In our protocol we have tried to avoid the limitations of similar studies in the design and sample size. Because of that, if we can find a relationship between particular alterations or patterns in the EEG and NCSE prognosis, it would have a good and direct impact on the clinical practice. It would bring great benefit for the affected subjects and for the professionals who have to diagnose and treat them because the goals, that we have just explained, would be achieved.

For here on, as our study is a retrospective one, it could let to the development of new approaches to know NCSE prognosis and to open the doors to new prospective trials to improve NCSE knowledge, to extrapolate the results for the general population and maybe to develop new management protocols according to the prognostic information of the electroencephalogram and evaluate if with the outcome information and the new management approaches, there is an improvement in the mortality and sever sequels of NCSE patients.

This protocol can be reported by others future studies and can increase the pool of data available for analysis.

WORK PLAN

RESEARCH TEAM

It will consists of the study coordination or principal investigation team **(PI)** of the main centre, a monitor (**M**; that will act as a link between the PI and the researchers of each participating hospital); neurophysiologists (**NP**, they will work as the main researchers for each hospitals, one for centre, included the main centre) and statistical specialist (**SS**). Moreover when the participating centres and the NP in each one will be selected, we will create a consensus committee (**CC**) it will be composed for 3 of the 12 neurophysiologists of the study and they will be selected for the principal investigation team and the monitor.

TASKS

PHASE 1: PREPARATION AND COORDINATION

ELIGIBILITY OF COLLABORATING CENTERS [PI, M]. Approach and selection of hospitals participating in the study. Collaborating centres have to meet the criteria explained before In order to ensure the appropriateness of their participation.

STUDY RESEARCH PROPOSAL AND EVALUATION BY ETHICAL COMMITEE [PI, NP, CEIC]: it has to be evaluated and accepted by the ethical committee (CEIC) and for all participating hospitals.

IN-PERSON MEETING 1: coordination of all centres and researches teams. A first in person meeting will take place with the monitor (M) and the principal investigation team (PI) and all investigators (NP) of each hospital in order to explain the project design and execution plan, the system and procedures of patient's selection, anonymous methods, data management and recruitment and central data monitoring. During the study, regular feedback will be provided to each hospital participating in this study and adequate methods of communication will be established between the monitor (M) and each hospital.

PHASE 2: FIELD WORK AND DATA COLLECTION

PATIENTS RECRUITIMENT AND DATA COLLECTION [NP]: At least six months will be required to collect all the information from the medical records. Each investigator (NP) in each centre is responsible for ensuring that all data is complete and exact, in an accurate and appropriate manner, following the anonymous method and guarantee that it will be centralized and available for the PI and for the M. Patients will be included until the sample size for every group will be achieved. The doubtful or questionable cases have to be sent to the consensus committee.

TELECONFERENCE MEETING [NP, M]. Weekly meetings will be held with the membership of the neurophysiology service responsible for the collection of information for the different hospitals and the principal investigation team and monitor. This teleconference meeting will be to review and evaluate the recruiting, the quality and homogeneity of data collected and to discuss the progress of the study. The first one will be at the beginning of the recruitment period and the second one in the middle of that phase.

EVALUATION OF CORRECT DATA COLLECTION [PI, M]. A following evaluation and validation of the data collection will be required, thus defining and classifying the information obtained using the guidelines described in the variables section of this protocol. Within all this period the Monitor will perform controls with all the hospitals to ensure adequate data collection (the two teleconference meetings explained before); he has to ensure that the protocol is followed, he has to notify any incidence or modification on the data collection, establish a proper communication system between itself and every main investigator of each centre, and he has to be in contact with them. Moreover both the monitor and the principal investigation team have to be accessible for all participant staff.

UNIFY CRITERIA IN DOUBTFUL CASES: during the data collection the Consensus Committee will work to unify criteria in doubtful and questionable cases of NCSE.

PHASE 3: DATA ANALYSIS AND FINAL EVALUATION

IN PERSON MEETING 2 [M, NP]: A second in person meeting will take place with the monitor (M) and all investigators (NP) of each hospital in order to explain the evaluation of the data collection.

STATISTICAL ANALYSIS AND ANALYSIS, INTERPRETATION AND DISCUSSION OF THE RESULTS[S, PI, NP]: At least four months will be required to perform the statistical analysis exposed, to interpret the statistical analysis performance, and to discuss the results with all participating centres in the third in-person meeting.

Three month will be needed to write the article and evaluate it. Results and conclusions will be analysed and the investigators will perform the final discussion in the last in-person meeting [PI, NP].

PHASE 4: ARTICLE PUBLICATION AND SCIENTIFIC DIFFUSION

As a multicentre clinical trial, each investigator can be responsible for local dissemination. We will send the article to a Neurophysiological magazine, journal articles and reports for its official publication and we will present the results of our work at annual conferences both in the state and also international.

CHRONOGRAM SCHEME

TASKS	2015				2016												2017	PERSONAL
	S	O	N	D	G	F	M	A	M	J	J	A	S	O	N	D		
PREPARATION AND COORDINATION PHASE																		
Bibliographic research, literature review, protocol elaboration and evaluation																		PI
Selection of the centres that will participate in the study																		PI, M
Study research proposal evaluation by ethical committee and all participating hospitals.																		PI, NP, CEIC
In-Person meeting 1																		PI, M, NP
FIELD WORK AND DATA COLLECTION																		
Patient's recruitment and data collection.																		NP
Teleconference meetings																		PI, M, NP
Evaluation of correct data collection																		PI, M
Unify criteria in doubtful cases																		CC
DATA ANALYSIS AND FINAL EVALUATION																		
In-Person meeting 2																		M, NP
Statistical analysis																		S
Analysis and interpretation of the results																		PI
Discussion of the results (In-Person meeting 3)																		PI, NP
Final report elaboration																		PI
Final report evaluation																		PI, NP
PUBLICATION AND SCIENTIFIC DIFFUSION																		
Scientific publications																		PI
Attendance to congresses																		

BUDGET

				TOTAL (€)
	Cost	Quantity	Time/nº	
STAFF				
Statistical analysis	35€/h	1	30h	1050
MATERIALS				
Articles and other literature material, printing and paper packs...	100€	-	-	100
MEETINGS				
In-personal meetings (food, transport, conference room rental)	40€/person	14 persons	3 meetings	1680
Teleconference meetings (conference room rental)	20€/meeting	-	2 meetings	40
PUBLICATION				
Article publication (publishing fees)	1500	1	-	1500
DISEMINATION				
2016 European congress on clinical neurophysiology	300€/person	1	1	300
12th European Congress on Epileptology – Prague 2016	300€/person	1	1	300
Travel expenses (transport, accommodation, food and miscellanea)	200€/person	1 person	2 congress attendance	400
		TOTAL COSTS (IVA include)		5370€

Staff: one or several neurophysiologists from the neurophysiology service of each hospital, will make, in their free time during the normal work hours, the research in the computer database program of the hospital, searching those patients who meet the inclusion and exclusion criteria required and specified in this protocol and a thorough reading of the EEG, correctly defining the characteristics of these tests, in order to divide the patients into different groups, according to the definition of variables mentioned earlier in this protocol. They will not receive any financial compensation for they contribution to the study but all in-personal meetings and conference meetings will be payed and they will appear as a collaborating staff in published articles and conferences.

The principal investigation team will carry out all the tasks of coordination, interpretation and dissemination of results and writing articles, we will appear as the principal investigators in published articles and conferences. We will not receive any financial compensation for our contribution to the study.

A statistical is required for the analysis of all the data, according to the statistical analysis section in this protocol.

Material resources: no extra money will be needed for the clinical techniques necessary for the study, since all of them were made in the ordinary way, following the current protocol of the hospital, and all the information will be obtained from data base of the hospitals.

Publications and dissemination: the principal investigator team will write the final work, but we will need money for its publication in magazines, and money for the conferences in which we will explain the results widely, it has been also taken into account the indirect costs of the dissemination plan (travel expenses, publishing fees…).

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ANNEXES

ANNEXE 1. Characteristics of NCSE subtypes

NCSE SUBTYPES	
Typical ASE	Prolonged generalised state of consciousness alteration with or without changes in behaviour. Impaired cognition associated with other manifestation. Patients may be able to eat and drink, withdraw from pain, walk, and respond to simple commands. Duration going from minutes to days or weeks. EEG findings are generalised and regular spike-wave discharges of 1-4Hz or more irregular and slow. It is typical in patients with idiopathic generalised epilepsies (absence epilepsy or juvenile myoclonic epilepsy) it may occur from once in a lifetime to 10 to 20 times per year. The triggers can be inappropriate AED, fever, hyperventilation, grief, excitement, fatigue, or can be associate with menstrual or sleep-wake cycles. ASE is generally associated with a benign outcome.
Atypical ASE	Difficult to differentiate of typical ASE. Consciousness alteration is more severe than in typical ASE. The EEG is very similar, but interictal background activity is commonly slow. Typical in Lennox-Gastaut syndrome, idiopathic generalised epilepsy.
Late onset de novo absence	Prolonged states of confusion or assumed psychiatric disorders in elderly patients with variables degrees of altered contact with environment, stupor or only mild amnesia. EEG is characterised by irregular spike-wave discharges with a frequency of 0·5-4 Hz. Typical in patients with remitted idiopathic generalised epilepsy or in patients without any seizure history. Triggered by psychotropic substance intoxication or detoxication.
SPSE	Seizures that are localized to a discrete cortical region, there is not altered contact with the environment and consciousness is preserved. Depending on the activated area, clinical characteristics are different and indicate the region of onset. The symptoms could be: acoustics, aphasia, dysesthesia, gustatory, olfactory, psychic, vegetative, visuals... The EEG is variable: focal spikes and spike-waves complexes restricted in space. Typical in epilepsia partialis continua (which typically presents unilateral, repetitive, and rhythmic twitching of the limb or face), patients with pre-existing lesional or non-lesional localisation-associated epilepsy, or de novo due to acute, progressive, or remote CNS injuries.
CPSE	Difficult to differentiate from ASE and rarely reported in children. It is characterised by a gradual development of symptoms after a prolonged or serial auras of any kind and altered contact with the environment. Depending on the affected area the clinical manifestations are different. The seizure activity can be originated mainly in frontal or temporal lobe affecting the limbic cortex. CPSE is typical in patients with temporal lobe or lesional epilepsies. The EEG is similar to SPSE but less restricted in space. o Frontal lobe: disinhibition, inappropriate smiling or laughter, and confabulation, angry, aggressively, anxiety with less consciousness impairment. It can be separated in two categories: a) unilateral frontal status (affective disinhibition or indifference with little or no

	confusion); b) bifrontal status with confusion and impaired consciousness. o Temporal lobe: variable confusion, agitation, receptive aphasia, psychosis, impairment ranges from mild clouding to coma or have an impaired consciousness state called "twilight state" with confusion, partial amnesia, speech arrest, automatisms, vocalizations, strange behaviour.
Subtle SE	It occurs in the aftermath and resolution of CSE, and is not an infrequent subtype, NCSE persist in 14% of patients after control of GCSE (15). For others authors it represents the borderland between NCSE and comatose NCSE. Is characterised by loss consciousness; no or subtle movements such as rhythmic twitching of the arms, legs, trunk, or facial muscles, tonic-eye movement, tonic-eye deviation, or nystagmoid eye jerking. In the EEG we can find generalised or lateralised spike or spike-wave discharges or flat periods. In some cases comatose and subtle SE can be overlap, because the endpoint of difficult-to-treat or advanced untreated convulsive SE may be a coma although in subtle SE sometimes could be a drug induce coma, or only a loss of consciousness. Moreover is important that coma SE have a worse prognosis than subtle SE, for that reason it is important to differentiate them.
Comatose SE	We define coma as unarousable psychologic unresponsiveness in which the subject lies with closed eyes. Status epilepticus is not uncommon in patients in coma and is overdiagnosed because clinical symptoms are often subtle and easy to miss, and the only way to diagnose it is with the EEG. There is enough information about this entity that demonstrate that there are sufficient differences between comatose form of NCSE and proper form (the rest of subtypes of NCSE), so we decided to adopted as a different subtype. It could be generalized and lateralized. It has a poor prognosis. The most frequent aetiologies are diffuse primary or secondary brain disturbances (like cerebral hypoxia-ischemia after cardiorespiratory arrest) for coma-GED, and focal cortical lesions for coma-LED.

References (3,5,12,13,16,21)

ANNEXE 2: List of aetiologies that may cause status epilepticus (2)

1 Cerebrovascular diseases
- a Ischemic stroke
- b Intracerebral bleeding
- c Subarachnoid bleeding
- d Subdural hematoma
- e Epidural hematoma
- f Sinus venous thrombosis and cortical venous thrombosis
- g Posterior reversible leukoencephalopathy syndrome
- h Vascular dementia

2 CNS infections
- a Acute bacterial meningitis
- b Chronic bacterial meningitis
- c Acute viral encephalitis (including Japanese B encephalitis, herpes simplex encephalitis, human herpesvirus 6)
- d Progressive multifocal leukoencephalopathy (PML)
- e Cerebral toxoplasmosis
- f Tuberculosis
- g Neurocysticercosis
- h Cerebral malaria
- i Atypical bacterial infections
- j HIV-related diseases
- k Prion diseases (Creutzfeldt-Jakob disease, CJD)
- l Protozoal infections
- m Fungal diseases
- n Subacute sclerosing panencephalitis
- o Progressive Rubella encephalitis

3 Neurodegenerative diseases
- a Alzheimer's disease
- b Corticobasal degeneration
- c Frontotemporal dementia

4 Intracranial tumors
- a Glial tumors
- b Meningioma
- c Metastases
- d Lymphoma
- e Meningeosis neoplastica
- f Ependymoma
- g Primitive neuroectodermal tumor (PNET)

5 Cortical dysplasias
- a Focal cortical dysplasia (FCD) II, tuberous sclerosis complex (TSC), hemimegalencephaly, hemihemimegalencephaly
- b Ganglioglioma, gangliocytoma, dysembryoplastic neuroepithelial tumor (DNET)
- c Periventricular nodular heterotopia (PNH) and other nodular heterotopias
- d Subcortical band heterotopia spectrum
- e Lissencephaly
- f Familial and sporadic polymicrogyria
- g Familial and sporadic schizencephaly
- h Infratentorial malformations (e.g., dentate dysplasia, mamillary dysplasia, etc.)

6 Head trauma
- a Closed head injury
- b Open head injury
- c Penetrating head injury

7 Alcohol related
- a Intoxication
- b Alcohol withdrawal
- c Late alcohol encephalopathy with seizures
- d Wernicke encephalopathy

8 Intoxication
- a Drugs
- b Neurotoxins
- c Heavy metals

9 Withdrawal of or low levels of antiepileptic drugs

10 Cerebral hypoxia or anoxia

11 Metabolic disturbances (e.g., electrolyte imbalances, glucose imbalance, organ failure, acidosis, renal failure, hepatic encephalopathy, radiation encephalopathy, etc.)

12 Autoimmune disorders causing SE
- a Multiple sclerosis
- b Paraneoplastic encephalitis
- c Hashimoto's encephalopathy
- d Anti-NMDA (*N*-methyl-D-aspartate) receptor encephalitis
- e Anti–voltage–gated potassium channel receptor encephalitis (including anti–leucine–rich glioma inactivated 1 encephalitis)
- f Anti-glutamic acid decarboxylase antibody associated encephalitis
- g Anti–alpha–amino–3–hydroxy–5–methylisoxazole–4–propionic acid receptor encephalitis
- h Seronegative autoimmune encephalitis
- i Rasmussen encephalitis
- j Cerebral lupus (systemic lupus erythematosus)
- k CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia) syndrome
- l Adult-onset Still's disease
- m Goodpasture syndrome
- n Thrombotic thrombocytopenic purpura (Moschcowitz syndrome, Henoch Schönlein purpura)

13 Mitochondrial diseases causing SE
- a Alpers disease
- b Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)
- c Leigh syndrome
- d Myoclonic encephalopathy with ragged red fibers (MERRF)
- e Neuropathy, ataxia, and retinitis pigmentosa (NARP)

14 Chromosomal aberrations and genetic anomalies
- a Ring chromosome 20
- b Angelman syndrome
- c Wolf-Hirshhorn syndrome
- d Fragile X syndrome
- e X-linked mental retardation syndrome
- f Ring chromosome 17
- g Rett syndrome
- h Down syndrome (trisomy 21)

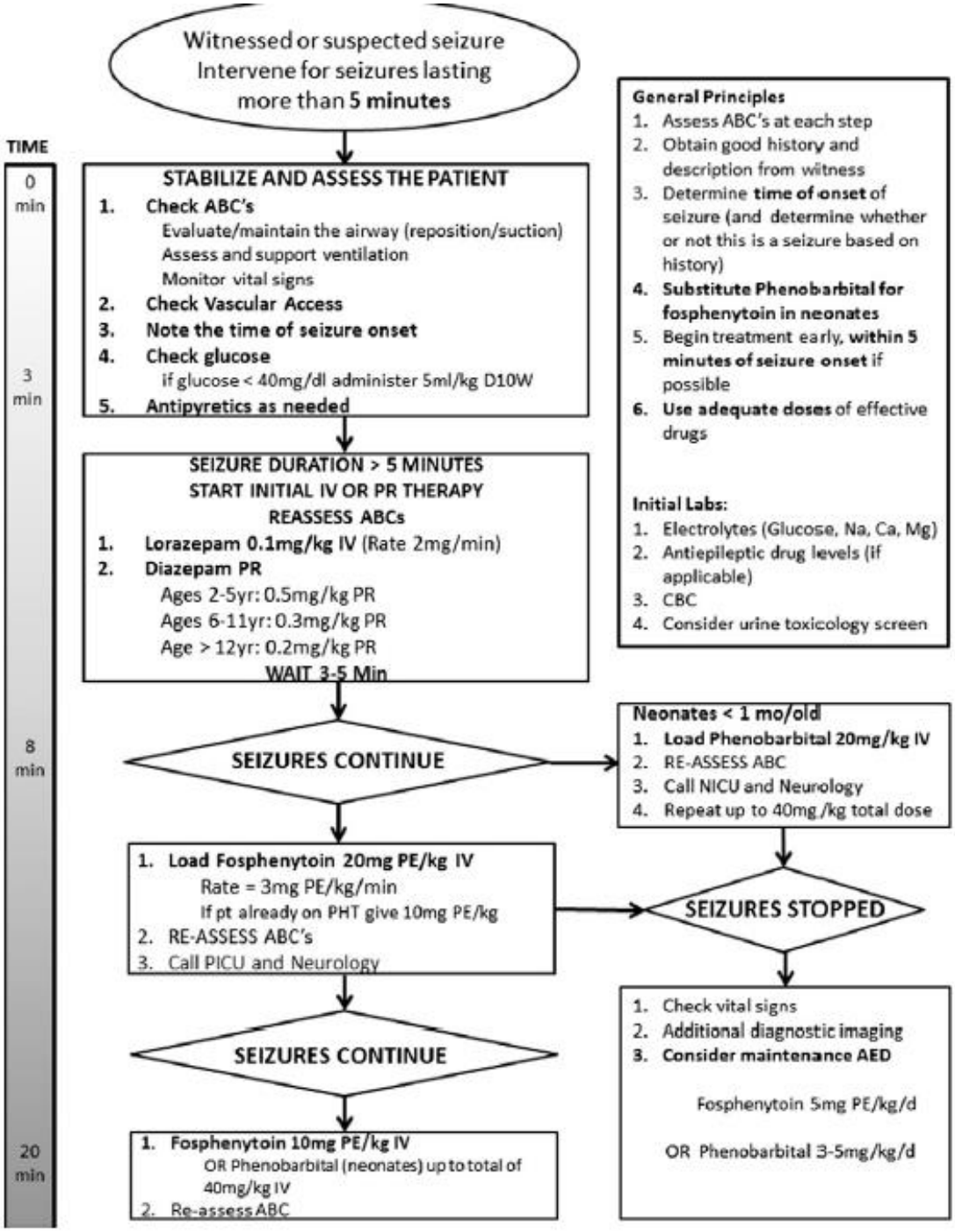
15 Neurocutaneous syndromes
- a Sturge-Weber syndrome

16 Metabolic disorders
- a Porphyria
- b Menkes disease
- c Wilson disease
- d Adrenoleukodystrophy
- e Alexander disease
- f Cobalamin C/D deficiency
- g Ornithine transcarbamylase deficiency
- h Hyperprolinemia
- i Maple syrup urine disease
- j 3-Methylcrotonyl Coenzyme A carboxylase deficiency
- k Lysinuric protein intolerance
- l Hydroxyglutaric aciduria
- m Metachromatic leukodystrophy
- n Neuronal ceroid lipofuscinosis (types I, II, III, including Kufs disease)
- o Lafora disease
- p Unverricht-Lundborg disease
- q Sialidosis (type I and II)
- r Morbus Gaucher
- s Beta ureidopropionase deficiency
- t 3-Hydroxyacyl Coenzyme A dehydrogenase deficiency
- u Carnitine palmitoyltransferase deficiency
- v Succinic semialdehyde dehydrogenase deficiency

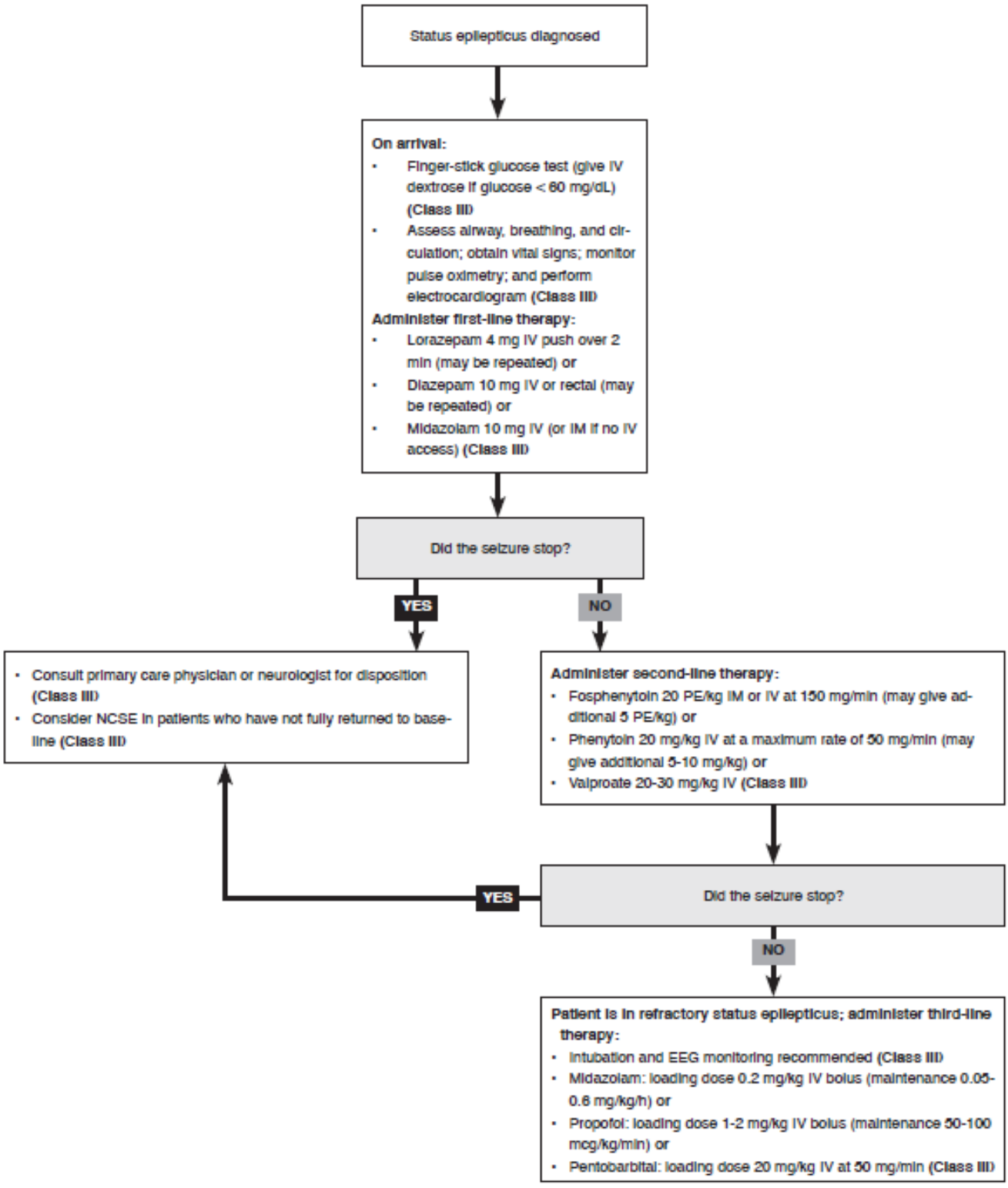
17 Others
- a Familial hemiplegic migraine
- b Infantile onset spinocerebellar ataxia (SCA)
- c Wrinkly skin syndrome
- d Neurocutaneous melanomatosis
- e Neuroserpin mutation
- f Wolfram syndrome
- g Autosomal recessive hyperekplexia
- h Cockayne syndrome
- i Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
- j Robinow syndrome
- k Malignant hyperpyrexia

ANNEXE 3. Treatment in patients with SE (8,11)

Algorithm for treatment in paediatric population:



Algorithm for treatment in adult population with SE:



Abbreviations: EEG, electroencephalography; IM, intramuscular; IV, intravenous; PE, phenytoin equivalents; NCSE, nonconvulsive status epilepticus.
For class of evidence definitions, see page 14.

ANNEXE 4. Systemic complications of status epilepticus (29)

Table 1
Systemic complications of status epilepticus.

Early systemic complications	Complications relating to treatment	Complications of prolonged intensive care unit care
Acidosis (respiratory > metabolic) • Increased CO_2 production • Decreased CO_2 removal • Depletion of glycogen stores	Nonanesthetic drugs • Benzodiazepine — respiratory depression, and sedation • Valproic acid — platelet and clotting dysfunction and hyperammonemia • Fosphenytoin/phenytoin — cardiac arrhythmias and hypotension • Levetiracetam — sedation • Lacosamide — PR prolongation, sedation, angioedema, and rash	Venous thromboembolic disease • Pulmonary embolism • Deep venous thrombosis
Hypoxia • Apnea • Upper airway obstruction • Aspiration of gastric contents • Mucous plugging • Neurocardiogenic pulmonary edema	Propofol • Propofol infusion syndrome • Hypotension	Pulmonary complications • Recurrent mucous plugging • Pleural effusions • Atelectasis • Tracheostomy Ventilator-associated pneumonia
Hyperadrenergic state • Hyperpyrexia • Hypertension • Tachycardia • Hyperglycemia • Peripheral leukocytosis	Midazolam • Accumulation in obesity and renal or hepatic dysfunction • Hypotension	Other infectious complications • Catheter-associated urinary tract infections • Sepsis • Bloodstream infections • Pseudomembranous colitis
Cardiac injury • Left ventricular stunning • Cardiac arrhythmias • Cardiac troponin elevation • Electrical conduction abnormalities • Cardiac contraction band necrosis	Barbiturates • Hypotension • Paralytic ileus • Increased risk of infection • Propylene glycol toxicity • Hepatic toxicity • Pancreatic toxicity • Lingual edema • Prolonged half-life	Skin complications • Skin breakdown • Yeast infections
Musculoskeletal injury • Tongue bites • Long bone fractures • Vertebral body compression fractures • Posterior shoulder dislocation	Ketamine • Tachyarrhythmias	Intensive care unit acquired weakness • Critical illness myopathy • Critical illness neuropathy
Renal injury • Rhabdomyolysis and acute renal failure	Inhalational anesthetics • Hypotension • Increased risk of infection • Paralytic ileus Hypothermia • Acid base and electrolyte disturbances • Coagulopathy • Impaired immunity • Cardiac arrhythmias • Paralytic ileus • Thrombosis	

ANNEXE 5. Modified Salzburg Consensus Criteria for NCSE (mSCNC) (20,34)

A. Patients without known epileptic encephalopathy

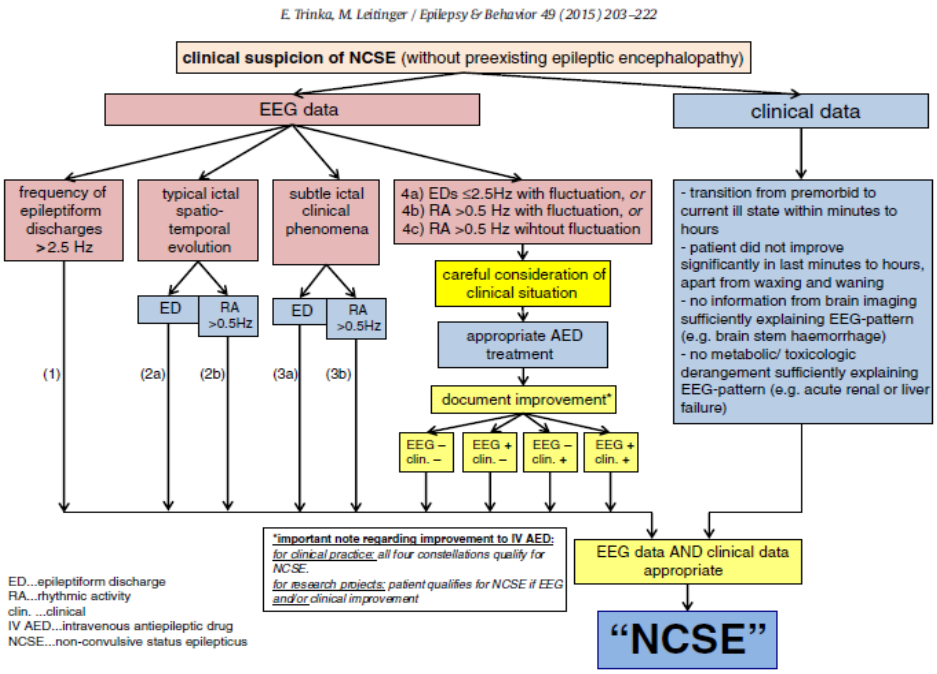
1. EDs (Repetitive focal or generalized spikes, polyspike, sharp waves, spike-and-wave, or sharp-slow-wave complexes) at >2'5 Hz.
2. EDs </= 2'5 Hz or rhythmic delta/theta activity (>0'5Hz) AND one of the following:
   a) EEG and clinical improvement after IV AED with increase in EEG reactivity and appearance of EEG background activity.
   b) Subtle focal ictal symptoms (e.g., facial twitching, gaze deviation, nystagmus, limb myoclonus).
   c) Typical spatiotemporal evolution:
      - Incrementing onset (increase in voltage with changes in frequency) or
      - Evolution in patterns (change in frequency >1Hz or change in location) or
      - Decrementing termination (voltage or frequency); or
      - Post-periodic epileptiform discharges background slowing or attenuation

B. Patients with known epileptic encephalopathy

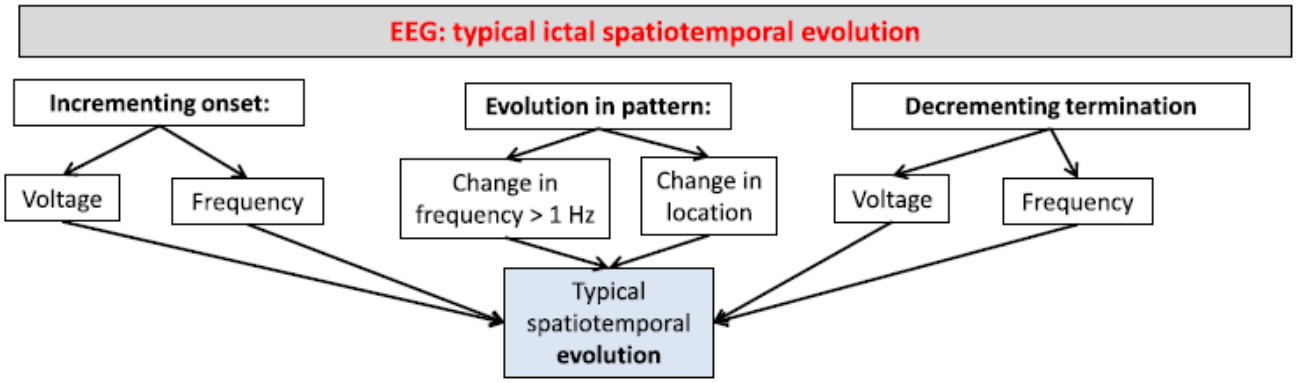
1. Frequent or continuous generalized spike-wave discharges, which show an increase in profusion or frequency when compared to baseline EEG with observable change in clinical state.
2. Improvement of clinical or EEG features with IV AEDs.

*There are not changes/ no reactivity in the pattern with arousal or noxious stimulation.

Algorithm for diagnosis of nonconvulsive status epilepticus with the mSCNS for NCSE (20)



EEG definition of typical spatiotemporal evolution and defeinitions required for mSNCS (20)



Evolution: *Incrementing onset (increase in voltage and change in frequency), or evolution in pattern (change in frequency >1 Hz and change in location), or decrementing termination (voltage and frequency).* ***AND ACNS criterion for "evolving" (ACNS-evolving)*** *"at least 2 unequivocal, sequential changes in frequency, morphology or location defined as follows: Evolution in frequency is defined as at least 2 consecutive changes in the same direction by at least 0.5/s, e.g. from 2 to 2.5 to 3/s, or from 3 to 2 to 1.5/s; Evolution in morphology is defined as at least 2 consecutive changes to a novel morphology; Evolution in location is defined as sequentially spreading into or sequentially out of at least two different standard 10-20 electrode locations. In order to qualify as present, a single frequency or location must persist at least 3 cycles (e.g. 1/s for 3 seconds, or 3/s for 1 second)"[2].*

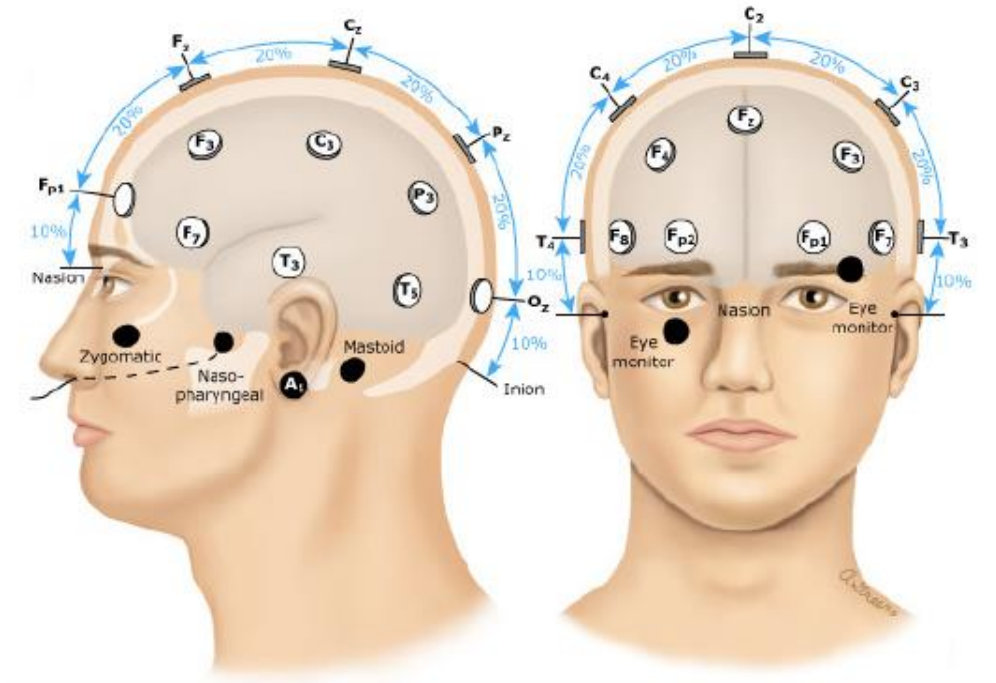
ACNS-criterion for Rhythmic Delta Activity (ACNS-RDA) *"Rhythmic = repetition of a waveform with relatively uniform morphology and duration, and without an interval between consecutive waveforms. RDA = rhythmic activity < 4 Hz. The duration of one cycle (i.e., the period) of the rhythmic pattern should vary by <50% from the duration of the subsequent cycle for the majority (>50%) of cycle pairs to qualify as rhythmic." [2].*

Subtle ictal clinical phenomena: *minor twitching of mouth, periorbital region or extremities should appear in close temporal relation to EEG-pattern (be cautious concerning non-epileptic involuntary movements as mimicks, e.g. Parkinsonian tremor, drug induced myoclonus (e.g. opioids), serotonin syndrome,...),*

Reactivity to IV AEDs*: within 10 minutes after AED fully applied; clinical presentation tested: improvement is defined as better performance in one of five domains (i) "say your surname", (ii) "repeat 1,2,3", (iii) "raise your arms"(first tell, if no response demonstrate), (iv) patient opens eyes to i - iii, (v) patient looks at the examiner in response to i - iii. If no response repeat procedure after strong tactile stimuli on both sides of the body. EEG tested: improvement is defined as reduction to "occasional", i.e. 1-9% of epoch.*

ACNS criterion for fluctuation (ACNS-fluctuation) *" >3 changes, not more than one minute apart, in frequency (by at least 0.5/s), >3 changes in morphology, or >3 changes in location (by at least 1 standard inter-electrode distance), but not qualifying as evolving. This includes patterns fluctuating from 1 to 1.5 to 1 to 1.5/s; spreading in and out of a single electrode repeatedly; or alternating between 2 morphologies repeatedly." [2]).*

ANNEXE 6. International electrode placement system (32).



The location of electrodes for recording electroencephalograms from the scalp, nasopharyngeal, and external ear sites are shown. The leads placed on the zygomatic arch beneath the eye allow for monitoring of eye movements.

Adapted from: Jasper HH. Report of the committee on methods of clinical examination in electroencephalography: 1957. Electroencephalogr Clin Neurophysiol 1958; 10:370.

Graphic 78990 Version 2.0

ANNEXE 7. Registration characteristics and triggering during EEG (18)

Tabla XVII. Recomendaciones técnicas del electroencefalograma en epilepsia

Recomendaciones técnicas para un EEG basal

- Registros de 16 canales (mínimo 8 canales).
- Mínimo: 21 electrodos (sistema 10-20).
- Montajes: referenciales y bipolares.
- Disposición: longitudinal y transversal.
- Impedancias: inferior a 5 kohms.
- Filtros: 50-100 µV.
- Sensibilidad: Baja frecuencia no > 1 Hz y de alta frecuencia no < 70Hz.
- Velocidad: 15-30 mm/s.
- Duración: 30 min (mínima 20 min).
- Reactividad: ojos abiertos/cerrados (OA/OC).

	Recomendaciones técnicas	Utilidad diagnóstica
HV	• Duración estándar: 3 min + 2 min post-HV (5 min en sospecha de EGI). • Frecuencia: entre 18-24 rpm. • Mantener OC. • Realizar a mitad o final registro. • Continuar registro al menos 1 min después de acabar HV. • Contraindicaciones: – Hemorragia intracraneal reciente. – Enfermedad cardiopulmonar. – Anemia depranocítica. – HTA no controlada.	• E. con ausencias: 80 % PO 3Hz • Tiene más valor HV durante 5 min que registro continuo de 6 horas. **NE III**[56]. • E. generalizadas sintomáticas (SLG): 40 % POLenta 2-2,5 Hz. • E. mioclónicas: brotes de punta y polipunta. No es el mejor método de activación (ELI). • E. focal: 6-9 % DEI y 4 % CE. • Hipoglucemia.-PO 3 Hz.
ELI	• Realizar con luz ambiental mínima para ver al paciente. • Distancia del flash a 30 cm del paciente. • Secuencia de frecuencias de estimulación (+): 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 60, 50, 40, 30 y 25 Hz. • Duración: trenes de 10 s, con una frecuencia con intervalos mínimos de 7 s. • 1.° (+) con OA; tras 5 s OC. • Duración aprox.: 6 min.	• Respuesta fotomiogénica o fotomioclínica: – 0,3 % sanos y 3 % epilépticos. • Respuesta fotoparoxística (RFP): – 30 % de pacientes con fotosensibilidad. – 30 % E. mioclónica juvenil. – 18 % E. ausencias de la infancia. – 15 % E. generalizadas idiopáticas. – 3 % E. parciales. • Respuesta a baja frecuencia (1-5 Hz) – Enfermedades neurodegenerativas (epilepsias mioclónicas progresivas).
Privación de sueño		La combinación de registro de sueño tras privación parcial de sueño aumenta la rentabilidad diagnóstica entre un 30 % y un 70 %.
Tareas cognitivas[58,59]	Etiopatogenia: hiperexcitabilidad difusa cortical y subcortical (± genético). Cálculo matemático. Puzles (praxias): 30 min. Lectura/escritura: 30 min en voz alta y de redacción leído.	Pueden precipitar actividad PO generalizada; útil: DD entre EF y EGI. Epilepsias reflejas.

HV: hiperventilación; ELI: estimulación lumínica intermitente; DEI: descargas epilépticas interictales; PO: punta-onda; DD: diagnóstico diferencial.

ANNEXE 8. EEGs patterns examples (20)

Figure 1: Atypical absence status

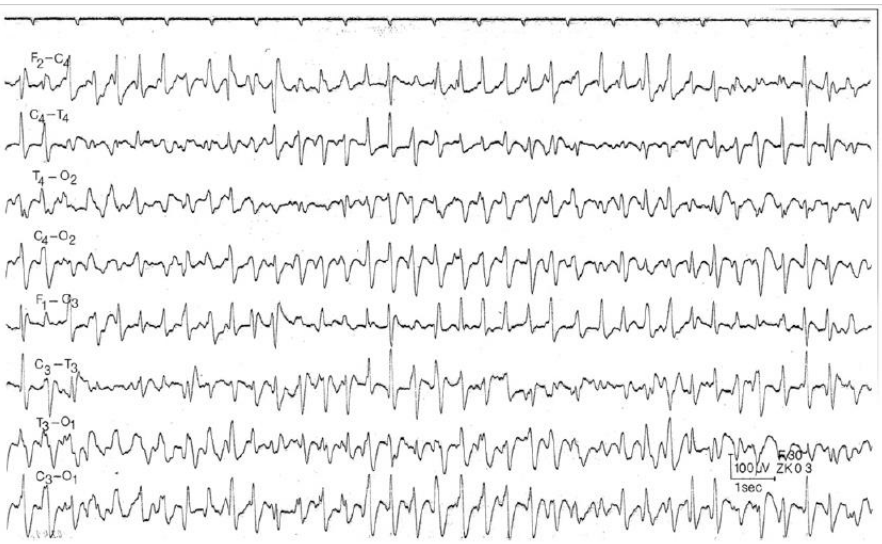


Fig. 6. Man, 33 years of age. Atypical absence status in late-onset (16 years) Lennox–Gastaut syndrome. Obtunded, withdrawn, inadequate reaction for 3 weeks. Continuous 2/s sharp and slow waves with triphasic appearance. Recovered after 3 weeks.

Figure 2: PLDs

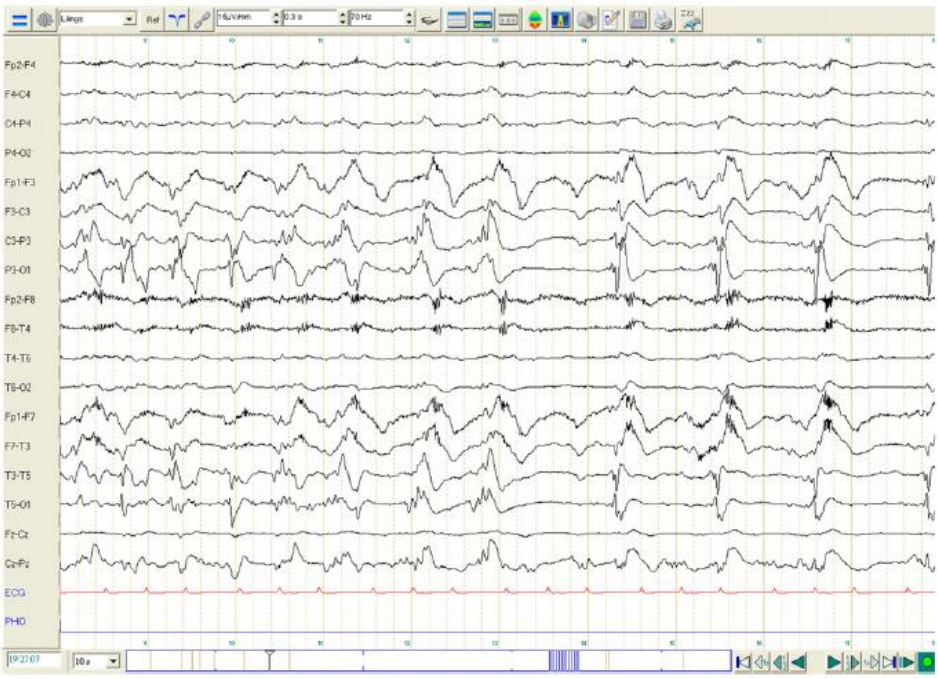


Fig. 7. (a–i): woman, 89 years of age. Nonresponsive, ongoing chewing-like movements. Hemiplegia L due to remote large media territory infarction. IV MDZ: 5 mg. In hospital: LZP: 4 mg, LEV: 2000, VPA: 2000 — failed to respond due to general bad condition (many comorbidities), no escalation of treatment. Lateralized periodic discharges left temporoparietal with fluctuating intervals between the discharges. Flat periods with 0.5- to 2-second duration. Outcome: died.

ANNEXE 9. Cerebral performance category (CPC) (12,35)

CPC 1. No sequelae and good recovery of the patients. Conscious, alert, oriented able to work. Normal cognitive functions, or only a mild neurologic or psychologic deficit.
CPC 2. Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life, no institutionalization is required. Able to work in sheltered environment and able to participate in activities of the daily living, but work and social life are compromised because of mental or physical disability.
CPC 3. Severe disability: conscious, dependent on others for daily support because of impaired brain function, institutionalization is required. Able to follow commands but cannot live independently. Ranges from ambulatory state to severe dementia or paralysis.
CPC 4. Coma or persistent vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if he appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness.
CPC 5: death or brain death: apnea, areflexia, EEG silence, etc

ANNEXE 10. Modified Rankin Score (mRS) (12,30)

0 = No symptoms at all. No limitations and no symptoms
1 = No significant disability. Symptoms present but no other limitations**.** Able to carry out all usual duties and activities.
2 = Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance. Limitations in participation in usual social roles, but independent for daily life activities.
3 = Moderate disability requiring some help with some instrumental ADL but not basic ADL. Able to walk unassisted.
4 = Moderate severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance. Not requiring constant care.
5 = Severe disability; bedridden, incontinent, and requiring constant nursing care and attention. Someone needs to be available at all times
6= death

ANNEXE 11. Pediatric Cerebral Performance Category Scale (PCPC)(36)

PCPC 1. Normal: at age-appropriate level; school age child attending regular school classroom.
PCPC 2. Mild disability**:** conscious, alert, and able to interact at age-appropriate level; school-age child attending regular school classroom but grade perhaps not appropriate for age; possibility of mild neurologic deficit.
PCPC 3. Moderate disability: conscious; sufficient cerebral function for age-appropriate independent activity of daily life; school-age child attending special education classroom and/or learning deficit present.
PCPC 4. Sever disability: conscious; dependent on others for daily support because of impaired brain function.
PCPC 5. Coma or vegetative state: any degree of coma without the presence of all brain death criteria; unawareness; even if awake in appearance, without interaction with environment; cerebral unresponsiveness and no evidence of cortex function (not aroused by verbal stimuli); possibility of some reflexive response, spontaneous eye-opening, and sleep-wake cycles.
PCPC 6. Brain death: apnea, areflexia, and/or electroencephalographic silence.

ANNEXE 12. Status epilepticus severity score (26)

	Features	STESS
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type	Simple-partial, complex-partial, absence, myoclonic*	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Total		0–6

* complicating idiopathic generalized epilepsy

ANNEXE 13. Epidemiology Based Mortality Score in Status Epilepticus (28)

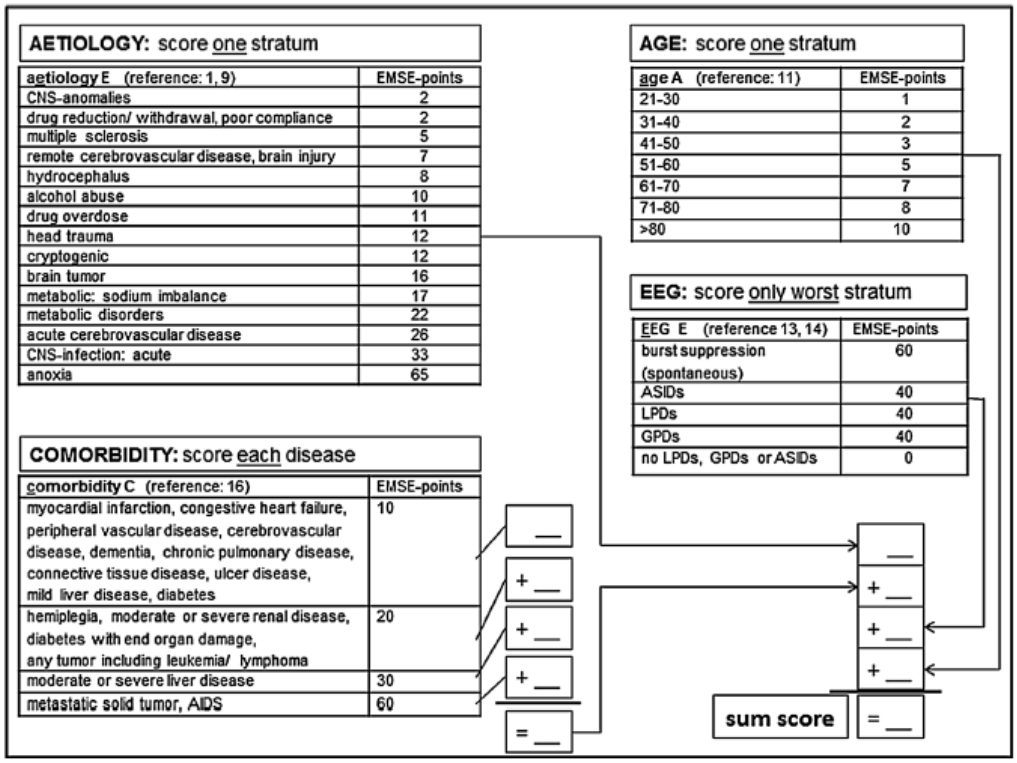


Fig. 2 Evaluation sheet example for making the sum score for a particular combination of parameters, demonstrated here is the combination aetiology-*a*ge-comorbidity-*E*EG (EACE)