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Title: Serum Neuron Specific Enolase: a new tool for seizure risk monitoring after status epilepticus

Short running title: Neuron Specific Enolase in status epilepticus

Authors:

Aurélie Hanin, PharmD^{1,2}, Sophie Demeret, MD³, Jérôme Alexandre Denis, PharmD, PhD^{4,5}, Vi-Huong Nguyen-Michel, MD², Benjamin Rohaut, MD, PhD^{1,3,4}, Clémence Marois, MD^{3,6}, Françoise Imbert-Bismut, PharmD, PhD⁷, Dominique Bonnefont-Rousselot, PharmD, PhD^{7,8}, Pierre Levy, MD⁹, Vincent Navarro, MD, PhD^{1,2,4,10*}, Virginie Lambrecq, MD, PhD^{1,2,4*}

* These authors contributed equally to the manuscript.

¹Sorbonne Université, Paris Brain Institute – Institut du Cerveau, ICM, INSERM U1127, CNRS UMR 7225, Paris France

²AP-HP, Clinical Neurophysiology Department, Pitié-Salpêtrière Hospital, Paris, France

³AP-HP, Neuro-Intensive care Unit, Pitié-Salpêtrière Hospital, Paris, France

⁴Sorbonne Université, Paris France

⁵AP-HP, Endocrine and Oncological Biochemistry Department, Pitié-Salpêtrière Hospital, Paris, France

⁶Groupe de Recherche Clinique en REanimation et Soins intensifs du Patient en Insuffisance Respiratoire aiguE (GRC-RESPIRE), Sorbonne Université

⁷AP-HP, Metabolic Biochemistry Department, Pitié-Salpêtrière Hospital, Paris, France

⁸Unité des Technologies Chimiques et Biologiques pour la Santé (UTCBS), INSERM U1267, CNRS UMR 8258, Université de Paris, Paris, France

⁹AP-HP, Public Health Department, Tenon Hospital, Paris, France

¹⁰AP-HP, Center of Reference for Rare Epilepsies, Pitié-Salpêtrière Hospital, Paris, France

Correspondence to: Vincent Navarro

Affiliation: Sorbonne Université, Paris Brain Institute – Institut du Cerveau, ICM, Inserm U1127, CNRS UMR 7225, Paris France and AP-HP, Clinical Neurophysiology Department, Pitié-Salpêtrière Hospital, Paris, France

Address/City/Country: 47-83 Boulevard de l'Hôpital, Paris 75013, France

Telephone: + 33 1 42 16 18 11

Email: vincent.navarro@aphp.fr

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Summary

Objective: There is a need for accurate biomarkers to monitor EEG activity and assess seizure risk in patients with acute brain injury. Seizure recurrence may lead to cellular alterations and subsequent neurological sequels. We investigated whether Neuron Specific Enolase (NSE) and S100-beta (S100B), brain injury biomarkers, can reflect EEG activity and help to evaluate the seizure risk.

Methods: We included 11 patients, admitted to an intensive care unit for refractory status epilepticus, who underwent a minimum of 3 days of continuous EEG, concomitantly with daily serum NSE and S100B assays.

We investigated on 103 days the relationships between serum NSE and S100B levels and two EEG scores to monitor the seizure risk. We looked for biochemical biomarker thresholds able to predict seizure recurrence.

Results: Only NSE levels positively correlated with EEG scores. Similar temporal dynamics were observed for the time courses of EEG scores and NSE levels. NSE levels above 17 ng/mL were associated with seizure in 71% of patients. An increase of more than 15% of NSE levels was associated with seizure recurrence in 80% of patients.

Conclusions: Our study highlights the potential of NSE as a biomarker of EEG activity and to assess risk of seizure recurrence.

Abbreviations:

cEEG = continuous electroencephalography; EaSiBUSSEs = EEG-based seizure build-up score in status epilepticus; ICU = intensive care unit; LMM = linear mixed model; NSE = Neuron Specific Enolase; ROC = receiving operating characteristics; S100B = S100-beta protein; SE = status epilepticus

Introduction

Status epilepticus (SE) is a life-threatening prolonged epileptic seizure.(1) Around 25% of SE are refractory to adequate antiepileptic drugs and require anesthetics. Non-convulsive seizures and non-convulsive SE occur frequently after a convulsive SE (33.5% and 20.2% respectively).(2)

Seizures may be preceded by electroencephalography (EEG) changes, which fluctuate both spatially and temporally. Currently, continuous EEG (cEEG) is the only way to monitor patients admitted after refractory SE. It allows the diagnosis of the persistence or recurrence of non-convulsive seizures in anesthetized and curarized patients. The management of refractory SE without cEEG monitoring exposes the patients to complications induced by unnecessary aggressive sedative treatments and brain lesions related to untreated SE.(3) SE recurrence may lead to cellular alterations (e.g. neuronal loss and glial activation) that could induce subsequent neurologic sequelae and even death.(4) Neuron Specific Enolase (NSE) and S100-beta (S100B) protein, two proteins that reflect brain injury, have been proposed as seizures or SE biomarkers.(5) NSE is present in neurons and neuroendocrine cells. An increase of serum NSE levels was first reported after an isolated seizure, with a peak level occurring within six to twelve hours after seizure onset.(6–9) Increased serum NSE levels were reported in patients with sustained SE.(10,11) S100B is present in high concentrations in glial cells and Schwann cells. S100B peaked in serum within one to six hours after an isolated seizure, and was not previously studied in human SE.(9)

Here, we assessed whether NSE and S100B could reflect the EEG activity by investigating the relationships between EEG scores, able to monitor the seizure risk, and serum NSE and S100B levels. Secondly, we assessed if serum NSE and S100B levels could be used to evaluate the seizure risk recurrence after SE and if we could propose biological thresholds for their clinical use.

Methods

Study design, setting and participants

We prospectively enrolled consecutive patients admitted in the Neuro intensive care unit (ICU) of Pitié-Salpêtrière Hospital for refractory SE, between December 2017 and July 2019 and who underwent at least 3 days of cEEG recording, concomitantly with daily blood analysis. Patients with post-anoxic SE were excluded. We also excluded patients for whom NSE and S100 levels were only measured during periods of induced burst-suppression EEG pattern. For other patients who required induced burst suppression, we started the study after burst suppression was over.

The protocol was approved by the local ethic committee (2012, CPP-Paris-VI). Patients or relatives were informed and provided their consent.

Seizure risk assessment with EEG analyses

EEGs were independently and blindly scored with two quantitative tools (2HELPS2B and EaSiBUSSEs) developed to monitor the seizure risk.(12–14) The 2HELPS2B score (range 0-7) is calculated, for a given time period, by a point system using one clinical and five EEG variables.(12) It was shown to efficiently assess the seizure risk in critically ill patients.(12) The EaSiBUSSEs score (range 1-7) is based on the morphology and the prevalence of EEG patterns and tailored to repeatedly monitor the progressive build-up leading to seizure recurrence (Supplementary Fig1, reprinted from *Continuous EEG monitoring in the follow-up of convulsive status epilepticus patients: A proposal and preliminary validation of an EEG-based seizure build-up score (EaSiBUSSEs)* (p.6), Aurélie Hanin, 2021, Neurophysiologie Clinique/Clinical Neurophysiology).(14)

EEG were scored every day within 3 consecutive time windows of 3 hours, before the blood draw (Fig.1A). The 3 hours' time-window was chosen to be able to assess efficiently the prevalence of EEG patterns.(15) The mean of the 3 scores for each day was calculated, allowing to score EEG for 9 hours before blood sample. This global time-window was chosen because NSE levels reach a peak between six and twelve hours after seizure onset.

Serum samples and assays

Blood samples were drawn daily at 6 am. Blood was centrifuged at 3500 rpm for 10 min. Hemolytic samples (hemoglobin concentration up to 47 mg/dL) were excluded. Serum NSE and S100B assays were performed daily using respectively immunofluorimetric assays and electrochemiluminometric sandwich immunoassays (Kryptor® and Modular®E170, Roche Diagnostics). The lowest detections were 0.8 ng/mL for NSE and 0.005 ng/mL for S100B. The coefficients of variation were found to be lower than 5% for all controls used.

Statistical analysis

To evaluate the relationship between serum NSE or S100B levels and EEG scores, we computed a linear mixed model (LMM) using successively NSE or S100B levels as the dependent variable; 2HELPS2B or EaSiBUSSEs as the fixed effect explanatory variables; and patients, time and the second biological variable (successively S100B or NSE) as random effects. The levels of correlation were obtained with Spearman analysis.

To assess the ability of biological markers to identify patients who would present a seizure in the next 24 hours, we computed the area under the receiver operating characteristics (ROC) curve and reported the values of sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) for the best cut-off defined accordingly to the Youden's index.(16)

All statistical tests were two-sided with a type I error rate of 5%. Analyses were performed using the R software V.3.5.0.

Data availability

All anonymized data are available on request.

Results

We screened 17 consecutive patients who were admitted to the Neuro-ICU for refractory SE and underwent long-term cEEG recording. We excluded 5 patients because their EEG was monitored for less than 3 days and 1 patient for whom NSE and S100 levels were only measured during periods of induced burst-suppression EEG pattern. We included the 11 remaining patients for a total of 103 days with both cEEG recording (more than 950 hours of EEG records) and daily NSE and S100B assays.

Demographic and clinical data of the population and etiologies of SE are shown in Table 1.

1. Association between EEG scores and serum NSE or S100B levels

Patients underwent a mean of 14 days of cEEG monitoring. Serum NSE levels positively correlated with 2HELPS2B ($\rho=0.31$; $p=0.0017$; $p=0.10$ once corrected for patient, time and S100B effect; Fig.1B) and EaSiBUSSEs scores ($\rho=0.27$; $p=0.0066$; $p=0.030$ once corrected for patient, time and S100B effects; Fig.1C). Conversely, S100B levels did not correlate with either 2HELPS2B ($\rho=-0.026$; $p=0.80$; Fig.1D) or EaSiBUSSEs ($\rho=-0.048$; $p=0.64$; Fig.1E). A closer look at the time courses of serum NSE levels and EaSiBUSSEs score showed a correlation ($\rho=0.24$; $p=0.023$; $p=0.091$ once corrected for patient effect), regardless of SE

etiology (see Fig.2 for details of the etiologies). No correlation was found between the evolution of NSE levels and 2HELPS2B ($p=0.66$).

2. Biological markers to assess the seizure risk

Serum NSE and S100B levels were able to assess the seizure risk with a mild discrimination (AUC=0.608; 95% CI 0.481-0.736 and AUC=0.592; 95% CI 0.471-0.712, respectively). Nevertheless, NSE levels above 17 ng/mL were associated with a higher risk of seizures (PPV=71.1%, NPV=57.1%, Se=60.0%, Sp=68.6%), along with an increase of 15% between two successive measures (PPV=80.0%, NPV=50.0%, Se=32.0%, Sp=89.5%).

We did not find efficient thresholds to assess the seizure risk with S100B (PPV<50%).

Discussion

Serum NSE levels correlated well with both EEG scores predicting the risk of seizure recurrence: low NSE levels were associated with EEG epochs including rare or no sporadic epileptiform discharges, whereas high NSE levels were associated with epochs including frequent to continuous periodic discharges and seizures. Increased serum NSE levels was previously reported after isolated seizures, with a peak occurring between six and twelve hours after seizure onset.(6–9) Our results are in agreement with previous publications. However, the underlying mechanisms are still not well known. Increased serum NSE levels may be related to neuronal death, and may explain the prognosis value of this biomarker.(10) Indeed, patients with periodic discharges had higher NSE levels and poorer outcome than patients with sporadic epileptiform discharges.(17) Nevertheless, despite their better prognosis in comparison to patients with periodic discharges, patients with seizures had the highest NSE levels.(17) Therefore, we may hypothesize that increased serum NSE levels might also be related to the

opening of the blood-brain barrier related to seizures. A mixed scenario combining opening of the blood-brain barrier and neuronal death may explain elevated level of NSE in SE.

The time course of serum NSE levels correlated well with that of the EaSiBUSSEs, regardless of the SE etiology. The correlations were lower for NSE and 2HELPS2B. This could be explained by a lower range of variation within each patient for 2HELPS2B score, possibly because the prevalence of EEG patterns (i.e. sporadic epileptiform discharges, periodic discharges) is not accounted for this score.

Higher NSE levels as well as increased NSE levels between two successive measures were associated with a higher risk of seizure. We found notably that more than 70% of patients with NSE above 17 ng/mL and 80% of patients for whom NSE increased of more than 15% between two successive measures would present seizures in the next 24 hours. Therefore, we assume that an NSE level kinetics could be relevant to identify periods of uncontrolled SE.

Our study highlights the potential of NSE as a biomarker reflecting EEG activity and its interest to assess the seizure risk. It is a simple effective bed-side investigation, that does not require interpretation expertise.

We found no correlation between S100B levels and EEG scores. We can make the hypothesis that either the short half-time of this protein is not appropriate for daily evaluation or that glial cell activation is delayed and inconstant.

Although our population sample was small with various SE etiologies, this is the first study which performed daily NSE and S100B measurements and a detailed analysis of cEEG recording with two EEG scores for long-term monitoring patients (14 days in average per patient and a total of 103 days).

Multimodal monitoring is increasingly recommended to monitor patients in ICU and to assess the pathophysiological pathways involved in secondary brain events. A multimodality monitoring with cEEG and NSE assays might have an added value to assess the seizure risk. Further studies are needed to confirm the interest of NSE in SE follow-up and to assess the performance of a multimodal monitoring in critically ill patients after SE as well as in other acute brain injury patients.

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Conflicts of Interest

Vincent Navarro reports personal fees from UCB Pharma, Eisai, GW Pharma and LivaNova, outside the submitted work.

Other authors report no disclosures.

Author contributions

Name	Contribution
Aurélie Hanin	Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, validation, visualization, writing original draft preparation
Sophie Demeret	Conceptualization, investigation, methodology, project administration, supervision, validation, writing original draft preparation
Jérôme Alexandre Denis	Data curation, investigation, methodology, validation, visualization, writing original draft preparation
Vi-Huong Nguyen-Michel	Investigation, validation, writing original draft preparation
Benjamin Rohaut	Investigation, validation, writing original draft preparation
Clémence Marois	Investigation, validation, writing original draft preparation
Françoise Imbert-Bismut	Data curation, investigation, methodology, validation, visualization, writing original draft preparation
Dominique Bonnefont-Rousselot	Investigation, project administration, supervision, validation, writing original draft preparation
Pierre Levy	Data curation, formal analysis, visualization
Vincent Navarro	Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, validation, visualization, writing original draft preparation
Virginie Lambrecq	Conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, visualization, writing original draft preparation

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Figures Legends

Fig.1: Correlations between Neuron Specific Enolase, S100B and the EEG scores and their assessing performance.

The Fig.1A represents the analysis protocol for each patient.

The Fig.1B and 1C show the relations between serum NSE levels and 2HELPS2B and EaSiBUSSEs, respectively. The Fig.1D and 1E show the relations between serum S100B levels and 2HELPS2B and EaSiBUSSEs, respectively. The correlations were assessed with the Spearman test.

Fig.2: Time course of EEG-based seizure build-up score in status epilepticus (EaSiBUSSEs) and NSE levels for 11 patients.

The time course of serum NSE levels is represented with red lines while the time course of EaSiBUSSEs score is represented with black lines. The dotted lines represent non-continuous data. We observed a very good correlation for 8 patients (A-H). A and B represent the time courses for 2 patients with autoimmune encephalitis (AE), C and D the time courses for 2 patients with a posterior reversible encephalopathy syndrome (PRES), E and F the time courses for patients with metabolic SE (MET), G and H the time courses for 2 patients who had been previously diagnosed with epilepsy (myoclonic astatic epilepsy, MAE and Lennox-Gastaut, LG). The correlation was weaker for 3 patients with New-Onset Refractory Status Epilepticus (NORSE) for whom no etiology had been found after careful evaluation (I-K).

Table1: Clinical characteristics of the study population

Data for the eleven patients are represented with mean or percentages and standard deviation. Abbreviations: AEDs = antiepileptic drugs; CBZ = Carbamazepine; CLO = Clobazam; CLZ = Clonazepam; FOS = Fosphenytoin; IgIV = intravenous immunoglobulin; KET = Ketamine;

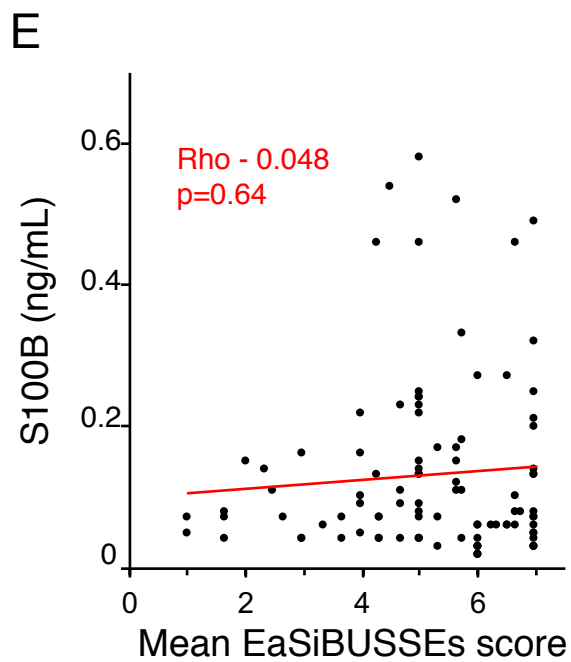
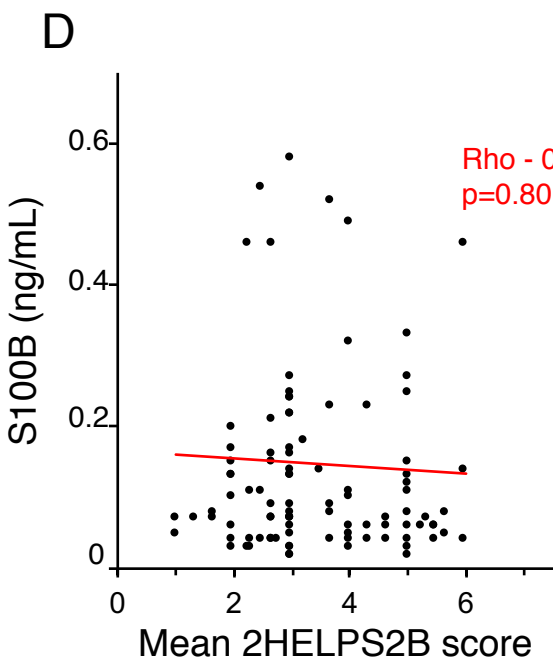
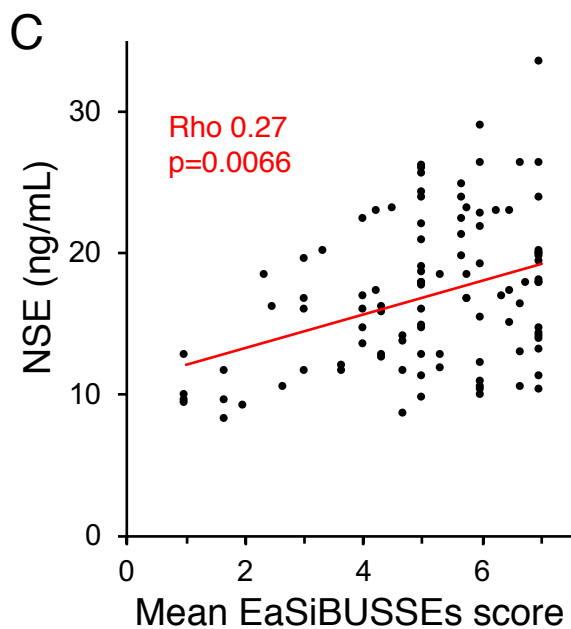
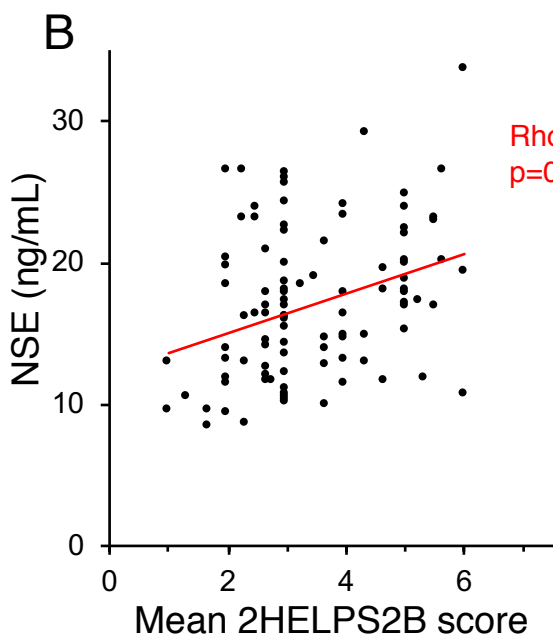
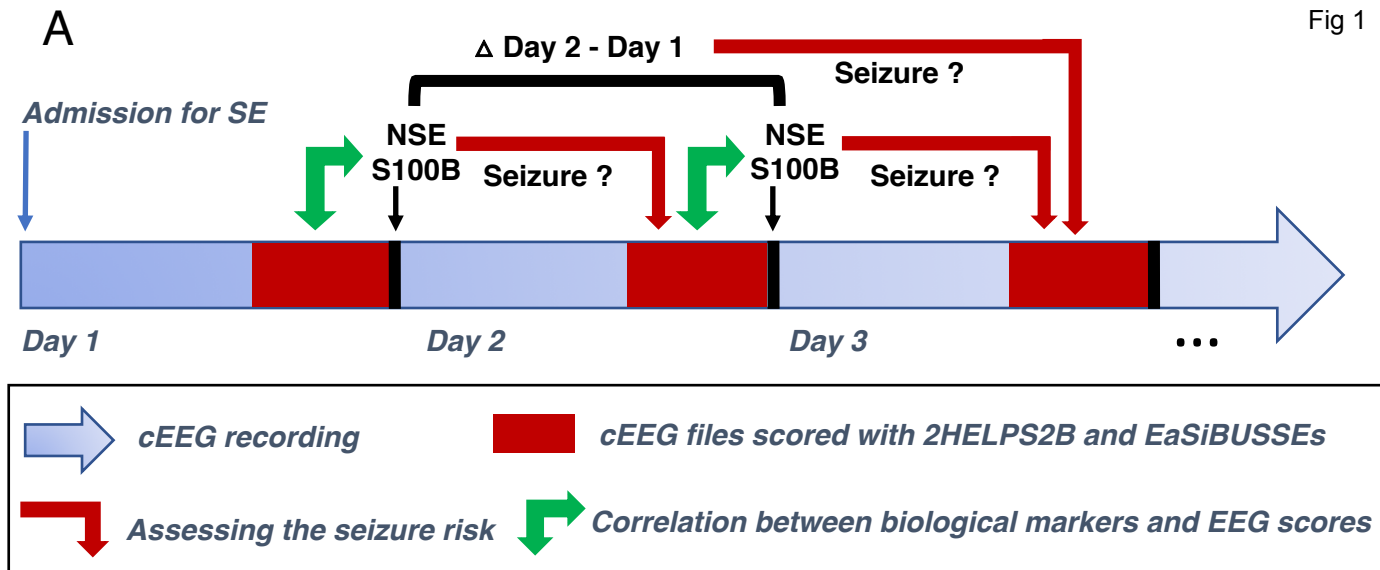
LCS = Lacosamide; LTG = Lamotrigine; LVT = Levetiracetam; MDZ = Midazolam; NORSE = New-Onset Refractory Status Epilepticus; NSE = Neuron Specific Enolase; PB = Pentobarbital; PER = Perampanel; PGB = Pregabalin; PHB = Phenobarbital; PHE = Phenytoin; PPF = Propofol; PRES = Posterior Reversible Encephalopathy Syndrome; RFM = Rufinamide; S100B = S100-beta; SE = Status Epilepticus STP = Stiripentol; TP = Thiopental; TPM = Topiramate; VPA = Valproate

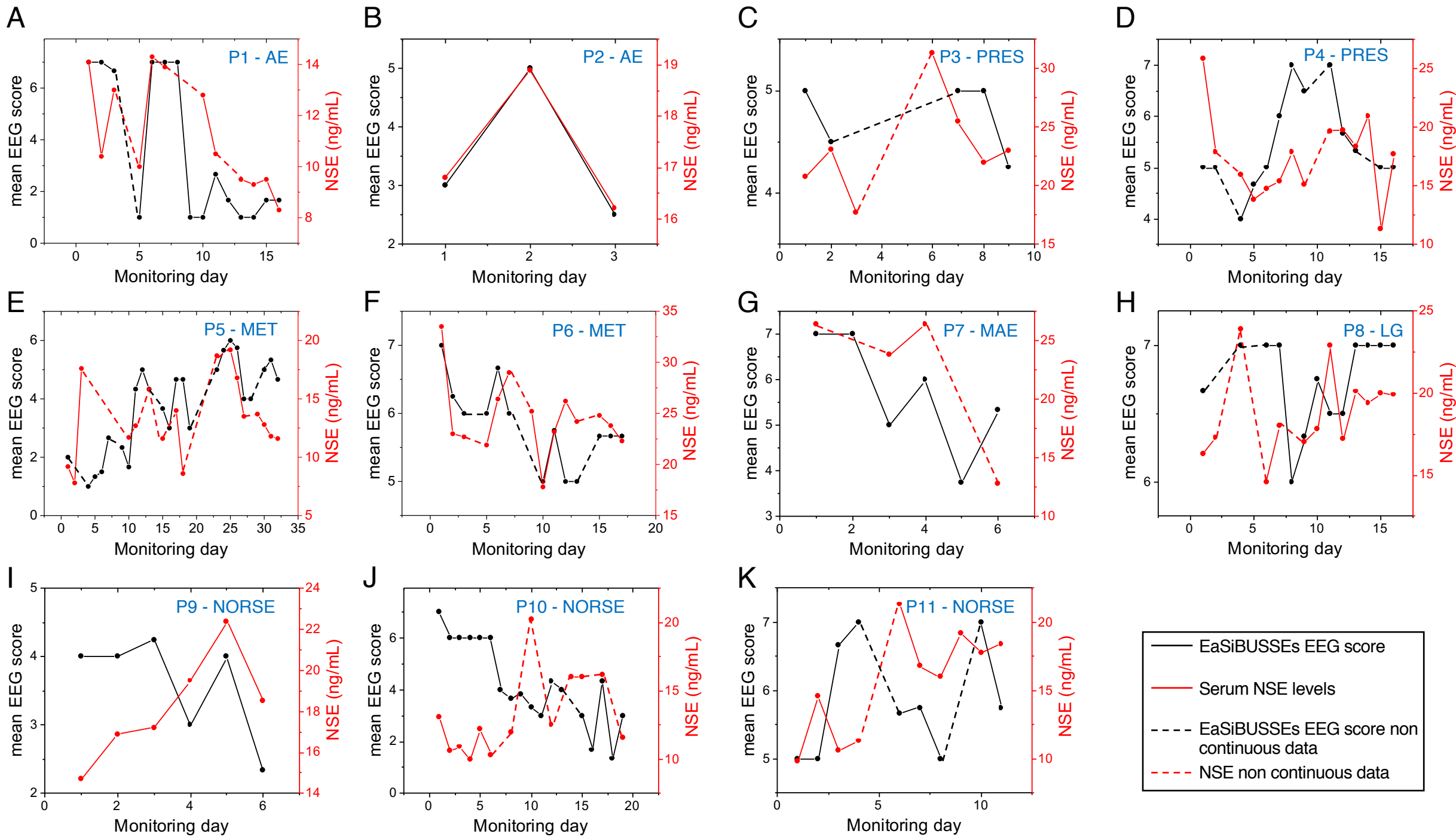
*AEDs: usual treatment

Patient	1	2	3	4	5	6	7	8	9	10	11	Mean or % ± sd
Age (years)	20	54	52	68	58	24	26	27	75	27	20	41.0 ± 20.6
Previous epilepsy	No	No	No	No	No	Yes	Yes	Yes	No	No	No	27%
SE etiology	NMDA encephalitis	Seronegative autoimmune encephalitis	PRES	PRES	Metabolic	Metabolic	Myoclonic-astatic epilepsy	Lennox-Gastaut syndrome	NORSE	NORSE	NORSE	-
SE clinical subtype	Focal	Focal	Focal	Focal	Focal	Focal	Focal	Focal	Focal	Generalized	Generalized	-
Intubated	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	82%
Anesthetics	MDZ PPF	MDZ PB PPF	PPF	MDZ PPF	KET MDZ PPF TP	-	KET MDZ	KET MDZ PPF	MDZ	KET MDZ PPF	KET MDZ PPF	-
AEDs	CLO CLZ FOS LVT	CLO LCS LVT PHB	CLO FOS LCS LVT PGB	LCS LVT	CBZ LCS LVT TPM	CBZ CLO CLZ FOS LTG* LVT PER PHB PHE PGB VPA*	CLO* LTG* LVT RFM* TPM* VPA*	CBZ* CLO LTG* STP* TPM* VPA	LCS LVT	CLO FOS LCS LVT PER TPM	FOS LVT PER PHB TPM	-
IgIV or corticoids	Yes	Yes	No	Yes	No	No	No	No	Yes	Yes	Yes	55%
SE duration before inclusion (days)	0	21	14	35	34	1	3	13	10	9	22	14.7 ± 12.1
Duration of monitoring (days)	16	3	9	16	32	17	6	16	6	19	11	13.7 ± 8.08
Duration of monitoring with NSE/S100B assays (days)	12	3	5	13	14	13	4	12	6	12	9	9.4 ± 4.1
Highest NSE value (ng/mL)	14.3	18.9	25.5	25.9	19.2	33.5	26.4	23.9	22.4	20.2	21.3	22.9 ± 5.05
Highest S100B value (ng/mL)	0.21	0.16	1.62	0.27	0.15	0.24	0.04	0.13	0.16	0.07	0.52	0.32 ± 0.45


Abbreviations: CBZ = Carbamazepine; CLO = Clobazam; CLZ = Clonazepam; FOS = Fosphenytoin, KET = Ketamine; LCS = Lacosamide; LTG = Lamotrigine; LVT = Levetiracetam; MDZ = Midazolam; PB = Pentobarbital; PER = Perampanel; PGB = Pregabalin; PHB = Phenobarbital; PHE = Phenytoin; PPF = Propofol; RFM = Rufinamide; STP = Stiripentol; TP = Thiopental; TPM = Topiramate; VPA = Valproate


Table 1







Score	Definition		Model
1	Background EEG with no interictal or ictal epileptiform discharges		
	Background EEG activity with non-specific EEG abnormalities (including focal or generalized slowing)		
2	Background EEG activity with lateralized or generalized, sporadic (rare < 1%, occasional 1-9% to frequent 10-49%) interictal epileptiform discharges (including spikes, polyspikes)		
3	Background EEG with lateralized or generalized, abundant (50-89%) interictal epileptiform discharges (including spikes, polyspikes)		
4	Background EEG activity with frequent (10-49%) periodic discharges (LPDs, GPDs, BiPDs) or LRDA without spatial or temporal organization, from 0.1 to 1.5/s	Scattered activities	
		Grouped activities	
5	Background EEG activity with abundant (50-89%) periodic discharges (LPDs, GPDs, BiPDs) or LRDA, without spatial or temporal organization from 0.1 to 1.5/s. Rare (<1%) BRDs, above 1.5/s, without spatial or temporal organization may occur	Scattered activities	
		Grouped activities	
6	(a) Continuous ($\geq 90\%$) periodic discharges (LPDs, GPDs, BiPDs) or LRDA, without spatial or temporal organization from 0.1 to 1.5/s; with occasional (1-9%) BRDs, above 1.5/s; no background activity		
	(b) Seizure burden less than 20%		
7	(a) Continuous ($\geq 90\%$) periodic discharges (LPDs, GPDs, BiPDs) or LRDA, without spatial or temporal organization from 0.1 to 1.5/s, with frequent (10-49%) BRDs, above 1.5/s; no background activity		
	(b) Seizure burden more than 20%		


Legend
 Background activity

 Focal or generalized slowing

 Sporadic epileptiform discharges

 PDs (LPDs, GPDs, BiPDs) and LRDA

 BRDs

 Seizure

*The GRDA and SIRPIDs were not included in this score, because they were shown not to be associated with seizures⁴³

Supplementary Fig.1:

Definition and model of the EEG-based seizure build-up score in status epilepticus (EaSiBUSSEs).

Reprinted from *Continuous EEG monitoring in the follow-up of convulsive status epilepticus patients: A proposal and preliminary validation of an EEG-based seizure build-up score (EaSiBUSSEs)* (p.6), Aurélie Hanin, 2021, Neurophysiologie Clinique/Clinical Neurophysiology.(14)

Seven EEG subscores were defined from the pattern least associated with seizure risk (no interictal activity) to the most severe one (focal or generalized SE). They depict the morphology and prevalence of EEG patterns in EEG epochs. The grey boxes represent the background activity. The green lines represent the focal or generalized slowing, the black lines the sporadic epileptiform discharges, the blue lines the PDs (BiPDs, LPDs and GPDs) and LRDA, the purple lines the BRDs and the red lines the seizures. The seizure burden is estimated as the total duration of seizures out of the total duration of cEEG recording.

Abbreviations: BiPDs = bilateral independent periodic discharges; BRDs = brief rhythmic discharges; GPDs = generalized periodic discharges; LPDs = lateralized periodic discharges; LRDA = lateralized delta rhythmic activity.