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Full title: Neuron Specific Enolase, S100-beta protein and progranulin as diagnostic biomarkers of status epilepticus

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Summary

Status epilepticus (SE) is a life-threatening prolonged epileptic seizure. A rapid diagnosis is fundamental to initiate antiepileptic treatment and to prevent the development of neurological sequels. Several serum and cerebrospinal fluid biomarkers have been proposed to help in the diagnosis of SE. Nevertheless, previous studies were conducted on too small patient cohorts, precluding the utilization of interesting biomarkers for the SE diagnosis.

Here, we aimed to assess the ability of Neuron Specific Enolase (NSE), S100-beta protein (S100B) and progranulin to help in the diagnosis of SE in a large cohort of patients (36 control patients, 56 patients with pharmaco-resistant epilepsy and 82 SE patients).

Blood NSE, S100B and progranulin levels were higher in SE patients when compared with control patients or patients with pharmaco-resistant epilepsy. Both NSE and progranulin levels were higher in cerebrospinal fluid from SE patients when compared with control patients. The receiver operating characteristics curves revealed good accuracy at detecting SE for serum S100B (AUC 0.748) and plasma progranulin (AUC 0.756). The performances were lower for serum NSE (AUC 0.624). Eighty-four percent of patients with serum S100B levels above 0.09 ng/mL presented with a SE whereas ninety percent of patients without SE had serum S100B levels lower than 0.09 ng/mL. Serum S100B levels were not significantly different according to SE etiology, SE semiology or SE refractoriness.

Our results confirm that NSE, S100B and progranulin levels are increased after SE. We suggest that serum S100B levels might be added to clinical evaluation and electroencephalogram to identify difficult-to-diagnose form of SE.

Key words: Status epilepticus – Diagnosis – Etiology – Neuron Specific Enolase – S100-beta protein – Progranulin

Abbreviations: CONT = Control patients; CSF = Cerebrospinal Fluid; EEG = electroencephalogram; EPI = pharmaco-resistant epileptic patients; ICU = Intensive Care Unit; NPV = Negative Predictive Value; NSE = Neuron Specific Enolase, NRSE = Non-Refractory Status Epilepticus; PPV = Positive Predictive Value; PSRSE = Prolonged Super-Refractory Status Epilepticus; ROC = Receiver Operating Characteristics; RSE = Refractory Status Epilepticus; S100B = S100-beta protein; SE = Status Epilepticus

Introduction

Status epilepticus (SE) is a life-threatening prolonged epileptic seizure, related to various etiologies and with heterogeneous clinical presentations [1]. Sustained SE may lead to brain injury and is associated with worse clinical outcomes and higher mortality [2]. The rapid diagnosis of SE is fundamental to urgently initiate antiepileptic treatments [3]. Diagnosis of convulsive SE is mostly based on clinical examination. In contrast, the diagnosis of non-convulsive SE requires an electroencephalogram (EEG) recording [4]. Here, we looked for the impact of SE on three biochemical markers levels and we wondered if these biochemical markers could be used to identify difficult-to-diagnose form of SE.

We considered Neuron Specific Enolase (NSE), S100-beta protein (S100B) and progranulin, which have previously been proposed as SE biomarkers [5]. They reflected respectively the neuronal injury (NSE), the astroglial injury (S100B) and the activation of microglia (progranulin) that occur in SE. Increased cerebrospinal fluid (CSF) NSE levels were reported in patients with cryptogenic or remote SE [6]. Increased serum NSE levels were also reported in patients with sustained SE with a peak between 24 and 48 hours after the SE onset [7, 8]. Despite good characteristics (good neuronal specificity, stability in the body fluids, a rapid and reliable biochemical assessment), NSE is not currently used as a diagnosis SE biomarker. This can be explained as most previous studies were conducted on too small patient cohorts (between 2 to 31 patients) precluding the utilization of NSE as a validated diagnosis biomarker for SE [9]. S100B was mostly studied in isolated seizures but increased CSF S100B levels were reported in a rat model of SE [10–12]. S100B was not previously studied in human SE. Nevertheless, its rapid assessment and its ability to distinguish isolated epileptic seizures from psychogenic non-epileptic seizures make S100B a promising biomarker for SE diagnosis [12]. A higher expression of progranulin was observed in activated microglia and macrophages following pilocarpine-induced SE in rats [13]. However, progranulin levels in CSF were not significantly increased compared to patients who underwent a lumbar puncture after a single tonic-clonic seizure [14].

Here, we evaluated the diagnosis value of these three biomarkers in a large cohort of patients. They were measured in blood samples from SE patients, control patients and patients with pharmaco-resistant epilepsy as well as in CSF samples from some SE patients and control patients.

Firstly, we assessed the ability of NSE, S100B and progranulin to identify SE patients.

Secondly, we investigated the impact of SE etiology, SE semiology and the delay of blood or CSF collection after the ongoing SE onset on the biomarker's levels

Methods

Study design, setting and participants

We prospectively enrolled adult patients admitted in intensive care unit (ICU) and neurology units of the Pitié-Salpêtrière Hospital, from February 2013 to March 2021. The protocol was approved by our local ethic committee (2012, CPP Paris-VI) and sponsored by INSERM (C16-16, 20152482). Patients or relatives were informed and gave their consent. The study design and report are in accordance with the STROBE statement [15].

Eligible SE patients were patients aged at least 18 years, with an ongoing SE, either a generalized convulsive SE, either a focal convulsive or focal non-convulsive SE diagnosed according to the International League Against Epilepsy criteria [1]. The SE end was defined as the absence of seizures after the anesthetic's withdrawal. Physicians from ICU and neurology units excluded: patients with a subtle SE defined by minor and erratic myoclonic movements in patients with severely impaired consciousness; patients with post-anoxic SE; patients whose SE was linked to a pathological condition, such as trauma or subarachnoid aneurysmal hemorrhage, who needed immediate surgery and for whom the biomarkers could be elevated due to the underlying disease [16, 17]. Patients for whose parent, guardian or other reliable person refused permission or patients who refused themselves permission were also excluded. Enrolled patients were divided into four groups according to their SE etiology: acute, progressive, remote and cryptogenic [18]. The type of SE was further categorized into three groups: non-refractory SE (NRSE), refractory SE (RSE) and prolonged super-refractory SE (PSRSE) [19]. The RSE was defined as a failure of at least two appropriately selected and dosed parenteral medications including a benzodiazepine, without any specific SE duration [19]. The PSRSE was defined as a RSE that persists for more than 7 days, with ongoing need for anesthetics [19]. The type of SE was further categorized into three groups according to the SE semiology: generalized convulsive SE, focal convulsive SE and focal non-convulsive SE. None of the patients had a generalized non-convulsive SE.

Eligible patients with pharmaco-resistant epilepsy (EPI) were aged at least 18 years and hospitalized for a video-EEG monitoring pre-surgical evaluation (n=17) or for a resection of the epileptic focus (n=39). Patients who refused permission and patients for whose the date of the last seizure cannot be reported were excluded.

Eligible control patients (CONT) were aged at least 18 years and hospitalized in neurology units for non-acute disorders and for whom a clinical neurological evaluation and a lumbar puncture were performed. Patients with previous history of epilepsy or patients whose symptoms were linked to an acute pathological condition (trauma, hemorrhage) were excluded as well as patients with an abnormal lumbar puncture (i.e. pleocytosis, increased protein levels, intrathecal synthesis). The diagnosis for these patients were psychogenic disorders or non-inflammatory peripheral neuropathies.

Biochemical assays

Blood and CSF samples were centrifuged at 3500 rpm for 10 min. Hemolytic samples (hemoglobin concentration above 47 mg/dL) were excluded.

The NSE and S100B assays were performed using respectively immunofluorimetric assays and electrochemiluminometric sandwich immunoassays (Kryptor®, Brahms 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 (CV) were found to be lower than 5% for all controls used. Progranulin measurements were performed using the progranulin-human-ELISA kit (Adipogen, Coger SAS, France). All the samples were analyzed in duplicated and progranulin measurements was repeated when CV between duplicated measures were higher than 15%.

Statistical analysis

Analyses were performed with R Software (R.3.5.0).

We first performed Kruskal-Wallis test to evaluate subgroups impact. Then, pairwise comparisons were performed using Student or Mann-Whitney when appropriate. The Benjamini-Hochberg test procedure was used to correct for multiple comparisons. Correlations between blood levels and the time between SE onset and blood sampling were evaluated by calculating respective Spearman's rho values and their level of significance. To assess the ability of biomarkers to diagnose SE, we computed the area under the receiver operating characteristics (ROC) curve and reported sensitivity and specificity for the best cut-off which was defined accordingly to the Youden's index [20]. Quantitative variables were expressed as mean with standard deviation. All statistical were two-sided with a type I error rate of 5%.

Data availability

All anonymized data are available on request.

Results

The study cohort is represented in Fig.1A. Main demographic data are shown in Table.1. Blood samples were collected for 36 CONT patients, 56 EPI patients and 82 SE patients. CSF samples were collected for 38 CONT patients and 34 SE patients.

Blood samples and CSF samples were collected respectively on average 7 (± 12) and 11 (± 17) days after the SE onset. All the blood and CSF samples were collected in patients with an ongoing SE. Twenty-nine EPI patients (52%) showed a seizure in the last forty-eight hours before the blood collection.

1. NSE, S100B and progranulin as diagnostic biomarkers of SE

1.1. Blood NSE, S100B and progranulin levels

Serum NSE levels were significantly higher in SE patients when compared with EPI patients and showed a non-significant increase as compared with CONT patients (Fig.1B, Table.2). Both serum S100B and plasma progranulin levels were higher in SE patients when compared with EPI patients and CONT patients (Fig.1B, Table.2). No significant difference of blood levels was found between CONT patients and EPI patients for any of the three biomarkers (Table.2).

1.2. CSF NSE, S100B and progranulin levels and CSF/blood ratios

Both CSF NSE and progranulin levels were significantly higher in SE patients when compared with CONT patients (Fig.1C, Table.2). No significant difference was found for CSF S100B levels (Table.2). Similarly, we observed in SE patients an increase in the CSF/blood ratios for progranulin, while the CSF/blood ratios tended to increase for NSE and no difference was found for CSF/blood S100B ratios (Table.2).

1.3. SE diagnosis value

The ROC curves revealed good accuracy at detecting SE for: (i) serum S100B levels (AUC 0.748 [CI 95% 0.669–0.827]), with a sensitivity of 59.7%, specificity of 90.2%, positive predictive value (PPV) of 83.6% and negative predictive value (NPV) of 72.8% when using the cut-off of 0.09 ng/mL; and (ii) plasma progranulin levels (AUC 0.756 [CI 95% 0.681–0.831]), with a sensitivity of 57.3%, specificity of 85.4%, PPV of 79.7% and NPV of 66.7% when using

the cut-off of 110 ng/mL (Fig.1D). Serum NSE levels can detect SE with a lower discrimination (AUC 0.624 [CI 95% 0.536–0.713]).

2. Biomarkers levels according to SE refractoriness, SE semiology and SE etiology

2.1. SE refractoriness

We next wondered if blood biomarkers levels differed according to SE refractoriness and to the delay between the ongoing SE onset and the blood collection. We found that only plasma progranulin levels differed according to the SE refractoriness ($p < 0.001$). Plasma progranulin levels were significantly higher for PSRSE patients when compared with RSE patients (177.1 ± 95.0 versus 107.7 ± 43.0 , $p < 0.001$) and NRSE patients (177.1 ± 95.0 versus 137.5 ± 63.2 , $p = 0.030$). Similarly, plasma progranulin levels were found correlated with the ongoing SE duration before the blood collection ($\rho = 0.360$, $p = 0.0032$) while no correlation was found for serum NSE and S100B levels (Fig.2A). We did not look for the impact of SE refractoriness on CSF biomarkers levels as lumbar puncture were mostly done for refractory SE.

2.2. SE semiology

We then researched if these three biomarkers behave differentially according to SE semiology. Forty-two (51%) patients had a generalized convulsive SE, 33 (40%) had a focal convulsive SE and 7 (9%) had a focal non-convulsive SE. The blood or the CSF levels were not significantly different according to SE semiology for all the three markers (data not shown).

2.3. SE etiology

We then researched if these three biomarkers behave differentially according to SE etiology. The SE etiologies were classified as acute for 28 patients (34%), progressive for 20 patients (24%), remote for 24 patients (29%) and cryptogenic for 10 patients (12%). The CSF levels were not significantly different according to SE etiology for all the three markers (data not shown). Serum NSE levels were not significantly different according to SE etiology whereas serum S100B and plasma progranulin levels tended to increase in acute SE (Fig.2B). We observed a high heterogeneity of serum S100B levels (0.03-0.70 ng/mL) and plasma progranulin levels (77-490 ng/mL) for the patients with acute etiology (Fig.2B). It might be explained by the heterogeneity of the underlying etiologies (encephalitis $n=19$, posterior reversible encephalopathy syndrome $n=3$, metabolic disturbances $n=2$, alcohol disorders $n=2$, subdural hematoma $n=2$).

Discussion

The identification of suitable biomarkers could help physicians to establish a more accurate diagnosis quickly, especially for difficult-to-diagnose form of SE.

The SE patients had higher CSF NSE levels when compared with control patients and higher serum levels when compared with pharmaco-resistant epileptic patients. These results are in accordance with previous studies [7, 8] but were obtained in a larger cohort which support their accuracy. We showed, for the first time, that SE patients had higher S100B levels when compared with control (in serum and CSF samples) and pharmaco-resistant epilepsy patients (in serum samples). Similarly, SE patients had higher progranulin levels when compared with control patients (in plasma and CSF samples) and pharmaco-resistant epilepsy patients (in plasma samples).

We may wonder if the increase of the biomarkers levels is related to SE onset, and therefore biomarkers could be used for SE diagnosis; and/or if it reflects brain damage associated to SE. A mixed scenario can be considered with an unequal distribution according to the biomarkers. The NSE is a world-renowned biomarker to assess brain damage in acute neurological disorders or after cardiac arrest [16, 17, 21, 22]. Increased NSE levels following SE may be related to neuronal death and NSE could be preferentially used as a SE prognosis biomarker. Nevertheless, several arguments suggest that NSE could also be a SE diagnosis biomarker. Firstly, while brain damage increased with the SE duration, we did not observe a correlation between the serum NSE levels and the ongoing SE duration before the blood collection. Secondly, serum NSE levels were not significantly different according to SE semiology while generalized convulsive SE are known to be more severe than focal convulsive SE. Thirdly, we previously reported that patients with seizures had higher blood NSE levels when compared with patients with periodic discharges at EEG despite periodic discharges were associated with higher brain damage [23, 24]. It suggested that increased NSE levels may be related to seizures onset and NSE could be used as a SE diagnosis biomarker. The S100B is a marker of astroglial injury and found increased in several acute neurological disorders [17, 21, 25]. While it was reported a quickly and progressive gliosis after SE, the absence of correlation between serum S100B levels and the ongoing SE duration before the blood collection suggests that the increase of S100B levels could be merely related to SE onset and therefore this biomarker could be used for SE diagnosis.

In contrast, plasma progranulin levels were higher in patients for whom the blood was collected several days after SE onset and therefore for PSRSE patients. The increase of the progranulin levels occurs primarily in activated microglia [13]. However, the microglial activation only occurs few days after the SE onset which could explain the increased delay. The sustained SE may enhance the microglial activation and inflammation processes and therefore, the increase of plasma progranulin levels could reflect the SE duration and subsequent consequences. Plasma progranulin levels might further testify the brain damage than the occurrence of SE. Nonetheless, as a microglial activation frequently occurs in SE of autoimmune origin [26], we may wonder if this biomarker might be also used to identify patients with SE of autoimmune origin and therefore guide the early treatment strategy.

Despite these three biomarkers were all increased in the blood of SE patients, and NSE and S100B increased could be related to SE onset, we believe that S100B is the most promising marker for SE diagnosis. Indeed, S100B had a higher AUC value than NSE, and it could be quickly assessed contrary to progranulin. We identified a cut-off at 0.09 ng/mL, which was accurately associated with a SE diagnosis for 84% of the patients. As control and pharmaco-resistant epilepsy patients rarely had serum S100B levels above 0.09 ng/mL (less than 10% in our cohort), it might be interesting to use serum S100B levels as an emergency triage marker. If a patient without any acute brain injury (trauma, hemorrhage) is admitted to the emergency department with convulsive movements, confusion or decreased alertness and has serum S100B levels above 0.09 ng/mL, clinicians may be prompted to keep the patient in the hospital for medical and neurological observation and to request an emergency EEG. Nonetheless, we believe that clinicians will not rely solely on this biomarker to decide on a return home. Our study highlights the potential of these biomarkers for SE diagnosis and allows to propose a cut-off for the clinical use of S100B.

We found no association between the SE etiology and the levels of serum NSE, as previously reported [8]. However, we observed a high heterogeneity in S100B and progranulin levels for patients with an acute SE. It could be explained by a heterogeneity of SE etiologies classified as an acute SE accordingly to the International League Against Epilepsy Classification [18]. If this first classification is useful to categorize SE, it could be relevant to add biochemical biomarkers to this classification in order to distinguish acute SE with or without inflammatory underlying causes.

We investigated the potential of NSE, S100B and progranulin as SE biomarkers in a large cohort of patients for the first time. Although our population was heterogenous for SE etiology and for the delay of enrollment after the SE onset, we found promising results for the three biomarkers. We confirmed the increase of NSE levels in SE patients whatever the SE etiology. Serum S100B appears to be the most promising biomarker for SE diagnosis by using the cut-off at 0.09 ng/mL. Plasma progranulin could be an interesting biomarker to reflect inflammatory processes.

There are some limitations for this study: it was conducted in a single center, most SE patients were enrolled in the Neuro-Intensive care unit specialized for the management of prolonged super-refractory SE and therefore, the collection of blood and CSF samples was delayed for patients who were previously managed in another hospital. Due to the small number of patients, we were not able to specifically analyze the interest of blood and CSF biomarkers for non-convulsive SE patients. Nonetheless, the strengths of our study were to collect samples from a large cohort of patients and to provide cut-off for clinical use. Further studies are needed to investigate the diagnosis potential of the three biomarkers for non-convulsive SE and to investigate the ability of progranulin to specifically distinguish inflammation processes related to a sustained SE (i.e. consequences of SE) from inflammation processes involved in SE development (i.e. causes of SE) [27].

Statements and Declarations

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Conflicts of interest

Vincent Navarro reports personal fees from UCB Pharma, Eisai, GW Pharma and LivaNova, outside the submitted work. Sophie Demeret reports individual payment from UCB Pharma, Regeneron and ARGENX. The other authors report no disclosures.

Availability of data and material

All data are available on request upon the corresponding author.

Code availability

Not applicable.

Author's contributions

Drafting the manuscript for content: Aurélie Hanin, Vincent Navarro

Major role in the acquisition of data: Aurélie Hanin, Jérôme Alexandre Denis, Valério Frazzini, Françoise Imbert-Bismut, Benoît Rucheton, Clémence Marois, Virginie Lambrecq

Study concept and design: Aurélie Hanin, Dominique Bonnefont-Rousselot, Sophie Demeret, Vincent Navarro

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Ethics approval

The protocol was approved by our local (2012, CPP Paris-VI) and by the INSERM ethic committees (C16-16, 20152482). The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to participate

Patients or relatives were informed and give their consent.

Consent for publication

Patients or relatives were informed and give their consent.

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Figures Legends

Fig.1 Neuron Specific Enolase, S100-beta protein and progranulin as diagnosis biomarkers of status epilepticus

The Fig.1A represents the number of patients for each group (CONT, EPI, SE) and each biological compartment (blood, CSF).

The Fig.1B and Fig.1C represent respectively the distribution of NSE levels (up), S100B levels (middle) and progranulin levels (down) in blood (Fig.1B) and in CSF (Fig.1C). The violin plots show the density of the data at different levels. The white point represents the median of the data, the dark box indicates the interquartile range and the two end points represent respectively the maximum and the minimum values (except for outliers).

The Fig.1D shows the ROC curves for serum NSE (red), serum S100B (blue) and plasma progranulin (black) to identify patients with SE. The table below represents the values of sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) for the best cut-off of each biological marker, defined according to the Youden's index.

Fig.2 Progranulin as a biomarker of inflammatory status epilepticus

The Fig.2A shows the relations between serum NSE levels (up), serum S100B levels (middle) and plasma progranulin levels (down) and the time between the SE onset and the blood sampling. The correlations were assessed with the Spearman test.

The Fig.2B represents the distribution of serum NSE levels (up), serum S100B levels (middle) and plasma progranulin levels (down) according to the SE etiologies. The white points represent the median of the data, the dark boxes indicate the interquartile ranges and the two end points represent respectively the maximum and the minimum values (except for outliers).

Table.1 Demographic characteristics of the study cohort.

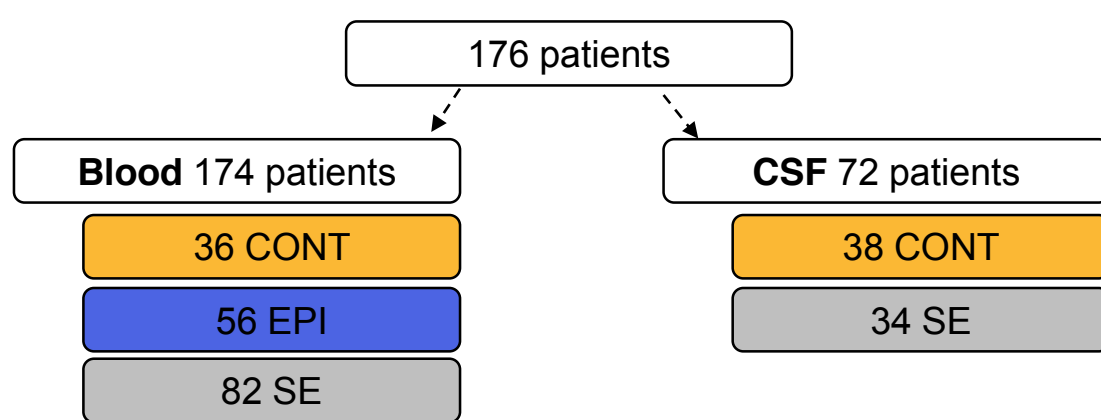
Data are represented as percentages or mean \pm standard deviation (sd)

Abbreviations: CONT = Control patients; EPI = pharmacoresistant Epileptic patients; F = Female; M = Male; SE = Status Epilepticus.

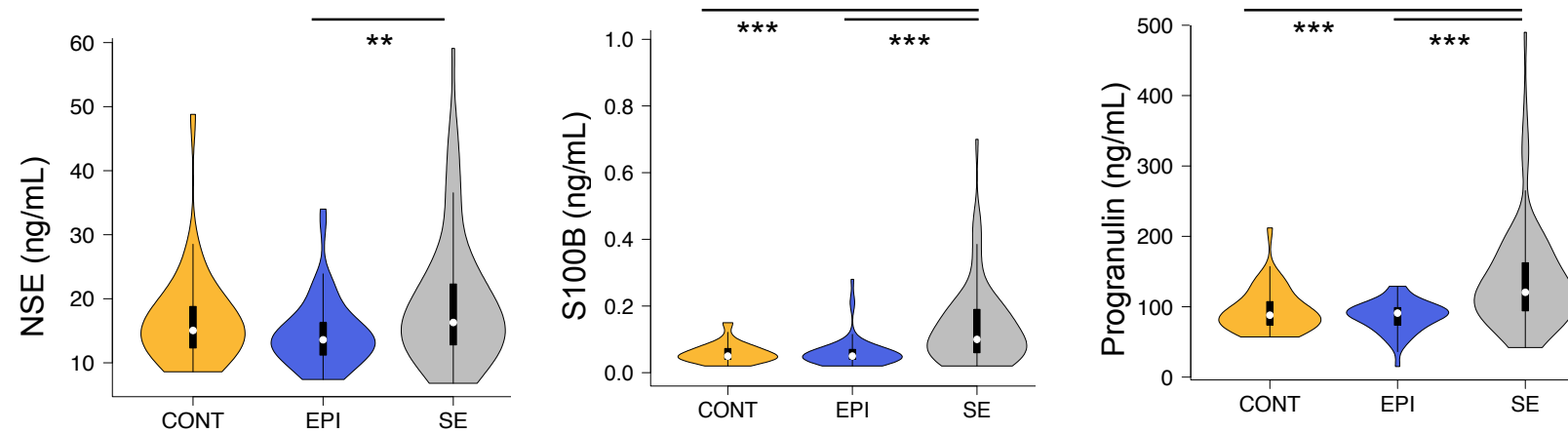
Table 2: Blood, CSF, CSF/blood ratio of NSE, S100B and progranulin in SE patients, control patients and EPI patients.

Data are represented as mean \pm standard deviation (sd).

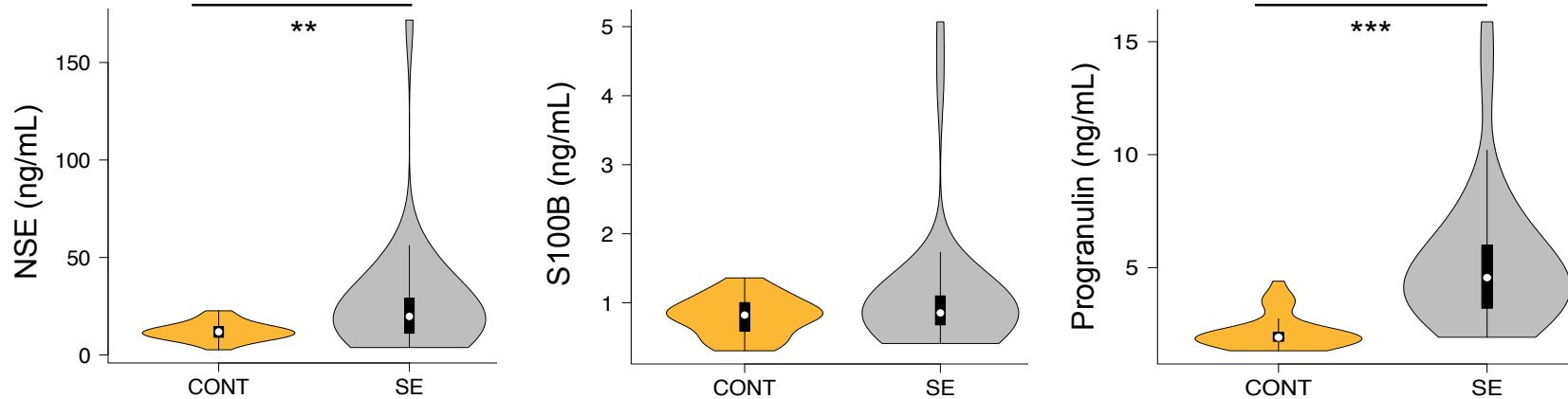
Abbreviations: AU = Arbitrary Units, CONT = Control patients, EPI = pharmaco-resistant Epileptic patients, SE = Status Epilepticus.



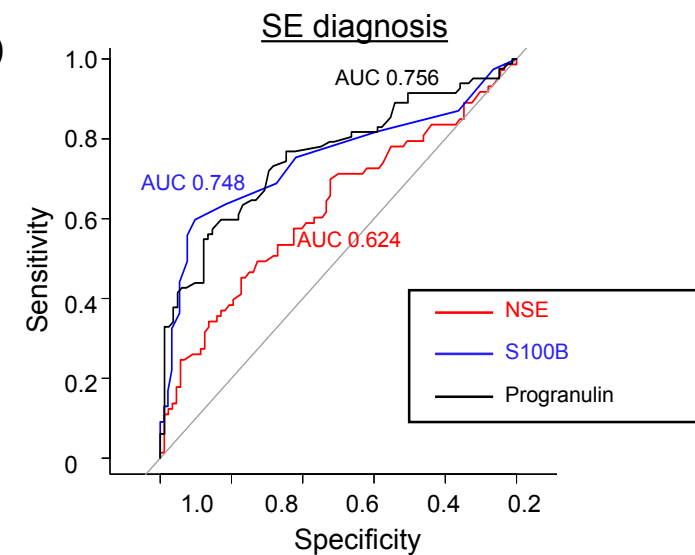
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C

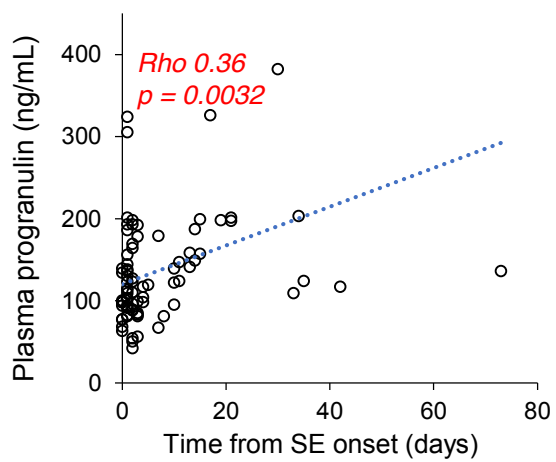
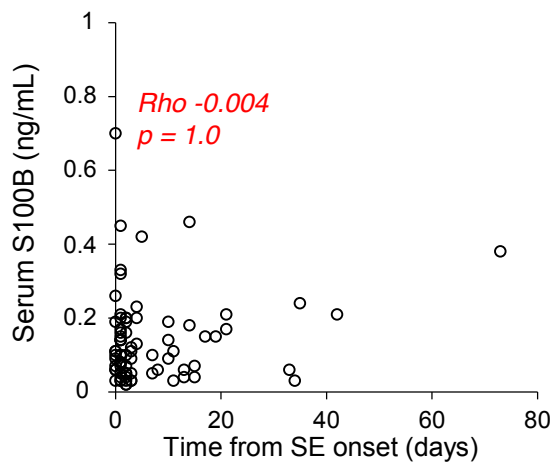
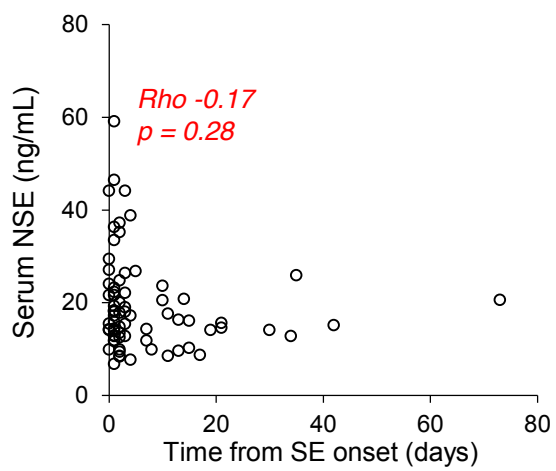


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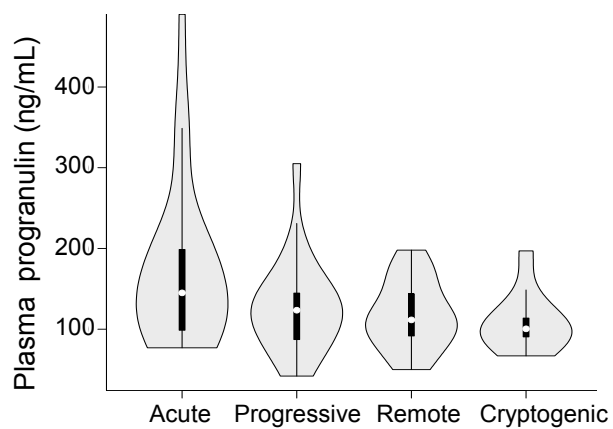
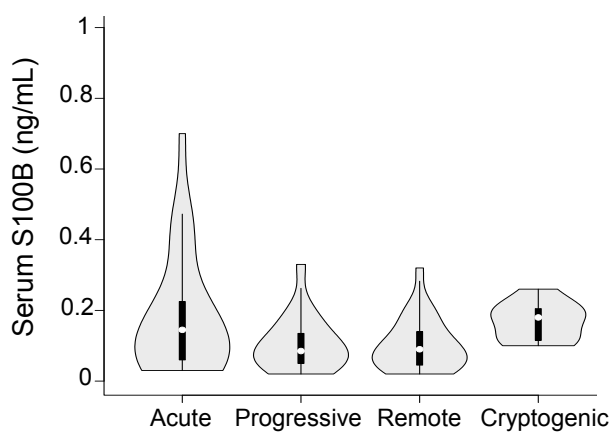
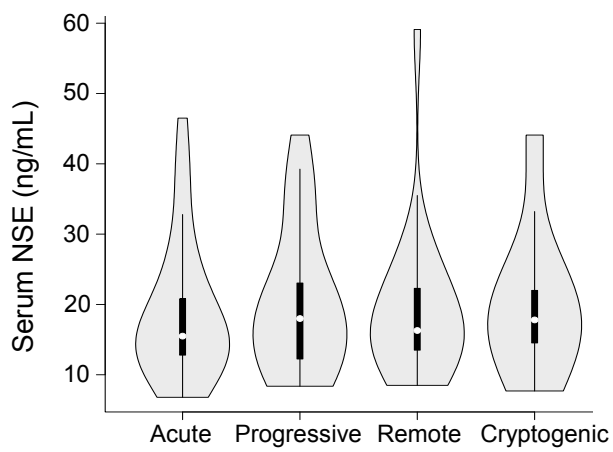


	Se (%)	Sp (%)	PPV (%)	NPV (%)
NSE 17.8 ng/mL	77.3	45.2	62.3	63.0
S100B 0.09 ng/mL	59.7	90.2	83.6	72.8
Progranulin 110 ng/mL	57.3	85.4	79.7	66.7

A



B



	Patients N (%)	Age (years \pm sd)	Ratio M/F (%)
SE patients	82	49.8 \pm 18.8	60
Acute	28 (34)	49.1 \pm 19.7	57
Progressive	20 (24)	52.4 \pm 19.8	70
Remote	24 (29)	48.8 \pm 19.1	54
Unknown cryptogenic	10 (12)	49.4 \pm 15.3	60
Patients who required immunomodulatory drugs	20 (24)	42.7 \pm 21.0	60
NRSE	25 (30)	55.5 \pm 16.7	64
RSE	32 (39)	51.3 \pm 18.8	63
PSRSE	25 (30)	42.2 \pm 18.8	52
EPI patients	56	35.9 \pm 11.2	48
CONT patients	36	54.1 \pm 20.7	50

Table 1: Demographic characteristics of the study cohort.

Data are represented as percentages or mean \pm standard deviation (sd)

Abbreviations: CONT = Control patients; EPI = pharmaco-resistant Epileptic patients; F = Female; M = Male; NRSE = Non-Refractory Status Epilepticus; PSRSE = Prolonged Super-Refractory Status Epilepticus; RSE = Refractory Status Epilepticus; SE = Status Epilepticus

	Blood			CSF			CSF/blood		
	NSE (ng/mL ± sd)	S100B (ng/mL ± sd)	Progranulin (ng/mL ± sd)	NSE (ng/mL ± sd)	S100B (ng/mL ± sd)	Progranulin (ng/mL ± sd)	NSE (AU)	S100B (AU)	Progranulin (AU)
SE	19.4 ± 10.2 (n=73)	0.14 ± 0.12 (n=77)	137.9 ± 73.5 (n=82)	27.0 ± 31.4 (n=28)	1.087 ± 0.953 (n=33)	5.30 ± 3.08 (n=28)	1.98 ± 2.93 (n=21)	13.40 ± 12.51 (n=25)	0.041 ± 0.027 (n=27)
CONT	16.6 ± 7.37 (n=34)	0.059 ± 0.030 (n=36)	94.6 ± 31.3 (n=36)	12.1 ± 4.63 (n=34)	0.805 ± 0.283 (n=38)	2.15 ± 0.766 (n=31)	0.75 ± 0.36 (n=26)	16.75 ± 9.84 (n=32)	0.024 ± 0.0076 (n=31)
EPI	14.5 ± 5.29 (n=54)	0.061 ± 0.046 (n=56)	86.6 ± 21.9 (n=46)	-	-	-	-	-	-
Pvalue SE-EPI Wilcoxon-test	0.0085	< 0.001	< 0.001	-	-	-	-	-	-
Pvalue SE-CONT Wilcoxon-test	0.39	< 0.001	< 0.001	0.0067	0.46	< 0.001	0.087	0.20	0.019
Pvalue CONT-EPI Wilcoxon-test	0.25	0.67	1	-	-	-	-	-	-

Table 2: Blood, CSF, CSF/blood ratio of NSE, S100B and progranulin in SE patients, control patients and EPI patients.

Data are represented as mean ± standard deviation (sd).

Abbreviations: AU = Arbitrary Units, CONT = Control patients, EPI = pharmaco-resistant Epileptic patients, SE = Status Epilepticus.