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Neuro-glial degeneration in Status Epilepticus: Exploring the role of serum levels of Neurofilament light chains and S100B as prognostic biomarkers for short-term functional outcome

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ABSTRACT

Background: The last ILAE definition of Status Epilepticus (SE) highlights that the persistence of the epileptic activity per se could determine irreversible brain damages that could be responsible for long-term consequences. The measurement of neuro-glial injury biomarkers could help in the identification of those patients who will eventually develop short- and long-term consequences of SE. At present none of the already studied biomarkers has been validated to be used in everyday clinical practice. In this study, we explore the role of NfL and S100B as a prognostic biomarkers to identify patients who will develop short-term disability after an episode of SE.

Methods: This is a retrospective assessment of the serum levels of both NfL and S100B in a cohort of 87 adult patients with SE prospectively collected in our SE registry (Modena Status Epilepticus Registry – MoSER –) at Baggiovara Civil Hospital (Modena, Italy). All samples were acquired during SE within 72 hours of SE diagnosis. The comparison groups were: healthy controls (HC, n = 27) and patients with epilepsy (PWE, n = 30). Demographic, clinical, and therapeutical information and thirty-days follow-up information regarding disability development were acquired for every included patient and analyzed in relation to NfL and S100B values.

Results: Serum levels of NfL were significantly higher in SE compared to those of PWE (median 7.35 pg/ml, IQR 6.4, $p < 0.001$) and HC (median 6.57 pg/ml, IQR 9.1, $p < 0.001$); S100B serum levels were higher in SE (median 0.11 ug/L, IQR 0.18) compared to PWE (median 0.03 ug/L, IQR 0.03, $p < 0.001$) and HC (median 0.02 ug/L, IQR 0.008, $p < 0.001$). However, only NfL serum levels were found to be an independent predictor of 30 days functional outcome whereas S100B levels did not.

Conclusions: Our results suggest that NfL measurement in serum during SE could help predict the short-term functional outcome.

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1. Introduction

Status Epilepticus (SE) is a common neurological emergency characterized by high short-term morbidity and mortality. The last ILAE definition of Status Epilepticus considers SE as "a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point t1); It is a condition that can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures" [1]. From this definition, it is evident that the persistence of the epileptic activity per se could determine brain damage that could be responsible for long-term consequences such as epilepsy development, cognitive, and behavioral deficits.

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Thus, besides clinical-electroencephalographic evaluation, a multimodal approach, based on the measurement of neuro-glial injury biomarkers could help in the identification of those patients who will develop short- and long-term consequences of SE.

Many different potential biomarkers of neural and glial degeneration have been studied so far both in serum and CSF of patients with epilepsy and SE [2–4] but, at present none of those has been validated to be used in everyday clinical practice.

Among them, Neurofilament light chains (NfL) are proteins especially present in the axons of the myelinated neurons where they play a structural role in establishing cross-bridging with other filaments and at the synaptic level where they maintain synaptic plasticity. Their role as a marker of neurodegeneration has been established in many different neurological diseases [5–9] and has been already evaluated in a previous exploratory study in SE by our group [10].

S100B is a protein particularly expressed by glial cells and by astrocytes where it plays the role of a calcium-sensor protein intervening in the regulation of many different processes involving proliferation, survival, and differentiation. Many different studies have recognized it as a sensitive biomarker of active astrocyte distress and at high extra-cellular concentrations it actively participates in the processes accompanying neural injury. Previous studies demonstrated elevated serum levels both in patients with epilepsy [3,11–15] and SE [16,17].

In this study, we explore the role of NfL and S100B as prognostic biomarkers to identify those who will develop short-term disabilities after an episode of SE.

2. Materials and methods

2.1. Study design, setting, and patients

We retrospectively measured the serum levels of NfL and S100B in a cohort of 87 adult patients with SE prospectively collected in our SE registry (Modena Status Epilepticus Registry – MoSER –) at Baggiovara Civil Hospital (Modena, Italy) from September 1, 2013 to December 31, 2021 [10]. All samples were acquired during SE within 72 hours of the diagnosis. All aetiologies were included but patients with post-anoxic encephalopathy.

Before 2015, SE was considered a continuous seizure that lasts 5 min or longer or two or more discrete seizures without complete recovery of consciousness between them [18]. After 2015, the definition given by the International League Against Epilepsy (ILAE) was systematically adopted and prospectively applied [1] and patients were included if they presented an episode of SE lasting more than 5 min for tonic-clonic SE, 10 min for focal SE with impaired consciousness, and 10–15 min for absence SE. All cases of SE that occurred before 2015 were reviewed by two authors (SM and GG) to ensure that all met the ILAE diagnostic criteria. The cases of non-convulsive SE were diagnosed according to the Salzburg electroencephalographic (EEG) criteria [19,20].

Demographic, clinical, and treatment information were acquired for every included patient examining the hospital informatic database. A SE episode was defined as responsive to treatment.

If it was controlled by the infusion of a benzodiazepine alone or followed by a single anti-seizure medication. Cases not controlled were considered refractory to treatment (RSE). A quote of these cases needed admission to the intensive care unit (ICU) and the administration of third lines/ anesthetic drugs. Those cases persisting despite the application of third lines drugs for 24 hours or reappearing at the weaning of anesthesia were considered Super-Refractory (SRSE).

Thirty-day follow-up information was acquired through hospital informatics database examination, clinical visits as well as telephone interviews. Disability level was measured using the Modified Rankin Scale (mRs). A worsening of the clinical condition was defined as an increase of at least one point in mRS at 30 days follow-up compared to the level of disability present before SE.

Serum levels of investigated biomarkers were compared to those of two comparison groups: healthy controls (HC, n = 27) without any neuropsychiatric condition and negative family history for neurodegenerative diseases whose blood samples have been donated and stored in the "Modena NeuroBiobank" (a biobank dedicated to research for neurological disorders active since 2018) and patients with epilepsy (PWE, n = 30) whose blood samples were collected after isolates seizures during the stay in the Epilepsy Monitoring Units. Both groups were age and sex-matched with the SE group.

2.2. Biomarkers measurements

Serum NfL concentrations were determined through the immune-enzymatic test on Simple Plex NfL Assay (ProteinSimple) on an Ella instrument, according to the manufacturer's instructions, and calibrated using the in-cartridge factory standard curve.

S-100B serum levels were measured through chemiluminescence immunoassay (CLIA, LIASON, DiaSorin).

2.3. Statistical analysis

IBM SPSS Statistics Version 26 was used for statistical analysis. We described categorical variables as percentages and proportions, and continuous variables as mean and standard deviation (SD) or as the median and interquartile range (IQR), depending on the underlying distribution. Univariate comparisons were performed with Fisher's Exact test, the chi-square test, and the Mann–Whitney test. Linear regression analysis was used to determine the predictors of serum levels of Nfl and S100B. Logistic regression analysis was used to determine predictors of 30 days functional outcomes. To find the best cut-off for these biomarkers for the analyzed outcome, ROC curves were calculated. The statistical threshold for all the analyses was set at a p-level of 0.05.

3. Results

We measured the serum levels of NfL chains and S100B in an adult population of 87 patients (female 54–62%- median age 70) with a clinical or electro-clinical diagnosis of SE. Samples were acquired during SE, within 72 hours from its diagnosis (median: 24 hours; IQR: 48). The clinical characteristics of the analyzed population are presented in the **supplementary material (Table S1)**.

Status Epilepticus patients showed great variability in serum levels of NfL (median 64.7 pg/ml, IQR 139.2). The levels of NfL were independently associated with female gender (B = 0.634 95% CI 0.072–1.195, p = 0.027), stupor/coma before treatment (B = 0.815 95% CI 0.249–1.382, p = 0.005) and refractoriness to treatment (B = 1.015 95% CI 0.359–1.671, p = 0.003) when adjusted for the other variables (duration of SE and age). Significantly higher levels were found in females (median 90.85 pg/ml, IQR 151.8, p = 0.012), stuporous and comatose patients (median 163 pg/ml, IQR 392.8, p = 0.001), and in those with refractory and super-refractory forms of SE (median 113, IQR 204.1, p < 0.001). No differences in NfL serum levels were found between patients with samplings acquired within 24 hours and those acquired after 24 hours from SE beginning (p = 0.168) **(**Table1**).**

The levels of S100B showed a median value of 0.11 ug/L with an IQR of 0.18. They were associated with stupor/coma before

Table 1
Variables influencing the levels of NfL.

Variables	B coefficient	95% CI	p
SE duration > 24 h	−0.068	−0.743 – 0.606	0.841
Gender (Female)	**0.634**	**0.072 – 1.195**	**0.027**
Stupor/Coma before treatment	**0.815**	**0.249 – 1.382**	**0.005**
Age	0.271	−0.008 – 0.550	0.057
Refractoriness to treatment	**1.015**	**0.359 – 1.671**	**0.003**

Table 2
Variables influencing the levels of S100B.

Variables	B coefficient	95% CI	p
Gender	0.519	−0.029 – 1.067	0.063
Etiology	−0.412	−0.939 – 0.116	0.124
Stupor/Coma before treatment	**0.913**	**0.365–1.461**	**0.001**
Age	0.222	−0.058 – 0.502	0.119

treatment (B = 0.913 95% CI 0.365–1.461, p = 0.001) independently from the other variables (etiology, age, and gender). In particular, levels of S100B were significantly higher in stuporous and comatose patients compared to alert or somnolent ones (median 0.19 ug/L, IQR 0.50 p = 0.001). No differences in S100B serum levels were found between patients with samplings acquired within 24 hours and those acquired after 24 hours from SE beginning (p = 0.778) **(**Table 2**).**

3.1. Biomarkers in SE compared to controls' control populations

The clinical characteristics of the PWE and HC populations are presented in the **supplementary material** **(Tables S2 and S3)**. Since age and gender could influence NfL and S100B levels and the comparison groups were younger compared to SE patients, a case-control matching analysis to balance the group in relation to age and gender was performed. In the SE group, serum levels of NfL were significantly higher compared to those of PWE (median 7.35 pg/ml, IQR 6.4, p < 0.001) and HC (median 6.57 pg/ml, IQR 9.1, p < 0.001). No differences were found between PWE and HC (p = 0.936). The same was observed for the S100B serum levels: SE (median 0.11 ug/L, IQR 0.18), PWE (median 0.03 ug/L, IQR 0.03, p < 0.001), HC (median 0.02 ug/L, IQR 0.008, p < 0.001). On the contrary, serum levels of S100B were significantly higher in PWE compared to HC (p = 0.002).

3.2. Serum biomarkers and 30 days disability

The median value of mRS pre-SE was 1. An overall worsening of the clinical conditions was observed in 57 patients (66%) and the median mRs value at hospital discharge and 30 days was 4 points.

Serum levels of NfL were significantly higher in patients who worsened after SE compared to those who completely recovered (median 97.20 pg/ml, IQR 167.80 vs median 26.15 pg/ml, IQR 90.74, p = 0.001). The same results were observed for serum levels of S100B (median 0.14 pg/ml, IQR 0.32 vs 0.09 pg/ml, IQR 0.10, p = 0.018) (Fig. 1). At the univariate analysis, only the NfL serum levels were found to be a predictor of 30 days functional outcome whereas S100B levels did not. Through the ROC curve, an accuracy of 71.8% (95% CI 60–84) for NfL in predicting 30 days of disability was found. The Youden index calculation, showed a value of 33.4 pg/ml as the best-cut off for 30 days of disability prediction (Sensitivity 77%, Specificity 60%). The multivariate analysis showed that NfL with the abovementioned cut-off, was an independent predictor of 30 days disability after correction for age (OR 3.9 95% CI 1.41–10.64 p = 0.009) (Fig. 2).

4. Discussion

In this study, we confirmed that the measurement of serum levels of S100B and NfL in the first hours from SE diagnosis could give insights into the neuro-glial degeneration related to the presence of sustained seizures. Pre-clinical evidence from animal models of SE in favor of this aspect are well defined [21,22]. In humans, this important point is still poorly studied. As has been previously highlighted by another previous study [23], electrographic SE after cardiac arrest is associated with higher levels of serum NfL compared to those found in post-anoxic patients without SE, which may indicate a potential secondary neuronal injury caused by electrographic SE.

In the present study, we found that both biomarkers were significantly elevated in SE patients compared to levels found after a single epileptic seizure in PWE and to those found in healthy controls. This result confirms our previous findings [10] and the results of a recent study on children with convulsive SE [16] in which serum S100B levels measured in the first 24 hours from SE diagnosis were found to be significantly elevated compared to those found in healthy children. Moreover, as regards to isolated seizures in PWE, in line with previous findings, we found that only serum S100B levels appeared to increase compared to levels found in healthy controls [3,12–15] while serum NfL levels did not differ [24,25]. This result suggests that single seizures could determine a more prominent glial perturbation rather than neuronal damage.

We already know that SE is a condition that could determine a bad short-term prognosis both in terms of death and disability.

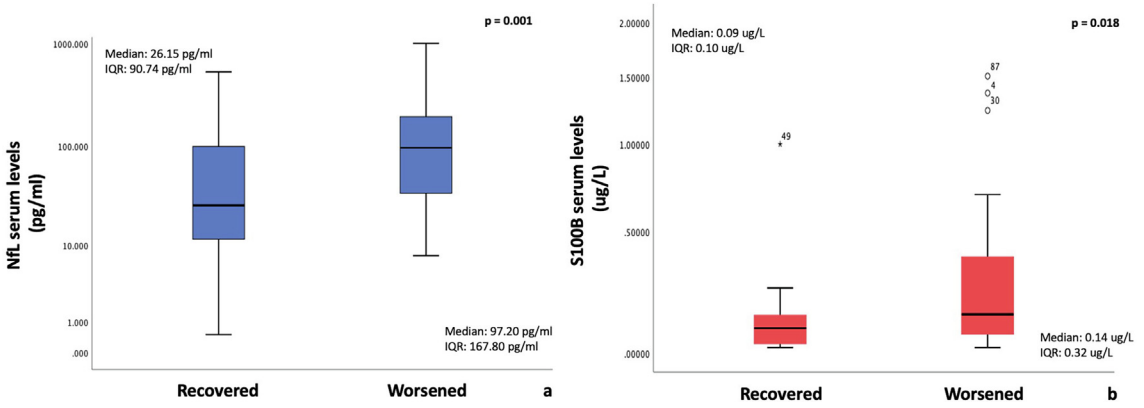

Fig. 1. (a) Comparison of serum levels of NfL between patients who completely recovered after SE and those who presented worsening clinical conditions. (b) Comparison of serum levels of S100B between patients who completely recovered after SE and those who presented worsening clinical conditions.

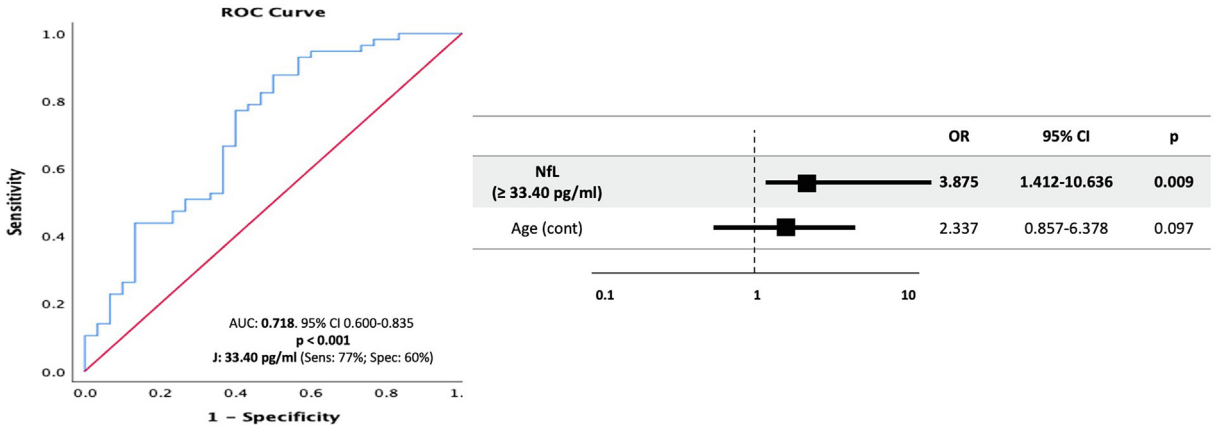

Fig. 2. ROC curve for 30 days disability development. The AUC for NfL was 0.718. The Jouden index calculation shows the best cut-off at 33.40 pg/ml giving a sensitivity of 77% and a specificity of 60%. Multiple regression analysis showed that NfL ≥ 33.40 pg/ml is an independent predictor of 30 days of disability development.

Many patients who survived a SE episode will never regain the performance status present before the SE episode. Thus, it is particularly important to predict the patient functional outcome. The literature lacks studies addressing specifically this point and no potential serum biomarker has been studied so far trying to answer this question. Moreover, the majority of existing clinical prognostic scores for SE are directed toward the determination of the risk of death after a SE episode [26–28] and not toward the functional outcome. In our study, 66% of patients worsened after SE. Worsening patients showed increased serum levels of both studied neuroglial degenerative biomarkers compared to those found in patients with a full recovery. In line with these results, a recent study showed that S100B was higher in those SE episodes with a high degree of MRI, potentially irreversible abnormalities [17]. However, our results suggest that only serum levels of NfL could predict disability development after SE, while S100B levels did not. To the best of our knowledge, this is the first study to address this question in SE. In accordance with our results, in the BISTRO study serum S100B levels after a single epileptic event appeared poorly predictive for seizure recurrence, mortality, and re-hospitalization within seven days from the first event [29].

5. Conclusions and future perspectives

Our results suggest that NfL measurement in serum during the first hours of SE could help predict the short-term functional outcome. In the future, it will be important to try to replicate these results in other different populations and to try to incorporate these results in clinical prognostic scoring systems.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2023.109131.

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