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Brain damage serum biomarkers induced by COVID-19 in patients from northeast Brazil

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Abstract

Neurological symptoms have been often reported in COVID-19 disease. In the present study, we evaluated brain damage associated with the increase of serum levels of neurological biomarkers S100B and neuron-specific enolase (NSE) induced by SARS-CoV-2 infection, in a population from Northeastern Brazil. Thirty-six healthy control (G1) individuals and 141 patients with confirmed COVID-19 were enrolled in this study. Positive-COVID-19 patients were divided into two groups according to the severity of illness by the National Institute of Health (NIH) criteria, 76 patients with mild symptoms for COVID-19 and (G2) and 65 with acute respiratory conditions requiring supplemental oxygenation via intensive care unit (ICU) admission (G3). A follow-up study was conducted with 23 patients from G2 14 (D14) and 21 (D21) days after the onset of symptoms. Serum levels of NSE and S100B were measured using the enzyme-linked immunoassay method (ELISA). Results revealed a significant positive association between G3 patients and S100B serum expression ($p = 0.0403$). The serum levels of NSE were also significantly enhanced in the G3 group compared to the control ($p < 0.0001$) and G2 group ($p < 0.0001$). In addition, clinical features such as symptoms and oxygenation status were not correlated with NSE or S100B serum expression. The follow-up study demonstrated a decrease over time (21 days) in NSE serum expression ($p < 0.0001$). These results suggest that brain damage is followed by acute virus exposure, with no long-term effects. Future work examining COVID-19 recovery will shed light on chronic neurological damage of SARS-CoV-2 infection.

Keywords Biomarker · COVID-19 · Follow-up · NSE · S100B

Introduction

Since early 2020, the world population has shared efforts to contain the spread of COVID-19, an infectious disease caused by the SARS-CoV-2 virus (Chen et al. 2020). The infection not only induces respiratory complications but also registers a variety of neurologic symptoms including ataxia, anosmia, ageusia, dizziness, headache, impaired consciousness, stroke, and viral encephalitis (Garg et al 2021; Flumignan 2020; Mao et al. 2020). A variety of studies have reported the ability of the virus to infect the central nervous system (CNS). First, retrograde transsynaptic transport has been proposed (Meinhardt et al. 2021). Second, the virus-induced inflammation disrupts the blood–brain barrier (BBB) which provides access to the CNS. Then, in the brain, SARS-CoV-2 directly interacts with endothelial cells through the Angiotensin Conversor Enzyme (ACE2), a transmembrane protein that acts as a receptor (Buzhdygan et al. 2020).

The study of biomarkers for neuronal damage has been revealing crucial insights into acute and long-term effects of brain dysfunction related to several diseases. For instance, the neuron-specific enolase (NSE) protein is a glycolytic enzyme highly specific for neurons and peripheral neuroendocrine

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cells. Usually, NSE localizes inside the cellular cytoplasm. Nevertheless, increased levels of the protein in the serum or cerebrospinal fluid (CSF) have been detected in cases of brain tissue damage, such as traumatic brain injury (TBI) and stroke (Lu et al. 2015; Thelin et al. 2016). S100B is a calcium-binding protein induced by neurological inflammations and infections which has robust expression in the nucleus and cytoplasm of astrocytes (Michetti et al. 2021).

The presence of either protein in CSF or serum has been associated with mild TBI patients and has been demonstrated to be of value for the screening of intracranial injury in the medical clinic field (Thelin et al. 2017).

In the context of the COVID-19 pandemic, the literature has revealed an association between NSE serum values and COVID-19 severity (Fiori et al. 2021; Wei et al. 2020; Ganti et al. 2020). Furthermore, S100B expression in COVID-19 patients suggests multiple inflammation-related neurological symptoms during acute infection (Aceti et al. 2020; Sahin et al. 2022).

In this context, the present study aimed to investigate the serum expression of NSE and S100B in COVID-19-positive patients. Further, here we also evaluate the association between the neurological biomarkers for brain injury with clinical manifestations of the disease, in a population from Northeastern Brazil.

Overall, we suggest that biomarkers of neuronal damage provide a more refined follow-up for COVID-19 patients in order to avoid long-term neurologic consequences from the SARS-CoV2 infection.

Methods

Volunteers recruitment

Thirty-six healthy individuals negative for COVID-19 formed the control group (G1).

This study recruited 141 patients from the COVID-19 screening at Clinics Hospital – the Federal University of Pernambuco, and Mestre Vitalino Hospital of Caruaru city to participate. All the clinical information of patients and blood samples were collected from the 2nd semester of 2020 to the 1st semester of 2021. To conduct the experimental analysis, 76 patients positive for SARS-CoV-2 with mild neurological symptomswere grouped as G2. The common symptoms for G2 were headache, anosmia, ageusia, and myalgia. Sixty-five positive patients with supplemental oxygenation at the intensive care unit (ICU) were grouped in G3. Both G2 and G3 groups were classified using the National Institutes of Health (NIH) symptom severity criteria as mild and severely ill, respectively. The date of disease onset was defined as the day when symptoms appeared. A follow-up study was conducted with 23 patients from the G2 group. Patients had their serum samples collected after 14 and 21 days of the onset of the disease.

Reverse-transcription polymerase chain reaction (RT-PCR) assay for SARS-CoV-2

Nasopharyngeal swab samples were collected from patients suspected of COVID-19. Following RNA extraction, two target genes of SARS-CoV-2 were tested for RT-PCR assay, RNA-dependent RNA polymerase (RdRP) and SARS-CoV2 envelope protein (E). The detection used a nucleic acid detection kit according to the manufacturer's protocol (Charité protocol, Biomanguinhos, Brazil). RT-PCR assay was performed under the following conditions: incubation at 50 °C for 15 min and 95 °C for 5 min, 45 cycles of denaturation at 94 °C for 15 s, and extension/collection of fluorescence signal at 55 °C for 45 s. A cycle threshold value (Ct value) of less than 39 was defined as positive.

Biomarkers measurement

Peripheral venous blood was collected into a serum separator tube (SST). Samples were centrifuged at 700 × g for 10 min to collect serum samples and stored at − 80 °C. A single run of ELISA assay was carried out for NSE and S100B in serum samples. Enzyme-linked Immunosorbent Assay (ELISA) kits were used according to the manufacturer's instructions to determine S100B (DY1820-05) and NSE (DY5169-05) (R&D Systems). The data are presented as median values.

Statistical analysis

Student's *t*-tests were used for statistical analysis in which p values of < 0.05 were considered statistically significant. The serum level values for both biomarkers and demographic parameters are expressed as the median, maximum, and minimum. Friedman's test was used to evaluate whether changes in serum NSE values occurred within groups over time. All quantitative data were plotted with GraphPad Prism® 8.4.2.

Results

Recruitment, clinical and demographic evaluation of research volunteers

The study included 141 patients with a positive diagnosis for COVID-19 by the RT-PCR method. The median age was 43 (± 13) years. The total number of patients represents 44% women ($N = 62$) and 56% men ($N = 79$). The control group (G1) had a median age of 53 years old. Positive individuals for COVID-19 were divided into Group 2 (G2) (53%, $N = 76$) which presented only mild symptoms such as headache, myalgia, ageusia, anosmia, and Group 3 (G3) (47%, $N = 65$) which required hospitalization in the

ICU due to the severe condition of COVID-19. Among G3 individuals, patients required not only supplemental oxygenation (due to SpO_2 status), but also tracheal intubation (TI) or breathing mask (NRM).

Looking at the side of symptoms, headache (66%, $N=50$) and anosmia (59%, $N=45$) were the most reported symptoms in G2, while dyspnea (69%, $N=45$) in G3. Table 1 shows the clinical data from patients recruited in the present study.

Serum measurement of S100B and NSE in control group (G1), mild COVID-19 (G2), and ICU patients (G3)

The S100B was detected in the serum samples of 8 (22%) of the 36 individuals in G1 (median value of 58.00 (38.50–121.73) pg/mL), 5 (6%) of the 76 patients (median of 64.00 (47.62–279.05) pg/mL) in G2, and in 6 (9%) of the 65 patients admitted to the ICU (median 144.00 (59.36–510.07) pg/ml) in G3.The levels of S100B did not differ from G1 and G2 ($p=0.4126$). The statistical analysis revealed a significant difference between the S100B serum levels in G1 and in G3 groups ($p=0.0403$). However, no substantial increase in S100B levels was quantified among G3 patients when compared to G2 patients ($p=0.4286$) (Fig. 1).

The serum expression of NSE was detected in 140 of 141 samples from COVID-19-positive patients (99%). The NSE was detected in 26 (70%) of the 36 serum samples (median value 3440.00 (395.56–8862.22) pg/mL) in G1, in 75 of the 76 serum samples (99%) (median value 3378.00 (578.00–13,078.00) pg/mL) in G3, and in G3 NSE was detected in all serum samples (median value of 5523.00 (432.67–13,739.33) pg/mL). No statistical difference was computed between G1 and G2 ($p=0.2136$). A significant difference was quantified between NSE serum levels in G1 and G3 ($p<0.0001$), and between G2 and G3 ($p<0.0001$) (Fig. 2).

Table 1 Clinical parameters of patients positive for COVID-19 and healthy controls

Clinical parameters	Control group (G1) ($N=36$)	Mild COVID-19 (G2) ($N=76$)	Severe COVID-19(G3) ($N=65$)
Women, N (%)	14 (39%)	41 (54%)	21 (32%)
Men, N (%)	22 (61%)	35 (46%)	44 (68%)
Median age (SD)	53 (22–77)	37 (22–73)	51 (21–81)
Comorbidities, N (%)			
Hypertension		11 (14%)	13 (20%)
Diabetes		-	5 (8%)
Others		3 (4%)*	1 (1,5%) **
Symptoms, N (%)			
Dyspnea	-	11 (17%)	45 (69%)
Myalgia	-	28 (43%)	16 (24%)
Headache	-	50 (66%)	19 (30%)
Anosmia	-	45 (59%)	-
Ageusia	-	38 (50%)	-

*Asthma

**Cardiovascular disease

Association and correlation of clinical parameters of positive COVID-19 patients with the levels of the S100B and NSE

Table 2 associates the clinical manifestation of patients positive for COVID-19 and NSE serum levels. Nevertheless, in our population, clinical parameters did not correlate with the serum expression of NSE. No association was computed between S100B and clinical manifestations of COVID-19.

Analysis of NSE serum levels for 21 days post-COVID-19 in individuals with mild symptoms of the disease

A follow-up analysis revealed a decline in NSE serum expression over time in 23 patients from G2. The NSE serum levels were measured on the 14th (D14) and 21st (D21) days after the onset of COVID-19 symptoms (Table 3).

Figure 3 discloses the individual values of NSE for each of the 23 participants during the follow-up study. All patients

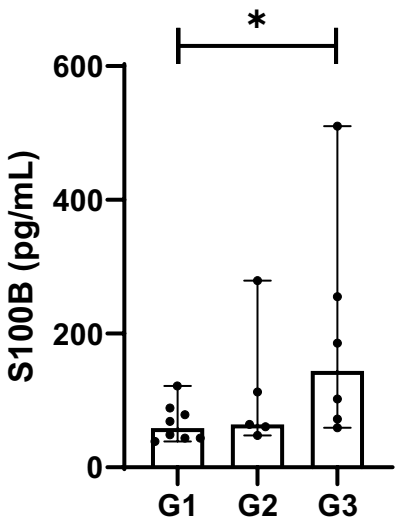

Fig. 1 Serum expression of S100B among COVID-19-positive patients and healthy controls. G1 — healthy individuals, control group. G2 patients are positive for COVID-19 with mild neurological symptoms. G3 patients positive for COVID-19 were admitted to the ICU. *$p<0.05$ was considered significant compared to G1

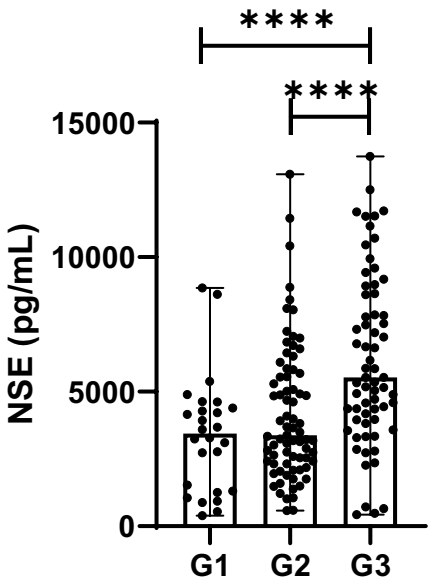

Fig. 2 Serum expression of NSE among COVID-19-positive patients and healthy controls. G1 — healthy individuals, control group. G2 patients are positive for COVID-19 with mild neurological symptoms. G3 patients positive for COVID-19 were admitted to the ICU. ****$p < 0.0001$ was considered significant compared to G1

except one exhibited the highest serological values for NSE during the onset of COVID-19 symptoms (D1). In D14, 7 (30%) and in D21, 9 (39%) patients did not show detectable levels of serum NSE. The comparisons among D1, D14, and D21 revealed significant difference of NSE serum expression in D0 and D14, and in D0 and D21 ($p < 0.0001$). However, no difference was quantified between D14 and D21 ($p > 0.999$).

Discussion

In the present study, we confirmed that patients with severe COVID-19 symptoms showed elevated serum expression of brain damage biomarkers NSE and S100B in a population from Northeast Brazil. On top of that, patients with mild symptoms of COVID-19 (G2) also showed an elevation in NSE serum levels compared to healthy volunteers (G1). Nonetheless, the results did not demonstrate a positive association between COVID-19-specific neurological symptoms and NSE. Finally, a follow-up study showed that after 21 days of post-COVID-19 infection, the levels of NSE significantly decreased, suggesting no long-term neurological dysfunction associated with the disease.

The levels of S100B have been evaluated in COVID-19 patients (Aceti et al. 2020; Sahin et al. 2022; Mete et al. 2021; Savarraj et al. 2021; Kokkoris et al. 2022). To date, S100B expression has been associated with neurological conditions and neurological damage as a marker of astrocytic injury (Arrais et al. 2020). Nevertheless, the association between S100B and COVID-19 severity remains under investigation. Sahin et al. (2022) and Aceti et al. (2020) have demonstrated that the levels of S100B did not increase in the blood of severe COVID-19 patients that had neurological symptoms during COVID-19 infection in a population from Turkey and Italy, respectively. Consistently, patients positive for COVID-19 have revealed a minimal expression of the virus in glial cells (Meinhardt et al. 2021). In line with these findings, our study did not reveal significant expression of S100B in mild COVID-19-positive patients compared to control in a population from Northeast Brazil.

Nevertheless, severe cases from G3 showed a significant increase in S100B compared to mild cases. Correspondingly, Kokkoris et al. (2022) have also revealed that the serum levels of S100B and NSE correlated with the severity of COVID-19 disease via induction of IL-6 and CRP.

One must assume that the levels of S100B or NSE possibly correlate with individual factors such as genetic variants, race, geological location, and genotype, for instance (Ben Abdesselam et al. 2003; Liu et al. 2005; Miao et al. 2020). Thus, such variants must be considered for the validation of biomarkers. Of note, the Scandinavian Neurotrauma Committee guidelines determine the absence of S100B in CSF and serum state for non-neural impairment even with

Table 2 The association of serum levels of NSE and clinical parameters of COVID-19 positive patients. Values are expressed in pg/mL. $p > 0.05$ was considered significant

Clinical features	G2		G3		*P* value < 0.05
	Yes	No	Yes	No	
Ageusia	3698	3218	-	-	0.2628/-
Anosmia	3498	3438	-	-	0.9937/-
Headache	3358	3238	4373	5866	0.8451/ 0.0835
Dyspnea	-	-	6633	5039	-/0.1463
Fever	4898	3178	-	-	0.1537-
Myalgia	3738	3338	4366	5696	0.839/0.1023
Intubated	-	-	4406	5529	-/0.2771

Table 3 Serum levels of NSE in COVID-19-positive individuals ($n = 23$) on day one (D1), D14, and D21 after the onset of symptoms

Clinical parameters	N		
Women, N (%)	9 (40%)		
Men, N (%)	14 (60%)		
Median (SD)	35 (22–44)		
Days of study	NSE (pg/mL)	C.I. 95%	I.Q.R
1st day (D1)	5748.0	[5852.0–5784.0]	[905–2075]
14th day (D14)	762.6	[814.8–776.3]	[478–806]
21st day (D21)	1018	[596.0–550.7]	[809–1300]

C.I. confidence interval, *I.Q.R.* Interquartile range

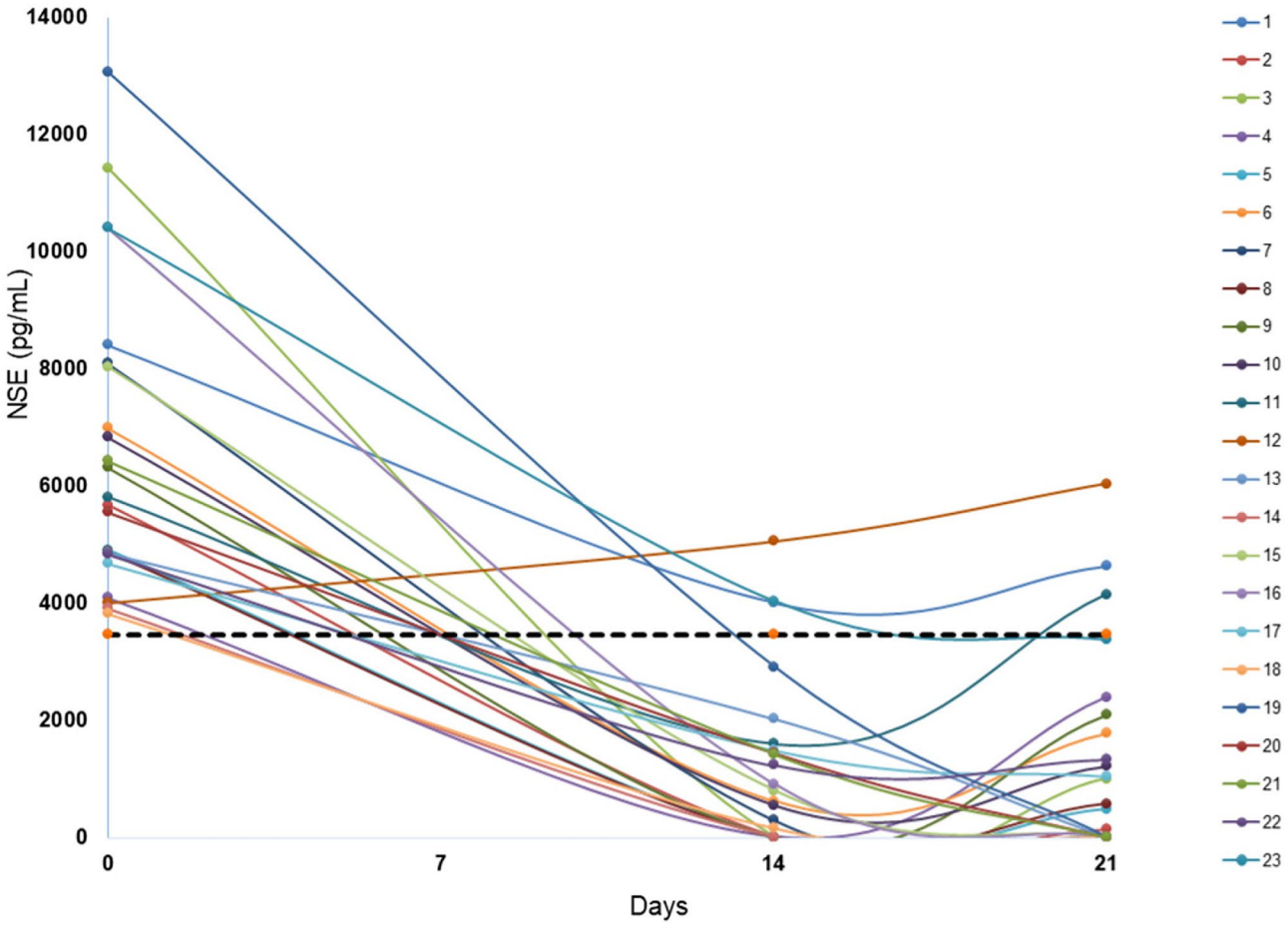

Fig. 3 Twenty-one days of serum quantification of NSE after the onset of the COVID-19 disease. Time trajectory of NSE levels in the serum of participants at three different times, D0, D14, and D21. All patients had NSE levels above the upper limit of the reference range on D0, 3 individuals on D14, and 4 individuals on D21. Dashed line = Upper reference limit calculated for the group with mild COVID-19 (G2). Upper reference limit = 3456.5 pg/mL

suggestive clinical evidence. The committee also highlights that S100B levels ≥ 0.1 ng/mL may indicate brain damage resulting from mild trauma (Ananthaharan et al. 2018). Here, a total of 4 individuals from G3 had S100B levels above this value (highest value of 0.51 ng/mL). Although fewer patients, this result might indicate a mild level of neural injury according to the values proposed by the Committee and therefore, restate the importance of monitorization of patients that required ICU admission.

Neuron-specific enolase (NSE) is a well-known cell-specific glycolytic enzyme. The elevation of NSE levels is a sensitive indicator of neuronal cell damage (Isgrò et al. 2015). In the context of COVID-19, the levels of NSE have been found elevated in individuals hospitalized because of COVID-19 infection (Fiori et al. 2021; Wei et al. 2020; Ganti et al. 2020; Savarraj et al. 2021; Cione et al. 2021). In the present study, we also quantified elevated serum expression of NSE post-COVID-19 infection in severe patients compared to control or mild patients.

The brain susceptibility to SARS-COV2 infection has been explained by multiple signalings (Kaneko et al. 2021; Erickson et al. 2021). Symptoms such as anosmia and ageusia have been described as determinant characteristics of neurological manifestation (Kaye et al. 2020). Our results corroborate with Blanco-Palmero et al. that neurologic symptoms during acute COVID-19 infection did not correlate with NSE serum expression. In contrast to our results, Cione et al. (2021) reported a strong correlation between dyspnea and enhanced NSE in the serum of Italian COVID-19-positive patients. In addition, our data showed a decline in NSE serum levels after 21 days of SARS-CoV2 exposure, suggesting that the protein may represent a neuro marker for COVID-19 recovery.

The understanding of COVID-19 neurological development is yet incipient, especially concerning the diversity among populations. These findings strengthen the emerging consensus that the outlook on the effect of the virus in the CNS may optimize patient care and follow-up monitoring.

Furthermore, our results unveil for the first time the role of NSE and S100B serum expression in patients positive for COVID-19 in Northeast Brazil, and suggest that NSE lodged a capacity to monitor neurological dysfunction and the recovery of COVID-19 patients.

Conclusion

Taken together, this study has provided an initial biological understanding of the role of S100B and NSE in COVID-19-positive patients in a population from Northeast Brazil. The elevation of S100B and NSE in the serum of severe patients suggests CNS damage related to acute virus exposure. The follow-up study with NSE confirmed no long-term CNS injury. Neurological symptoms of COVID-19 did not associate with NSE and S100B expression.

The mechanism underpinning CNS vulnerability to SARS-CoV2 infection has been difficult to dissect. Nevertheless, the present study is the first to characterize the expression of these molecules in inhabitants of Northeast Brazil, as well as the longest prospective cohort study, carried out with brain damage biomarkers in COVID-19 patients.

Even though our study has some limitations according to the number of patients enrolled and fewer patients expressing S100B in the serum, the results shed light on the monitorization of brain signaling in response to acute and post-21 days of SARS-CoV2 infection. On top of that, the results also held the view that NSE may provide insight into the recovery of patients from COVID-19. Future studies must clarify the neurological alterations caused by short and long-term COVID-19 infection.

Author contribution We assume that all authors have contributed to the submitted work, and approve the manuscript and its submission to the journal.

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