Original

Association of Serum S100b with Prognostic Factors in Acute Ischemic Stroke Patients at the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria

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Article history: Received 20 November 2023, Reviewed 21 December 2023, Accepted for publication 23 December 2023

How to cite this article:
Ajala AO, Ajose OA, Komolafe MA, Adedeji TA, Omisore AD, Busuyi SJ, Tajudin AA. Association of Serum S100b with Prognostic Factors in Acute Ischemic Stroke Patients at the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria; A Case-Control Study. The Nigerian Health Journal 2023; 23(4):961 - 967. DOI: https://www.doi.org/10.60787/tnhj-753

Abstract

Background: Stroke is a life-threatening neurological condition due to impairment in blood supply to the brain. In addition to clinical acumen, diagnosis and monitoring of stroke requires technical radiological imaging procedures. Researchers have sought serum biomarkers to aid the diagnosis and monitoring of stroke patients.

Method: Serum S100B was measured in 33 patients with acute ischemic stroke to evaluate its relationship with prognostic factors in stroke: severity estimated with the National Institute of Health Stroke Scale (NIHSS), functional outcome evaluated using the modified Rankin score (mRS), and infarct volume on computed tomography (CT) scan.

Result: A population of 33 test subjects with stroke were recruited into the study together with apparently healthy age and gender matched control subjects. S100B was assayed in all the participants with an Enzyme Linked Immuno-Sorbent Assay method (ELISA). The stroke patients were assigned NIHSS scores; functional outcome was assessed using the mRS. Infarct volume on CT scan was measured with the scanner volumetry program.

Conclusion: Elevated serum S100B is associated with increased clinical severity in acute ischemic stroke patients. S100B may thus be a suitable biomarker for monitoring patients with ischemic stroke.

Keywords: Ischemic stroke, S100B, National Institute of Health Stroke Scale: NIHSS, modified Rankin Score: mRS

Introduction

Stroke is defined as rapidly developing clinical signs of focal or global disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.[1] It can be broadly classified into ischemic or haemorrhagic types.

Ischemic stroke occurs when there is a compromise in blood supply to a region of the brain due to an obstruction of the vessels by a thrombus or embolus. Haemorrhagic stroke occurs due to vessel rupture and haemorrhage into the brain and can be classified as cerebral haemorrhage, or subarachnoid haemorrhage, depending on the locus of the haemorrhage within the brain. Non-modifiable risk factors for stroke include age, gender, genetics, and ethnicity amongst others. Modifiable risk factors for stroke include diabetes mellitus, smoking, alcoholism, hypercholesterolemia and atrial fibrillation.[2]

Print ISSN: 0189-9287 Online ISSN: 2992-345X

African countries are undergoing an epidemiological transition involving an increase in non-communicable diseases and cardiovascular risk factors, due to socio-demographic and lifestyle changes. The incidence of stroke is rising in African countries, and other low- and middle- income countries (LMIC), and these countries contribute 86% of all stroke deaths globally.[3] Prevalence rate of stroke in Nigeria has been estimated to be about 1.31 per 1000(0.13%).[4]

Diagnosis of stroke is usually carried out clinically and confirmed by neuro-imaging techniques such as Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI). Also, neuro-imaging techniques are often not available in areas with limited resources. Repeat imaging tests which are often inconvenient and costly, may be required to monitor stroke patients during illness. Furthermore, clinical evaluation is usually subjective and clinical diagnosis of stroke may not always be reliable in inexperienced physicians' hands.

As palliative to these drawbacks, researchers have carried out a considerable number of studies on biomarkers in stroke.[5-9] The availability of specific biomarkers in evaluation of stroke patients will aid in the diagnosis and monitoring of the disease, as well as reduce total costs incurred during management.

S100B, a member of the S100 super family of proteins; so called because of their 100% solubility in ammonium sulphate, is one of such biomarkers.[10] S100 proteins have 2 subunits: A and B. The S100A is produced in skeletal and cardiac muscle, and kidney. S100B protein is found in astrocytes, oligodendrocytes, and Schwann cells.[11] It is involved in regulating the intracellular processes of growth, transcription, and differentiation, and may play a reparative role following cell damage.[12] It is easily quantified in blood, cerebro-spinal fluid, and urine. It is stable for up 48 hours at room temperature and is not degraded by freezing to – 70˚c.[13]

Studies have demonstrated increased concentration of S100B in stroke, degenerative central nervous system (CNS) disorders, and in CNS trauma.[5,8,14] Increased serum levels in malignant melanoma have also been described.[15,16] Other researchers have specifically described significant correlation between serum S100B and severity, functional outcome, and lesion volume in stroke.[17-20]

This study was carried out to assess the usefulness of S100B as a biomarker to aid the diagnosis and monitoring of stroke patients. It specifically aimed at evaluating serum S100B to determine the nature of its relationship with clinical prognostic factors of stroke: clinical severity estimated with the NIHSS, and functional outcome evaluated with the mRS in patients with ischemic stroke.

Method

Study Design

The study was a cross-sectional study done at the OAUTHC from September 2018 to November 2019. Ethical approval was given by the Ethics and Research committee of OAUTHC (Protocol no. ERC/2018/08/18). Thirty-three (33) adult patients with first occurrence of acute ischemic stroke diagnosed clinically and confirmed with neuroimaging (CT scan) presenting at the emergency unit of the OAUTHC, Ile-Ife were recruited into the study via consecutive non-probability sampling. The average time of presentation of the stroke patients from onset of symptoms was 3 days. Age- and gender-matched apparently healthy individuals were recruited as control subjects to serve as the comparison group in the study.

To prevent confounding by other possible causes of S100B elevation, exclusion criteria for the study included adults presenting later than 4 days from onset of symptoms, haemorrhagic stroke, previous history of stroke or transient ischemic attack**,** individuals with clinical history suggestive of central nervous system tumour, seizure disorder, neurodegenerative disorders e.g. Alzheimer's disease, Parkinson's disease, and Amyotrophic lateral sclerosis. Individuals with history suggestive of malignant melanoma were also excluded.

A detailed history and physical examination were carried out on all patients. 5ml of venous blood was collected by venepuncture under strict aseptic conditions into plain bottles and allowed to stand for adequate clotting and retraction to occur. Serum was obtained from clotted blood after full clot retraction by centrifuging at 3000 revolutions per minute for 10 minutes, transferred into plain bottles, and immediately stored frozen at – 20 ˚C until analysis.

Biomarker analysis

Analysis of S100B was carried out by a sandwich ELISA method using reagent kit supplied by Eagle Biosciences (DKO074), 20A Northwest Blvd, suite 112, Nashua, New Hampshire, USA.

The S100B ELISA test is based on the binding of S100B by two antibodies, one immobilized on microwell plates and the other conjugated with horseradish peroxidase (HRP). The assay involves a two–step binding procedure

Print ISSN: 0189-9287 Online ISSN: 2992-345X

with incubation. After every incubation step, separation of unbound components is performed by simple solid phase washing. The enzyme HRP in the bound fraction reacts with hydrogen peroxide (H_20_2) in the substrate while the tetramethyl benzidine (TMB) in the substrate develops a blue colour that turns yellow when the stop solution (H_2SO_4) is added. The colour intensity is proportional to the S100B concentration in the sample.

Neurological assessment

Stroke severity was assessed in all patients using the National Institute of Health Stroke Scale (NIHSS) at first contact within 4 days of onset of symptoms. The NIHSS uses an 11-item scoring system to assess deficits in cranial nerves, cortical, and subcortical functions. Scored items include level of consciousness, visual fields, gaze, facial palsy, motor and sensory function, limb ataxia, and tests of language. Scores increase with severity, with a total possible score of 42, and a least score of 0 in the complete absence of neurological deficit. A stroke severity grading of the scale is as follows: ≤ 4: mild, 5 – 15: moderate, 16 – 20: moderately severe, 21 – 42: severe. The stroke patients were dichotomized into groups based on their NIHSS scores with patients with score ≤ 15 classified as mild-moderate stroke and those with score > 15 classified as having severe stroke.

Functional outcome in patients was determined using the modified Rankin Scale (mRS) on day 30 from onset of symptoms. The mRS is a clinical outcome scale for measuring the degree of disability and dependence on others in patients who have had stroke. There are 7 outcome severity scores on the mRS from 0 – 6. A score of 0 is given for the absence of symptoms; a maximum score of 6 is given for fatal cases.

Radiological imaging

All participants with stroke had cranial Computed Tomography scan (Revolution ACT 16-slice machine, GE® model: 5492001) within a week of onset of symptoms. Mean time to CT scan was 5 days after onset of symptoms. All patients had CT scan after blood samples for biomarker analysis had been obtained. The lesions (infarct) were reviewed for size and volume measurement on soft tissue window for CT. The axial section with the largest dimension of the lesion was assessed and the longest lesion axis measured as 'A' with the ruler tool on CT console. 'B' was taken as the widest diameter perpendicular to A. 'C' was calculated by multiplying the number of axial slices on which the lesion is seen by the slice thickness for contiguous slices without any interslice gap in between them. Infarct volume was estimated in all patients using the ABC/2 (ellipsoid) formula.

The axial section with the largest dimension of the lesion was assessed by visual inspection, and the longest lesion axis measured as 'A' with the ruler tool on CT console. 'B' was taken as the widest diameter perpendicular to A. 'C' was calculated by multiplying the number of axial slices on which the lesion is seen by the slice thickness for contiguous slices without any interslice gap in between them. Non-contiguous slice acquisitions were avoided in the study.

All measurements were done by a consultant radiologist to reduce inter-rater variability.

Statistical analysis of data

Data collected were analysed with computer software: IBM SPSS Statistics for Windows, Version 20.0. (IBM Corp, Armonk, NY. U.S.A). Continuous variables were described using means and standard deviations (SD), or medians (med) and interquartile ranges (IQR), while categorical variables were expressed as percentages. Frequency distribution of continuous variables was tested for normality using the Shapiro-Wilk test. The student's t-test was used to compare normally distributed variables; otherwise, the Mann-Whitney U test was used. Spearman's correlation co-efficient was used to assess the degree of correlation between study variables. Statistical significance was set at a p-value of < 0.05. Biomarker accuracy in detecting stroke severity was carried out with receiver operating characteristic (ROC) curve analysis.

Results

There were 33 cases with ischemic stroke with age- and gender-matched healthy controls recruited into the study. The mean age of the stroke cases was 69.7 years (SD: 12.0) and mean age of controls was 67.8 years (SD: 10.9). There was no significant difference in age between the two groups: t=-0.30, p=0.976.

Among the stroke cases, 26(79%) were hypertensive, 5(15%) were diabetic, and 3(9%) had dyslipidemia. There was no patient with established ischemic heart disease or cardiac arrhythmias in the study. There were no smokers among the patients.

Demographic and clinical characteristics of study participants are shown in Table 1. The mean NIHSS score on admission was 17; (standard deviation [SD]: 10.9), mean day 30 mRS score was 4; (SD: 2.0)), mean volume of infarct on CT scan was 25.1mm^3; (SD: 26.5) Serum S100B was higher in the stroke cases than in controls: median(med): 27.73pg/ml; Inter-Quartile Range (IQR): 19.23-46.39pg/ml vs median: 201.2pg/ml; IQR: 14.07-29.93pg/ml. χ=2.36, p=0.018. A box-plot

Print ISSN: 0189-9287 Online ISSN: 2992-345X

diagram showing the levels of serum S100B in cases and controls is shown in Figure 1.

There was a significant positive relationship between serum S100B and the NIHSS: r=0.324, p=0.043. A scatterplot of serum S100B and the NIHSS in stroke cases is shown in Figure 2. There was however no significant relationship between serum S100B and the mRS: r=0.151, p=0.217 or infarct volume: r=0.155, p=0.210

On ROC analysis, serum S100B of 28.14pg/ml (Area Under Curve [AUC]: 0.753, 95% 0.569-0.937, p=0.031) was able to differentiate mild-moderate stroke from severe stroke with a sensitivity of 70%, and specificity 65%. ROC curve showing diagnostic performance of serum S100B in differentiating mild-moderate stroke from severe stroke based on the NIHSS is shown in Figure 2. The likelihood ratio of positivity for stroke severity at this serum level was 2.0, while likelihood ratio for negativity was 0.46.

Table 1: Demographic and clinical characteristics of study participants

Study Participants	Cases	Controls
N	33	33
Male, n(%)	14 (41)	14 (41)
Female, n(%)	19 (59)	19 (59)
Mean age(SD)	69.7(±12.0)	67.8(±10.9)
Hypertension, n(%)	26(79)	
Diabetes, n(%)	5(15)	
Dyslipidemia, n(%)	3(9)	
Ischemic heart disease/arrhythmia	Nil	
History of smoking	Nil	
S100B, med(IQR)[pg/ml]	27.73(19.23-46.39)	20.12(14.07-29.23)
NIHSS	16.7(10.9)	
mRS	3.7(2.0)	
infarct volume [mm³]	25.1(26.5)	

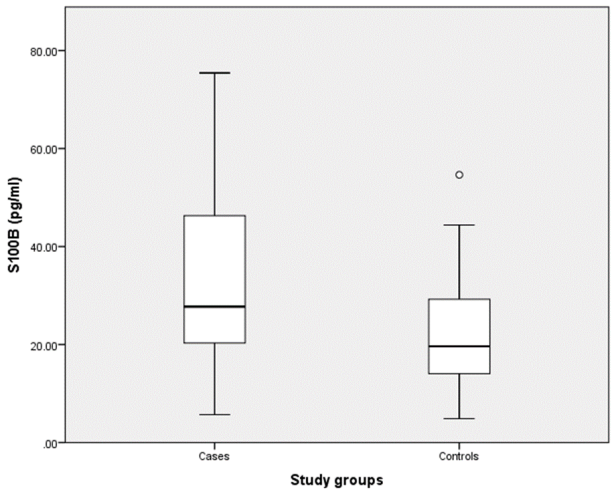

Figure 1: Box-plot diagram showing levels of serum S100B in cases and controls. Cases (med)27.73pg/ml; (IQR)19.23-46.39pg/ml vs controls (med)201.2pg/ml; (IQR)14.07-29.93pg/ml. p=0.018.

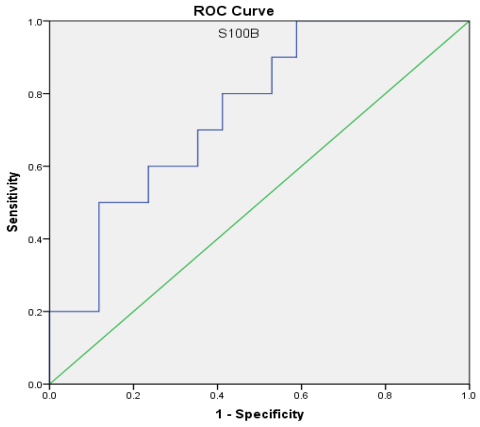

Figure 2: ROC curve showing diagnostic performance of serum S100B in differentiating mild-moderate stroke from severe stroke. AUC: 0.753, 95% C.I: 0.569-0.937, p=0.031.

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Discussion

In this study, serum S100B was significantly higher in cases than in controls. This is similar to findings by earlier researchers who measured S100B in ischemic stroke cases and healthy controls.[21-24] S100B is a relatively glial-specific protein and is released following neuronal damage. Its release is however not specific to stroke but also occurs in a variety of CNS disorders. As such it may only serve as a practical aid to the diagnosis of stroke where other factors; clinical, radiological, or biochemical have been established.

This study found a significant positive relationship between serum S100B and stroke severity measured with the NIHSS. Several studies have described the positive correlation of serum S100B with the NIHSS in ischemic stroke patients. Abdel-Ghaffar et al measured S100B on days 1 and 3, and found a significant positive correlation between S100B and the NIHSS on day 3 alone.[18] Hermann et al found a significant positive correlation between S100B and the NIHSS on all days of sampling 32 patients with ischemic stroke over 4 days from onset of symptoms.[25] Similarly, Wunderlich et al studied neurobiochemical markers: S100B and neuron-specific enolase in ischemic stroke and found both markers showed the highest positive significant correlation with the NIHSS on day 4 of admission of the stroke patients.[26] Other studies that measured S100B and assessed stroke severity with the NIHSS also found a significant positive correlation between the two parameters.[23,27]

The NIHSS is used to assess the degree of neurological deficit in stroke patients. Neurological deficit in stroke may be closely related to the degree of cellular damage as more neurons damaged would result in more symptoms manifesting in patients. S100B released from damaged glial cells in stroke is possibly responsible for the increased serum levels with increasing NIHSS scores in this study.

Selcuk et al, however reported a lack of significant correlation between S100B and the NIHSS, and postulated that the site of neuronal damage may also be a contributing factor to the severity of symptoms and subsequent NIHSS score in stroke patients.[19]

There was no significant correlation between S100B and day 30 mRS in the study. This is in agreement with the data reported by Bielewicz et al regarding the relationship between these variables in ischemic stroke.[28] Abdel-Ghaffar et al did not also find a significant correlation between day 1 S100B and day 14 mRS, but its relationship was positive with day 3 S100B. It may be that other factors outside of the extent of neuronal damage contribute to functional outcomes in ischemic stroke; factors such as standard of care, presence of co-morbidities, or availability of psychosocial support. Other researchers have however reported a positive relationship between S100B and functional outcome in ischemic stroke assessed using the mRS or other outcome scoring scales.[19,22,23,25,27,29]

Serum S100B also showed no significant correlation with lesion volume on CT scan in this study. This is unlike the findings in the study by Onatsu et al where a significant positive correlation was found between S100B and infarct volume measured on CT carried out at day 10; mean infarct volume was 40.6(SD: 70.65)mm^3.[20] Wunderlich et al found a similar positive association in a study where CT was carried out within a week of admission with mean infarct volume: 36.6mm^3.[26] Mean time to CT scan from onset of stroke symptoms in our study was 5 days, and mean infarct volume in the stroke cases was 25.1(SD: 26.5)mm^3. It is probable that having CT scans on the patients at later dates would have allowed lesions to form more completely as was seen in the study by Joana et al were day 10 CT scans gave more information than scans performed earlier in the same patients.[28]

The finding of a significant association between S100B and severity of stroke in this study underscores it as a promising biomarker of stroke. This strengthens its potential for clinical utility particularly in the monitoring of stroke patients instead of repeated radiological imaging. Our study suffered certain limitations. Blood samples were collected only once from the study participants; serial sampling of the patients at specific intervals would have given a more comprehensive picture of serum S100B dynamics in the stroke patients. In the absence of material constraints, a larger sample size would have been preferable for a better powered study.

Conclusion

This study was carried out to determine the relationship between serum S100B and prognostic factors in patients with ischemic stroke. S100B showed a significant positive relationship with stroke severity estimated with the NIHSS but not with functional outcome or infarct volume in patients with ischemic stroke. Further studies may prove S100B to be a suitable surrogate marker for stroke severity useful in clinical monitoring of patients with ischemic stroke.

Declarations

Print ISSN: 0189-9287 Online ISSN: 2992-345X

Ethical consideration: The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Ethical approval was obtained by the Ethics and Research Committee of the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife.
Informed consent to participate was obtained from all individual participants included in the study or from their legal guardians.
Consent for publication of research findings from the study was obtained from all study participants or their legal guardians.

Authors' contribution: AA, AO, KM, and AT were responsible for conceptualization and design of the research work.
AA, AT, OA, TA, and BS selected the cases and controls, carried out blood sampling, clinical examination, laboratory investigations, and radiological imaging, as well as statistical analysis of study data.
AA, TA, and BS wrote the original draft of the manuscript.
AA, BS, AO, KM, TA, and OA carried out revision and editing of the original manuscript.
AO, KM, AT, and OA provided general supervisory roles over the research work.
All authors read and approved the final version of the manuscript.

Conflict of interest: The authors have no relevant financial or non-financial interests to disclose.

Funding: No funding was received for conducting this study.

Acknowledgement: The authors like to thank the staff of the Department of Chemical Pathology, Obafemi Awolowo University Teaching Hospitals Complex for logistic support during the study, and the participants of the study who gave consent and subjected themselves to the terms of the study.

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Print ISSN: 0189-9287 Online ISSN: 2992-345X