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# Protein S100B: a potential biomarker that correlates with clinical neurological variables in pediatric patients with congenital heart disease?

## Abstract

**Objectives:** S100B protein has been proposed as a brain injury biomarker in several clinical scenarios. We aimed to determine whether a correlation exists between S100B serum levels and clinical variables at the pre-operative period of paediatric patients with congenital heart disease.

**Methods:** A prospective case-control study was designed including paediatric patients from one month to with congenital heart disease admitted for surgical treatment during a 3-month period. We studied 44 patients at the pre-operative period and divided them in two groups: 20 with clinical neurological variables and 24 without them. Clinical paediatric neurological variables were obtained, and serum levels of S100B protein were measured using the ELISA "sandwich" technique.

**Results:** The cut-off for S100B serum level in patients with clinical neurological variables was 16pg/ml, with sensibility and specificity values of 70% and 70.8%, respectively. S100B protein levels greater than 16pg/ ml correlated with clinical neurological variables (p=0.014, OR=2.556, and 95% CI=1.205 -5.418)

Neurological clinical variables before operation may modify operative resilience and the risk of neurological complications.

**Keywords:** biomarkers, neurological variables, congenital heart disease

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Luis Antonio Pando Orellana,[1,2] Juan Calderón Colmenero,[2] Nancy Lucero Martínez Rodríguez,[2] Leonardo Del Valle Mondragón,[3] Víctor Manuel Espinoza Gutiérrez,[2] Jorge Luis Cervantes Salazar,[2] Juan Verdejo Paris,[2] Alfonso Buendía Hernández,[2] Armando Vega López,[1] Pedro José Curi Curi[2]

[1]Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, México

[2]Departamento de Cardiología Pediátrica, Instituto Nacional de Cardiología Ignacio Chávez, México

[3]Departamento de Farmacología, Instituto Nacional de Cardiología Ignacio Chávez, México

**Correspondence:** Pedro José Curi Curi, Juan Badiano No.1, Col. Sección XVI, Del. Tlalpan, 14080, México D.F., México, Tel 01(52) 5573 2911, Fax 55(55) 5573 0994, Email pcuricuri001@gmail.com

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**Abbreviations:** PET/CT, computed tomography combined with positron emission tomography; SPECT, single positron emission tomography; RAGE, advanced glycation end products

## Introduction

S100B belongs to the calmodulin family and is an EF-hand protein discovered by Moore in 1966 as a fraction of the brain in a 100% sulphur solution. S100B is a universal animal protein and probably functions as a neural growth factor.[1,2] Congenital heart diseases are the most frequent malformations in the paediatric population, with a prevalence of 6 to 8 cases per 1000 live births.[3] Advances in diagnosis and surgical techniques have allowed many patients to reach adulthood, but the risk of central nervous system damage continues to be one of the most feared morbidities in cardiovascular surgery.[4,5] but only 8 per 1000 new-borns have a congenital heart disease[3,5-11] and that are at the postoperative period on a long term basis,[3,5,7,10-15] The first diagnostic approach for neurological disorders is made by means of a clinical neurological examination and history. Ideally, such as computed tomography, PET/CT (CRANIAL) and SPECT. These studies cannot be performed immediately in the new-born or infant period due to haemodynamic instability, ventilator-dependent patients, unavailability or increased costs. In addition to these factors, the studies can lead to quantifying neurological damage as a whole to predict clinical outcome. Infrastructure and expertise also require major medical facilities; therefore, a biological maker could facilitate the task by selecting candidates to the complete functional imaging tests, neurophysiological protocols, and 3D anatomical imaging with the correct biomarker or biomarkers for a proper triage before referral to level III of medical attention.

A biomarker is therefore needed not only to detect brain damage but also to predict the clinical brain metabolic outcome. The S100B protein, which was identified in the brain, is produced by astrocytes in physiological conditions in children with congenital heart disease[16] and in different clinical scenarios, such as cranial trauma, cerebral ischaemia, neurodegenerative disorders, chronic inflammatory cerebral disease, cardiac arrest, and cardiopulmonary bypass.[7,8,10-14,17-26] The aim of this study is to determine any correlation between S100B protein serum concentration levels and clinical neurological abnormal variables or risk factors at the pre-operative period in paediatric patients with congenital heart disease.

## Methods

### Study design

We designed a prospective case-control study that included all paediatric patients (one month to 16 years old) with congenital heart disease admitted to our institution (National concentration heart disease institution) for surgical treatment in a 3-month period of time. The only exclusion criterion was: previous cardiac surgery or emergency surgery. A clinical neurological history was obtained with the informed consent of the parent, relative or closest person responsible for the patient. We emphasized obstetrical antecedents, such as prenatal control, perinatal, paediatric, cardiovascular and neurological parameters and considered major positive antecedents as follows: a history or report of pre-eclampsia, eclampsia, and APGAR score <8 at baseline and 5 minutes. Post-natal neurological variables considered as major positive variables included neurodevelopmental deficit, epilepsies (partial), syndromatic phenotype and/or genotype,

and clinical neurological motor .Definitions of these terms were obtained from the respective clinical practices, particularly the neurodevelopmental unit of the Hospital Infanfil de México "Dr. Federico Gomez", of which the first author was chairman, and the Consejo Mexicano de Pediatría (National Board of Pediatrics).

The remaining clinical factors, considered minor positive criteria, including demographic, anthropometric and complementary data, such as gender, weight, height, congenital heart disease type, and pre-operative oxygen saturation, were also registered but do not add to the article except as cyanotic or acyanotic disease because of it´s very complex terminology and at the end has to do just with these very generic terms in our data base and the purpose of the paper. Patients were divided in two groups: those with clinical positive variables and those without them. To include patients with clinical neurological positive variables, we required one positive major peri-natal criterion (antecedent before, during or after labour up to a month of age) and a positive major post-natal criterion (meaning from the second month on) or also at least two positive perinatal and/or two post-natal minor criteria. This study was approved by our institution´s ethics committee, and signed consent was provided for every case enrolled.

### Determination of protein S100B serum concentration level

Peripheral blood samples were obtained from all patients at the pre-operative period and centrifuged at 3000 rpm for 15minutes at room temperature. Sample plasma aliquots were obtained and frozen at-80°C until analysis. S100B serum levels were measured by an ELISA technique (S100B [Human] ELISA KIT, ABNOVA; KA0037) in two incubation periods for a total period of 120minutes. During the first incubation period, a monoclonal specific antibody was added (biotinylated anti S100B antibody) for 60minutes. Afterwards, HRP-streptavidin was added. After 30minutes of incubation and washing, the substrate solution was added. The reaction was stopped by the addition of an acid solution, and the absorbance of the resulting product was measured. The results were obtained using a standard curve of S100B in accordance with manufacturer's directions and were expressed as µg/L.

### Statistical analysis

All data were registered in a checklist at the pre-operative period. Information was stored in an electronic Excel page and processed with an SPSS statistical software version 21.0 (SPSS Inc., Chicago, Ill, USA). Quantitative variables are presented as means and variability ranges (minimum and maximum). Categorical data are presented by terms of frequency and percentages in relation to the population at risk. S100B protein serum concentration levels were plotted using a ROC curve for both groups of patients, and the area under the curve (AUC) was determined to compare them. Comparison of categorical variables between patients with clinical neurological background and the patients without it was performed by means of a Fisher´s exact test. Odds ratios were also calculated with a 95% confidence interval (CI). For comparing quantitative variables that were normally distributed, we performed a Student t-test. Values of $p<0.05$ were considered statistically significant.

## Results

We included 44 patients divided in two groups in the final analysis: 20 with clinical neurological antecedents as defined and 24 without clinical neurological antecedents. The group with clinical neurological antecedents exhibited a significant difference in the presence of clinical neurological (35%, n=7, p=0.015) compared with the group without clinical neurological antecedents. The remainder of variables did not exhibit significant differences, which lead to an appropriate comparability between groups (Table 1) (Table 2). The area under the curve (AUC) was 0.685 for the group with clinical neurological antecedents as defined and of 0.315 for the group without clinical neurological antecedents as defined. The cut-off S100B serum level to identify patients with clinical neurological antecedents was 16pg/ml, with sensibility and specificity values of 70% and 70.8%, respectively. Correlation between S100B protein serum level and clinical neurological antecedents is presented in Table 3. High S100B protein serum concentration levels>16pg/ml correlate significantly with the presence of clinical neurological clinical variables or antecedents (p=0.014) with a 2.556 odds ratio (OR) and 95% confidence interval of 1.205 to 5.418.

**Table 1** Demographic categorical characteristics

| Variable | | With clinical neurological antecedents/history (Low Apgar, Fetal Suffering, Neurological lateralization, Seizures, Neurodevelopment alterations) | Without clinical neurological antecedents/history (Low Apgar, Fetal Suffering, Neurological lateralization, Seizures, Neurodevelopment alterations) | p |
|---|---|---|---|---|
| | | n (%) | n (%) | |
| Gender | Female | 11 (55%) | 12 (50%) | 0.771 |
| | Male | 9 (45%) | 12 (50%) | |
| Congenital disease type | Non cianotic | 12 (60%) | 15 (62.5%) | 1.000 |
| | Cianotic | 8 (40%) | 9 (37.5%) | |
| Syndromatic antecedents (Down, 22 delecion) | | 4 (20%) | 4 (16.7%) | 1.000 |

Table Continued

| Variable | | | With clinical neurological antecedents/history (Low Apgar, Fetal Suffering, Neurological lateralization, Seizures, Neurodevelopment alterations) | Without clinical neurological antecedents/history (Low Apgar, Fetal Suffering, Neurological lateralization, Seizures, Neurodevelopment alterations) | p |
|---|---|---|---|---|---|
| | | | n (%) | n (%) | |
| Peri-natal neurological antecedents (history) | Fetal suffering | | 8 (40%) | | |
| | Pre-eclampsia | | 4 (20%) | | |
| | Eclampsia | | 1 (5%) | | |
| | APGAR (first minute) | 5 | 1 (5%) | | |
| | | 6 | 1 (5%) | | |
| | | 7 | 2 (10%) | | |
| | | 8 | 8 (40%) | 6 (25%) | 0.418 |
| | | 9 | 3 (15%) | | |
| | APGAR (5 minutes) | 7 | 1 (5%) | | |
| | | 8 | 4 (20%) | | |
| | | 9 | 8 (40%) | 6 (25%) | 0.312 |
| | | 10 | 2 (10%) | | |
| | Neuro-development | Deficient | 14 (70%) | 15 (62.5%) | 0.752 |
| | | Normal | 6 (30%) | 9 (37.5%) | |
| Post-natal neurological antecedents (history) | Epilepsia (partial) | | 1 (5%) | | |
| | Clinical neurologic compromise (lateralization/paresia) | | 7 (35%) | 1 (4.2%) | 0.015 |

**Table 2** Demographic numerical characterisctics

| Variable | With clinical neurological antecedents/history (Low Apgar, Fetal Suffering, Neurological lateralization, Seizures, Neurodevelopment alterations) | Without clinical neurological antecedents/history (Low Apgar, Fetal Suffering, Neurological lateralization, Seizures, Neurodevelopment alterations) | P |
|---|---|---|---|
| | Mean±SD (Min-Max) | Mean±SD (Min-Max) | |
| Age (years) | 6±4.812 (1-16) | 6.54±4.89 (1-15) | 0.714 |
| Weight (kg) | 17.64±12.25 (3-51) | 23.75±17.78 (5-60) | 0.201 |
| Height (cms) | 103.63±31.64 (55-162) | 110.63±31.87 (64-160) | 0.471 |
| Preoperative oxygen saturation **(%)** | 84.95±11.27 (63-98) | 87.17±10.35 (63-98) | 0.501 |

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**Table 3** Correlation between S100B protein serum concentration levels and clinical neurological variables

| S100B serum concentration level (pg/ml) | Wih clinical neurological antecedents (history) n (%) | Without clinical neurological antecedents (history) n (%) | p | OR (CI 95%) |
|---|---|---|---|---|
| High (>16pg/ml) | 14 (70%) | 7 (29.2%) | | 2.556 |
| Low (≤16pg/ml) | 6 (30%) | 17 (70.8%) | 0.014 | (1.205-5.418) |

## Discussion

A great variety of developmental disorders have been identified in up to 50% of the paediatric population in Latin America, but only 8 per 1000 new-borns have a congenital heart disease that modifies their development and resilience before, through and after cardiopulmonary bypass. These other factors include underweight, lower percentiles in height (in a Mexican population)[12] and cognition deficits[6,27,28] that are typically detected during the postoperative period on a long- term basis. We observed that S100B protein levels greater than 16 pg/ml correlate with clinical abnormal neurological variables (p=0.014, OR=2.556, and 95% CI=1.205- 5.418) and therefore may modify operative resilience and risk of neurological complications which have been reported in several articles[3,5,29,30] Functional imaging studies cannot be performed immediately in the new-born or infant period because of haemodynamic instability, ventilator dependent patients, unavailability of infrastructure or costs. In addition to these factors, these studies can lead to quantify neurological damage as a whole to predict clinical outcome. Infrastructure and expertise require major medical facilities; therefore, as a biological maker, the S100B protein could facilitate the task by selecting patients who could be candidates for complete functional imaging tests, neurophysiological protocols, and 3D anatomical imaging. Thus selecting patients and costs in poor countries. The fact that S100B is comparable with neurological variables opens a line of research to consider how this correlation is involved given its role in the possible operative risk in patients who need cardiac surgery because of congenital heart disease cyanotic clinical (unsaturated with pulse oximetry: actually undergoing correlation with saturation under 80%) and non-cyanotic clinical,(actually undergoing saturation above 80%) clinical research; as well as with IOS index . This question should be of particular interest to the non-specialist because the diagnosis of congenital heart disease is at least suspected at the first and second level of health systems. Physicians that refer this group of patients to specialized centers must have access to an inexpensive biomarker to prioritize and alert the health system of risk factors, to improve triage referral protocols and to notify highly specialized centers of their behaviour while facing cardio-pulmonary bypass with possible insult to the brain and/or complications (3-7%) according to our series[3,12] Clinical anamnesis to obtain neurological data is difficult in paediatric populations with congenital heart disease for several reasons. Because of young age, physicians must ask to parents, relatives, closest persons or general paediatricians or even gynaecologists and obstetricians of the patient. Unfortunately, this is a problem that neurologists, cardiologists and physicians in general must address, particularly in developing countries.[2,5,7,9,18,20,31,32] S100B engages with RAGE receptors[5] given that it is a cofactor in nitrogen reactive species. We are convinced that clinical correlations are trying to tell us something. However, given that children are different, it does not go alone. Previous communications tell us that the population under study must be stratified by age and that metabolic pro- and antioxidative items should be considered in addition to this important clinical-molecular correlation; the objective is to re-evaluate the value of S100B as a true and integral marker that can assess potential risks before congenital heart disease surgery and the inevitable and necessary comprehension of chronic hypoxia to fully understand the correlations established here between S100B and neurological variables.[33-53]

## Author contributions

a. Luis Antonio Pando-Orellana, MD: Concept/Design, Data analysis/interpretation, Drafting article, Critical revision of the article, Approval of article, Statistics, Overall-Data collection, Funding, and Responsible researcher.

b. Juan Calderón-Colmenero, MD: Data analysis/interpretation, Drafting article, Critical revision of the article, Approval of article, and overall Data collection

c. Nancy Lucero Martínez–Rodríguez, PhD: Data analysis/interpretation, Drafting article, Critical revision of the article, Approval of article, Statistics, and laboratory Data collection

d. Leonardo Del Valle-Mondragón, PhD: Data analysis/interpretation, Critical revision of the article, Approval of article, and laboratory Data collection

e. Víctor Manuel Espinoza-Gutiérrez, MD: Data analysis/interpretation, Critical revision of the article, Approval of article, and Data collection

f. Jorge Luis Cervantes-Salazar, MD: Critical revision of the article, Approval of article, and Data collection

g. Juan Verdejo-Paris, MD: Critical revision of the article and Approval of the article

h. Alfonso Buendía-Hernández, MD: Critical revision of the article, Approval of article, and Data collection

i. Armando Vega-López, PhD. Critical revision of the article and Approval of article.

j. Pedro José Curi-Curi, MSc. Operative aspects, statistical collaboration and analysis and Approval of article

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## Conflicts of interest

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