S100 failes to predict post stroke epilepsy, data from BIOSIGNAL study

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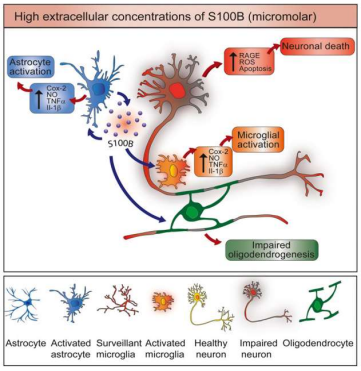
Background & Aim

Background:

- **Ischemic stroke (IS) is the leading cause of epilepsy in elderly patients. Blood biomarkers acquired in the acute phase may contribute to early prediction and risk stratification for post stroke epilepsy (PSE), thus identifying vulnerable patients that are most likely to benefit of antiepileptic treatment.**
- **Increased permeability of blood-brain barrier and neuro-inflammation are crucial in the process of epileptogenesis. S100-B is a calcium-binding cytokine mainly released by astrocytes that is involved in controlling astrocytes proliferation, neuron differentiation and apoptosis.**



Michetti F, D'Ambrosi N, Toesca A, et al. The S100B story: from biomarker to active factor in neural injury. *J Neurochem*. 01 2019;148(2):168-187. doi:10.1111/jnc.14574

- **Elevation of S100-B serum levels is a marker of cell damage, studies with murine models and with large collectives of human patients have been already proposed this protein as a prognostic biomarker for PSE [1,2].**

Aim:

- **We aim to assess and validate the predictive value for PSE of S100-B using a large well characterized acute IS cohort.**

Patients & Methods

Setting:

Within the multicenter BIOSIGNAL (Biomarker Signature of Stroke Aetiology) study (ClinicalTrial.gov NCT02274727), we consecutively included 1165 ischemic stroke patients at the stroke center of the university hospital of Zurich 24 hours of symptom onset

Work-up during hospitalization:

- **Medical history, physical examination**
- **Clinical risk scoring using NIHSS**
- **Blinded S100-B measurement within 24 hours of symptom onset**
- **Routine laboratory tests & imaging (CT and /or MRI)**
- **Aetiology work up (ECG, Echocardiography, Ultrasound)**

Endpoint:

- **Primary Endpoint: late seizure more than 7 days after stroke during one year and long term follow up (follow-up median duration 5 year, IQR 1 year)**
- **Secondary Endpoint: any seizure during one year and long term follow up (follow-up median duration 5 year, IQR 1 year)**

Analysis:

Logistic regression and Cox proportional hazards models were fitted to estimate odds ratio (OR) and 95% confidence interval (CI) for the association between log-S-100B and the outcome measure while extreme gradient boosting techniques were used to assess optimal, predictive multivariable models.

Results

Baseline Characteristics

Table 1. Baseline Characteristics of All Patients as well as Stratified by seizure

	All Patients (*n* = 1001)	No seizure (*n* = 942)	Seizure (*n* = 61)	*P* Value
Demographic data				
Age, median (IQR), y	72 (18–100)	70 (18–100)	70 39–90)	0.91
Women, *n* (%)	422 (42)	397 (42)	25 42)	0.54
Medical history, *n* (%)				
Hypertension	713 (71)	664 (70)	49 (83)	**0.02**
Current smoking	269 (27)	256 (27)	13 (22)	0.24
Diabetes mellitus	151 (15)	136 (14)	15 (25)	**0.02**
Dyslipidemia	722 (72)	680 (72)	42 (71)	0.49
Clinical data, median (IQR)				
NIHSS at admission (points)	7 (0–30)	6 (0-30)	10 (0–27)	**<.001**
OCSP				
Cortical involvement	35 (10.6)	8 (4.1)	27 (20.2)	**<.001**
ACA	150 (45.6)	87 (44.6)	63 (47.0)	0.74
MCA	67 (20.4)	42 (21.5)	25 (18.7)	0.58
PCA	89 (27.1)	61 (31.3)	28 (20.9)	**0.04**
Laboratory values, median (IQR)				
S100*	0.12 (0.0215-0.29)	0.12 (0.02-4.29)	0.14 (0.03-0.60)	**0.04**
Therapy				
i.v thrombolysis	416 (42)	392 (42)	24 (71)	0.81
i.a thrombolysis	80 (8)	75 (8)	5 (8)	0.52
TOAST subtype, *n* (%)				
Large-vessel disease	156 (16)	144 (15)	12 (20)	0.19
Cardioembolic	283 (28)	269 (29)	14 (24)	0.26
Small-artery disease	121 (12)	120 (13)	1 (2)	**0.004**
Other known	68 (37)	59 (6)	9 (15)	**0.02**
Undetermined	374 (37)	351 (37)	23 (39)	0.45

Footnote: IQR, interquartile range, meaning range between the first and third quartile; NIHSS, National Institute of Health Stroke Scale; ACS, Anterior Circulation Stroke; MCA, Medial Circulation Stroke; PCA, Posterior Circulation Stroke; TOAST, Trial of Org 10172 in Acute Stroke Treatment.[1] * Normalized copy number per µL of plasma; iv: intravenous; i.a: intraarterial

Univariate Regression Analysis

- In the univariate logistic regression log10S100-B was associated with any seizure after one year follow up [OR 2.12, 95% CI 1.01–4.42, P = 0.046, per unit log10S100-B increase], no associaton was found in the long term follow up.

Multivariate Regression Analysis

In the multivariate logistic regression log10S100-B was not associated with any seizure after one year [OR 0.88, 95% CI 0.37–2.06, P = 0.76, per unit log10 S100-B increase] (shown in the table) or in the long term follow up[OR 0.66, 95% CI 0.26–1.70, P = 0.39, per unit log10 S100-B increase]

	Seizure			
Predictors	**OR**	**95% CI**		***P***
log10 S100*	0.88	0.37	– 2.06	0.76
hypertension	2.25	1.07	– 4.74	4.74
diabetes	2.00	1.05	– 3.80	0.04
NIHSS at admission (per point)	1.09	1.05	– 1.14	<0.001
Small-artery disease	0.25	0.03	– 1.90	0.18
cortical	2.39	0.00	– 0.03	<0.001

Footnote: NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; CI, confidence interval; * log10-transformed values were used in these analyses. See the "Statistical Analysis" section for details.

Conclusions

Despite previous studies[1,2] we were not able to find an independent significant prognostic contribution of S-100B for late or any seizures. Other candidate biomarkers should be further evaluated for this important clinical question.

1. Vezzani A, Maroso M, Balosso S, Sanchez MA, Bartfai T. IL-1 receptor/Toll-like receptor signaling in infection, inflammation, stress and neurodegeneration couples hyperexcitability and seizures. Brain Behav Immun. Oct 2011;25(7):1281-9. doi:10.1016/j.bbi.2011.03.018

2. Abraira L, Santamarina E, Cazorla S, et al. Blood biomarkers predictive of epilepsy after an acute stroke event. Epilepsia. 10 2020;61(10):2244-2253. doi:10.1111/epi.16648