S-100B protein: An early prognostic marker after cardiac arrest

Karolina Wojtczak-Soska, Małgorzata Lelonek

Department of Cardiology, 1st Chair of Cardiology and Cardiac Surgery,
Medical University of Lodz, Poland

Abstract

The identification of a good prognostic factor of neurological outcome after cardiac arrest is needed. S-100B protein seems to be a promising early predictor of brain damage. Yet it is necessary to reach a consensus on cut-off values, time of blood sampling and the predictive accuracy of S-100B protein. The present review summarizes the data about the clinical implications of S-100B protein after brain injury, especially in patients after cardiac arrest. (Cardiol J 2010; 17, 5: 532–536)

Key words: S-100B protein, cardiac arrest, brain damage

As the techniques of cardiopulmonary resuscitation (CPR) become more effective, the number of patients surviving cardiac arrest (CA) increases. High mortality and frequent brain damage are characteristic of these patients but there are no precise and generally accepted diagnostic rules to predict early and overall outcomes. The identification of a good prognostic factor of the neurological outcome after CA is needed to decide on further therapeutic management and to avoid futile medical treatment.

To predict cerebral outcomes following CA, modern medicine has at its disposal neuroimaging data, electrophysiological data and blood or cerebrospinal fluid examination data. Neuroimaging and electrophysiological data, however, are insufficient in the early stage to appraise brain injury following CA and are not as helpful as early biochemical markers, which are easy to obtain and assess [1]. Many investigators have been looking for the most accurate predictor [2–5]. S-100B protein and neuron-specific enolase (NSE) appear to be the most promising factors. The present review focuses on the role of S-100B protein as an earlier marker than NSE in predicting early neurological outcomes following CA.

S-100B is a calcium-binding, low molecular weight (LMW) protein produced by activated glia in the central nervous system. Its name S-100B originates from its solubility in a 100%-saturated solution with ammonium sulphate at neutral pH [6]. S-100B is produced early after metabolic injury by astrocytes activated by oxygen or glucose deprivation [7]. It is released into the extracellular space, into cerebrospinal fluid and further into the bloodstream when the blood-brain barrier loses its integrity, mechanically or during inflammatory response after CA. It may also be released from mechanically damaged cells. In nanomolar concentrations, S-100B is trophic to neurons and has a reparative role but when it is overproduced, in micromolar concentrations can enhance neuroinflammation and cause further neurologic injury by evoking neuronal apoptosis [8]. Serum levels of S-100B increase after CA and are positively correlated with dimension of brain injury [7, 8]. S-100B is measured in blood serum and remains stable for several hours. It has a short half-life (approximately 30 min) so its measurement is very useful in the emergency and intensive care units.

Many different sensitive immunoassays are available to determine the serum levels of S-100B protein, both automatic and manual [9, 10]. One of the most popular tests, Can Ag S100 EIA (Can Ag

---

Table 1. Studies on S-100B levels, with cut-off values, specificity, sensitivity and time of sampling in patients following cardiac arrest.

Authors	No. of patients	Data	Outcome	Cut-off values [µg/L]	Specificity (%)/ Sensitivity (%)	Time of sampling
Martens et al. [16]	64	S-100, NSE	Remained in coma	0.7	96/55	24 h
Rosén et al. [25]	41	S-100	Death	0.2		Day 1
				0.2		Day 2
			No return to independent daily life	0.2		Day 2
Böttiger et al. [13]	66	S-100B	Death	0.2		24 h
			Brain damage	> 1.1	NM/100	48 h
Hachimi-Idrissi et al. [15]	58	S-100B	Remained in coma	0.7	85/67	OA
				0.7	88/100	24 h
Mussack et al. [18]	20	S-100B, Il-8	No return to independent daily life	0.76	100/54	Day 1
Pfeifer et al. [11]	97	S-100B, NSE, time of anoxia, GCS score	Remained in coma	1.5	96/34	Day 3
Miao et al. [14]	25	S-100B, NSE	Remained in coma	0.165	100/94.4	2 h
Grubb et al. [17]	143	S-100B, NSE	In-hospital death Memory impairment	1.20 > 0.29	100/44.8 100/42.8	Day 2
Prohl et al. [2]	80	S-100B, NSE, sensory-evoked potentials, neuropsychological assessments	Remained in coma	2.1	100/17	Day 1
Shinozaki et al. [12]	107	S-100B, NSE	CPC 3–5	1.41	100/20.9	24 h

NSE — neuron specific enolase; Il-8 — interleukin-8; GCS — Glasgow Coma Scale; CPC — cerebral performance categories; NM — not mentioned; OA — on admission

Diagnostics AB, Gothenburg, Sweden) contains reagents for 96 tests and has to be stored at 2–8°C. The estimations of S-100B are done at room temperature, and among other things require microplate spectrophotometer and microplate shaker. Calibrators and patient samples are incubated together with Anti-S-100B monoclonal antibody in Streptavidin-coated microstrips for two hours. After incubation they are washed and incubated with two more reagents. If S-100B is present, a blue color will develop during the enzyme reaction. The intensity of this color is proportional to the amount of S-100B in the samples. The absorbance is read at 620 nm in a microplate spectrophotometer.

Another of the many tests available is the popular two-site immunoassay Liaison® Sangtec 100 (DiaSorin AB, Bromma, Sweden). It's a two-step immunoluminometric sandwich assay using directly coated magnetic microparticles and it allows 100 determinations of S-100B to be carried out. The time of incubation is 20 minutes.

Many studies on the S-100B protein as an early predictor following CA have been published (Table 1).

Pfeifer et al. [11] investigated the prognostic value of S-100B protein, NSE, and Glasgow Coma Scale (GCS) in 97 patients following CA. Serum levels over $1.5 \, \mu g/L$ for S-100B increased the risk of a poor outcome (death/persistent vegetative state) by 12.6 times. A combination of GCS < six and elevated serum levels of S-100B and NSE at 72 hours after CPR predicted poor outcome with 100% specificity.

A Japanese study by Shinozaki et al. [12] compared serum levels of S-100B and NSE at six and 24 hours following CA in 107 patients. Serum levels of S-100B and NSE in the group of patients with a poor neurological outcome (CPC3 to CPC5 in the Glasgow-Pittsburgh cerebral performance categories: CPC, Table 2) were higher than those in patients with a favorable neurological outcome (CPC1 and CPC2; p < 0.01). Cut-off values of S-100B predictive of poor neurological outcome were 1.41, 0.21, and 0.05 ng/mL. They corresponded to sensitivities of 20.9%, 62.8%, and 100%. These values were higher than these for NSE. S-100B assessed 24 hours after CA is recognized as a better early predictor of poor neurological outcome than NSE.

Table 2. Comparison of Glasgow-Pittsburgh cerebral performance categories (CPC) and Glasgow Outcome Scale (GOS) scores.

CPC grade	CPC specification	GOS specification	GOS grade
1	Good cerebral performance: conscious and alert, with normal neurological function or only slight cerebral disability	Good recovery: able to return to work or school	5
2	Moderate cerebral disability: conscious and sufficient cerebral function for part-time work in sheltered environment or independent activities of daily life	Moderate disability: able to live independently but unable to return to work or school	4
3	Severe cerebral disability: conscious and dependent on others for daily support because of impaired brain function	Severe disability: able to follow commands but unable to live independently	3
4	Coma, vegetative state		2
5	Dead or brain dead		1

Also Böttiger et al. [13] determined serum levels of S-100B and NSE in 66 patients after CA, immediately afterwards, and after 15, 30, 45 and 60 minutes; again after two, eight, 24, 48, and 72 hours; and seven days after CPR (NSE was not determined before two hours after CA). During the entire study period, S-100 and NSE levels were lower in patients surviving without brain damage (CPC1) than in the group with documented brain damage. Within two hours after CA, the maximum S-100 level in patients with documented brain damage was $3.70 \pm 0.77\,\mu g/L$ (p < 0.05), and in patients without recovery of spontaneous circulation (ROSC) $3.44 \pm 0.58\,\mu g/L$ (p < 0.05), whereas in patients with no brain damage S-100 level was $0.90 \pm 0.29\,\mu g/L$. Investigators concluded that S-100B is an early and sensitive marker of severe brain damage and short-term outcome following CA.

Moreover, Miao et al. [14] in a study from China compared serum levels of S-100B and NSE at two, 12, 24, 48 and 72 hours after ROSC, in a group of seven healthy volunteers and in 25 patients divided into two groups: patients who regained consciousness during the six months following CA, and patients who did not. Serum levels of both NSE and S-100 were higher in the group who did not regain consciousness. Serum S-100 protein cut-off was $0.165\,\mu g/L$, with a sensitivity of 94.4%, and a specificity of 100%.

Serum levels of S-100B were assessed at admission in a group of 58 patients who had CA by Hachimi-Idrissi et al. [15]. In patients who did not regain consciousness, serum levels of S-100B were higher $4.66 \pm 0.61\,\mu g/L$ than in the patients who regained consciousness $0.84 \pm 0.21\,\mu g/L$ (p < 0.01). Serum S-100 cut-off value of $> 0.7\,\mu g/L$ 24 hours after CA was found to be a predictor of poor prognosis (specificity of 88% and sensitivity of 100%), was recently reported by Martens et al. [16] with higher specificity of 96%.

Furthermore, Grubb et al. [17] obtained S-100 and NSE levels in 143 survivors following CA, at 12, 24–48 and 72–96 hours after the event. Cut-off values of S-100 resulting 100% specificity for in-hospital death were $1.20\,\mu g/L$ (sensitivity 44.8%); and for moderate to severe memory impairment $> 0.29\,\mu g/L$ (sensitivity 42.8%).

In turn, Mussack et al. [18] compared S-100 and Il-8 levels in 20 patients after CA and 20 patients after brain injury. In CA-patients, the S-100 level measured 12 hours after CA was an independent predictor for unfavorable neurological outcome (in Glasgow Outcome Scale score Table 2).

A very interesting systematic review of 31 papers discussing S-100B and NSE was presented by Shinozaki et al. [1]. Investigators compared cut-off levels, definitions of poor and good outcomes, and time of sampling. Their study showed that the measurement of serum levels of S-100B within the 24 hours following CA might be more relevant than those of NSE in predicting neurological outcomes.

S-100B is also useful in determining the outcome after trauma and stroke. Researchers concluded that serum levels of S-100B indicate the severity of brain damage and are correlated to neurological prognosis after trauma [19, 20]. They also showed

that integration of S-100B within existing management routines can reduce the need for computed tomography scans after minor head injury by 30% [21]. When it comes to the outcome prediction after stroke, most investigators agree that S-100B is a useful marker [22, 23]. They also suggest that S-100B may have a promising role as an additional tool for identifying patients at increased risk of specific early neurological complications after stroke in non-specialist hospitals [24].

The presented investigations have some limitations. The main one is the small number of studied patients. The second is the time course, but no study has presented the time-course of S-100B in a large number of human subjects at the same time. Future studies should focus on it in a larger group of patients.

Clinically, S-100B could be used to determine patients with a low risk of brain damage which does not require further diagnostic management. On the other hand, in patients with a high risk of brain damage, it could prevent the use of pointless therapy. It could be assessed at admission, then between six and 12 hours, and finally 24 hours after CA.

Most investigators agree that S-100B is an early and specific predictor of poor neurological outcome, and that it does this more accurately than NSE [1, 11–13, 15–18, 25–29]. But for the moment, a wide variety of cut-off values and different definitions of poor and good outcomes present a barrier to applying S-100 protein to clinical practice. It's necessary to set cut-off values, time of blood sampling, and to establish a coherent definition of poor and good outcomes. From then on, serum levels of S-100B can give us useful information about neurological outcomes in cardiological patients following CA.

Conclusions

S-100B protein seems to be a good early prognostic factor of brain damage after CA and other conditions bringing about brain injury, such as stroke and trauma.

Acknowledgements

References

1. Shinozaki K, Oda S, Sadahiro T et al. S-100B and neuron-specific enolase as predictors of neurological outcome in patients after cardiac arrest and return of spontaneous circulation: A systematic review. Crit Care, 2009; 13: R121.

2. Prohl J, Röther J, Kluge S et al. Prediction of short-term and long-term outcomes after cardiac arrest: A prospective multivariate approach combining biochemical, clinical, electrophysiological, and neuropsychological investigations. Crit Care Med, 2007; 35: 1230–1237.

3. Roine RO, Somer H, Kaste M, Viinikka L, Karonen SL. Neurological outcome after out-of-hospital cardiac arrest. Prediction by cerebrospinal fluid enzyme analysis. Arch Neurol, 1989; 46: 753–756.

4. Usui A, Kato K, Murase M et al. Neural tissue-related proteins (NSE, G0 alpha, 28-kDa calbindin-D, S100b and CK-BB) in serum and cerebrospinal fluid after cardiac arrest. J Neurol Sci, 1994; 123: 134–139.

5. Dauberschmidt R, Zinsmeyer J, Mrochen H, Meyer M. Changes of neuron-specific enolase concentration in plasma after cardiac arrest and resuscitation. Mol Chem Neuropathol, 1991; 14: 237–245.

6. Sedaghat F, Notopoulos A. S100 protein family and its application in clinical practice. Hippokratia, 2008; 12: 198–204.

7. Gerlach R, Demel G, König HG et al. Active secretion of S100B from astrocytes during metabolic stress. Neuroscience, 2006; 141: 1697–1701.

8. Van Eldik LJ, Wainwright MS. The Janus face of glial-derived S100B: Beneficial and detrimental functions in the brain. Restor Neurol Neurosci, 2003; 21: 97–108.

9. Smit LH, Korse CM, Bonfrer JM. Comparison of four different assays for determination of serum S-100B. Int J Biol Markers, 2005; 20: 34–42.

10. Heizmann CW. S100B protein in clinical diagnostics. Ass Spec Clin Chem, 2004; 50: 49–51.

11. Pfeifer R, Börner A, Krack A, Sigusch HH, Surber R, Figulla HR. Outcome after cardiac arrest: predictive values and limitations of the neuroproteins neuron-specific enolase and protein S-100 and the Glasgow Coma Scale. Resuscitation, 2005; 65: 49–55.

12. Shinozaki K, Oda S, Sadahiro T et al. Serum S-100B is superior to neuron-specific enolase as an early prognostic biomarker for neurological outcome following cardiopulmonary resuscitation. Resuscitation, 2009; 80: 870–875.

13. Böttiger BW, Möbes S, Glätzer R et al. Astroglial protein S-100 is an early and sensitive marker of hypoxic brain damage and outcome after cardiac arrest in humans. Circulation, 2001; 103: 2694–2698.

14. Miao WL, Li HL, Wang HD et al. Role of neuron specific enolase and S100 protein in evaluation of brain damage in patients resuscitated from cardiac arrest. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue, 2007; 19: 749–752.

15. Hachimi-Idrissi S, Van der Auwera M, Schiettecatte J, Ebinger G, Michotte Y, Huyghens L. S-100 protein as early predictor of regaining consciousness after out of hospital cardiac arrest. Resuscitation, 2002; 53: 251–257.

16. Martens P, Raabe A, Johnsson P. Serum S-100 and neuron-specific enolase for prediction of regaining consciousness after global cerebral ischemia. Stroke, 1998; 29: 2363–2366.

17. Grubb NR, Simpson C, Sherwood RA et al. Prediction of cognitive dysfunction after resuscitation from out-of-hospital cardiac arrest using serum neuron-specific enolase and protein S-100. Heart, 2007; 93: 1268–1273.

18. Mussack T, Biberthaler P, Kanz KG et al. Serum S-100B and interleukin-8 as predictive markers for comparative neurologic outcome analysis of patients after cardiac arrest and severe traumatic brain injury. Crit Care Med, 2002; 30: 2669–2674.

19. Wiesmann M, Steinmeier E, Magerkurth O, Linn J, Gottmann D, Missler U. Outcome prediction in traumatic brain injury: Com-

parison of neurological status, CT findings, and blood levels of S100B and GFAP. Acta Neurol Scand, 2010; 21: 178–185.

20. Rainey T, Lesko M, Sacho R, Lecky F, Childs C. Predicting outcome after severe traumatic brain injury using the serum S100B biomarker: results using a single (24 h) time-point. Resuscitation, 2009; 80: 341–345.

21. Undén J, Romner B. A new objective method for CT triage after minor head injury-serum S100B. Scand J Clin Lab Invest, 2009; 69: 13–17.

22. Brouns R, De Vil B, Cras P, De Surgeloose D, Mariën P, De Deyn PP. Neurobiochemical markers of brain damage in cerebrospinal fluid of acute ischemic stroke patients. Clin Chem, 2010; 56: 451–458.

23. Nash DL, Bellolio MF, Stead LG. S100 as a marker of acute brain ischemia: a systematic review. Neurocrit Care, 2008; 8: 301–307.

24. Dassan P, Keir G, Brown MM. Criteria for a clinically informative serum biomarker in acute ischaemic stroke: A review of S100B. Cerebrovasc Dis, 2009; 27: 295–302.

25. Rosén H, Rosengren L, Herlitz J, Blomstrand C. Increased serum levels of the S-100 protein are associated with hypoxic brain damage after cardiac arrest. Stroke, 1998; 29: 473–477.

26. Püttgen HA, Geocadin R. Predicting neurological outcome following cardiac arrest. J Neurol Sci, 2007; 261: 108–117.

27. Ekmektzoglou KA, Xanthos T, Papadimitriou L. Biochemical markers (NSE, S-100, IL-8) as predictors of neurological outcome in patients after cardiac arrest and return of spontaneous circulation. Resuscitation, 2007; 75: 219–228.

28. Rosén H, Sunnerhagen KS, Herlitz J, Blomstrand C, Rosengren L. Serum levels of the brain-derived proteins S-100 and NSE predict long-term outcome after cardiac arrest. Resuscitation, 2001; 49: 183–191.

29. Snyder-Ramos SA, Böttiger BW. Molecular markers of brain damage: Clinical and ethical implications with particular focus on cardiac arrest. Restor Neurol Neurosci, 2003; 21: 123–139.