Clinical Article

Serum levels of S100B, S100A1B and S100BB are all related to outcome after severe traumatic brain injury

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Summary

Objectives. S100B is an established marker of brain damage. Used in the context as a biochemical marker, S100B denotes a measurement of all S100 proteins, including at least one S100B monomer, i.e. the sum of the two dimers S100A1B and S100BB. Almost all published studies are based on this “sum concentration”. However, the brain specificity of S100B has been questioned and increased serum levels have also been reported after trauma without head injury. Since the S100B monomer dominates in the brain, we hypothesised that the S100BB dimer should be better related to outcome after severe traumatic brain injury than S100A1B or the “sum concentration”.

Methods. Daily serum samples were collected from 59 patients with severe traumatic brain injury. Three different ELISA methods were used for measurements of S100B, S100A1B and S100BB respectively. Outcome was assessed after one year and categorised according to the Glasgow Outcome Scale.

Results. Serum levels of S100B, S100A1B and S100BB followed the same temporal course, with early maximum and rapidly decreasing values over the first days after the trauma. Maximum serum concentrations of each of the parameters were increased in the patient group with an unfavourable outcome compared with those with a favourable outcome (p = 0.01, 0.006 and 0.004, respectively).

Conclusion. Both S100A1B and S100BB were related to outcome after severe traumatic brain injury. Even though this study is small, it seems unlikely that separate analyses of the dimers are of any advantage compared with measuring S100B alone.

Keywords: S100B; S100A1B; S100BB; traumatic brain injury; outcome; biochemical brain damage markers.

Introduction

Numerous studies of patients with severe traumatic brain injury (TBI) have shown an association between serum levels of S100B and outcome [12, 14, 19]. Elevated serum S100 B levels are not necessarily associated with neuroglia damage but may also reflect the ongoing failure of the blood brain barrier [6, 7]. However, the brain specificity has also been questioned and Anderson and co-workers concluded that trauma, even in the absence of head trauma, results in high serum concentrations of S100B. Among their trauma patients, serum S100B levels were highest after bone fractures and/or thoracic
contusions, but also burns and minor soft-tissue damage caused increased serum S100B levels [1]. Since S100B is expressed not only in the brain but also in several extracerebral tissues, release from these tissues seems probable.

S100B is not a defined protein but instead denotes collectively the measurement of all S100 dimers that contain at least one B-monomer subunit. No B-containing dimers other than BB homodimers or A1B heterodimers are known [2]. The B subunit has attracted the greatest attention, as it is mainly found in astroglial and Schwann cells. However, it has also been found in adipocytes, chondrocytes and melanocytes. The A1 subunit is mainly found in astroglial cells, together with a B subunit (S100A1B), and as a homodimer (S100A1A1) in striated muscle, heart and kidney [15]. In the human brain, S100B accounts for a much larger part of the S100 fraction than S100A1 [4, 5].

Analysis of the S100 B subunit has been commercially available for a long time. Used in the diagnosis of brain damage it is often inconsistently referred to and has been called S100, S100B, S100 or S100/B. In this paper, we use the name S100B for the analysis method measuring the summed concentration of dimers containing at least one B subunit (and the B monomer clearly expressed as a subunit). An assay measuring the A1 subunit in S100A1B has recently been developed (Fujirebio Diagnostics AB). Only few previous studies have measured S100A1B and S100BB separately and, to our knowledge, none has focused on severe TBI. We hypothesised that separate analyses of the dimers might be superior to S100B as biochemical markers after severe TBI.

Patients and methods

All the patients with severe TBI admitted to the Neuro-intensive Care Unit (NICU) at Sahlgrenska University Hospital between October 2000 and December 2002 were considered for inclusion in this prospective study. The criteria required for inclusion were Glasgow Coma Scale (GCS) ≤8, a therapeutic indication to monitor intracranial pressure (ICP), need for ventilator treatment and start of serum sampling on day 2 at the latest. (The calendar day of the trauma was defined as day 0). The GCS was estimated from ambulance and medical reports and graded retrospectively by the same neurologist (K N). The indication for ICP monitoring, ventilator treatment as well as the choice of further treatment strategy (evacuation of haematomas, decompressive craniectomy and so on) were based on clinical grounds by the neurosurgeon in charge of patient care. The patients were continuously monitored in the NICU and treated according to a clinical protocol designed to maintain an ICP of <20 mmHg and a cerebral perfusion pressure (CPP) of >60 mmHg. Vital signs and ICP were recorded on an hourly basis.

S100B, S100A1B and S100BB were determined in venous blood. The first sample was drawn as soon as possible after admission and then every morning on days 1, 2, 3, 4, 6, 8 and once in the period between days 11 and 14. All the samples were centrifuged and serum was frozen to −70°C and stored for analysis. The serum concentrations were measured using three different enzyme-labelled immunosorbent assay (ELISA) methods (Fujirebio Diagnostics AB, Göteborg, Sweden). Samples were processed according to the manufacturer’s specifications. The levels are normally very low in serum. The analytical detection limits for the assays are ≥0.010 μg/L (S100B), ≥0.020 μg/L (S100A1B) and ≥0.01 μg/L (S100BB).

Outcome was assessed after one year and categorised according to the Glasgow Outcome Scale (GOS) based on the results of a structural interview carried out face to face [16]. For non survivors death certificates and medical reports were reviewed. GOS 1–3 (dead, vegetative state or severe disability) was regarded as an unfavourable outcome and GOS 4–5 (moderate disability or good recovery) as a favourable outcome.

The initial CT was reviewed according to Marshall categories I–IV [8] by one neuroradiologist (blinded to clinical and laboratory data). Not only diffuse brain injury but also mass lesions were classified according to their relation to midline shift and compression of cisterns (but not according to a retrospective analysis of whether or not evacuation was performed). One neurologist (K N) collected and categorised the clinical data and performed the follow up interviews. She was blinded to the results of the biochemical markers and CT classification. The patient material has been described earlier [10] and some of the patients have also been included in a study analysing cerebrospinal fluid from ventricular drainage [20]. The medical ethics committee at the University of Göteborg approved the study and the next of kin gave their informed consent.

Means and medians were calculated for descriptive purposes. Statistical analyses were performed using non-parametric tests. For comparisons between two groups, the Mann–Whitney U-test was used for continuous variables and Fisher’s exact test for dichotomous variables. Van Elteren’s test was used to test differences between