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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

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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, S100b or S100 β. 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 Neurointensive 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) $\leq$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 $\geq$0.010 µg/L (S100B), $\geq$0.020 µg/L (S100A1B) and $\geq$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

two groups, adjusting for neurosurgery. Spearman's test was used for correlations. Univariate logistic regression analyses were performed to predict the outcome. From these analyses, the Area Under Curve (c-statistics) was calculated. All the tests were two-tailed and were conducted at a 5% significance level.

Results

Inclusion and clinical data

The inclusion was consecutive without breaks and only a few ($n = 3$) more patients could hypothetically have been included. Finally 44 men and 15 women were studied. Characteristics of the patients are shown in Table 1. Twenty-one patients were admitted directly to the NICU and 38 were transferred from other hospitals. The first sample was taken on day 0 in 17 patients (the shortest delay from trauma to sampling was 5.5 h), on day 1 in 29 and on day 2 in the remaining 13 patients. The initial CT of the brain was normal in one and pathological in the remaining 58 patients. A midline shift of >5 mm was seen in 21 patients. ICP was continuously recorded by an intraventricular catheter ($n = 57$) or intraparenchymatous microtransducer ($n = 2$). ICP was at least once, above 25 mmHg in 39 patients and CPP below 60 mmHg in 45 patients. In addition to insertion of the catheter, further neurosurgery, particularly evacuation of haematomas was indicated in 34 patients (day 0–9). Dichotomised outcome was not related to whether further neurosurgery was required or not. Patients with contemporary life-threatening trauma to other organs are generally treated at other intensive care units due to hospital routines. However, even though our study group was treated at a NICU, only 13 patients were regarded as having an ''isolated'' brain injury. Brain injury in combination with fracture (especially skull fracture) was most common. Dichotomised outcome at one year was not associated with whether or not the patient had an ''isolated'' brain injury.

Table 1. *Characteristics of 59 patients with severe traumatic brain injury*

	Number
Gender	
Men/women	44/15
Age, yrs	
Median	37
Range	8–81
Type of trauma	
''Isolated'' brain injury	13
Brain injury and fractures (including skull fractures)	28
Brain injury and fractures and trauma to internal organs	17
Brain injury and trauma to internal organs	1
Initial CT	
Type I (normal)	1
Type II (lesions, present cisterns, midline shift 0–5 mm	20
Type III (lesions, cisterns compressed, midline shift 0–5 mm	17
Type IV (midline shift >5 mm)	21
Neurosurgery	
Evacuation of haematomas Epidural (3) Subdural (9) Intracerebral (2) Multiple locations (3)	17
Evacuation of haematomas and decompressive craniectomy	12
Decompressive craniectomy	3
Revision of skull fracture	2
Outcome at one year	
GOS 1	11
GOS 2	1
GOS 3	16
GOS 4	20
GOS 5	11

Outcome

Three patients died during the first three days and another eight within six weeks after the trauma. All the deaths could be attributed to the brain injury, although respiratory failure was often a terminal event. Outcome after one year was available for all the patients. The outcome for the 48 survivors was scored using face-to-face interviews in 45 patients, by telephone in two (patients not living in the region) and from medical records alone in one (patient not living in the region and not able to answer questions by telephone). With a few exceptions ($n = 2$) all interviews were performed by the same neurologist (K N). A favourable outcome (GOS 4–5) was seen in 31 patients and an unfavourable outcome (GOS 1–3) occurred in 28 patients.

Biochemical markers

Maximum serum S100B, S100A1B and S100BB were increased in all but a few patients (Table 2). The three serum parameters followed the same temporal course, with early peak concentration (median day 1 for all three parameters), followed by rapidly decreasing values over the first few days (Fig. 1). As expected, S100B showed the highest values. Concentrations of S100A1B were

Table 2. *Maximum serum concentrations of S100B, S100A1B and S100BB in 59 patients after severe traumatic brain injury*

Parameter	Median (μg/L)	Range (μg/L)	Reference value (μg/L)
S100B	0.202	0.042–10.09	0.09
S100A1B	0.097	0.018–2.67	0.06
S100BB	0.078	0.009–4.65	0.02

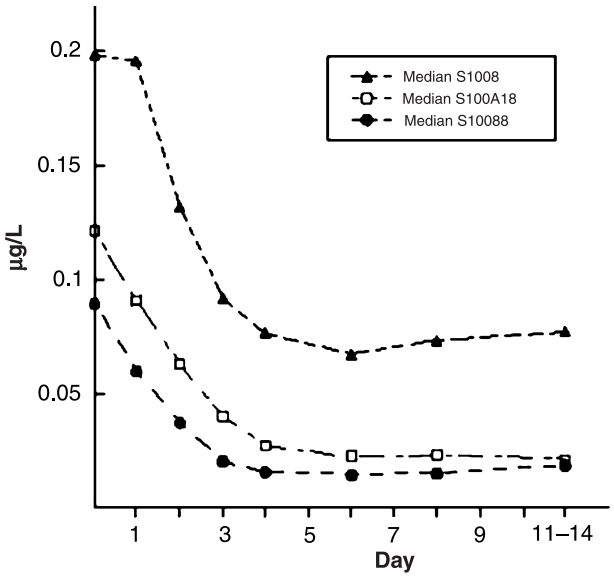

Fig. 1. Median serum concentrations of S100B, S100A1B and S100BB in 59 patients after severe traumatic brain injury in relation to day of sampling

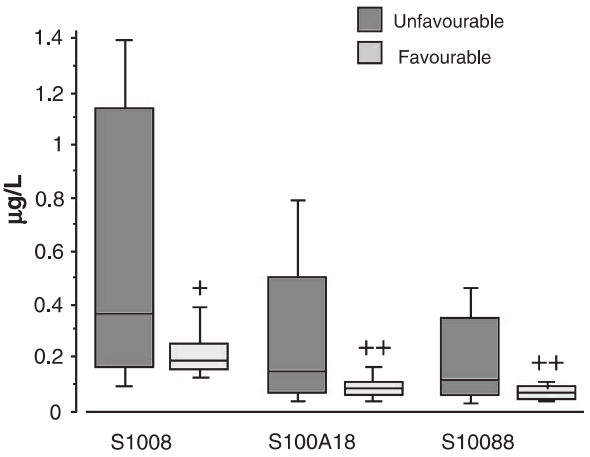

Fig. 2. Maximum serum concentrations of S100B, S100A1B and S100BB from 28 patients with unfavourable outcome compared with maximum serum concentrations from 31 patients with favourable outcome after severe traumatic brain injury. Each box plot shows the 10th, 25th, 50th, 75th and 90th percentile. Outliers are excluded. $^{+}p<0.05$, $^{++}p<0.01$. Mann–Whitney *U*-test

higher than those of S100BB. The sum of S100A1B and S100BB concentrations did not fully correspond to serum S100B (80% or less).

Patients with an unfavourable outcome had increased maximum serum S100B, S100A1B and S100BB levels compared with the group with a favourable outcome ($p=0.01$, 0.006 and 0.004 for S100B, S100A1B and S100BB respectively) (Fig. 2). The temporal profile with an early maximum and a rapid decrease was seen both in the group with a favourable outcome and in the group with an unfavourable outcome. The difference between favourable/unfavourable outcome was significant not only for the maximum values but also for the values on day 0 and on day 1. However, on these days the sample series were not complete (day 0: $n=17$, $p=0.001$, 0.002 and 0.006 for S100B, S100A1B and S100BB, respectively, day 1: $n=46$, $p=0.004$, 0.0008 and 0.005 for S100B, S100A1B and S100BB, respectively).

Maximum serum S100B, S100A1B and S100BB all increased in the patient group ($n=21$) with a midline shift of $\geq$5 mm on the first CT, compared with the remaining patients ($n=38$) ($p=0.008$, 0.001 and 0.0006 for S100B, S100A1B and S100BB, respectively). Maximum ICP correlated with maximum serum levels for all three parameters (S100B, $r=0.38$, $p=0.003$; S100A1B, $r=0.34$, $p=0.01$; S100BB, $r=0.37$, $p=0.004$). Patients requiring further neurosurgical operations, in addition to the insertion of an intracranial catheter ($n=34$), had increased maximum S100B, S100A1B and S100BB compared with the remaining patients ($n=25$) ($p=0.03$, 0.01 and 0.04, for S100B, S100A1B and S100BB, respectively). However, the differences in maximum concentrations between unfavourable and favourable outcome remained significant regardless of whether or not neurosurgery was performed ($p=0.03$, 0.008 and 0.008 for S100B, S100A1B and S100BB, respectively, Van Elteren's test). All three markers increased in the few patients ($n=2$) in whom serum samples were obtained before any neurosurgery was performed. One patient had normal levels (for all three S100 parameters), following the insertion of an intracranial catheter, and another patient also had normal levels after evacuation of an epidural haematoma. Maximum S100B, S100A1B and S100BB were not significantly increased in the patient group with multiple trauma compared with the small group with ''isolated brain injury''. Two patients turned out to have a secondary serum peak with extremely high values on days 11–15 (none of them were operated upon later than day 1). Both these patients died from herniation within the next two days (Fig. 3).

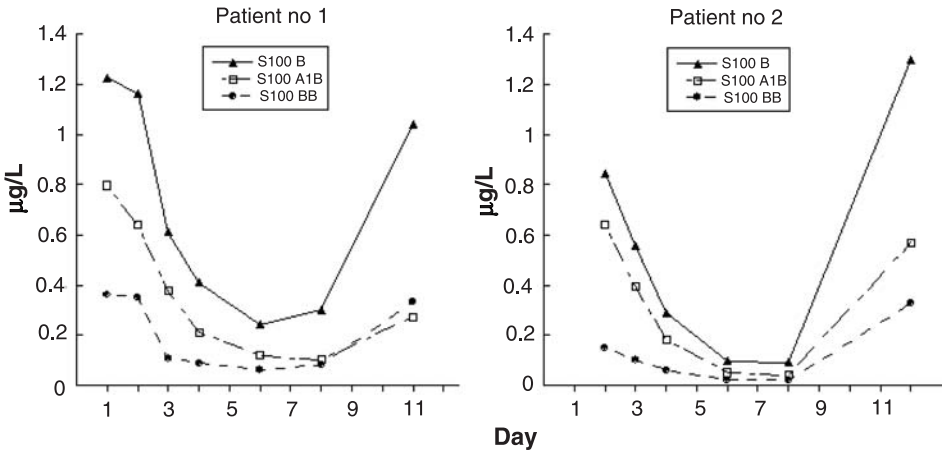

Fig. 3. Daily serum concentrations of S100B, S100A1B and S100BB from two patients with severe traumatic brain injury (day 0) and death from herniation within two weeks

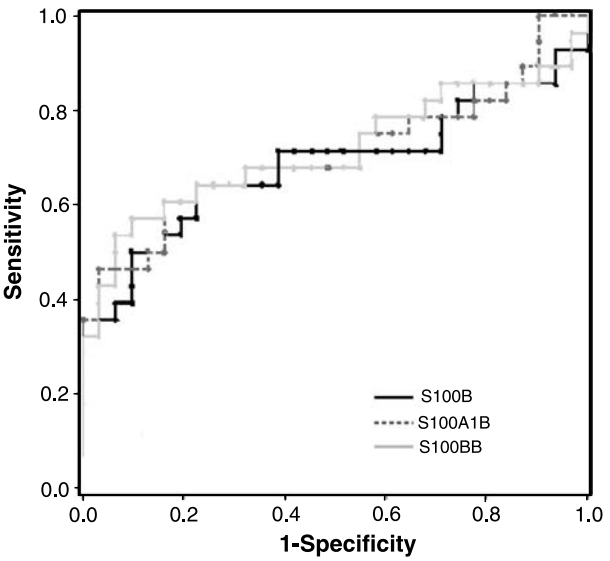

Fig. 4. Receiver operating characteristic curves for S100B, S100A1B and S100BB in serum for unfavourable outcome at one year after severe TBI. Cut off values for 100% specificity: 0.55 µg/L (S100B), 0.30 µg/L (S100A1B) and 0.17 µg/L (S100BB). Cut off values for 80% specificity: 0.30 µg/L (S100B), 0.13 µg/L (S100A1B) and 0.10 µg/L (S100BB)

Logistic regression analyses with c-statistics revealed that the two dimers predicted outcome approximately as effective as S100B (c-statistics for S100A1B = 0.71 (95% CI 0.57–0.85), for S100BB = 0.72 (95% CI 0.57–0.86) and for S100B = 0.69 (95% CI 0.54–0.83)). Area under curve (c-statistics) are as shown in Fig. 4.

Discussion

The main findings in the present study were the relationships between serum concentrations of S100B, S100A1B and S100BB, respectively and the long-term outcome after severe TBI. Our aim was to include patients in whom the brain injury was critical and requiring attention at a specialised NICU for more than just observation or post-operative care. To select these patients, we added the need for ventilator treatment and the indication to monitor ICP to our inclusion criteria for severe TBI. Patients with brain injury in combination with life threatening trauma to other organs were cared for at other intensive care units and were not included in this study. Accordingly, we studied patients with critical brain injuries and only ''relatively mild'' trauma to other organs. The principal strengths of the study were the almost complete inclusion and follow-up after one year carried out with face to face interviews by the same neurologist. The principal shortcomings were the relatively few serum samples taken very early and before the urgent neurosurgical intervention, but once started, the series were almost always complete (fewer than 5% of samples missing).

The S100 parameters were not only related to outcome, but also to ICP and CT findings. Even if the concentrations of all three of the markers were associated with these ''brain specific phenomena'', a possible extracerebral contribution cannot be ruled out. The present study was not designed to answer the question about the extracerebral contribution of the different S100 types. This would have required immediate sampling in trauma patients without headinjuries. However, we regarded all fractures, including skull fractures, as trauma to multiple ''organs/tissues'' (classified as ''multiple trauma''), since serum S100B levels are known to increase after bone fractures in particular [1, 11, 16]. We did not find any significant differences in the concentrations on day 0 or 1, maximal concentration or temporal course of the three S100 parameters (not shown) in these patients, compared with those with ''isolated brain

injury''. Also, extracerebral release has been shown to be of concern mainly during the first hours after the trauma and is probably less relevant when the half-life has cleared most of this contribution [1, 13]. Thus, the results in the present study with ''late'' serum samples correlating with outcome, was probably not influenced by extracerebral release.

We did not observe any noteworthy difference between the dimers after severe traumatic brain injury. A clear dominance of one of them would have been an advantage, when evaluating results from patients with TBI in combination with other trauma. Our results are complementary to previous studies by Anderson and co-workers. They analysed the dimers S100A1B and S100BB separately after cardiac surgery, with the expectation that the extracerebral S100B contribution seen after cardiac surgery would be predominantly either S100A1B or S100BB, and that the other would be more specific for cerebral tissue damage. However the separate analysis of the dimers did not either distinguish between S100B of cerebral or extracerebral origin [2]. Furthermore, in a study of trauma patients without head injuries, they showed that the concentration ratio of S100A1B/S100BB varied widely with no apparent type of trauma or tissue damage [1].

Neurosurgically operated patients (in addition to the ICP device) had increased serum levels of the S100 parameters compared with those, who did not undergo further surgery. This was probably attributable to a more severe clinical picture in the patient group requiring further neurosurgery. The association between maximal serum concentrations of all three S100 parameters and outcome also remained significant after adjustment for neurosurgery. Only a few samples were taken before surgery, but we noted increased concentrations in two patients and also normal concentration after neurosurgery in two others, indicating increase secondary to the trauma and not to the surgery itself. Two patients had a secondary peak of all three S-100 parameters (S100B, S100A1B and S100BB), with extremely high values in serum taken more than a week post injury and neurosurgical interventions. In these, confounding factors are supposedly excluded, and the increase in all three parameters is of cerebral origin. Undén and co-workers have reported on one patient in whom the S100B levels appeared to peak immediately prior to cerebral herniation [17]. Increase prior to worsening of the clinical condition or ICP increase may add information influencing management decisions. However, in the present study we did not sample frequently enough to know if one of the dimers increased more rapidly than the other.

S100BB has been suggested to be most specific for brain-associated diseases, since the S100B monomer is regarded as the dominant isoform in the CNS [4, 5]. Our hypothesis was that S100BB would be better associated with brain injury and outcome after severe TBI, but surprisingly S100BB and S100A1B gave similar results. We noticed that serum concentrations of S100BB were lower than those of S100A1B. This result was in agreement with those from mild traumatic brain injuries [9]. Furthermore, Anderson and co-workers reported a normal dominance of S100A1B in both serum and CSF and the dimers (S100A1B and S100BB) increased proportionally in one patient with stroke and in one patient with spinal damage following repair of aorta aneurysms [3]. The dominance of S100A1B in serum and CSF in these studies, as well as in the present study, is somewhat contradictory to the fact that S100BB dominates in the brain. The reason for this discrepancy is not clear to us. Besides difficulties in estimating the concentrations of the dimers speculative hypothesis can be differences in the pathophysiological processes in the injured brain. Similarly, it is uncertain why the sum of S100A1B and S100BB values only equal 80% of the values of the S100B assay. Possibly this might be related to the properties of the antibodies or to other methodological factors of the assays.

To summarise, our data indicate that both serum S100A1B and serum S100BB increase after severe TBI and concentrations are associated with brain injury severity and long-term outcome. We also confirm the association between serum levels of S100B and outcome after severe TBI. In the clinical setting, as selected in this study, neither S100B, S100A1B nor S100BB appeared to have significant advantages over the others. Based on the findings from the present small study, the results of previous studies of S100B after severe TBI would probably not have been different if one of the dimers had been measured instead. It seems unlikely that separate analysis of the dimers are of any advantage compared with measuring S100B alone after severe TBI. This information may be of interest for all those who have measured only S100B after TBI and also for forthcoming studies.

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Comment

This is an interesting study. Most of the papers published with protein S-100 measurements have used S-100B. Analysis of the S100B subunit has been commercially available for a long term. The authors hypothesised that separate analyses of the dimers (S100B, S100A1B and S100BB) might be superior to S100B as a biochemical marker after severe traumatic brain injury.

Interestingly, neither S100B, S100A1B nor S100BB appeared to have significantly advantages over the others. Their data indicate that both serum S100A1B and serum S100BB are associated with brain injury severity and long-term outcome after severe head injury. Based on their findings it seems unlikely that separate analyses of the dimers are of any advantages compared with measuring S100B alone. For those who have measured only S-100B in brain injury patients for many years this information is of great interest and also of importance for forthcoming studies.

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