Outcome after severe head injury is determined by both primary and secondary injury. Despite experimental evidence of considerably more complex mechanisms, clinicians focus mainly on cerebral ischemia as the central mechanism leading to secondary brain damage. Prevention and early treatment of high intracranial pressure (ICP), low cerebral perfusion pressure (CPP), hypocapnia, hypoxia, and vasospasm are thought to reduce the incidence of secondary insults and to improve outcome after severe head injury.

The S-100B protein is a small cytosolic protein that is found in astroglial or Schwann cells. It is highly specific for brain tissue and is increasingly being investigated as a diagnostic tool to assess the neurological damage after head injury, stroke, subarachnoid hemorrhage, and cardiopulmonary bypass.

The authors report on three patients with severe head injury with otherwise normal cerebral perfusion pressure, SaO₂, PaCO₂, and controlled intracranial pressure (ICP), in whom a secondary excessive increase in serum S-100B was observed. In all cases, the S-100B increase was followed by an increase in ICP. All three patients died within 72 hours after the excessive increase in S-100B. These findings indicate that major secondary brain damage may occur at a cellular level without being identified by current neuromonitoring techniques.

Key Words • S-100 protein • severe head injury • secondary brain damage • intracranial pressure

Case Reports

Case 1

This 55-year-old man was brought to the hospital after a traffic accident. He was intubated at admission and received ventilation. His postresuscitation Glasgow Coma Scale (GCS) score was 6. Computerized tomography (CT) scanning performed 2 hours postinjury revealed a 35-cm³ right frontal contusion. An intraparenchymal ICP sensor was placed in the patient, and when ICP levels increased 25 mm Hg, the patient was initially treated with mannitol and moderate hyperventilation (PCO₂ 33–40 mm Hg). Serum S-100B concentrations were measured daily. There were no documented periods of CPP decrease to less than 60 mm Hg or ICP increase to greater than 25 mm Hg during Days 1 to 3. However, a secondary increase of serum S-100B was seen on Day 3 (1.8 μg/L). No other abnormality was found at this time. On Day 4, there was a massive increase in S-100B of 5.9 μg/L (Fig. 1). Again, no pathological levels of CPP, ICP, PCO₂, or SaO₂ were found at this time. Twelve hours after the marked increase in S-100B a gradual secondary rise in ICP to greater than 25 mm Hg occurred. Emergency CT scanning performed on Day 4 revealed increased contusion volume (50 cm³), brain edema, and compressed basal cisterns. The patient’s elevated ICP was refractory to mannitol, moderate hyperventilation, barbiturates, and hypothermia on Day 5. The patient died of intracranial hypertension 6 days postinjury.
Case 2

This 17-year-old boy was brought to the hospital after a traffic accident. He was intubated at admission, received ventil-ation, and had a postresuscitation GCS score of 6. Admission CT scanning revealed diffuse injury III (swelling) according to the Marshall classification. An intraparenchymal ICP sensor and a brain tissue oxygen (PtiO2) sensor were placed in the patient. The PaCO2 was kept between 35 and 40 mm Hg and CPP above 70 mm Hg. The ICP was 20 mm Hg on the day of injury but decreased to below 15 mm Hg in the following 4 days. Brain PtiO2 was higher than 20 mm Hg during Days 1 to 5. Despite normal CPP, ICP, PCO2, and PtiO2 values, initially slightly elevated serum S-100B levels increased further in the following days.

On Day 5, another marked increase in serum S-100B up to 5.1 μg/L was found. Five hours later the patient experienced a secondary increase in ICP, which required treatment with mannitol. On Day 6, ICP was refractory to treatment and increased to 35 mm Hg. No other abnormality was found except leukocytosis and hypernatremia (157 mmol/L). Bilateral mydriasis was found on Day 6 postinjury. On Day 9 postinjury the patient died on Day 11 postinjury.

Case 3

This 41-year-old man was treated in the emergency room of our hospital after a fall. On admission, he demon-strated abnormal flexion (GCS score of 5) and was intubated and received ventilation. A CT scan obtained 3 hours postinjury revealed a right-sided subdural hematoma with a midline shift of 5 mm. The hematoma was removed the same day. Despite the mass lesions and the operative procedures, S-100B remained only slightly elevated at less than 0.3 μg/L. During the following 6 days the patient demonstrated abnormal flexion (GCS score of 5) and normal pupillary reactivity to light, CPP levels greater than 60 mm Hg, and ICP of less than 25 mm Hg. On Day 9 postinjury he showed a marked increase in serum S-100B protein but normal ICP, CPP, and PCO2 levels. There was no other reason that could be related to the increase in S-100B. On Day 10 his ICP increased to 35 mm Hg, CPP decreased to less than 50 mm Hg, and his body temperature rose to 39°C due to pneumonia. On Day 10 postinjury he developed hypoten-sion refractory to catecholamine treatment and bilaterally dilated pupils unresponsive to light. The patient died on Day 11 postinjury.

Discussion

There is evidence that much of the neural damage that follows head injury is caused by a cascade of neurochemical and pathophysiological events set in motion by the primary mechanical insult. With a half-life of just 2 hours, in minor head injury serum S-100B normally returns to baseline levels within hours. In a cohort of 84 patients with severe head injury, we found that serum S-100B gradually returned to baseline within 3 to 9 days. Secondary increases of S-100B to 2.5 μg/L or more were associated with a mortality rate of 100%. In many of these patients the increase in S-100B may be explained by a concomitant increase in ICP, a decrease in CPP, or other secondary brain insults.

However, after excluding all patients with any possible association between the massive secondary increase and other findings including those yielded by neuromonitoring, CT scanning, transcranial Doppler recording, extracranial diseases, or surgical manipulations, three patients remained in whom no event was found that could explain the S-100B increase. In all three cases, there was a strong association between the rise in serum S-100B and a secondary increase in ICP. However, raised serum S-100B preceded the ICP increase. We speculate from these observations that the S-100B increase may have been caused by major secondary brain insults occurring at the cellular level. These insults were not caused by, but resulted in, an ICP increase. At least in these cases, we think the ICP increase was an epiphenomenon.

The main criticism of this hypothesis is that we simply might have missed insults that would have been found by using other monitoring techniques such as measurement of jugular venous saturation. In analyzing their 112 episodes of jugular desaturation (jugular venous saturation values < 50%), Rob-ertson, et al. found intracranial hypertension associated with 53 episodes, cerebral vasospasm in one episode, systemic causes such as hypotension, hypoxia, hypocarbia, and anemia associated with 51 episodes, and both systemic and cerebral causes in the remaining seven episodes of jugular desaturation. Thus, no single episode of jugular desaturation occurred without an obvious change in other parameters.

Massive S-100B increases may be explained by exten-
Secondary S-100B increase

sive cell damage of astrocytes, massive secretion from cells, or extensive damage to the blood-brain barrier; however, the exact mechanism remains unclear. In the three cases presented here, there were no pathological findings that might explain the S-100B increase. Thus, it may indicate the existence of pathophysiological mechanisms that lead to major secondary brain damage at a cellular level without being detected by our current diagnostic tools.

References


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