Editorial

Giuseppe Lippi and Gianfranco Cervellin

Protein S100B: from cancer diagnostics to the evaluation of mild traumatic brain injury

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A traumatic brain injury (TBI), conventionally defined as an injury impairing physiological brain function, is mostly attributable to bumps, blows, jolts to the head or penetrating injuries [1]. It should be hence distinguished from the simple head trauma, due to the substantial diagnostic and prognostic differences. According to the most recent statistics of the US Centers for Disease Control and Prevention (CDC), TBI accounts for nearly 2.5 million emergency department (ED) visits, hospitalizations, and deaths in the US, either as isolated injury or associated with other types of trauma [2]. It is also estimated that up to 5.3 million persons in the US live with significant TBI-related disabilities. Notably, the populations more likely to have TBI-related ED visits and to be hospitalized for this reason are children aged 0–4 years or adolescents aged 15–19 years, along with adults aged 75 years or older [2]. Hence, it is not surprising that TBI is now regarded as a major public health issue in the US, as well as in many other countries around the globe.

The current paradigm for diagnosing TBI in the ED entails a thoughtful neurological examination accompanied by brain imaging through a computed tomography (CT) scan or other less commonly available imaging techniques [3]. The initial neurological assessment is based on different approaches, although the most widely used is the Glasgow Coma Scale (GCS). This scoring system entails a 15-point scale capable of rapidly assessing the neurological status, based on motor response, verbal response, and eye opening (Table 1). Patients with a GCS score of 3 are totally unresponsive and have the worst prognosis, whereas patients with a score of 15 display almost normal neurologic performance. Conventionally, patients exhibiting a GCS ≤ 8 are defined as having severe TBI, those exhibiting a GCS score comprised between 9 and 12 (or 13, depending on the guideline) are defined as having moderate TBI, and those with a GCS ≥ 13 (or 14, depending on the guideline) as having mild TBI [4]. Importantly, a CT scan is usually recommended for all those patients who, 4 h after the injury, have a GCS score <15, are not clinically improving, and have suspected open or depressed skull fracture, ≥2 episodes of vomiting and are aged 65 years and older. Similar indications have been provided in children and adolescent with TBI, wherein a CT scan may be indicated for timely identification of acute hydrocephalus, fractures or different types of intracranial injury requiring neurosurgical intervention [5].

Despite that these recommendations are followed nearly worldwide, emerging evidence attests that even when using low-dose ionizing radiation protocols, CT scans are nothing if not safe. A large epidemiological survey including as many as 10.9 million people aged 0–19 years, identified from Australian Medicare records and who were followed up for a mean period of 9.5 years, revealed that the overall incidence of future cancer was 24% higher for subjects exposed to CT than for unexposed people in a fully adjusted analysis [6]. Notably, the excess rate ratio of brain cancer after brain CT was found to be 0.021 (95% CI, 0.014–0.029) per mGy of brain dose. This translates into an incidence rate ratio of brain cancer after brain CT comprised between 1.74 and 3.24, with the highest ratio reported for children aged 1–4 years. Thus a crucial question emerges: what can laboratory medicine do to improve the diagnosis of TBI and concomitantly reduce the risk of CT-related cancer?

The S100 calcium-binding protein B (S100B) is one of the various members of the S-100 protein family. This 92 amino-acid protein is encoded by the *S100B* gene located on chromosome 21q22.3 [7]. Although S100B is mainly produced by astroglial and Schwann cells, additional extracerebral sources have been identified [8]. As protein S100B expression is considerably increased in several types of cancers, mainly of neuroectodermal origin, this biomarker is now used for follow-up and therapeutic monitoring of a variety of malignancies including melanoma, malignant peripheral nerve sheath tumors, Schwannomas, paraganglioma stromal cells, histiocytoma, and clear cell sarcomas [8]. Importantly, the European Society for Medical Oncology (ESMO) has recently concluded that protein S100B is the most accurate blood test in the follow-up of melanoma patients [9].

Table 1: Glasgow Coma Scale for assessing the severity of traumatic brain injury (TBI).

Mild TBI (13–15):
– Loss of consciousness up to 30 min
– Loss of memory for events immediately before or after the accident for as much as 24 h
– Alteration of mental state at the time of the accident
– Focal neurologic deficits that might or might not be transient
– Posttraumatic amnesia longer than 24 h
Moderate disability (9–12):
– Loss of consciousness >30 min
– Physical or cognitive impairments which may or may not resolve
– Benefit from rehabilitation
Severe disability (3–8):
– Coma: unconscious state
– No meaningful response, no voluntary activities
Vegetative state (<3):
– Sleep wake cycles
– Arousal, but no interaction with environment
– No localized response to pain

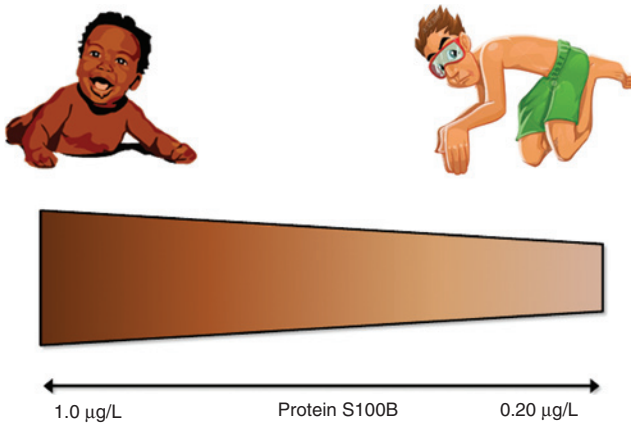

Figure 1: Biological influence of age and skin color on the serum concentration of protein S100B.

In recent years, the clinical usefulness of protein S100B has extended far beyond the boundaries of cancer diagnostics. A meta-analysis of 22 studies concluded that the sensitivity of this biomarker is as high as 98.7% for a positive CT scan in patients with mild TBI, with a value of specificity approximately 51% [10]. Further decreasing the cut-off value to 0.20 µg/L would allow identifying brain injury with 99.6% sensitivity and 47.0% specificity. Importantly, it was recently demonstrated that the high negative predictive values of protein S100B at ED admission would safely allow withholding CT scans in up to 50% of patients with mild TBI, so decreasing the total healthcare cost for patient management by approximately 30% [11]. It is also noteworthy that the measurement of S100B has consistently overwhelmed that of other potential biomarkers of brain injury, especially neuron-specific enolase (NSE) [12, 13].

Despite this promising evidence, a major drawback remains. The cut-off value used for ruling out a positive CT scan in patients with mild TBI varied widely across different studies, with thresholds comprised between 0.10 and 0.60 µg/L. This is mostly attributable to different study populations and the analytical techniques used for measuring protein S100B. In this issue of the journal, Bouvier et al. measured the serum concentration of protein S100B by a commercial chemiluminescent immunoassay in a population of 409 healthy children aged 0–16 years [14], reporting that the serum value decreased in parallel with the age, i.e. from 0.97 µg/L in children aged 0–3 months, to 0.58 µg/L in those aged 4–9 months, 0.31 µg/L in those aged 10–24 months, and 0.20 µg/L, in children aged 2–16 years, a value that was found to be virtually identical to that of the adult population (Figure 1). Indeed, this is an essential information, wherein different protein S100B cut-offs should be used for assessing the risk of brain lesions in children according to their age. Another important finding that emerged from the study of Bouvier et al. is that the two commercially available chemiluminescent immunoassays display a satisfactory correlation (r=0.92), but the overall bias remains too high to permit using identical diagnostic thresholds (i.e. values were found to be 27% higher with the DiaSorin than with the Roche immunoassay). This is not surprising, as similar information has also been published by the STIC-S100 study group [15]. Notably, Bouvier et al. also observed that the reference range of protein S100B in serum was significantly higher in healthy black-skinned than in healthy white-skinned volunteers, thus highlighting further the need to personalize the diagnostic cut-offs of this biomarker (Figure 1).

Indeed, the future of TBI diagnostics is still unwritten, and other innovative biomarkers such as the neurofilament medium polypeptide (NFM) protein may soon be ready for prime time [16]. In the meanwhile, it seems reasonable to conclude that the measurement of protein S100B represents a valuable perspective for evaluating both children and adults presenting to the ED with mild TBI, provided that an optimal diagnostic cut-offs for ruling out brain lesions can be settled.

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Corresponding author: Prof. Giuseppe Lippi, Section of Clinical Biochemistry, University Hospital of Verona, P.le LA Scuro 10, 37134 Verona, Italy, E-mail: giuseppe.lippi@univr.it. http://orcid.org/0000-0001-9523-9054; and Associate Editor of *Clinical Chemistry and Laboratory Medicine*, Italy
Gianfranco Cervellin: Emergency Department, Academic Hospital of Parma, Parma, Italy