

Use of Biomarker S100B for traumatic brain damage in the emergency department may change observation strategy

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ABSTRACT

INTRODUCTION: The revised Scandinavian Neurotrauma Committee (SNC) guidelines on management of patients with head trauma include an option for measurement of S100B in peripheral blood with 100% sensitivity for neurosurgical intervention. A medical technology assessment was conducted to evaluate any impact of using S100B on the use of computed tomographies (CT) of the brain and admission for observation.

MATERIAL AND METHODS: Patients referred for assessment of head injury over a period of 1.5 months had their blood sampled for measurement of S100B in serum. Results were not available to the treating physician and treatment was conducted according to existing practice. Patient records were reviewed retrospectively and post hoc divided into two groups depending on whether the SNC criteria for taking the blood sample were met. The use of CT and admission was analysed.

RESULTS: A total of 39 patients had their blood sampled for analysis. In all, 12 patients were excluded in pursuance of SNC guidelines, which left 27 patients for analysis. A total of 15 patients had abnormally high S100B levels. Using the SNC criteria, only eight of these qualified a priori for blood sampling. Furthermore, seven of the 11 patients who were admitted had normal S100B levels.

CONCLUSION: The number of patients with an above-threshold concentration of S100B was almost equally distributed between those fulfilling the SNC criteria for S100B assessment and those who could have been discharged without further evaluation. Using S100B as a screening tool may lead to an increase in the use of CTs of the brain. In relation to admission, measurement of S100B may contribute to the adoption of an appropriate observation strategy.

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TRIAL REGISTRATION: not relevant.

February 2013 saw the publication of the revised guideline of the Scandinavian Neurotrauma Committee (SNC) on initial treatment of patients who have sustained minor head trauma [1].

The guideline has subsequently been disseminated in the respective medical journals of the Scandinavian countries [2-4]. In line with previous revisions of these

guidelines, patient evaluation using the Glasgow Coma Scale (GCS) remains of paramount importance. As a novel feature, the guideline introduces the possibility of evaluating patients scoring GCS 14 or 15 – with or without vomiting and/or loss of consciousness – through a blood sample that measures the concentration of the neurobiomarker S100B in peripheral blood. Patients scoring below GCS 14, patients with focal deficits as well as patients exhibiting a number of clinical features are, however, not eligible for this test [1]. A distinct advantage of the biomarker is its independence of intoxication, e.g., alcohol [5, 6]. In addition, it is not associated with any adverse effects in contrast to CT, which exposes the patient to radiation.

S100B is a glia protein that does not penetrate the blood-brain barrier, and which is therefore not found in peripheral blood under normal circumstances [7]. Head trauma with structural lesions causes a disruption of this barrier, which, in turn, produces measurable amounts of S100B in peripheral blood. The elimination rate of S100B from peripheral blood, and the fact that – under normal circumstances – children have higher S100B serum concentrations than adults, has so far meant that the test has only been validated for use in adults (patients aged >15), and only if the blood was sampled within six hours after the trauma was sustained [1, 8]. A S100B serum concentration below 0.1 micrograms per litre excludes structural brain lesions with a sensitivity of 99% and is regarded as having 100% sensitivity for neurosurgical intervention [5, 6]. Given the low specificity of the test, levels above 0.1 microgram per litre do not per se indicate structural brain damage.

Prior to the introduction of routine use of the biomarker, a local medical technology assessment was conducted at our institution. Using post hoc analysis, the purpose of the study was to assess any impact on the management of patients with minor head trauma compared with existing practice. The main parameters were the use of CT of the brain and admission for observation. The present study may also be seen as a response to the wishes of the authors of the primary publication who invited external clinical validation of the revised SNC guidelines [1].

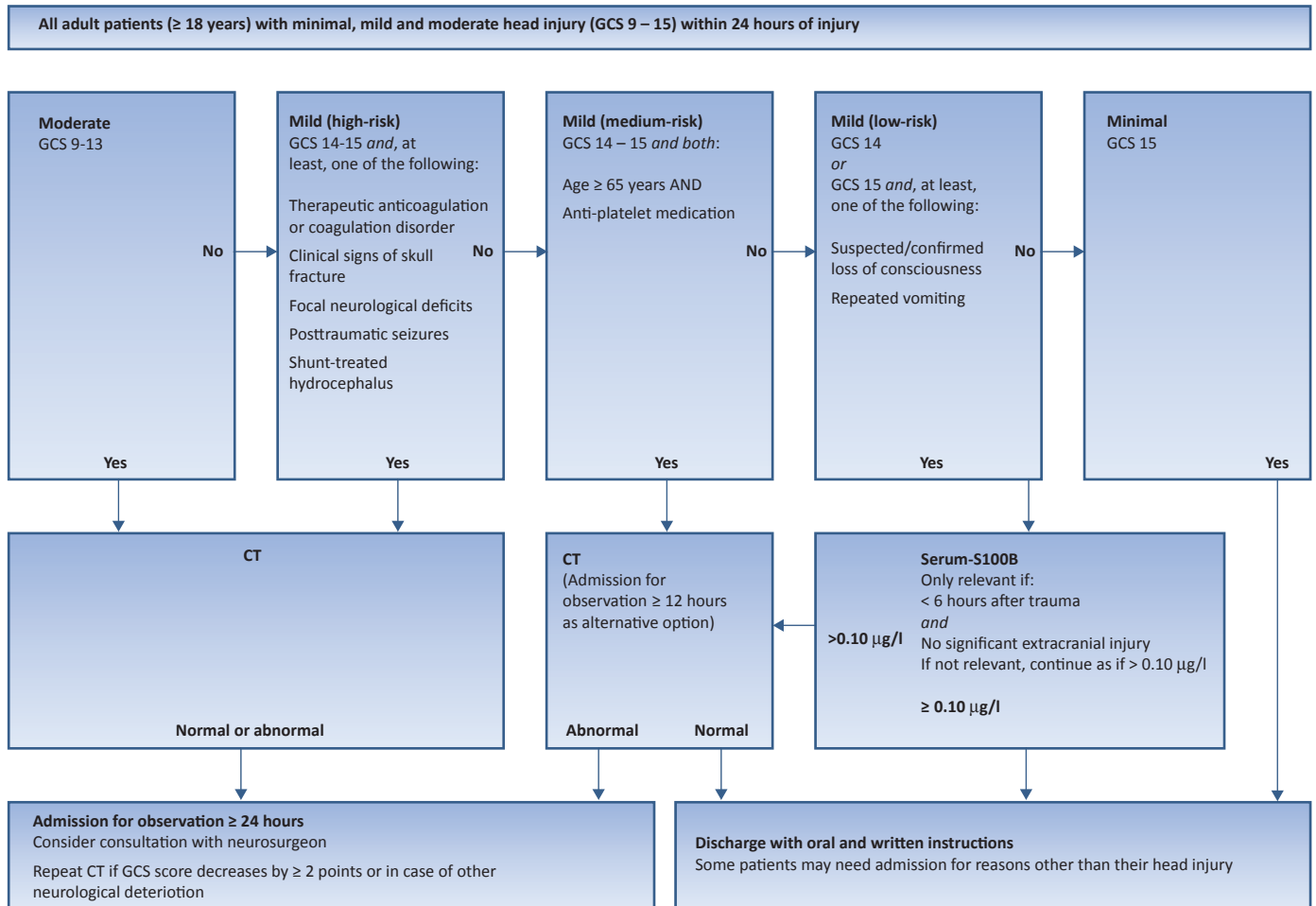
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FIGURE 1

Flow chart illustrating the emergency management of patients with minor head trauma according to the revised 2013 guidelines of the Scandinavian Neurotrauma Committee. Adapted with permission from [2].



CT = computed tomography; GCS = Glasgow Coma Scale.

MATERIAL AND METHODS

The study was conducted as a medical technology assessment. The main aim was to perform a retrospective post hoc analysis of a patient cohort addressing the following question: What would the clinical consequences have been of uncritically measuring the S100B concentration in peripheral blood after minor head trauma?

In the period from 4 July to 14 August, 2013 patients who were evaluated after minor head trauma at the Emergency Department at Koege Hospital had their blood sampled for measurement of S100B concentration in peripheral blood on a random spot basis. Blood was only sampled after the patients had provided informed consent. Blood samples were analysed at the Department of Clinical Biochemistry, Koege Hospital, using Cobas e411 apparatus (Roche Diagnostics). For valida-

tion, the samples were also analysed at the Department of Clinical Biochemistry at Rigshospitalet using Cobas 8000 apparatus (Roche Diagnostics). Agreement between test results was analysed using the Bland-Altman method [9].

The patients were managed according to our existing practice. The result of the blood sample was not available at the time treatment decisions were made, and hence did not influence the choice of treatment.

Using the SNC recommendations as a key for the post hoc analysis, patient records were assessed registering the following parameters:

- *Age*: Patients younger than 18 years of age were excluded.
- *Time from trauma to blood sampling*: Delay from

trauma to the sampling was calculated using ambulance registration forms or from phone contact to the department. Cases in which more than six hours had elapsed from trauma to admission, or in which data were insufficient, were excluded.

- *Estimated GCS*: Patients having a score lower than 14 were excluded.
- *Clinical signs*: Patients with de novo focal deficits, seizures, clinical signs of a skull base fracture or a dislocated convexity fracture were excluded.
- *Prior medical history*: Patients with ventriculoperitoneal shunts, who were in warfarin anticoagulant therapy (or related drugs), or who were known to have coagulopathy were excluded. Also, patients aged 65 or above who were in treatment with antiplatelet agents were excluded.
- *Significant extracranial injury*: Patients with significant extracranial injury were excluded.
- *Suspected or confirmed loss of consciousness*.
- *Vomiting, including number of episodes*.
- *CT of the brain performed and its result*.
- *Admission for observation after concussion*: Qualitatively, an estimate was made to establish whether the reason for admission was strictly observation for intracranial traumatic pathology or whether admission was done for other reasons.

For characterisation of the patients in terms of the SNC criteria for evaluation through measurement of S100B concentration, the cohort was divided into two groups defined by whether or not the SNC criteria for measuring S100B concentration were met. Each of these groups was then analysed to determine whether or not S100B concentrations were above the threshold value. The group who did not meet the SNC criteria for measuring S100B concentration is equivalent to the right hand column in **Figure 1** as patients sustaining only minimal head injury. The group containing patients who met the SNC criteria for measuring S100B is equivalent to the second column from the right in **Figure 1** as patients having low-risk mild head injury.

The post hoc analysis was performed on the presumption that irrespective of the clinical condition or compliance with SNC criteria, elevated levels of S100B would have triggered a CT of the brain or admission for observation.

Trial registration: not relevant.

RESULTS

In the study period, a total of 39 patients had their blood sampled for measurement of their S100B concentration. A total of 12 patients were excluded from further ana-

lysis. Two patients had a history of seizure, two patients were on anticoagulant therapy, in four cases more than six hours had elapsed from trauma to admission, one patient did not have a history of head trauma, two patients were below the age of 18 years, and in one case, the identity of a patient could not subsequently be confirmed and therefore the patient record could not be accessed.

The remaining 27 patients, who were included for study, were on average 51 years of age (range: 18-86 years). Eight of the patients were female. In total, seven patients had a CT of the brain performed; none of these displayed traumatic pathology.

In total, 11 patients were admitted for observation. None of these had progression in symptoms. In four of the 11 admissions, the patient records allowed us to conclude that the purpose of admission was much broader than the detection of any structural lesions of the brain. Due to data insufficiency it could not, however, be concluded that in the remaining seven patients the motif for admission was the detection of any structural brain lesion exclusively. All patients admitted were scored for brain concussion.

In total, 14 patients had an S100B concentration above the defined threshold.

Of the seven patients who had a CTs performed, four had a normal S100B concentration. Of the 11 patients admitted for observation, seven had a normal S100B concentration.

Post hoc stratification according to the SNC inclusion criteria for measurement of S100B concentration showed that, retrospectively, 15 of the patients satisfied the criteria for evaluation through measurement of their S100B concentration. Eight of these patients had a concentration of S100B above the defined threshold. This post hoc group of patients also comprised all of the patients who had a CT of their brain performed as well as nine of the 11 patients who were admitted for observation.

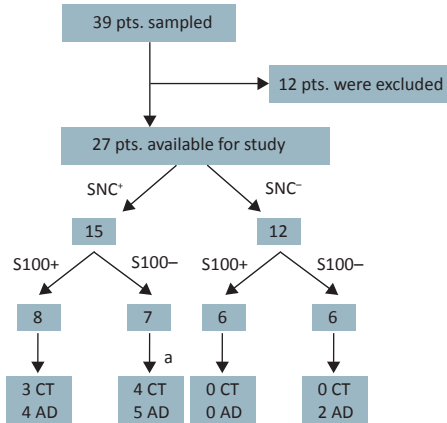
The stratification data are summarised in **Figure 2**. The mean difference between the test results ob-



Assessment of a head trauma patient.

 **FIGURE 2**

Stratification of the cohort according to whether or not the criteria of the revised guidelines of the Scandinavian Neurotrauma Committee on use of the S100B concentration in patient management were met (GCS 14-15 and possible/confirmed loss of consciousness and/or more than one episode of vomiting). The distribution of patients having a concentration of S100B above the threshold seems not to depend on whether Scandinavian Neurotrauma Committee criteria were met. In the last line of the diagram, the clinical fate is shown in terms of computed tomography of the brain being done and/or admission for observation. Discharges are not shown.



AD = admitted; CT = computed tomography; pts. = patients; SNC = Scandinavian Neurotrauma Committee

a) Two patients had a computed tomography and were admitted; hence, the total is nine rather than seven.

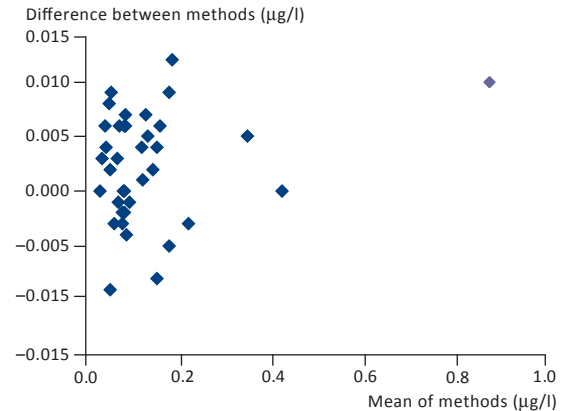
tained locally and those reported by the validation laboratory was 5%, ranging from 0 to 15%. A Bland-Altman plot of the differences observed is shown in **Figure 3**.

DISCUSSION

At the Emergency Department of Koege Hospital, clinical decision-making regarding patients with minor head trauma has so far been rooted in the so-called Canadian Head CT rules from 2001 [10]. In the five years the department has existed, routine audit has not given reason to believe that structural brain damage has been overlooked systematically. In other words, current practice is deemed to be safe. The intention of introducing biomarker S100B as part of the revised SNC guidelines was to improve patient safety, while reducing both cost and the use of imaging [1, 5]. Retrospectively applying the revised SNC principles for management of patients with head trauma in the cohort in terms of use of the S100B biomarker shows that eight CTs of the brain should have been performed. In practice, seven scans were performed; a number comparable to the theoretical eight CTs calculated. Among the seven patients in whom a CT of the brain had been performed, four had normal S100B levels, which ruled out structural lesions to the brain. On the other hand, four patients in the group of patients who satisfied the SNC criteria had an S100B se-

 **FIGURE 3**

Bland-Altman plot presenting the agreement between S100B measurements done locally and at a reference laboratory.



rum concentration exceeding the threshold, but, nevertheless, did not have a CT performed. It seems apparent that measurement of S100B would have improved the indication for performing CTs.

As for admission of patients for observation after concussion, the results show that reasons for admitting patients often extend beyond the scope of detecting a structural brain lesion. Retrospectively, it was not possible to discern these reasons in detail, but the patients admitted were scored for brain concussion; a clinical tool designed for the detection of any structural brain lesion. Scoring patients involves frequent observation which constitutes a burden on the patient, who needs to be awoken repeatedly, and it is costly in terms of nursing staff resources. Seven of the 11 patients had normal S100B concentrations. Of the remaining four, two had a normal CT of the brain. By definition, these patients (given that they do not exhibit any of the characteristics that would cause them to be excluded from this study, e.g. ventriculoperitoneal shunt or warfarin anticoagulant therapy, Figure 1), do not need scoring after concussion. Rather, the strategy for observation in such cases should reflect other clinical reasons for admission. In the present series, it may therefore be concluded that S100B measurement would clearly have had a positive impact on resource allocation during admission.

The flowchart illustrating the use of the guidelines (Figure 1) presupposes clinical evaluation of the patient prior to deciding whether or not to obtain a blood sample from him or her. However, the common mode of patient reception in emergency departments is to perform blood sampling upon arrival so that results may be available when the physician takes the patient history and does the physical examination. This mode of operation has also to be taken into account when introducing bio-

marker S100B; and here Figure 2 clearly shows a precipitous conflict. Thus, the S100B threshold values were exceeded in half of the patients who did not satisfy the SNC criteria for S100B measurement, i.e. in those who could have been immediately discharged on clinical grounds with written and oral information according to the revised SNC guideline. Using S100B as a screening tool was definitely not intended by the SNC guidelines. Thus, this study shows that lack of diligence in selecting patients for S100B, or simply using the standard approach for reception of patients in the Emergency Department, may well leave the treating physician facing a substantial number of falsely positive S100B patients (in the SNC sense). In the present study, uncritical acceptance of these false positives would have produced a total of 14 CTs, representing a 100% increase.

The current study was undertaken without a control group and, combined with the limited size of the study group, the ability to extrapolate to other types of practice is, indeed, very limited. Although improving clinical diagnostics remains a mainstay of any clinical practice, it must also be borne in mind that awaiting a clinical diagnosis prior to the decision to take out a blood sample and then waiting for the result before deciding for or against a CT will possibly place an unacceptable burden on patient logistics. When admitting patients for e.g. pneumonia, a standard panel of blood tests are sampled from the patient. Experience has shown that odd off values that do not fit into the clinical picture may be benefit from a wait-and-see approach. In the example given, slightly elevated liver enzymes are not likely to change the clinical course taken. The question is whether there is a case for S100B to be measured for screening purposes, and, then, in case elevated values are observed, guideline principles may be used to decide whether or not these values should carry clinical significance.

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LITERATURE

1. Unden J, Ingebrigtsen T, Romner B. Scandinavian guidelines for initial management of minimal, mild and moderate head injuries in adults: an evidence and consensus-based update. *BMC Med* 2013;11:50.
2. Eskesen, V, Springborg JB, Unden J et al. Guidelines for the initial management of adult patients with minimal to moderate head injury. *Ugeskr Læger* 2014;176:V09130559.
3. Unden, J, Bellander B M, Romner B. Updated management of adults with head injuries. Scandinavian Neurotrauma Committee's new guidelines provide guidance at minimal, mild and moderate injuries. *Läkartidningen* 2013;110:1868-9.
4. Sundstrom T, Wester K, Enger M et al. Scandinavian guidelines for the acute management of adult patients with minimal, mild, or moderate head injuries. *Tidsskr Nor Lægeforen* 2013;133:E1-E6.
5. Springborg JB, Unden J, Ingebrigtsen T et al. Brain injury marker S100B can reduce the use of computer tomography in minor head injuries – secondary publication. *Ugeskr Læger* 2009;171:978-81.
6. Unden J, Ingebrigtsen T, Romner B. Management of minor head injuries with the help of a blood test. S100B analysis can reduce the number of CT examinations and patient admissions. *Läkartidningen* 2008;105:1846-8.
7. Zongo D, Ribereau-Gayon R, Masson F et al. S100-B protein as a screening tool for the early assessment of minor head injury. *Ann Emerg Med* 2012;59:209-18.
8. Jonsson H, Johnsson P, Hoglund P et al. Elimination of S100B and renal function after cardiac surgery. *J Cardiothorac Vasc Anesth* 2000;14:698-701.
9. Bland JM, Altman D G. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307-10.
10. Stiell IG, Wells G A, Vandemheen K et al. The Canadian CT Head Rule for patients with minor head injury. *Lancet* 2001;357:1391-6.