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Mild traumatic brain injury and biomarkers of acute brain injury

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Head computed tomography (CT) is currently the standard diagnostic tool for evaluating intracranial damage in patients with traumatic brain injury (TBI) and for identifying patients who should undergo immediate surgery. Despite the general consensus on using head CT in patients with severe or moderate TBI, there is no agreement on whether CT is needed for those with mild TBI (Glasgow Coma Scale [GCS] scores from 13–15) given the low prevalence of intracranial abnormalities detected by CT and the low mortality linked to mild brain injury. Two blood- and plasma-based biomarkers for rapid detection—glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase L1 (UCH-L1)—are helpful for making decisions about adult patients with GCS scores between 13 and 15 in the first 12 hours after the TBI, since they can indicate the need for CT or help rule out unnecessary imaging.
Negative findings for GFAP and UCH-L1 within the first 12 hours after a mild TBI allow CT to be ruled out in patients with a GCS score of 15 who have symptoms and/or risk factors, or in patients with GCS scores of 13 or 14. Such patients can be discharged to home observation if they have recovered sufficiently and are asymptomatic. If more than 12 hours have passed since the TBI or if at least one biomarker is positive, a scan should be performed and the usual protocols subsequently followed in accordance with the CT findings and clinical picture.

Keywords: Traumatic brain injury. Biomarkers. Acute brain injury. GFAP, UCH-L1.

Mild head trauma and biomarkers of acute brain injury

Cranial computed tomography (CT) is the standard diagnostic tool for evaluating brain injury in patients with craniocerebral trauma and for identifying patients who should undergo immediate surgery. In spite of the general consensus on using cranial CT in patients with severe or moderate trauma, there is no agreement on whether CT is needed for those with mild injuries (Glasgow Coma Scale [GCS] scores, 13-15) given the low prevalence of intracranial abnormalities detected by CT and the low associated mortality. Two blood- and plasma-based biomarkers, glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase L1 (UCH-L1) are helpful for making decisions about adults with GCS scores between 13 and 15 in the first 12 hours after head injury because they can indicate the need for CT or help rule out unnecessary imaging. The negative predictive value of negative findings for GFAP and UCH-L1 within 12 hours of trauma allows CT to be ruled out in patients with GCS 15 scores who have symptoms and/or risk factors or in patients with GCS scores of 13 or 14. Such patients can be discharged to home observation if they have recovered sufficiently and are asymptomatic. If more than 12 hours have passed since the head injury or if one of the biomarkers is positive, a scan should be obtained and the usual protocols followed in accordance with the CT findings and clinical picture.

Keywords: Craniocerebral trauma. Biological markers. Brain injuries, acute. Glial fibrillary acidic protein (GFAP). Ubiquitin C-terminal hydrolase L1 (UCH-L1).

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Managing patients with mild traumatic brain injury

Concern about identifying patients with mild traumatic brain injury (TBI) and a high risk of acute intracranial injury (AII), coupled with the lack of objective tools available during the assessment to determine patients' neurocognitive status, has led to an exponential increase in head computed tomography (CT) requests at hospital emergency departments (HED)[1–11]. This lack of objectivity is more evident in certain patients, where there may be some confusion as to whether the symptoms are caused by TBI or due to drug or alcohol abuse, or even to the presence of underlying diseases (e.g. Alzheimer's disease) or other neurodegenerative diseases that do not allow the incident, the associated symptoms or the injury mechanism to be understood with certainty.

Some of the main effects of mild TBI are immediate and occur within a few hours of injury, although signs and symptoms may peak in severity at any time from hours to months after the TBI. Cognitive impairment is common, particularly visual and motor reaction time, information processing, memory and attention. However, in a minority of cases it can also appear as intracranial lesions that are visible on a CT[12]. Only 7–10% of patients with mild TBI (Glasgow Coma Scale [GCS] between 13 and 15 points) have CT-detected intracranial abnormalities, of which fewer than 1% are estimated to require neurosurgical intervention. Mortality, meanwhile, is a very rare outcome (0.1%)[1,12,13]. Specifically, the lesions considered to have a low risk of progression requiring neurosurgical intervention are: mild convexity subarachnoid hemorrhage, intraparenchymal hematoma or hemorrhagic contusion in a single location, and subdural or epidural hematoma, all measuring less than or equal to 4 mm[1].

Therefore, the low percentage of patients with these characteristics and the very low mortality associated with mild TBI—together with the increase in associated costs, HED overload and the risks of radiation exposure (especially important in young people under 20 years of age)—have challenged the widespread use of urgent head CT in mild TBI[1,14,15].

There is consensus on performing a head CT in patients with moderate or severe TBI, but controversy remains over which mild TBI patients should undergo this diagnostic test[16]. These facts and the goal of reducing unnecessary testing have driven the search for tools that can effectively and safely identify patients at low risk of AII. Various protocols and clinical guidelines have been developed for groups with specific risk factors or criteria, aimed at the early identification of patients who may have AII, and therefore require neuroimaging tests or hospital observation[1,16-22]. However, the lack of clinical specificity and the need for more evidence in certain population groups that have risk factors, enable a degree of justification for the differences between guidelines and their limited impact on reducing the number of CTs performed. The sensitivity of these criteria for identifying patients at low risk of intracranial injury following a mild TBI may be lower than originally described[17,18,23–25]. Therefore, there are currently no universally accepted standards and the use of these protocols in Spain is center-dependent, with no common consensus or protocol for managing patients with mild TBI.

In short, one of the main challenges in managing these patients is the need to optimize resources through more detailed risk stratification in order to define the best approach for each patient.

Markers of acute brain damage

There have been significant advances in recent decades within the study of blood biomarkers that improve the diagnosis and clinical characterization of patients with possible brain damage. This in turn has presented an important opportunity to gain understanding of the pathophysiology of the illness, and to better support clinical decision-making.

Direct impact or acceleration-deceleration forces applied to the head can cause both immediate and delayed impairment of the blood-brain barrier/gliovascular unit. The injury causes oxidative stress and primary vascular damage that leads to protein leakage into the blood. In addition, the production of proinflammatory mediators increases and cell adhesion molecules are overexpressed on the surface of the cerebral endothelium, promoting the entry of inflammatory cells into the injured brain parenchyma and the extravasation of red blood cells[26.27].

More than 20 brain proteins have been identified in blood, some of which have been shown to predict head CT results in mild TBI (Table 1)[28–30]. Origin and release kinetics are two key factors in the study of these molecules and their usefulness as biomarkers.

Specifically, the S100ß protein has been one of the most studied blood biomarkers, and has even been included in some clinical guidelines and triage areas for the initial care provided to patients with mild TBI within Europe[19,25,31]. Although several studies have demonstrated its high sensitivity and negative predictive value for acute head CT[30], the use of S100ß has not become widespread in clinical practice. Some of the reasons for this are: elevated protein in the absence of TBI, depending on the injury mechanism, due to the existence of extracranial sources (adipose tissue, musculoskeletal tissue and melanocytes); the time course of the biomarker in peripheral body fluids (its presence must be determined within 3 hours of the trauma); and the robustness of existing data[29,32–39].

Other biomarkers studied are glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase L1 (UCH-L1) and, specifically, the combination of both for evaluation in the acute period following a TBI.

UCH-L1 is one of the most abundant proteins in the brain. It represents 1–2% of total brain protein and is located exclusively in neurons. It is involved in the elimination of degraded and denatured proteins following oxidative phenomena.

GFAP is a protein derived from astrocyte tissue, whose expression and release is specific to the brain. This quality makes it unique as a biomarker of brain injury in various situations, such as traumatic damage, ischemic events and certain neurodegenerative disorders[40]. It is a monomeric protein with a molecular weight of 52 kDa, released into the blood through the blood-brain barrier

Table 1. Potential blood biomarkers in traumatic brain injury

Origin	Neuronal	Glial	Axonal injury

Biomarker	NSE	UCH-L1	GFAP	S100ß	NfL	Tau
Point of release	Acute: minutes to hours		Acute: minutes to hours		Subacute to chronic: hours to months	
Significant extracranial contribution	Erythrocytes	Some expression in gonads, adrenals	Very specific to the brain	Adipose tissue, muscle, skin	Axonal	Liver, kidney, testicles, peripheral nerves
Characteristics	Blood levels depend on hemolysis	Hyperacute – acute	Very specific to the brain	Elevated in extracranial lesions	May remain elevated for months	Long-term outcome biomarker (dementia)

GFAP: Glial fibrillary acidic protein; NfL: Neurofilament light; NSE: Neuron-specific enolase; UCH-L1: Ubiquitin C-terminal hydrolase L1.

when its integrity is affected by traumatic injury. There is an early plasma peak on the first day and a progressive decrease during the first week from the third day of progression[29,34,41].

GFAP and UCH-L1 levels are measurable in the peripheral blood from the first hour after the TBI and reach their highest levels at approximately 20 and 8 hours, respectively[14]. Both values decrease over time; however, GFAP values remain elevated beyond 72 hours[14] (Figure 1). The difference in origin and kinetics of both markers determines the importance of measuring both proteins together when evaluating patients in the acute phase after TBI.

The results of the study by Bazarian *et al.* showed a sensitivity of 95.8%, a negative predictive value of 99.3% and a specificity of 40.4% for the rapid serum/plasma test for the specific biomarkers GFAP and UCH-L1 for mild TBI[30]. These findings indicate that the test can reliably predict the absence of AII displayed on a CT scan. This represents a paradigm shift in how the condition is evaluated, with the availability of a test that—when performed on adults over 18 years of age within 12 hours after the trauma—could reduce unnecessary head CT scans by up to 38%[16].

The authors indicate that its use in clinical practice may mean: shortened hospital waiting times for patients, leading to improved HED efficiency and quality of care perceived by patients; reduced exposure to radiation from head CT scans; improved evaluation of patients who are intoxicated, or have underlying disease or other neurodegenerative pathologies; and, finally, less overload of the services and health care workers involved.

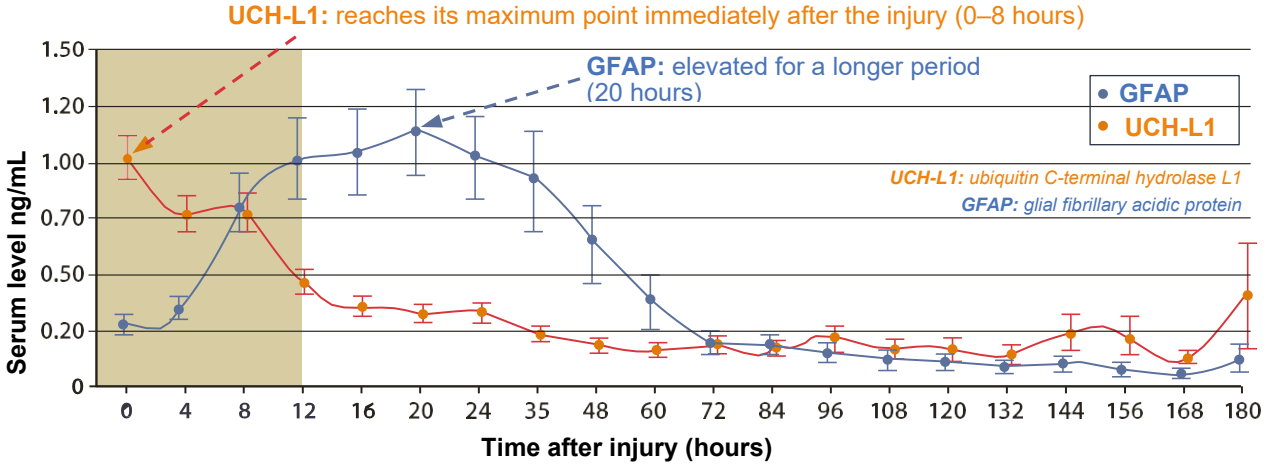

Figure 1. Time course of GFAP and UCH-L1 in patients with mild/moderate traumatic brain injury on CT (modified from Papa L, *et al.*[14]).

Clinical stratification and evaluation of mild traumatic brain injury

The aim of this evaluation is to identify the presence of symptoms and risk factors for AII, avoiding neuroimaging tests in patients for whom the risk is very low or non-existent[1,44]. This is especially important in the evaluation of patients with mild TBI because around 90% of requested head CT scans are normal[1,12,13].

After assessment, patients with GCS 15 with no symptoms or risk factors (Table 2) can be discharged for home observation with verbal and written information on recommendations about things to monitor and the possible progression of the injury. Based on medical criteria, the patient can undergo observation in the HED for between 6 and 24 hours. In addition, based on medical criteria and the individual clinical situation, the GFAP and UCH-L1 combination can be tested if fewer than 12 hours have elapsed since the trauma, in order to rule out the need for a head CT scan.

Acute brain damage study

During the evaluation of adult patients with mild TBI (GCS 13–15), rapid serum/plasma testing of the specific GFAP and UCH-L1 biomarkers serves as a complementary tool to assist in decision-making regarding the need for a head CT.

Testing the GFAP and UCH-L1 combination is requested within the first 12 hours after trauma in patients with:

– GCS 15 with symptoms and/or risk factors (Table 2).

– GCS 14 or GCS 13.

The process for using the test involves conventional processing of the samples that arrive at the laboratory, with results obtainable after 30 to 60 minutes. A negative result from analysis of GFAP and UCH-L1 biomarkers in the first 12 hours after trauma is associated with the absence of intracranial lesions due to the high negative predictive value of these biomarkers. These patients may be discharged for home observation with verbal and written information on recommendations to follow in the event of potential progression, provided that the patient has recovered and asymptomatic (Figure 1).

All interventions should be assessed based on the individual needs of each patient. The recommended observation period varies from 6 to 24 hours, depending on the findings, associated risk factors and patient progress. In any case, the patient is discharged with verbal and written information on recommendations for dealing with potential progression of the injury, provided that they are clinically well and there are no post-traumatic risk factors other than age alone.

If more than 12 hours have elapsed since the trauma or the biomarker result is positive, a CT head should be performed.

Table 2. Risk factors for poor clinical outcomes in mild traumatic brain injury

– Neurological deficit.
– Bleeding disorder, hemorrhagic disorder, taking anticoagulants or antiplatelet agents, excluding acetylsalicylic acid monotherapy if not accompanied by other signs or symptoms[18].
– ≥ 65 years.
– Intoxication (alcohol or drugs).
– Vomiting (≥ 2).
– Headache.
– Post-traumatic seizures.
– Short-term memory loss or amnesia of episode.
– Evidence of head or neck injury.
– Previous brain injury/neurosurgery.
– Dangerous injury mechanism, considered to be the ejection of occupants from or the overturning of a motor vehicle, collision with a pedestrian or cyclist, or falling from heights greater than one's own height or five steps.

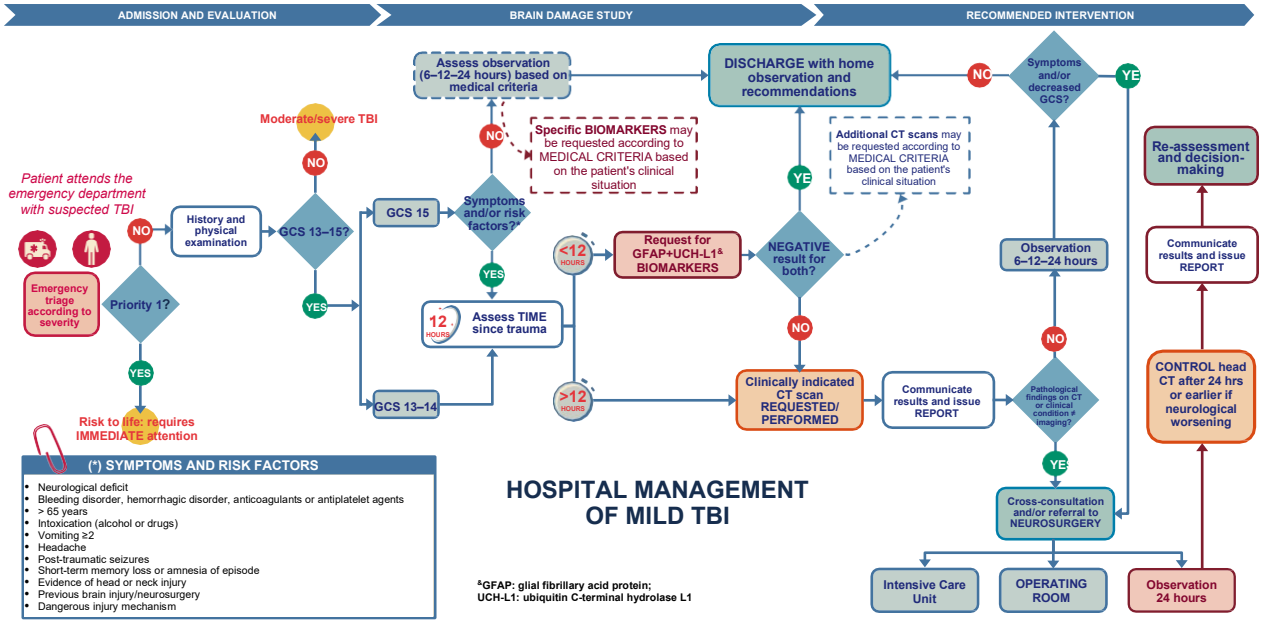

Figure 2.

Table 3. Recommended intervention in the use of biomarkers and computed tomography

– More than 12 hours after the trauma (with Glasgow score of 15 and risk factors/symptoms, or Glasgow score of 13–14), or after a positive GFAP and UCH-L1 biomarker analysis, urgent head CT is indicated.
– If there are no pathological findings on the CT, patients may be discharged for home observation, provided that they are clinically well and free of post-traumatic risk factors other than age alone.
– Consult the Neurosurgery Department if the CT reveals pathological findings or when the patient's clinical condition is inconsistent with the radiological findings.
– Request a control CT: • If an initial CT reveals pathological findings, regardless of the patient's good clinical condition and after a 24-hour observation period. • If symptoms persist or the patient experiences neurological deterioration during the observation period.

CT: computed tomography.

However, a CT scan can be requested regardless of the biomarker results, based on medical criteria and the clinical situation of each patient (Table 3).

Precautions in patients receiving anticoagulants

It is necessary to ascertain the coagulation status of patients with mild TBI who are undergoing antithrombotic therapy. This means requesting a standard INR clotting test for patients on vitamin K antagonists (VKA); renal function and the time of last drug intake should also be ascertained for patients taking direct acting oral anticoagulants (DOACs). If uncertain about DOAC intake, a DOAC level test or specific clotting tests may be requested if available[47].

If pathological findings (bleeding) appear on CT, it is recommended that anticoagulant drugs be immediately stopped and reversed:

– VKAs (if INR > 2) with prothrombin complex concentrate (PCC) and vitamin K. Fresh frozen plasma (FFP) may be used if no PCC is available.

– If the patient is taking thrombin inhibitor (dabigatran), its specific reversal agent (idarucizumab) should be used. If not available, use PCC.

– If treating with XABANS—otherwise known as direct factor Xa inhibitors (apixaban, edoxaban or rivaroxaban)—use PCC, as the specific reversal agent (andexanet alfa) is not yet marketed in our setting.

Once the observation time has elapsed in cases with normal CT results, the anticoagulation regimen can be continued by assessing whether it is necessary to adjust the dose according to the INR in the case of VKAs or according to renal function for DOACs. Communication and coordination with the hematologist may be necessary for this patient profile.

Conclusion

Clinical history (with particular attention to risk factors for poor TBI progression) and physical examination are the basis for decision-making in the clinical management of mild TBI. Within the first 12 hours, head CTs can be replaced for these TBIs by testing the GFAP and UCH-L1 combination. A negative result for both has sufficient negative predictive value to discharge the patient and to proceed with home observation. However, as in any emergency care process, medical judgment and the patient's individual clinical situation take precedence in decisions regarding discharge and clinical observation, or the need for a head CT scan.

Annex

Document endorsed by: SEMES (Sociedad Española de Medicina de Urgencias y Emergencias — Spanish Society of Emergency Medicine and Emergencies), SENEC (Sociedad Española de Neurocirugía — Spanish Society of Neurosurgery), SERAM (Sociedad Española de Radiología Médica — Spanish Society of Medical Radiology), SERAU (Sociedad Española de Radiología de Urgencias — Spanish Society of Emergency Radiology), SEQC-ML (Sociedad Española de Medicina de Laboratorio — Spanish Society of Laboratory Medicine).

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