REUE | Review Article

Mild head trauma and biomarkers of acute brain injury

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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. These biomarkers 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. CT can also be avoided 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).

Traumatismo craneoencefálico leve y biomarcadores de lesión cerebral aguda

Actualmente, la tomografía computarizada (TC) craneal es la herramienta de diagnóstico estándar para evaluar la lesión intracraneal de pacientes con traumatismo craneoencefálico (TCE) e identificar aquellos que necesitan tratamiento quirúrgico inmediato. Existe un consenso generalizado sobre la realización de la TC craneal en los pacientes con TCE moderado o grave, pero no hay acuerdo sobre a qué pacientes con TCE leve (puntuación en la Escala de Coma de Glasgow –GCS– entre 13-15) se debe realizar esta prueba, por la baja prevalencia de anomalías intracraneales detectadas por TC y la excepcional mortalidad ligada al daño cerebral leve. Los biomarcadores de detección rápida en suero/plasma GFAP (Proteína Ácida Fibrilar Glial) y UCH-L1 (Ubiquitina C-terminal Hidrolasa L1) sirven de ayuda a la toma de decisiones durante la evaluación de pacientes adultos con GCS 13-15 en las primeras 12 horas desde el TCE. Permiten determinar la necesidad de realizar una TC, reduciendo su uso a los casos necesarios.
Tras un TCE leve, en pacientes con GCS 15 con síntomas y/o factores de riesgo, GCS 14 o 13, un resultado negativo de GFAP y UCH-L1 en las primeras 12 horas, descarta la necesidad de realizar una TC craneal, con un valor predictivo negativo muy elevado. Estos pueden ser dados de alta para observación domiciliaria, siempre que estén recuperados y sin sintomatología. Si han transcurrido más de 12 horas del TCE, o al menos un biomarcador es positivo, se debe realizar una TC craneal y, tras ello, seguir los protocolos habituales según los hallazgos radiológicos y el estado clínico del paciente.

Palabras clave: Traumatismo craneoencefálico. Biomarcadores. Lesión cerebral aguda. GFAP, UCH-L1.

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Article Information: Received: 21-11-2023. Accepted: 25-11-2023. *Online:* 21-12-2023.
Editor in Charge: Guillermo Burillo-Putze.

Management of patients with mild traumatic brain injury

Concern over identifying patients with mild traumatic brain injury (TBI) who are at high risk of presenting an acute intracranial injury (AII), together with the lack of objective tools available during assessment to determine the patients' neurocognitive status, has led to an exponential increase in requests for cranial computed tomography (CT) scans in emergency departments (EDs).[1-11] This lack of objectivity is even more evident in certain patients in whom there may be confusion as to whether symptoms are caused by the TBI *per se*, by drug or alcohol use, or by underlying conditions (e.g., Alzheimer's disease) or other neurodegenerative disorders that make it difficult to determine the event, associated symptoms, or mechanism of injury with certainty.

Some of the main effects of mild TBI occur immediately and appear within a few hours after injury, although maximum symptoms and signs may arise hours to months later. Cognitive changes are frequent—especially in visual and motor reaction time, information processing, memory, and attention—but only a minority of cases show intracranial lesions visible on the CT.[12] Only about 7–10% of patients with mild TBI (Glasgow Coma Scale [GCS] score 13–15) present CT-detectable intracranial abnormalities, and it is estimated that < 1% require neurosurgery, with mortality being exceptional (0.1%).[1,12,13] Specifically, lesions considered low risk for progression and neurosurgical need include: minimal convexity subarachnoid hemorrhage, single-site intraparenchymal hematoma or hemorrhagic contusion, and subdural or epidural hematomas ≤ 4 mm.[1]

Therefore, the low percentage of patients with these findings and the exceptionally low mortality associated with mild TBI—together with increased health care costs, ED overcrowding, and radiation exposure (particularly relevant in those younger than 20 years)—have led to questioning the routine use of urgent cranial CT in mild TBI.[1,14,15]

While there is consensus regarding CT scanning in moderate or severe TBI, controversy remains on which patients with mild TBI truly require this diagnostic test.[16] In this context, and to reduce unnecessary imaging, efforts have been made on developing tools to safely identify patients at low risk of AII. Several clinical protocols and guidelines have been developed with sets of criteria or risk factors aimed at early identification of patients who may present AII, for whom neuroimaging or hospital observation is indicated.[1,16-22] However, the lack of clinical specificity and limited evidence in certain high-risk subgroups partly explain the differences among guidelines and their limited impact on reducing CT utilization. The sensitivity of these criteria for identifying low-risk patients after mild TBI may be lower than originally described.[17,18,23-25] Therefore, there are currently no universally accepted standards, and in Spain, use of these protocols is center-dependent, without a unified national consensus for managing mild TBI.

In summary, one of the main challenges in managing these patients is optimizing resources through more detailed risk stratification, enabling the best individualized approach for each patient.

Markers of acute brain injury

Over recent decades, significant advances have been made in studying blood biomarkers that improve the diagnosis and clinical characterization of patients with possible brain injury, providing a valuable opportunity to better understand the pathophysiology and assist in clinical decision-making.

After direct impact or acceleration–deceleration forces to the head, both immediate and delayed dysfunction of the blood–brain barrier/gliovascular unit occurs. The injury induces oxidative stress and primary vascular damage, leading to protein leakage into the bloodstream, increased production of pro-inflammatory mediators, and overexpression of endothelial adhesion molecules, which promote inflammatory cell infiltration into the traumatized parenchyma and red blood cell extravasation.[26,27]

More than 20 brain-derived proteins have been identified in blood, some of which have been shown to predict CT findings in mild TBI (Table 1).[28-30] Their origin and release kinetics are key determinants of their usefulness as biomarkers.

Specifically, S100β protein is one of the most extensively studied blood biomarkers and has even been included in some clinical guidelines and triage protocols for the initial management of mild TBI in Europe.[19,25,31] Although several studies have shown its high sensitivity and negative predictive value for acute cranial CT,[30] the use of S100β in routine practice has not become widespread. Reasons include: its elevation in the absence of TBI depending on the mechanism of injury, extracranial sources (adipose, musculoskeletal tissue, and melanocytes), the temporal course of the biomarker (must be measured within 3 hours of trauma), and limitations in data robustness.[29,32-39]

Other biomarkers studied are the GFAP (glial fibrillary acidic protein) and the UCH-L1 (ubiquitin C-terminal hydrolase L1)—particularly their combined use in the acute evaluation after TBI.

UCH-L1 is one of the most abundant brain proteins, representing 1–2% of total brain protein, localized exclusively in neurons, and involved in degrading oxidatively damaged proteins.

GFAP, derived from astrocytic tissue, is expressed and released specifically in the brain, making it an exclusive biomarker of brain injury in diverse conditions, including trauma, ischemia, and certain neurodegenerative disorders.[40] It is a monomeric protein (52 kDa) released into the bloodstream through the disrupted blood–brain barrier, peaking within the first day and gradually declining during the first week.[29,34,41]

GFAP and UCH-L1 levels are measurable in peripheral blood within the first hour after TBI, peaking at approximately 20 and 8 hours, respectively.[14] Both decline over time, although GFAP remains elevated beyond 72 hours[14] (Figure 1). The different origins and kinetics of these two

Table 1. Potential blood biomarkers in traumatic brain injury

Origin	Neuronal		Glial		Axonal Injury	
Biomarker	NSE	UCH-L1	GFAP	Σ100β	NFL	Tau
Time of release	Acute: minutes to hours		Acute: minutes to hours		Subacute to chronic: hours to months	
Significant extracranial contribution	Erythrocytes	Some expression in gonads, adrenal glands	Highly specific to the brain	Adipose tissue, muscle, skin	Axonal	Liver, kidney, testes, peripheral nerves
Characteristics	Blood levels depend on hemolysis	Hyperacute – Acute	Highly specific to the brain	Elevated in extracranial injuries	May remain elevated for months	Long-term outcome biomarker (dementia)

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

biomarkers justify measuring both during acute-phase evaluation.

The study by Bazarian *et al.* showed a sensitivity of 95.8%, negative predictive value of 99.3%, and specificity of 40.4% for the rapid serum/plasma test combining GFAP and UCH-L1 in mild TBI.[30] These results suggest that the test can reliably predict the absence of AII on CT, representing a paradigm shift in TBI assessment. In adults > 18 years, testing within 12 hours of injury could reduce unnecessary CT scans by up to 38%.[16]

The authors indicate that its use in clinical practice may shorten patient waiting times in the hospital and, consequently, improve the efficiency of the ED, enhance the quality of care perceived by patients, reduce radiation exposure resulting from performing a cranial CT scan, improve the assessment of patients who are intoxicated or have underlying diseases or other neurodegenerative disorders, and, finally, mitigate the workload of the involved services and professionals.

Clinical stratification and evaluation of mild traumatic brain injury

The goal of this assessment is to identify the presence of symptoms and risk factors for AII, while avoiding neuroimaging in patients with very low or absent risk.[1,44] This is especially relevant because about 90% of cranial CT scans ordered for mild TBI are normal.[1,12,13]

After assessment, patients with GCS 15 and no symptoms or risk factors (Table 2) may be discharged home for observation, with verbal and written instructions on warning signs and expected evolution. If needed, a 6–24-hour observation period in the ED may be considered. Depending on clinical judgment and timing (< 12 hours post-injury), determination of combined GFAP and UCH-L1 levels may help rule out the need for cranial CT.

Management of the adult patient with traumatic brain injury

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

The determination of the combined GFAP and UCH-L1 biomarkers should be 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 procedure for the test follows the standard laboratory sample-processing workflow, and results can be obtained within 30 to 60 minutes. A negative result for GFAP and UCH-L1 biomarkers within the first 12 hours after trauma is associated with the absence of intracranial lesions, owing to their high negative predictive value. These patients may be discharged for home observation with verbal and written instructions on warning signs and follow-up recommendations, provided they have fully recovered and are asymptomatic (Figure 2).

All interventions must always be assessed according to each patient's individual needs. The recommended obser-

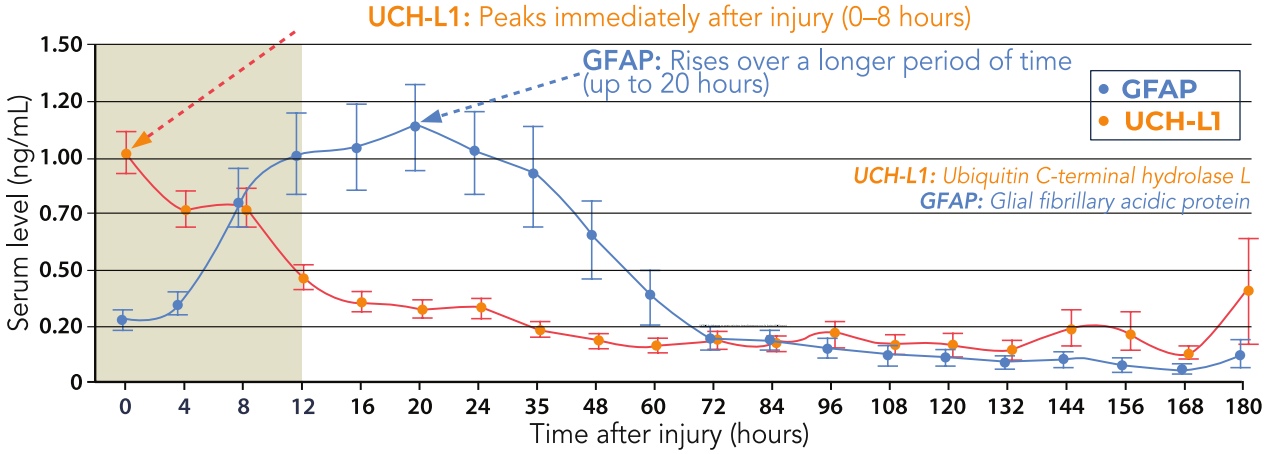

Figure 1. Temporal profile of GFAP and UCH-L1 in patients with mild/moderate TBI and traumatic brain injury (modified from Papa L, *et al.*[14]).

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

– Neurological deficit.
– Coagulopathy, bleeding disorder, or use of anticoagulant or antiplatelet therapy, excluding acetylsalicylic acid (ASA) monotherapy if not accompanied by other signs or symptoms.[18]
– Age ≥ 65 years.
– Intoxication (alcohol or drugs).
– Vomiting (≥ 2 episodes).
– Headache.
– Post-traumatic seizures.
– Short-term memory loss or amnesia of the event.
– Evidence of injury to the head or neck.
– History of brain injury or prior neurosurgery.
– Dangerous mechanism of injury, defined as ejection of vehicle occupants or vehicle rollover, pedestrian or cyclist struck by a motor vehicle, or a fall from a height greater than the patient's own height or > 5 steps.

Table 3. Recommended actions for the use of biomarkers and cranial computed tomography

– If > 12 hours have elapsed since trauma (GCS 15 with symptoms/risk factors or GCS 13–14) or if the GFAP and UCH-L1 biomarker test yields a positive result, an emergency cranial CT scan is indicated.
– If the CT scan shows no pathological findings, patients may be discharged for home observation, provided they are clinically stable and have no post-traumatic risk factors, except for age as an isolated criterion.
– Consult the Neurosurgery Department if the CT scan shows pathological findings or if the clinical presentation is inconsistent with radiological results.
– Request a follow-up CT scan: • SIf an initial CT scan revealed pathological findings, regardless of the patient's good clinical condition, after a 24-hour observation period. • SIf symptoms persist or the patient experiences neurological deterioration during the observation period.

CT: computed tomography; GFAP: Glial fibrillary acidic protein; UCH-L1: Ubiquitin C-terminal hydrolase L1; GCS: Glasgow Come Scale.

vation period ranges from 6 to 24 hours, depending on findings, associated risk factors, and clinical evolution. In all cases, the patient may be discharged with verbal and written information about warning signs and expected evolution, as long as they are clinically stable and have no post-traumatic risk factors, except for age as an isolated criterion.

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

However, based on clinical judgment and taking into consideration each patient's individual situation, a CT scan may be requested regardless of biomarker results (Table 3).

Precautions in patients on anticoagulant therapy

In mild TBI patients on antithrombotic treatment, it is essential to assess hemostatic status by requesting a standard coagulation panel and INR in those on vitamin K antagonists (VKAs). For patients taking direct oral anticoagulants (DOACs), renal function and the time of last dose must also be known. If there is uncertainty regarding DOAC intake, specific coagulation assays or DOAC level tests may be requested when available.[47]

If CT reveals pathological findings (bleeding), anticoagulant therapy should be suspended and reversed immediately as follows:

– VKAs (if INR > 2): use prothrombin complex concentrate (PCC) and vitamin K; if PCC is unavailable, use fresh frozen plasma (FFP).

– Dabigatran (thrombin inhibitor): use its specific reversal agent idarucizumab; if unavailable, administer PCC.

– Factor Xa inhibitors (apixaban, edoxaban, rivaroxaban): administer PCC, as the specific reversal agent andexanet alfa is not yet commercially available in our setting.

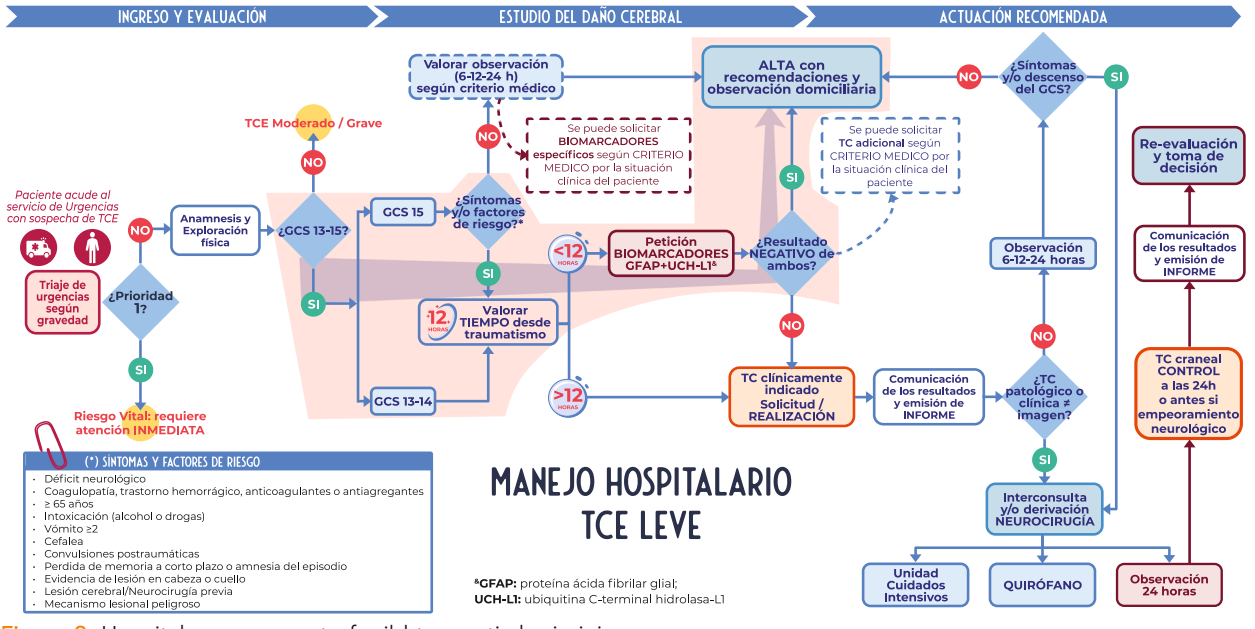

Figure 2. Hospital management of mild traumatic brain injury.

In cases with normal CT results, once the observation period has concluded, anticoagulation may be resumed, adjusting dosage as appropriate: according to INR for VKAs and renal function for DOACs. Coordination with a hematology specialist may be required for these patients.

Conclusions

Health history (with special attention to risk factors for poor TBI outcomes) and physical examination are the foundation for clinical decision-making in the management of mild TBI. In such cases, cranial CT within the first 12 hours can be substituted by the determination of combined GFAP and UCH-L1. A negative result for both biomarkers provides a sufficiently high negative predictive value to allow safe discharge and home monitoring. Nevertheless, as in any emergency care process, clinical judgment and the patient's individual condition always prevail in decisions regarding discharge, observation, or CT necessity.

Annex

This document has been endorsed by: Spanish Society of Emergency Medicine (SEMES), Spanish Society of Neurosurgery (SENEC), Spanish Society of Medical Radiology (SERAM), Spanish Society of Emergency Radiology (SERAU), Spanish Society of Laboratory Medicine (SEQC-ML), and Spanish Association of Football Team Physicians (AEMEF).

ARTICLE INFORMATION

Conflict of Interest Disclosures: None reported.

Funding: Abbott provided support for an independent external consulting team to coordinate and facilitate all study phases. No other funding was received for this research.

Ethical responsibilities: The authors have confirmed the maintenance of confidentiality and respect for the patient rights, agreement of publication, and transfer of rights to Revista Española de Urgencias y Emergencias.

Article not commissioned by the Editorial Board and with external peer review.

Note of the editors: This is a BOWMAN-generated English translation of the officially indexed Spanish-language article, which should be cited as Rev Esp Urg Emerg. 2024;3:31-36. In this translated version, the editors have supervised the process; however, it cannot be ruled out that some errors resulting from the artificial intelligence translation process may have gone unnoticed.

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