

Review Article

Neuroworsening: a concept in need of updating
Deterioro neurológico: un concepto que necesita actualización
Deterioração neurológica: um conceito que precisa de atualização

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Abstract

Assessment and follow up of patients with acute brain pathologies has traditionally been based on the identification of neuroworsening. Today, the central criteria for its detection include the value in the Glasgow Scale and evaluation of pupillary response, which are elements that are modified once the brain injury has progressed enough to alter the clinical status of the patient. This means that both clinical changes are detected late, delaying the response of the medical team. Currently, diverse noninvasive monitoring systems provide parameters and thresholds that could be integrated into a new concept of neuroworsening.

This approach would incorporate new criteria for an earlier identification of worsening in patients with acute stage brain injury. These new techniques and a set of criteria that could form part of a redefinition of neuroworsening are proposed. It is fundamental that this new definition be validated through clinical studies or expert consensus in order to deliver criteria that permit the minimization of the harmful effects of neuroworsening in the prognosis of patients with traumatic brain injury and other neurocritical conditions.

Keywords: Neuroworsening, acute brain injury, non-invasive neuromonitoring

Resumen

La evaluación y el seguimiento de pacientes con patologías cerebrales agudas han estado tradicionalmente basados en la identificación del empeoramiento neurológico. En la actualidad, los criterios centrales para su detección incluyen el valor en la Escala de Glasgow y la evaluación de la respuesta pupilar, los cuales son elementos que se modifican una vez que la lesión cerebral ha progresado lo suficiente como para alterar el estado clínico del paciente. Esto significa que ambos cambios clínicos se detectan tardíamente, retrasando la respuesta del equipo médico. Actualmente, diversos sistemas de monitoreo no invasivo proporcionan parámetros y umbrales que podrían integrarse en un nuevo concepto de empeoramiento neurológico. Este enfoque incorporaría nuevos criterios para una identificación más precoz del deterioro en pacientes con lesión cerebral en fase aguda. Se proponen estas nuevas técnicas y un conjunto de criterios que podrían formar parte de una redefinición del empeoramiento neurológico. Es fundamental que esta nueva definición sea validada mediante estudios clínicos o consenso de expertos, con el fin de establecer criterios que permitan minimizar los efectos perjudiciales del empeoramiento neurológico en el pronóstico de pacientes con traumatismo encefalocraneano y otras condiciones neurocríticas.

Palabras clave: Neurodeterioro, lesión cerebral aguda, neuromonitoreo no invasivo

Resumo

A avaliação e o acompanhamento de pacientes com patologias cerebrais agudas têm sido tradicionalmente baseados na identificação do declínio neurológico. Hoje em dia os critérios centrais para sua detecção incluem o valor na Escala de Glasgow e a avaliação da resposta pupilar, que são elementos modificados somente quando a lesão cerebral já progrediu o suficiente para alterar o estado clínico do paciente. Isso significa que ambas as alterações clínicas são detectadas tardiamente, atrasando a resposta da equipe médica. Atualmente, diversos sistemas de monitorização não invasiva fornecem parâmetros e limiares que poderiam ser integrados a um novo conceito de piora neurológica. Essa abordagem incorporaria novos critérios para uma identificação mais precoce do agravamento em pacientes com lesão cerebral em fase aguda.

Propõem-se o uso dessas novas técnicas e um conjunto de critérios que poderiam fazer parte de uma redefinição do declínio neurológico. É fundamental que essa nova definição seja validada por meio de estudos clínicos ou consenso de especialistas, a fim de estabelecer critérios que permitam minimizar os efeitos prejudiciais de declínio no prognóstico de pacientes com traumatismo cranioencefálico e outras condições neurocríticas.

Palavras-chave: Declínio neurológico, lesão cerebral aguda, neuromonitorização não invasiva

Introduction

Traumatic brain injury (TBI) can be defined as the disruption of brain function caused by an external physical force. The incidence of TBI is estimated at 50 million cases a year worldwide. The morbidity and mortality rates are higher in low- and middle-income countries and cost the world economy approximately 400 billion dollars, or 0.5% of the gross world product¹. In clinical practice, the severity of TBI is classified by the Glasgow coma scale (GCS): mild (GCS 14-15), moderate (9-13), and severe (3-8). Severe TBI has mortality rates between 30 and 60% and is associated with physical and cognitive sequelae that affect the patient and society as a whole. Patients with moderate TBI, while they do not suffer devastating primary injuries, have a mortality rate between 3 and 15% and the moderate-severe disability reaches up to 35%, according to different publications^{2,3}. It is important to note that for every severe TBI, there are 4 patients with a moderate TBI.

Traumatic brain injury provokes damage to the brain matter, loss of cerebral blood flow (CBF) regulation, alterations in metabolism, activation of inflammatory, oxidative stress and cellular cascades, necrosis, and neuronal apoptosis. These processes lead to increase cellular death, cerebral edema, and an increase in intracranial pressure (ICP)⁴. For these reasons, management strategies must be centered in prevention, early diagnosis, and aggressive treatment of the secondary brain injury to avoid more neuronal damage and a worse clinical result. In this context, neuroworsening is the term used to represent neurological deterioration that can be a sign of progression of the brain injury in the initial phase, especially in the first 48 hours from admission. We must take into account that this concept, and its criteria, have generally been adopted for other neurocritical pathologies such as aneurysmal subarachnoid hemorrhage (aSAH), ischemic stroke, and intracerebral hemorrhage, among others. The main cause of neuroworsening is an increase in ICP.

Current concept of Neuroworsening

A prospective cohort of 481 TBI patients showed that neuroworsening was considerably more likely to have a more injury load in computed tomography (CT) scan, neurosurgical intervention, in-hospital mortality and an unfavorable outcome. This study concluded that early neuroworsening is an indicator of the severity of TBI and an independent predictive element of unfavorable results at 3 and 6 months⁵. In 1998, Morris et al. defined neuroworsening as one or more of the following criteria: decrease of ≥ 2 points in the Glasgow motor score; new appearance of loss of pupillary response or development of pupillary asymmetry ≥ 2 mm, and or worsening of neurological state or CT scan, sufficient to justify immediate intervention⁶. The consensus working group of the Seattle International Consensus Conference (SIBICC)⁷ adapted it, and this criterion was later shared by the TBI management consensus without ICP monitoring (CREVICE)⁸.

Neuroworsening
Severe worsening in clinical neurological status as:
-Spontaneous GCS motor reduction ≥ 1 point (compared to previous examination)
-New worsening in pupillary response
-New pupillary asymmetry or bilateral mydriasis
-New focal deficit
-Herniation syndrome or Cushing triad that requires immediate attention

Table 1.- Neuroworsening criteria SIBICC consensus.

These clinical criteria have not been substantially modified in 26 years. But is known that GCS evaluation presents up to 30% interobserver variability, with a difference of 2 points in 17%⁹, and even though the motor GCS is the most reliable, there continues to be variation, especially in the intermediate scores (GCS motor 5, 4, and 3). Additionally, the frequent absence of periodic registers of the score, the administration of medications as sedatives, and conditions of the patients themselves can mask changes in the neurological state or induce errors in its evaluation.

On the other hand, the second pillar of clinical assessment of patients at risk of neuroworsening, the pupillary assessment using a penlight to evaluate pupil reactivity and a measuring tape to evaluate pupil size¹⁰. Asymmetric pupils measuring >1 mm in difference are considered pathologically significant. Reliance on manual measurements of pupillary size for symmetry comparisons, is subjective and entirely dependent on the skill of the observer. Subjectivity of size measurements leads to inconsistencies in the medical record of patient's pupillary exam. Even more, pupils are often categorized and registered in medical records as "sluggish" or "nonreactive", however, this is an incomplete evaluation of pupillary function⁵.

But beyond the inaccuracy and/or inconsistency of the pillars of neuroworsening detection, the greatest concern about the current definition is the debatable precocity to detect the progress of secondary brain injury and patient worsening, because at this point it is very likely that the damage could be irreversible.

The paradigm shift moves then to anticipating clinical worsening (GCS and pupils) through the use of new tools that allow early detection of the brain injury before it manifests clinically¹¹. Adding the information provided by these systems will contribute greater certainty and precocity to the clinical examination, allowing us to try to avoid the progression of secondary brain injury and its harmful effects on prognosis.

Clinical tools for a better definition of neuroworsening

The current definition of neuroworsening needs to be reconsidered, incorporating not only clinical parameters, but also tomographic ones, as well as including the different systems that are available such as pupillometry, optic nerve sheath diameter, transcranial doppler (TCD) and biomarkers, among others, that allow an earlier recognition of this group of patients that evolve with a worsening of a non-devastating primary brain injury. Each of these non-invasive neuromonitoring methods are easily applicable since admission and some of them have the advantage of being independent of the observer and reproducible, making possible to have a reliable temporal profile in the first hours of evolution.

Pupillometry is an automatized analysis of pupillary reflex through infrared light stimuli, which eliminates the subjectivity inherent in the manual evaluation carried out by the human eye. This method provides detailed information about the phases of pupillary reflex, including pupillary diameter before and after stimulation, latency, contraction velocity, and percentage of contraction, among others. From this data, specific algorithms generate a global indicator known as the neuro pupillary index (NPi), whose value <3.0 can be indicative of elevated ICP¹².

Recently, the ORANGE study was published. This is a multicentric, prospective, and observational cohorts study carried out in Europe and North America, that enrolled patients in intensive care units (ICU) after TBI, aSAH, and intracranial hemorrhage. Pupillometry was performed every 4 hours for the days following

admission to compute NP_i. The study concluded that the NP_i has a clinical prognostic value which is statistically significant for the neurological result and mortality following acute brain injury. This study also identified novel NP_i pathological thresholds (<4) following acute brain injury that could assist clinicians in detecting brain damage and monitoring the response to therapeutic interventions¹³. The pupillometer is a portable easy to use equipment that can be used both by the medical and nursing teams in emergency departments and ICUs.

TCD has multiple utilities in monitoring neurocritical pathologies, among others, to evaluate the presence of increased ICP. For this purpose, parameters such as the pulsatility index (PI) and the diastolic flow velocity (DFV) are considered. Both have an adequate correlation with the ICP values. Studies in patients with mild and moderate TBI have demonstrated that PI values of > 1,2 and DFV < 20 - 25 cm/s on admission are associated with greater incidence of neuroworsening¹⁴. Bouzat showed that moderate TBI patients with abnormal PI and DVF performed worse in disability scales in comparison with those patients with normal values. In this large study it was shown that the TCD was feasibly done on admission to emergency rooms following a mild to moderate TBI¹⁵. The sensitivity and specificity of TCD to detect early neurological worsening were acceptable in this context.

Ultrasound measurement of the diameter of the optic nerve sheath diameter (ONSD) is a simple and reproducible technique that can be done in emergency rooms and ICUs and require a brief training period. Its association with an increase in ICP is widely documented in the literature, although the reference values reported varies between 5 and 6 mm according to different studies. The interobserver variability is found to be between 0.2 to 0.3mm^{16,17}. Yic et al. focused on evaluating ONSD as a predictor of intracranial hypertension in comparison with the invasive measurement of ICP founded that values under 5.7mm were associated with a very low probability of ICP above 20 mmHg¹⁸.

The most used tomographic evaluation scales for TBI patients, as Marshall 19 and Rotterdam20 mainly consider criteria such as space occupying lesions > 25 ml, midline shift > 5 mm, and basal cisterns state, given that these are associated with intracranial hypertension and a worse prognosis. However, we consider that a CT images reinterpretation is necessary to allow an earlier prediction of worsening. In 2007, Maas et al. demonstrated that the relationship between the degree of displacement from the midline and the result at 6 months was essentially linear²¹. Thus, any increase in the displacement from the midline > 1 mm could be considered significant. For this, it is crucial to establish consensus at the anatomical references, for avoiding measurement errors. We usually use an axial plane at the level of foramen of Monro and measure the lateral displacement of the septum pellucidum from the straight line drawn between the anterior and posterior attachments of the falx to the inner table of the skull.

Regarding the basal cisterns, Marshall and Rotterdam scales differ in their interpretations, with the former considering only two states (visible or absent), while the latter considers three (present, compressed, and absent). This must be considered since traumatic coma data bank studies have shown that the state of the basal cisterns is associated with worse outcomes if they are absent, compressed but visible or normal²² (Figure 1). Both parameters can be used in admission CT, but can also be analyzed comparatively during evolution.

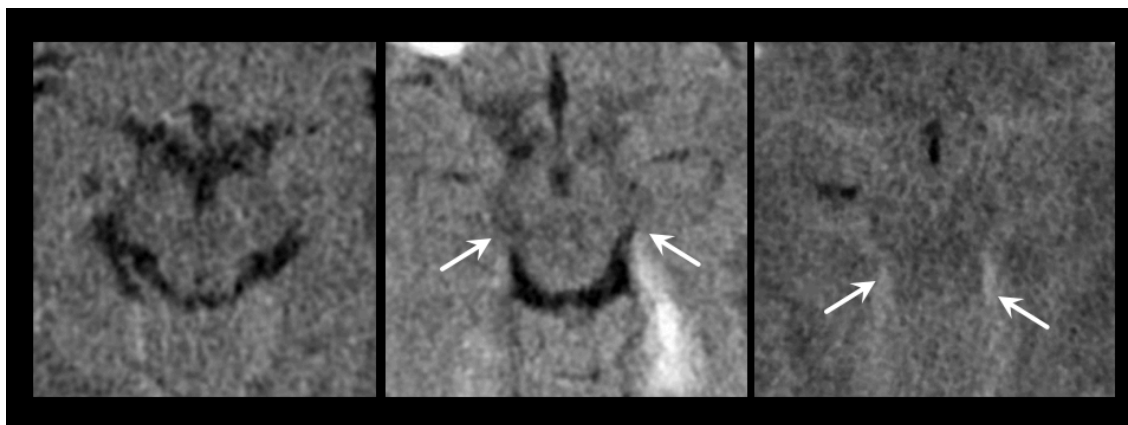


Figure 1. Peri mesencephalic basal cisterns in a) normal, b) compressed, but present, and c) obliterated. Note the variation in the angle of the interpeduncular cistern with progressive compression.

Brain contusions are the most complex intracranial lesions to evaluate for several reasons: 1) different presentations (hyperdense, hypodense, and mixed) 2) difficulty in volume measuring due to their irregular morphology and 3) because volume can increase in the first post trauma hours. Given this, it is reasonable to incorporate improvements in the imaging analysis, such as contusion volumetry that could be automatized or semi-automatized 23 or with perfusion CT, which permits a better estimation of the extension of these injuries compared to a simple brain CT, especially in the first hours (Figure 2). Therefore, considering the aforementioned in the criteria for neuroworsening, it would be possible to incorporate the increase in intraparenchymal lesions volume (more than 25 ml), the appearance of basal cisterns compression, or an increase in displacement from the midline in serialized CT.

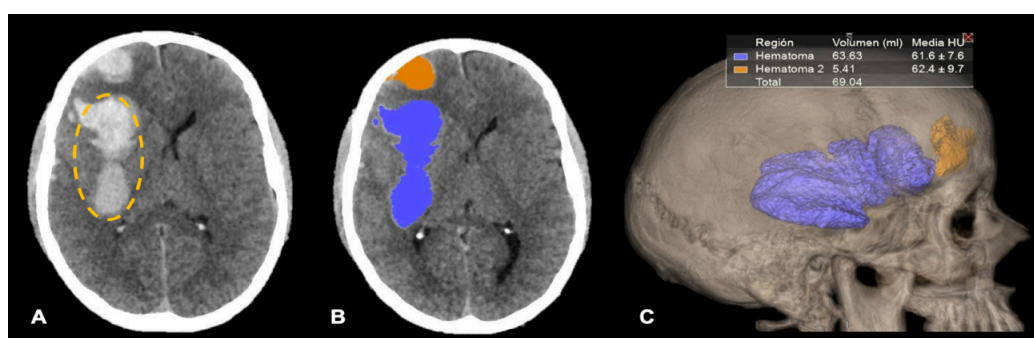


Figure 2. Analysis of the volume of a brain hematoma in a non-contrast CT. A) Irregular fronto-insular hematoma with heterogeneous density and satellite hemorrhage. Note the disagreement with the theoretical shape of the ellipse used for the manual estimation of volume. B) Semi-automatized postprocessing by segmentation of the primary hematoma densities and anterior satellite hemorrhage. C) Total volumetry of the segmented main hematoma plus satellite hemorrhage represented in 3D image with semi-transparent bone. (Analysis performed on Canon Vitrea® console)

Oertel et al.²⁴ showed that there are patients at high risk from the initial CT scan. A significant proportion of patients with moderate, severe, and even mild head injuries can exhibit a clinical-radiological

deteriorating evolution, up to 50% in the first post traumatic hours. Data based on severe and moderate patients collected by the European Brain Injury Consortium showed an evolution from a type I and type II diffuse injury to a mass lesion in 13% of cases ²⁵.

The advance in proteomics has permitted the study of a series of proteins that are identifiable and measurable following TBI. TBI biomarkers represent the different components of the neuro-glial-vascular unit. The most studied acute phase biomarkers are ubiquitin c-terminal hydrolase (UCHL-1), glial fibrillary acidic protein (GFAP), S100 Beta protein (S100B), and neurofilaments (NF), among others ^{26,27}. Their use would allow the serialized evaluation of patients, especially with moderate TBI, obtaining a temporal profile with a biomarkers panel, and the recognition of certain thresholds and trends that could be associated with unfavorable clinical evolution, before clinical neuroworsening occurs.

For example, a patient with an intermediate GCS (9-14), with an early CT showing traumatic temporal SAH will be differentiated from a similar patient with a biomarker profile of elevated UCHL-1, GFAP, S100B or that increases in the first 24 hours. This would make an earlier neuroworsening diagnosis before the GCS deterioration, pupillary reaction, or CT showing injury progression.

Finally, the non-invasive analysis of intracranial compliance, such as Brain4 care monitor developed in Brazil ²⁸ which through a sensor on the scalp detect cranial micro deformations making possible to acquire intracranial pressure waves. The relationship $P2/P1 > 1.2$, and time to peak (TTP) are associated with intracranial pressure values > 20 mmHg ²⁹. This is an easily installed, non-invasive equipment that allows real time intracranial compliance monitoring and probably predicts neuroworsening not only in patients with TBI.

Discussion

Including all these new non-invasive monitoring and CT scan reinterpretation to the classic neuroworsening definition would allow to be more aggressive and precise in the decision-making process in patients with an initial non-severe brain injury, in whom secondary injury progression will worsen prognosis if we don't take clinical decision timely.

CLINICAL	IMAGE (CT scan)	NMNI
Decrease in Glasgow motor ≥ 1 point	Increase MLS ≥ 1 mm	Pupillometry: NPi < 4.0 Difference NPi > 0.7
Decrease ≥ 2 points total Glasgow	Change in basal cisterns state considering 3 states	ONSD > 5.7 mm
New alteration of pupillary asymmetry.	Mass volume increase to more than 25 ml	TCD: PI $> 1,25$ DFV $< 20 - 25$ cm/s
New motor deficit	-----	Biomarkers: UCHL-1, GFAP, S100B levels, first 24 hours

Cushing Triad	-----	Brain4 Care: Relationship P2/P1 > 1.2 Altered TTP

Table 2. Different alternatives and thresholds that could be included in a new definition of Neuroworsening.

It is fundamental to continue studying the correlation of these new parameters with early neuroworsening probability to be able to establish which of them and in what combination would allow us to anticipate the appearance of neuroworsening. This aims to take more aggressive and earlier medical and neurosurgical actions in apparently mild or moderate cases before the secondary brain injury progresses and presents itself with clinical worsening.

The B-ICONIC consensus was recently published with recommendations for the use of noninvasive neuromonitoring for the management of intracranial hypertension in TBI patients, in the absence of invasive ICP monitoring. Among the noninvasive neuromonitoring systems and their criteria, several of those mentioned in this article are included, confirming that the use of these tools is feasible and that there is consensus among experts in the definition of thresholds³⁰.

In conclusion, neuroworsening is a very useful concept in everyday clinical practice in the evaluation and follow up of patients with acute neurological pathologies. It allows clinical detection of secondary injury progression. However, the current definition is obsolete and late because it only considers clinical parameters and for this reason must be updated. This update means incorporating parameters provided by the different non-invasive neuromonitoring systems currently available, in addition to the reinterpretation of CT scan. This new neuroworsening definition will allow us to detect before the clinical worsening those patients at risk of negative clinical evolution. It is essential to continue studying the most effective and efficient thresholds and combination of these criteria to validate a new definition of neuroworsening.

Abbreviations

The following abbreviations are used in this manuscript: aSAH: Aneurysmal Subarachnoid Hemorrhage; CBF: Cerebral Blood Flow; CREVICE: TBI Management Consensus Without ICP Monitoring; CT: Computed Tomography; DFV: Diastolic Flow Velocity; GCS: Glasgow Coma Scale; GFAP: Glial Fibrillary Acidic Protein; ICP: Intracranial Pressure; ICU: Intensive Care Unit; MLS: Midline Shift; NF: Neurofilaments; NP_i: Neurological Pupillary Index; ONSD: Optic Nerve Sheath Diameter; PI: Pulsatility Index; S100B: S100 Beta Protein; SIBICC: Seattle International Severe TBI Consensus Conference; TBI: Traumatic Brain Injury; TCD: Transcranial Doppler; TTP: Time to Peak; UCHL-1: Ubiquitin C-Terminal Hydrolase

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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Author Contributions

All authors reviewed and approved the final version of the manuscript for publication.

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