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REVIEW

Usefulness of biomarkers in the prognosis of severe head injuries☆

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Abstract Severe head injuries have a great socioeconomic and public health impact. Despite progress in diagnosis and treatment, no sufficiently reliable predictive models have been established for developing clinical trials and promoting effective therapeutic strategies capable of improving the prognosis. In the last decades, several brain damage biomarkers have been studied as potential diagnostic and prognostic tools in traumatic brain injury. However, all of them have limitations that preclude their universalized application. The properties of the known biomarkers – both those traditionally shown to correlate with severity and prognosis, and those recently announced as promising options – should be analyzed. New studies are needed to define their properties, both isolatedly and in combined use.

PALABRAS CLAVE
Biomarcadores;
Suero;
Lesión cerebral;
Trauma craneal

Utilidad de los biomarcadores en el pronóstico del traumatismo craneoencefálico grave

Resumen El traumatismo craneoencefálico grave es una entidad clínica con gran repercusión en términos socioeconómicos y de salud pública. Pese a los avances obtenidos en el ámbito del diagnóstico y tratamiento, no se han consolidado modelos predictivos suficientemente fiables que permitan desarrollar ensayos clínicos e impulsen estrategias terapéuticas efectivas que mejoren su pronóstico. En este sentido, durante las últimas décadas se han estudiado diversos biomarcadores de lesión cerebral con el fin de establecerlos como herramientas diagnósticas y pronósticas de la lesión traumática cerebral. Sin embargo, todos ellos presentan alguna

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limitación que impide su aplicación universalizada. Es necesario analizar las propiedades de los biomarcadores conocidos hasta la fecha, tanto los que tradicionalmente han demostrado correlación con la gravedad y pronóstico como aquellos que recientemente se anuncian prometedores. Para ello, convendría diseñar nuevos estudios que definan sus propiedades de forma aislada y que diluciden el papel de su uso combinado.

Introduction

Severe traumatic brain injury (TBI) remains an important public health problem, due to the large percentage of unfavorable outcomes involved (death and disabling sequelae) and the great associated treatment costs, compensations, disability pensions and years of work lost in affected individuals fundamentally belonging to the active population.[1,2]

Although TBI is an extremely complex condition,[3] there have been many advances in recent years in relation to the diagnosis, monitoring and treatment of the affected patients.[4,5] However, given the heterogeneity of severe TBI, there are still important shortcomings in our knowledge of the physiopathology of TBI and the development of reliable predictive models capable of offering an early orientation as to the patient outcome, with the purpose of improving the diagnostic and therapeutic strategies on an individualized basis. Likewise, we need valid predictive models in severe TBI in order to define efficacy endpoints in the evaluation of new drugs or treatment strategies–since the usual primary endpoints (death and disability) are widely recognized as being inadequate and could explain the discouraging results obtained with certain promising drugs.[6]

Considering the above, and in the same way as in other disease processes, such as ischemic heart disease, research is carried out to identify biological markers that could offer a more precise indication of the extent and severity of TBI, independently of the prior biological substrate and of other circumstances that accompany severe TBI–thereby contributing to homogeneously define different patient categories. Such markers would not only facilitate individualization of the intensity and timing of patient management but could also contribute to the development of strategies for preventing the consolidation of injury and enhancing neuroprotective effects capable of avoiding or minimizing secondary damage.

The present study offers a critical review of the main brain damage biomarkers studied till date.

Brain damage biomarkers

A biomarker is defined as a quantifiable biological indicator specific of a given physiological or pathological condition. Vos concluded that the use of biomarkers contributes to improve knowledge of the physiopathology of brain damage, affording essential complementary information for the diagnosis and for predicting the outcome of these patients.[7] However, the definition of a brain damage marker must establish differentiations with respect to other alterations, since the central nervous system (CNS) is very complex and can present a range of different lesions, which in turn can affect different target cells with variable degrees of severity. Furthermore, the existence of the blood–brain barrier (BBB) conditions the structural characteristics of these biomarkers, which must be able to cross the mentioned barrier in order to reach the bloodstream.

Over 20 years ago, the ideal TBI biomarker was defined as an indicator with high specificity and sensitivity for the brain tissue, with release occurring only after irreversible brain tissue damage, and with rapid appearance in both cerebrospinal fluid (CSF) and blood after damage. The marker moreover must reflect the extent and severity of the damage, following a known time course. In turn, the marker variations between age and gender groups must be minimal. On the other hand, the tools for analysis and immediate detection of the marker must be available and reproducible. Lastly, and most importantly, determination of the marker must be clinically relevant. It should be underscored that biomarkers are dynamic elements that experience changes in response to different inflammatory states, tissue necrosis phenomena and damage caused by oxidative stress.[3] Serial measurements rather than isolated or point determinations are thus required in order for the collected data to be of practical significance.

On the other hand, there is some controversy regarding the type of biological fluid that should be analyzed. Direct sampling of the damaged brain tissue or of brain tissue at risk is not plausible, though it would be the only source of biomarkers affording unequivocal and direct information on the changes occurring after severe TBI. The rest of the determinations are conditioned to the mechanism underlying biomarker release (passive or active), the crossing of membranes and barriers (cell membrane, BBB, etc.), and dilution phenomena once the systemic compartment has been reached.[8] In this regard, techniques such as microdialysis can be used to determine metabolites and biomarkers corresponding to the cerebral interstitial compartment or space.[9] On the other hand, the CSF compartment is located closer to the damage site; measurements at this level are therefore not conditioned by integrity of the BBB. However, the collection of CSF samples involves problems in terms of accessibility and availability, with the need for invasive maneuvers which are often contraindicated in patients with severe TBI. As a result, most biomarkers are studied in peripheral blood, since the technique in this case is simple,