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Invited review

Traumatic brain injury: Changing concepts and approaches

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ABSTRACT

Traumatic brain injury (TBI) represents a huge global medical and public health problem across all ages and in all populations. In this review, we discussed the changing concepts and approaches. Globally, the incidence is increasing and in high income countries epidemiologic patterns are changing with consequences for prevention campaigns. TBI should not be viewed as an event, but as a progressive and chronic disease with lifetime consequences. In the clinical field, precision approaches to treatment are being developed, which require more accurate disease phenotyping. Recent advances in genomics, neuroimaging and biomarker development offer great opportunities to develop improved phenotyping and better disease characterization. In clinical research, randomized controlled clinical trials are being complemented by large data collections in broad TBI populations in comparative effectiveness designs. Global collaborations are being developed among funding agencies, research organizations and researchers. Only by combining efforts and collaboration will we be able to advance the field by providing long-needed evidence to support practice recommendations and to improve treatment.

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Introduction

Traumatic brain injury (TBI) represents a huge medical and public health problem across all ages and in all populations.¹ It is considered as “the most complex disease in the most complex organ”, characterized by great heterogeneity in terms of etiology, mechanism, pathology, severity and treatment with widely varying outcomes. Falls and high velocity road traffic incidents cause different types of injury. TBI may consist of diffuse damage, contusion brain damage or intracerebral hematoma. The primary brain damage may be worsened by intrinsic pathophysiologic mechanisms and by systemic insults such as hypoxia and hypotension. The clinical severity ranges from minor to virtually unsurvivable. Large differences in outcome have been reported between centers with an up to 6-fold higher risk in poorer versus better centers after adjustment for chance effects and case mix.² We have also recognized that TBI should not be considered as an acute event but as a trigger of progressive injury which may occur over hours, days, weeks, months and even years.³ Whilst basic

research has increased our knowledge of the mechanisms involved, improvements of clinical management have not been kept pace. Although the implementation of guidelines for the treatment of TBI have improved standards of clinical care, they may have resulted in general approaches to treatment, without giving due recognition to the specific needs of individuals. Unidimensional and relatively insensitive approaches to the characterization of disease severity and outcome have contributed to a general lack of appropriate targeting of therapy. Much clinical research in TBI has focused on reductionistic approaches to target isolated disease mechanisms in clinical trials testing the efficacy of specific neuroprotective agents. As in clinical practice, failure to recognize the heterogeneity inherent to TBI has likely been a major factor contributing to the very high percentage of trials in TBI that failed to show benefit.⁴

We are currently witnessing major shifts in the direction of clinical research and practice approaches. Global collaborations are being established to improve the care for TBI patients. Indeed, TBI is a global disease that warrants a global approach. In this review we aimed to highlight these collaborative efforts and to discuss paradigm shifts in epidemiology, clinical practice and research.

Epidemiology

The incidence of TBI worldwide is increasing, mainly in middle income and low income countries due to the increased use of motor

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vehicles. WHO has estimated that by 2020, road traffic accidents will rank the third place as a global cause of death and disability. Vulnerable road users (pedestrians, cyclists, etc.) are particularly at risk. In high income countries improved traffic safety regulations have led to a decline in traffic-related TBI.⁵ The overall incidence of TBI in Europe is not clearly decreasing as more TBI is being reported from falls in elderly patients. In a systematic review, Tagliaferri et al⁶ calculated an overall incidence of 235/100 000 hospital admissions for TBI, which was in strong contrast to the reported incidence of 50/100 000 described in China.⁷ Globally great variations exist in the reported incidences.⁴ This variation is mainly due to differences in case ascertainment and definitions for TBI. Reliable epidemiological data should be considered essential to inform health care policy-maker and to target prevention campaigns appropriately. Standardized epidemiologic monitoring has been implemented in the US by the Centers for Disease Control and Prevention (CDC) but such monitoring is deficient in many parts of the world, including Europe. The development of high quality epidemiologic monitoring for reliable estimation of incidence, prevalence and outcome of TBI should become a global priority.

TBI: a progressive and chronic disease

TBI is no longer considered as an event, following which recovery may or may not occur. It is recognized that it is a progressive disease in which intrinsic pathophysiologic processes and systemic second insults (e.g. hypoxia and hypotension) aggravate the primary damage. For a long time, diffuse axonal injury was considered to be resulted from mechanical shearing of axons. However, work by Povlishock et al⁸ clearly demonstrated that axonal damage may be secondary to metabolic changes. This finding is extremely relevant as it opens a window for potential therapeutic interventions. Brain contusions are the most common type of structural damage that may be visualized on CT scanning. Expanding brain contusions may cause mass effect, raised intracranial pressure and brain herniation. Equally relevant is the toxic effect of brain contusions as demonstrated by experimental work in Japan.^{9,10} In an experimental model of TBI, bilateral brain contusions were induced. On one side, the contusion was excised and replaced by gelatin; in the later histologic analysis significantly more edema and mass effect were seen on the side of the intact contusion. Following this observation, renewed interest has arisen in early resections of contusions with a main intent to minimize toxic effects which could lead to further deterioration. A recent clinical trial on early surgery for traumatic contusions has however unfortunately been halted because of slow recruitment; in the analysis of the results, a strong tendency towards decreased mortality and more favorable outcome was reported in the treatment group undergoing early surgery.¹¹ The early termination of this trial has prohibited definitive conclusions which could reliably direct future treatment protocols. As a consequence, large variations between countries and centers will remain in the indications for surgical treatment of brain contusions.

TBI is not only a progressive disease in the early phase, but may also evolve into a chronic disease. Dementia occurs more frequently following TBI compared with the people without TBI and the risk appears to be dependent on the severity of the initial TBI.¹² Deposition of amyloid and tau, as well as auto-immune responses, has been postulated as the possible cause of these chronic effects. Whilst in the past protein deposits in the brain could only be detected by post-mortem examination, recent advances in PET scanning permit *in vivo* visualization.¹³ Such approaches further hold great potential for *in vivo* monitoring of the risk incurred from repetitive injuries to which sporters are especially prone. Particularly in the US, much attention has been focused on the syndrome

of chronic traumatic encephalopathy reported on patho-anatomic analysis of professional and amateur high risk sports in athletes dying from other causes.^{14,15} *In vivo* imaging is required to determine the clinical relevance.

Precision approach to treatment

Evidence-based medical approaches and the development of guidelines for multiple aspects of care for TBI patients have substantially improved the standards of care, but have also led to the uncritical adoption of standardized approaches aimed at an average patient. The “average” patient however does not exist and particularly in TBI there are many phenotypes. More accurate disease phenotyping is now facilitated by recent advances in genomics, neuroimaging and biomarker development. Recent evidence suggests that up to one third of patients with mild TBI (GCS 13–15) and a normal CT scan upon presentation will demonstrate structural abnormalities on later MR imaging.¹⁶ Specific MR sequences including susceptibility weighted imaging (SWI) and diffusions weighted imaging (DWI) are more sensitive for detecting smaller lesions such as microhemorrhages and traumatic axonal injury.¹⁷ Diffusion tensor imaging (DTI) and diffusion kurtosis imaging (DKI) hold potential for visualizing more complex microstructural changes in TBI, also when traditional MR sequences appear normal.¹⁸ The diffusion tensor characterizes the magnitude of water diffusion (ADC and mean diffusivity), its directional non-uniformity (fractional anisotropy, radial and axial diffusivity) and its orientation (the tensor eigenvectors). Besides enhanced possibilities for detecting structural damage, DTI with fractional anisotropy (FA) mapping or tractographic analysis can demonstrate white matter loss following TBI and structural disconnections that are likely the root cause of disability. Longitudinal imaging over time will further allow tracking of the progressive nature of TBI, particularly in patients who develop increasing symptoms over time. Despite the large potential of DTI and DKI imaging in TBI, we should recognize that FA values only reflect orientation dependant aspects of the microstructure of tissues and tractography only yields a virtual reconstruction. The exact biological and microstructural underpinning of DTI is not yet fully understood and interpretation is complex.¹⁹ Nevertheless, it is clear that MR offers great advantages for improved detection of structural damage offering better pathophysiological characterization from ictus to outcome.^{20,21}

Biochemical biomarkers are considered with a broad potential in TBI. They can differentiate between neuronal and glial damage,^{22,23} and provide insight into inflammatory neurodegenerative and regenerative processes. The field is rapidly evolving but produces relatively limited studies, which prohibits drawing definitive conclusions for clinical guidance. Three main directions on clinical research on biomarkers exist as follows: (1) aid in diagnosis and characterization of TBI; (2) tracking disease processes; (3) establishing prognosis.

In the search for specific biomarkers, interest was focused on glial fibrillary acidic protein (GFAP) and its breakdown product (GFAP-BDPs), myelin basic protein (MBP), ubiquitin c-terminal hydrolase (UCH-L1) on analysis of the TRACK-TBI data in the US. Okonkwo et al²⁴ discriminated the mild TBI patients with and without structural abnormalities on CT examinations and found a correlation between initial biomarker levels and clinical outcome, suggesting that biomarkers may facilitate identification of individuals at most risk for developing poor outcome and more severe complications. Various biomarkers have been considered for a molecular taxonomy of TBI including metabolomics. Metabolomics in TBI concerns the assessments of metabolic changes in the brain after trauma.²⁵ Work in this direction is ongoing in the context of an

EU-funded project TBIcare (www.tbicare.eu). Despite a large number of biomarker studies in TBI, we should recognize that biomarker development in TBI is still in its infancy and that translation into clinical diagnosis with wide-spread adoption remains a goal not accomplished yet. Specific challenges include not only the heterogeneous characteristics of TBI patients, but also the incomplete understanding of the underlying biology of the biomarkers and how they are transported from brain to blood as well as influences of sample handling and processing. Collaborations between basic and clinical researchers with improved standardization across analytical platforms will facilitate the translation of promise into practice.

However, it is not only advanced developments in the fields of neuroimaging and biomarkers that permit opportunities for better characterization of disease processes and understanding the pathophysiology in individual patients, but also the interpretation of more traditional monitoring. The recent BEST TRIP trial investigating effects of ICP monitoring in a clinical trial in South-America failed to show additional benefit of this implementation of therapy based upon ICP monitoring versus that based upon clinical evaluation and repeated CT scanning.²⁶ Unfortunately, these “negative” results have led to unintended adverse effects that some clinicians now withhold ICP monitoring and some health care authorities even retract reimbursements. We considered such reactions inappropriate and an example of evidence misinterpretation. Conceptually, the major asset of ICP monitoring is that it may provide an early warning for developing intracranial problems (and as such trigger additional CT scans) and a better understanding of what is going on within the brain of a specific patient. Such improved disease characterization is the basis for precision medicine approaches, a concept recently advocated by the National Academy of Science in the US (National Research Council 2011). We anticipated that such better understanding will facilitate the implementation of more targeted guidelines based on standardized approaches. Large sample size is further required to confirm them.

Global collaboration

Perhaps the biggest change in the field of TBI is a general move towards data sharing and establishment of international collaborations. In 2011, three major funding agencies (European Commission, US National Institute of Neurological Disorders and Stroke, and Canadian Institute of Health Research and its national funding partners) joined forces in research to improve the treatment of TBI by establishing InTBIR (International Initiative for Traumatic Brain Injury Research: <http://intbir.nih.gov/>).²⁷ InTBIR is an open community and welcomes the participation of other agencies and funding bodies. This collaboration of funding agencies is unique. Within the framework of InTBIR, various large scale collaborative projects have been instituted, including CENTER-TBI in Europe, TRACK-TBI in the US and ADAPT trial focused on severe pediatric TBI also in the US. Importantly, the investigators of these three major studies will harmonize efforts and work together. The three studies each have a slightly different focus but all are based on observational data collection in broad TBI populations including nearly 10 000 patients together. TRACK- and ADAPT-TBI have a main focus on improved characterization whilst CENTER-TBI additionally exploits the differences between countries, centers and participants in terms of organization of care, processes, management and outcome in a comparative effectiveness design to identify best practices. The concepts of these studies have attracted wide attention and are now evolving into global efforts. Linked projects are being set up in China, India and Australia. In this year, recruitment for a large scale

observational study in China modeled on CENTER-TBI concept is expected to start in 40 centers, based on the experience of Chinese head trauma data bank under the coordination by Jiang et al.²⁸ Importantly, the projects will undertake data collection according to commonly agreed standards and all investigators have agreed to facilitate individual patient data analysis across studies. The recognition that TBI is a global problem that requires a global approach is now being translated into research practice. Small and highly focused reductionistic approaches are being completed by large data collections in broad TBI populations in order to be applied in the real clinical practice. Only by combining efforts and collaboration in the analysis of results, will we be able to advance the field by providing long needed evidence to support practice recommendations and to improve treatment.

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