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IMPROVING THE DIAGNOSIS AND TREATMENT OF SECONDARY DIFFUSE BRAIN INJURY IN CHILDREN WITH ACUTE COMBINED TRAUMATIC BRAIN INJURIES

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Abstract

Background: Acute combined traumatic brain injury (TBI) in children represents a complex clinical condition characterized by the interaction of primary intracranial damage, extracranial traumatic injuries, and evolving secondary cerebral insults. Secondary diffuse brain injury may develop through interconnected mechanisms involving cerebral hypoxia, ischemia, impaired autoregulation, neuroinflammation, excitotoxicity, mitochondrial dysfunction, and diffuse cerebral edema. The developing brain exhibits age-dependent physiological characteristics that complicate neurological assessment, diagnostic interpretation, and intensive care management.Objective: To critically examine the mechanisms underlying secondary diffuse brain injury in pediatric patients with acute combined TBI and to develop an evidence-informed framework for improving early diagnosis, neurological monitoring, and therapeutic decision-making.Methods: A narrative synthesis of established pediatric severe TBI guidelines, neurocritical care principles, and relevant research on traumatic axonal injury, neuroimaging, cerebral perfusion, secondary injury mechanisms, and multimodal monitoring was undertaken. The analysis focused on clinically relevant diagnostic strategies, prevention of secondary insults, and individualized management in pediatric patients with associated extracranial trauma.Results: The available evidence supports an integrated diagnostic strategy combining serial neurological examination, urgent computed tomography when indicated, selective magnetic resonance imaging, physiological monitoring, and assessment of systemic injury. Magnetic resonance imaging, particularly susceptibility-sensitive and diffusion-weighted sequences, may reveal traumatic axonal abnormalities not apparent on conventional computed tomography. Prevention of hypoxemia, hypotension, intracranial hypertension, seizures, and systemic metabolic disturbances remains central to neuroprotective management. Advanced monitoring and selected biomarkers may provide complementary information, although their clinical utility and outcome benefits require further validation in pediatric populations.Conclusion: Improving the management of secondary diffuse brain injury in children requires early identification of evolving cerebral and systemic insults, age-appropriate neurocritical care, and multidisciplinary coordination. Diagnostic technologies should be integrated with physiological assessment rather than used as substitutes for clinical judgment. Further prospective research is necessary to establish validated pediatric risk-stratification models and

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determine which monitoring-guided interventions improve long-term neurological outcomes.

Keywords: pediatric traumatic brain injury; combined trauma; secondary brain injury; diffuse axonal injury; cerebral edema; neurocritical care; intracranial pressure; magnetic resonance imaging; neuroprotection.

Introduction

Traumatic brain injury remains a major cause of mortality and long-term neurological disability among children and adolescents. Unlike isolated neurological injury, acute combined traumatic brain injury frequently involves simultaneous damage to the brain and other anatomical regions, including the thorax, abdomen, extremities, and spinal structures. Such injuries produce complex interactions between intracranial pathology and systemic physiological disturbances, creating conditions in which secondary brain injury may develop rapidly despite initial stabilization. The resulting neurological deterioration may reflect not only the severity of the primary traumatic insult but also the cumulative effects of hypoxemia, systemic hypotension, inflammatory activation, coagulation abnormalities, and disturbances in cerebral perfusion [1,2].

The distinction between primary and secondary brain injury is fundamental to understanding pediatric neurotrauma. Primary injury occurs at the moment of mechanical impact and includes focal contusions, intracranial hemorrhage, vascular damage, and traumatic axonal disruption. Secondary injury develops subsequently through a dynamic sequence of molecular, cellular, vascular, and systemic events. These processes may extend beyond the original injury site and contribute to diffuse neuronal dysfunction, cerebral edema, impaired oxygen delivery, and progressive neurological deterioration [3].

The term secondary diffuse brain injury requires careful interpretation. Diffuse traumatic axonal injury primarily results from mechanical rotational and acceleration–deceleration forces at the time of trauma, whereas secondary diffuse injury refers more broadly to evolving widespread cerebral dysfunction caused by post-traumatic physiological and biochemical processes. Although these conditions may coexist and interact, they should not be considered interchangeable. Differentiating primary traumatic axonal abnormalities from secondary hypoxic–ischemic, edematous, or inflammatory changes is particularly important when interpreting neuroimaging findings and planning treatment.

The pediatric brain differs from the adult brain in several clinically significant respects. Age-related variations in cerebral blood flow, metabolic requirements, skull and intracranial compliance, vascular autoregulation, and neuronal maturation influence the response to traumatic injury. Moreover, the clinical manifestations of neurological deterioration may be difficult to recognize in preverbal children or in patients requiring sedation, analgesia, and mechanical ventilation. These characteristics emphasize the need for age-appropriate diagnostic criteria and individualized monitoring strategies [1,4].

The development of pediatric neurocritical care has improved the understanding of secondary cerebral insults. Nevertheless, considerable uncertainty remains regarding the

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optimal integration of conventional neuroimaging, advanced magnetic resonance techniques, invasive physiological monitoring, circulating biomarkers, and targeted therapeutic interventions. This uncertainty is especially relevant in children with combined injuries, where resuscitation priorities must balance the requirements of cerebral protection against the treatment of extracranial hemorrhage, respiratory dysfunction, and other life-threatening conditions.

The objective of this article is to analyze the principal mechanisms of secondary diffuse brain injury in children with acute combined traumatic brain injuries and to formulate an integrated diagnostic and therapeutic approach based on contemporary neurocritical care principles.

Materials and Methods

This article was developed as a narrative review and conceptual synthesis of established evidence concerning pediatric traumatic brain injury and secondary cerebral damage. The methodological framework was based on critical examination of pediatric severe TBI management guidelines, clinical and experimental studies of secondary injury mechanisms, neuroimaging literature, and research addressing cerebral physiological monitoring and neurological outcomes.Particular attention was directed toward the recommendations of the Brain Trauma Foundation for the management of pediatric severe traumatic brain injury, together with relevant studies describing traumatic axonal injury, post-traumatic cerebral edema, neuroinflammatory mechanisms, and systemic contributors to secondary neurological deterioration [1–6].The analysis was structured around the relationship between pathophysiological mechanisms, diagnostic approaches, therapeutic interventions, and clinical outcomes. Diagnostic modalities were assessed in terms of their potential contribution to the identification of intracranial lesions, diffuse axonal abnormalities, cerebral hypoperfusion, intracranial hypertension, and evolving neurological dysfunction.

Therapeutic approaches were considered according to their physiological rationale, established guideline recommendations, and limitations of the available pediatric evidence. Particular emphasis was placed on avoiding extrapolation from adult populations when pediatric-specific data are insufficient.

No original patient cohort was enrolled, no intervention was performed, and no new clinical outcome data were generated. Accordingly, the findings presented below represent an evidence-informed synthesis and proposed clinical framework rather than the results of an experimental or observational clinical investigation.

Results

Secondary diffuse brain injury develops through interacting biochemical, vascular, inflammatory, and metabolic pathways. Following the primary traumatic event, neuronal membrane disruption and altered ionic homeostasis may initiate excessive excitatory neurotransmitter release, calcium influx, mitochondrial dysfunction, and increased production of reactive oxygen species. These events can impair cellular energy metabolism and contribute to progressive neuronal and glial injury [3,5].Mitochondrial dysfunction plays a central role in the secondary injury cascade. Impaired oxidative phosphorylation

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reduces cellular energy availability, while disturbances in calcium regulation and oxidative stress further compromise neuronal viability. The resulting mismatch between metabolic requirements and energy production may contribute to cellular swelling, disrupted neurotransmission, and delayed neuronal death.Neuroinflammation constitutes another important component of secondary cerebral injury. Activation of microglia and astrocytes, recruitment of circulating inflammatory cells, and release of inflammatory mediators may contribute to blood–brain barrier dysfunction and altered vascular permeability. Although inflammatory responses also participate in tissue repair, excessive or prolonged activation may aggravate cerebral edema and secondary neuronal injury [5].Cerebral autoregulatory impairment further increases vulnerability to secondary insults. Under normal physiological conditions, cerebral blood vessels respond to changes in systemic arterial pressure to maintain relatively stable cerebral blood flow. Following severe TBI, autoregulatory mechanisms may become impaired, making cerebral perfusion more dependent on systemic hemodynamics. Consequently, hypotension, hypoxemia, or increased intracranial pressure may reduce oxygen delivery and promote secondary ischemic injury [1,2].In children with combined trauma, these mechanisms may be intensified by extracranial injuries. Thoracic trauma can impair pulmonary gas exchange, hemorrhage can compromise systemic perfusion, and severe inflammatory responses may alter microvascular function. Therefore, the severity of secondary cerebral damage cannot be evaluated independently of the patient's systemic physiological condition.Early neurological assessment remains essential in children with acute combined TBI. The Glasgow Coma Scale, including age-appropriate pediatric adaptations, provides a structured method for evaluating consciousness, although its interpretation may be affected by sedation, intubation, seizures, intoxication, and associated injuries.

Serial neurological examinations are generally more informative than an isolated assessment because secondary deterioration may develop after the initial injury. Changes in consciousness, pupillary responses, motor function, and seizure activity may indicate evolving intracranial pathology or systemic physiological compromise.Computed tomography (CT) is the principal emergency imaging modality for identifying acute intracranial hemorrhage, mass lesions, skull fractures, and other structural abnormalities requiring urgent intervention. Its advantages include rapid acquisition and broad availability. However, conventional CT may underestimate the extent of nonhemorrhagic traumatic axonal injury and other microscopic abnormalities.Magnetic resonance imaging (MRI) provides additional information when the patient's condition permits safe examination. Diffusion-weighted imaging may reveal abnormalities associated with altered water diffusion, while susceptibility-weighted imaging and related sequences are sensitive to small hemorrhagic lesions. These techniques can improve the detection and characterization of traumatic axonal injury, particularly in structures such as the corpus callosum and brainstem [6,7].Nevertheless, MRI abnormalities do not independently establish the timing or precise mechanism of injury. Diffusion restriction, for example, may occur in several pathological conditions, including traumatic, ischemic, and seizure-related processes. Interpretation therefore requires integration with clinical history, physiological observations, conventional imaging, and the temporal course of neurological findings.Advanced MRI techniques, including diffusion tensor imaging, may provide

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research-level information about white matter microstructure. However, variability in acquisition protocols, developmental changes in the pediatric brain, and limited individual-level diagnostic thresholds restrict their routine use as definitive clinical decision-making tools.

Physiological monitoring is particularly important in children with severe TBI because neurological examination may be limited by sedation, paralysis, or critical illness. Monitoring of oxygenation, ventilation, systemic blood pressure, temperature, electrolytes, and glucose provides information necessary for preventing systemic contributors to secondary brain injury.Intracranial pressure monitoring may be considered in severe pediatric TBI according to established guidelines and individual clinical circumstances. The Brain Trauma Foundation's pediatric guidelines recommend treatment of intracranial pressure above 20 mmHg and suggest maintaining cerebral perfusion pressure at a minimum of 40 mmHg, with consideration of values up to 50 mmHg in infants and younger children and potentially higher targets in adolescents [1]. These recommendations should be interpreted in the context of age, injury characteristics, and overall physiological status.Intracranial pressure and cerebral perfusion pressure represent important but incomplete measures of cerebral physiology. A patient may exhibit impaired regional oxygenation or altered cerebral metabolism despite apparently acceptable global pressure values. Accordingly, multimodal monitoring approaches have been investigated to provide additional information regarding cerebral oxygen delivery and metabolic function.

Brain tissue oxygen monitoring, transcranial Doppler ultrasonography, and cerebral microdialysis may offer complementary physiological information in selected settings. However, the evidence supporting routine use of these technologies in pediatric patients remains limited, and their application should depend on institutional expertise, clinical indications, and available resources.

The principal therapeutic objective in secondary diffuse brain injury is to prevent or minimize potentially reversible physiological insults while supporting cerebral perfusion and systemic homeostasis.Early stabilization of airway, breathing, and circulation is fundamental. Hypoxemia should be corrected promptly, and systemic hypotension should be avoided because both are associated with secondary cerebral injury. In children with combined trauma, hemodynamic management must also address extracranial bleeding and other sources of circulatory instability.Ventilation should aim to maintain appropriate oxygenation and carbon dioxide levels. Routine prophylactic severe hyperventilation is not recommended because excessive reduction of arterial carbon dioxide can produce cerebral vasoconstriction and potentially worsen ischemia. Temporary controlled hyperventilation may be considered in selected emergency circumstances, such as impending cerebral herniation, while definitive treatment is organized [1].Hyperosmolar therapy is an established component of intracranial hypertension management. The pediatric severe TBI guidelines provide recommendations for hypertonic saline in selected patients with elevated intracranial pressure, including specific concentration- and weight-based regimens. Such treatment requires close monitoring of serum sodium, renal function, hemodynamic status, and potential complications [1]. The selection of treatment should follow pediatric neurocritical care protocols rather than an undifferentiated approach to all patients with

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diffuse injury.Seizure prevention and management represent additional components of neurological protection. Early post-traumatic seizures may increase cerebral metabolic demands and contribute to physiological instability. Guideline-supported antiseizure prophylaxis may be considered in severe pediatric TBI to reduce early post-traumatic seizures, although prophylaxis has not been shown to prevent late post-traumatic epilepsy [1].Temperature management also requires careful attention. Fever may increase cerebral metabolic demand and worsen physiological stress. Controlled temperature management and avoidance of hyperthermia are therefore important supportive measures. Moderate hypothermia may be considered in specific circumstances under specialist protocols, but it should not be applied indiscriminately as a universal treatment for diffuse cerebral injury.Sedation and analgesia are necessary for comfort, mechanical ventilation, and control of physiological stress in selected patients. However, excessive sedation can obscure neurological examination and complicate assessment of evolving cerebral injury. Management should balance the requirements of intracranial pressure control, systemic stability, and neurological reassessment.Based on the reviewed evidence, an integrated framework for children with acute combined TBI can be conceptualized around three interdependent clinical domains: early identification of primary intracranial pathology, continuous surveillance for secondary cerebral insults, and individualized intervention directed at modifiable physiological abnormalities.

Discussion

The management of secondary diffuse brain injury in children with acute combined TBI requires a comprehensive understanding of the interaction between primary mechanical injury and subsequent physiological deterioration. Although modern neuroimaging and neurocritical care technologies have expanded diagnostic possibilities, prevention of secondary systemic and cerebral insults remains one of the most important aspects of clinical management.

A central challenge is the heterogeneity of pediatric TBI. Children differ substantially in developmental stage, cerebral physiology, injury mechanism, associated extracranial trauma, and capacity for neurological recovery. These differences complicate the establishment of universal diagnostic thresholds and treatment targets. Clinical approaches developed for adults cannot always be directly applied to pediatric populations without considering developmental physiology and the strength of pediatric-specific evidence.

The role of advanced neuroimaging deserves particular attention. MRI may identify traumatic axonal abnormalities and additional parenchymal lesions that are poorly visualized on CT. Nevertheless, increased lesion detection does not necessarily establish that MRI-guided intervention improves neurological outcomes. Imaging should therefore be used to complement clinical and physiological assessment, with attention to transport safety and the stability of critically injured children.

The relationship between intracranial pressure, cerebral perfusion, and secondary injury also remains complex. Intracranial hypertension is an important therapeutic target, but diffuse cerebral dysfunction may occur without sustained pressure elevation. Similarly, apparently adequate cerebral perfusion pressure does not guarantee normal regional

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microcirculation or tissue oxygenation. These limitations support continued investigation of multimodal monitoring approaches, although their benefits must be demonstrated through appropriately designed pediatric studies.

Systemic injury represents an additional source of clinical complexity. Children with thoracic trauma, hemorrhage, or other extracranial injuries may experience secondary neurological deterioration through impaired oxygen delivery and systemic inflammatory mechanisms. Management strategies must therefore integrate trauma surgery, pediatric intensive care, neurosurgery, radiology, and rehabilitation rather than focusing exclusively on intracranial pathology.

The development of predictive models may provide future opportunities for improving early risk stratification. Candidate predictors include age, injury mechanism, neurological examination findings, systemic physiological abnormalities, neuroimaging characteristics, and intracranial pressure trends. However, a clinically useful model must undergo transparent development, internal validation, and preferably external validation before implementation. The combination of multiple variables does not automatically improve prediction, and model complexity should be balanced against feasibility and clinical interpretability.

Circulating biomarkers, including glial fibrillary acidic protein and ubiquitin C-terminal hydrolase L1, have attracted increasing interest in TBI research. Their potential value lies in complementing clinical and imaging assessment, but interpretation in children is complicated by age-related biological variation, injury timing, and the influence of extracranial trauma. At present, such biomarkers should not be presented as definitive standalone diagnostic tools for secondary diffuse brain injury in pediatric patients.

Long-term outcome assessment is another essential dimension of management. Survival and early neurological stabilization do not necessarily indicate complete recovery. Children may subsequently develop cognitive, behavioral, emotional, educational, and functional difficulties that become apparent as developmental demands increase. Therefore, structured follow-up and rehabilitation should form part of a comprehensive pediatric neurotrauma pathway [8].

The present review has several limitations. It is a narrative rather than systematic review and does not include a reproducible database search, formal risk-of-bias assessment, or quantitative meta-analysis. The proposed integrated framework has not been tested in a clinical cohort, and its effects on mortality, intracranial pressure burden, neurological recovery, or long-term functional outcomes cannot be inferred. Furthermore, the evidence supporting several advanced monitoring technologies remains limited in pediatric populations.

Future research should prioritize multicenter prospective studies incorporating standardized definitions of secondary diffuse injury, age-specific physiological measurements, serial neuroimaging, and validated long-term outcome instruments. Such investigations could help determine whether integrated monitoring and individualized treatment pathways produce measurable improvements beyond established standard care.

Conclusion

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Secondary diffuse brain injury in children with acute combined traumatic brain injuries is a multifactorial pathological process involving interactions between primary cerebral damage, impaired perfusion, metabolic dysfunction, neuroinflammation, and systemic physiological disturbances. Its diagnosis requires careful integration of clinical examination, conventional neuroimaging, selective advanced imaging, and appropriate physiological monitoring.

The prevention of hypoxemia, hypotension, intracranial hypertension, seizures, and metabolic instability remains central to evidence-informed neuroprotective management. Advanced imaging and monitoring modalities may provide additional diagnostic information, but their use should be guided by clinical relevance, patient safety, and the limitations of available pediatric evidence.

An integrated multidisciplinary approach offers a rational framework for identifying evolving secondary insults and tailoring treatment to individual physiological needs. Further clinical validation is required to establish whether the proposed diagnostic and therapeutic framework improves neurological outcomes in children with acute combined TBI.

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