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Guest Editorial

Hypoxic-ischemic brain injury: Addressing the disconnect between pathophysiology and public policy

David B. Arciniegas[a,b,*]
[a]*Brain Injury Rehabilitation Unit, HealthONE Spalding Rehabilitation Hospital, Aurora, CO, USA*
[b]*Neurobehavioral Disorders Program, University of Colorado Denver, Aurora, CO, USA*

1. Introduction

Hypoxic-ischemic brain injury (HI-BI) denotes a physiologically significant disruption of brain function due to a deficient supply of oxygen to the brain resulting from a reduced level of circulating arterial oxygen or diminished blood-oxygen saturation or insufficiency of hemoglobin (i.e., hypoxia), failure of cerebral perfusion (i.e., ischemia), or a combination of these factors (i.e., hypoxia-ischemia) [9]. The causes and the neurological consequences of hypoxia and hypoxia-ischemia are complex, and they vary with the relative contributions of these pathophysiologic processes and their durations in a given individual [4]. The pathophysiologic, etiologic, and demographic heterogeneity of HI-BI is reflected in the wide variety of neurological, neurobehavioral, and functional outcomes associated with this category of brain injuries [2,8,10,12–14].

Although this general definition and understanding of HI-BI is used commonly by neurologists and neurorehabilitation specialists, it is important that we acknowledge at the outset of this issue of *NeuroRehabilitation* that there is no empirically-validated standard clinical case definition or formal diagnostic criteria for HI-BI. The set of clinical conditions that we regard as within the spectrum of HI-BI is identified in the International Classification of Diseases 9th Revision, Clinical Modification (ICD-9-CM) by the term 'anoxic brain damage' (348.1). The clinical terms 'anoxic brain injury' and 'anoxic encephalopathy' are often used interchangeably with this ICD-9-CM term and HI-BI, and also with the context-specific but related ICD-9-CM codes and terms listed in Table 1.

The principal problems with the terminology of the ICD-9-CM is that the 'anoxic brain damage [or injury],' in many cases, describes too narrowly the pathophysiology of brain injury and connotes too strongly its severity. In this issue of *NeuroRehabilitation*, we elected to favor the term HI-BI over anoxic brain damage (or equivalent terms) in light of the fact that many of these injuries do not involve anoxia *per se* but instead hypoxia or hypoxia-ischemia.

The converse of these problems is entailed by the inclusion of HI-BI, or at least a subset of such injuries, within the definition of 'traumatic brain injury' (TBI) adopted by the United States government in the TBI Act of 2008 [6]. In this Act, the definition of TBI is revised such that it "may include brain injuries caused by anoxia due to trauma including near drowning." This modified definition of TBI interprets the concept

*Address for correspondence: David B. Arciniegas, MD, Neurobehavioral Disorders Program, University of Colorado Denver, 13001 East 17th Place, Campus Box F546, Aurora, CO 80045, USA. Tel.: +1 303 724 4998; Fax: +1 303 724 3594; E-mail: David.Arciniegas@UCDenver.edu.

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Table 1
Terms in the International Classification of Diseases 9th Revision, Clinical Modification (ICD-9-CM) that may be used to denote hypoxic-ischemic brain injury (HI-BI)

ICD-9-CM Code	ICD-9-CM Descriptor	Comment
348.1	Anoxic brain damage (also sometimes coded as 'anoxic encephalopathy')	Coded with the condition that resulted in the HI-BI, such as cardiac arrest (427.5), respiratory arrest (799.1 and related codes), accidental poisoning by gases (E867-E868), accidents caused by submersion, suffocation, and foreign bodies (E910-E915), near-hangings (E953, E963, E913.8), etc.
997.01	Central nervous system complication – anoxic brain damage, cerebral hypoxia	Used when the HI-BI occurs during or as the result of a procedure (i.e. a complication of surgical or medical care)
639.8	Cerebral anoxia following conditions classifiable to 630–638	Used to describe HI-BI associated with (as a maternal complication of) various types of molar (630–631), ectopic (633), or missed (632), spontaneous (634), or induced (635–638) aborted pregnancies
669.4	Cerebral anoxia following cesarean or other obstetrical surgery or procedure, including delivery NOS	Excludes HI-BI following conditions classifiable to 630–638
768.7	Hypoxic-ischemic encephalopathy (HIE)	Denotes HI-BI originating in the perinatal period resulting from perinatal asphixia (768.5). In clinical practice, HIE is also used to denote HI-BI resulting from other causes of cardiorespiratory compromise after birth. 'Neonatal encephalopathy' (NE) is used instead of HIE by some authors to avoid the otherwise narrow attribution of HIE to perinatal asphixia alone
779.2	Cerebral ischemia NOS of newborn	Used to denote 'cerebral depression, coma, and other abnormal cerebral signs,' including HI-BI, resulting from cerebral ischemia in a newborn; may capture causes of NE not resulting from perinatal asphixia

'trauma' in TBI less specifically than is conventional in the clinical and scientific literature – i.e., the application of external physical force to the brain, including acceleration/deceleration and/or blast forces – and instead extends it to a much larger set of physical injuries (traumas), such as those denoted by ICD-9-CM codes E910-915, E953, 963, and 913.8, among others (see Table 1).

This redefinition is almost certainly motivated by the laudable goal of inclusivity as regards public policy affecting persons with TBI, their families, and the systems that serve them. However, incorporating HI-BI – and particularly only a trauma-related subset of such injuries – into the definition of TBI poses at least two serious risks for the science of both TBI and HI-BI as well as for the care of persons with these injuries. First, including only the trauma-related subset of HI-BI into TBI research, care, and public policy undertakings will leave unaccounted and unserved a substantial number of individuals with HI-BI – those with such injuries following cardiac arrest, obstetric, peri- and neonatal events, and surgical or medical procedures. Second, conflating the needs, study, and care of persons TBI and HI-BI presumes that these injuries are so similar in terms of their demographics, pathophysiologies, and treatment (including community reintegration) that addressing the issues relevant to persons with TBI will serve equally well persons with HI-BI.

Of particular concern is the heterogenity between and within these categories of brain injury. The subtypes of HI-BI differ not only in cause (hypoxia with preserved circulation versus cardiovascular collapse) but also in neuropathological consequences [4]. Moreover, the locations and types of gross anatomic and microscopic injury as well as the neurological and neurobehavioral sequelae of HI-BI differ from those produced by TBI [3,5,11–13], which is itself heterogeneous with respect to causes and consequences [1,7].

Time will tell whether this inclusive definition of TBI is useful with respect to the aims of the TBI Act of 2008, and particularly the work it supports through the national program for TBI registries, grants supporting state TBI surveillance systems or registries, TBI research programs administered by the Centers for Disease Control and the National Institutes of Health, and TBI service delivery systems supported by the Health Resources Services Administration. Given the success of these enterprises in the past, there is reason to be optimistic about the future of these works as they pertain to persons with conventionally-defined (i.e., mechanical) TBI. However, there are reasons to be concerned that the integration of TBI and HI-BI – two epidemiologically, neuropathologically, and functionally disparate types of brain injury – into the TBI Act of 2008 will not serve well the study of either condition, the people that they affect, and the systems of care developed

around them – and especially persons with HI-BI and their families.

Indeed, the study of HI-BI and also the development of neurorehabilitation systems of care for persons with this specific type of brain injury are necessary and important undertakings in their own right. These undertakings are limited by the relatively underdeveloped clinical research literature describing the evaluation and neurorehabilitative management of HI-BI, and particularly its neurological and neurobehavioral sequelae. Accordingly, the care of persons with this condition is guided in large measure by analogy to traumatic and other acquired brain injuries. As with the approach to HI-BI adopted in the TBI Act of 2008, applying a certain measure of care-by-analogy is understandable and unavoidable – doing so allows those of us working with persons with HI-BI and their families to organize and deliver care that supports their neurological and functional recovery, facilitates adaptation to disability, and, to the greatest extent possible, re-entry into the community and workforce. Nonetheless, our efforts to provide and improve the neurorehabilitation of persons with HI-BI will benefit from a more detailed knowledge of this condition, its sequelae, and the literature, limited though it may be, describing its neurological, neurobehavioral, and neurorehabilitative evaluation and management.

This issue of *NeuroRehabilitation* is intended to provide our readers, as well as others who might be interested, with just this type of information: a set of articles addressing HI-BI and reviewing the neuropathophysiology, neuroimaging assessment, and the evaluation and management of the neurological and neurobehavioral sequelae of these injuries in adults and children. Drs. Busl and Greer (Massachusetts General Hospital and Harvard Medical School) begin this issue with a review of the pathophysiology of HI-BI. Dr. Little and colleagues (University of Illinois College of Medicine) follow thereafter with a discussion of current neuroimaging techniques and their current and potential applications to the clinical evaluation of persons with HI-BI. Dr. Armstrong-Wells and her collaborators at The Children's Hospital and the University of Colorado Denver (UCD) then focus on these issues as they pertain to perinatal HI-BI, or neonatal encephalopathy. Returning to adults, Drs. Lu-Emerson and Khot (University of Washington) address the neurological sequelae of HI-BI and Dr. Anderson (Denver Veterans Affairs Medical Center and UCD) and I (HealthONE Spalding Rehabilitation Hospital and UCD) offer a review of the broad spectrum of post-hypoxic cognitive impairments and their treatments. Thereafter, Drs. Shprecher (University of Utah) and Mehta (Evergreen Neuroscience Institute) address the under-recognized problem of delayed post-hypoxic leukoencephalopathy. We also included in this issue reviews of two related topics: hypobaric (high-altitude) hypoxic cerebral injury and obstructive sleep apnea (OSA), contributed by Dr. Maa (Denver Health and Hospitals and also UCD) and Dr. Tsai (UCD), respectively. Hypoxia-related neurological dysfunction is a common consequence of exposure to high-altitude (particularly in the uninitiated and when extreme) as well as repetitive hypoxic stress due to OSA. Accordingly, both serve as models for the pathophysiology of HI-BI and the lessons learned from them may inform the evaluation and management of persons with HI-BI more generally.

We appreciate the interest in and support for the development of this issue offered by Drs. Zasler and Kreutzer, Editors of *NeuroRehabilitation*, as well as the organizational support for its development provided by the journal's Managing Editor, Ms. Oliver. We hope that our readers and others interested in this subject will find this issue informative and useful in their study of, neurological and neurorehabilitative care for, and advocacy on behalf of persons with HI-BI and their families.

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