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Lenticulostriate arterial distribution pathology may underlie pediatric anoxic brain injury in drowning

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ABSTRACT

Drowning is a leading cause of neurological morbidity and mortality in young children. Anoxic brain injury (ABI) can result from nonfatal drowning and typically entails substantial neurological impairment. The neuropathology of drowning-induced pediatric ABI is not well established. Specifically, quantitative characterization of the spatial extent and tissue distribution of anoxic damage in pediatric nonfatal drowning has not previously been reported but could clarify the underlying pathophysiological processes and inform clinical management. To this end, we used voxel-based morphometric (VBM) analyses to quantify the extent and spatial distribution of consistent, between-subject alterations in gray and white matter volume. Whole-brain, high-resolution T1-weighted MRI datasets were acquired in 11 children with chronic ABI and 11 age- and gender-matched neurotypical controls (4–12 years). Group-wise VBM analyses demonstrated predominantly central subcortical pathology in the ABI group in both gray matter (bilateral basal ganglia nuclei) and white matter (bilateral external and posterior internal capsules) ($P < 0.001$); minimal damage was found outside of these deep subcortical regions. These highly spatially convergent gray and white matter findings reflect the vascular distribution of perforating lenticulostriate arteries, an end-arterial watershed zone, and suggest that vascular distribution may be a more important determinant of tissue loss than oxygen metabolic rate in pediatric ABI. Further, these results inform future directions for diagnostic and therapeutic modalities.

1. Introduction

Drowning is the third leading cause of unintentional injury death worldwide, with the highest rates among children 1–4 years old. Defined as the process of experiencing respiratory impairment from submersion/immersion in liquid, it rapidly leads to cardiac and respiratory arrest (Topjian et al., 2012). Cases of nonfatal drowning, wherein the victim successfully receives cardiopulmonary resuscitation, are also most common in children less than four years old (Borse et al., 2008; Kriel et al., 1994). For every pediatric drowning death, at least two survivors are hospitalized from a drowning incident (Weiss, 2010). In these patients, nonfatal drowning damages many organs, but the most devastating disability results from brain injury (Ibsen and Koch, 2002).

Anoxic brain injury (ABI; also hypoxic-anoxic injury) can result from nonfatal drowning and cardiac arrest as the brain is exceptionally sensitive to the duration and intensity of oxygen deprivation (Topjian et al., 2012). Often used synonymously with hypoxic-ischemic brain injury (HI-BI, a more descriptive term), ABI involves a complex constellation of injuries to the brain from hypoxia, ischemia, cytotoxicity, and combinations thereof (Busl and Greer, 2010). With these insults, the brain is deprived not only of oxygen, but also of glucose and other nutrients that support neural metabolism. This triggers injurious biochemical cascades, including excessive neurotransmitter release leading to excitotoxicity, oxygen free radical formation, lactic acidosis, and

Abbreviations: ABI, anoxic brain injury; ACA, anterior cerebral artery; CT, computerized tomography; DTI, diffusion tensor imaging; HI-BI, hypoxic-ischemic brain injury; MCA, middle cerebral artery; MNI, Montreal Neurological Institute; MPRAGE, magnetization prepared rapid gradient echo; PLIC, posterior limb of the internal capsule; VBM, voxel-based morphometry.

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ultimately, neuronal death. Further, lactic acid and other cytotoxic agents that are normally removed by the circulation accumulate due to ischemia (Huang and Castillo, 2008). It has been widely reported that certain brain regions are more susceptible to HI-BI than others, a concept known as selective vulnerability (Huang and Castillo, 2008). Observed patterns of injury may reflect cellular metabolic demands, vascular distribution (e.g., watershed zones), or both (Hegde et al., 2011).

Several studies have concluded that brain tissues with higher densities of excitatory neurotransmitter receptors and higher metabolic demands are especially susceptible to damage from anoxic-ischemic insults (Huang and Castillo, 2008; Rabinstein and Resnick, 2009). Regions with high concentrations of glutamate or other excitatory amino acid receptors (gray matter) are more vulnerable to excitotoxicity. Increased synaptic activity in these tissues also results in greater energy demands, rapidly subjecting them to energy depletion and early injury with oxygen deprivation. Accordingly, the selective vulnerability of gray matter has been largely established across anoxic etiologies. Traditionally implicated regions include the basal ganglia, cerebellum, and hippocampi (Huang and Castillo, 2008; Rabinsten and Resnick, 2009; Souminen and Vähätalo, 2012). Movement, coordination, and memory deficits are consequently the most common sequelae in survivors (Topjian et al., 2012).

Vascular pathogenesis has also been suggested in ABI and implicates cerebral watershed regions. These border zones involve the junction of the distal fields of two nonanastomosing arterial systems and have decreased tolerance to ischemia. Classically, two distinct watershed zones are recognized: (1) cortical watershed: between the territories of the anterior, middle, and posterior cerebral arteries; and (2) internal watershed: in the white matter between the deep and superficial arterial systems of the MCA, or between the superficial systems of the MCA and ACA (Momjian-Mayor and Baron, 2005). The central subcortical gray and white matter comprising the vascular territory of the perforating lenticulostriate arteries has not collectively been proposed as a predominant site of injury with anoxia. Importantly, despite the suggested involvement of the above hypoxia-vulnerable areas, the full extent of consistent short- and long-term neuropathological consequences of drowning have yet to be established.

Neuroimaging modalities are particularly critical in the examination of post-drowning ABI, as there exist no systematic pathological (post-mortem) human studies in this disorder. CT and MRI have been extensively applied clinically following resuscitation from drowning. Acute anatomical imaging findings are often subtle or reported as normal, even in cases of severe ABI. Diffuse edema, which manifests as the loss of normal contrast between gray and white matter, is the most common early finding on CT and T1/T2-weighted MRI (Rafaat et al., 2008; Rabinsten and Resnick, 2009). Chronically, diffuse structural atrophy is frequently observed. Diffusion MRI methods are more sensitive in the detection of ABI; when focal pathology is present, basal ganglia and cerebellar damage are most commonly reported (and associated with poor outcomes) (Rabinsten and Resnick, 2009). Outcomes in pediatric nonfatal drowning can range from considerable recovery, to varying levels of neurological impairment, to minimally conscious and persistent vegetative states, to brain death (Christensen et al., 1997). Severe motor impairments, including loss of self-mobility, self-feeding, and communication capabilities are common post-drowning ABI consequences, and various movement disorders have been reported across other hypoxic-ischemic etiologies (Lu-Emerson and Khot, 2010).

It is important to note that reports of structural neuroimaging findings in pediatric ABI have relied solely on visual inspection. There exist no quantitative or group analyses of consistent gray and white matter damage with drowning. Determination of the extent, course, and uniformity of anatomical brain pathology from anoxia in these patients is necessary and could be highly valuable in establishing patterns of damaged versus intact neural tissue, in suggesting the underlying pathophysiological processes of ABI in drowning, in clinical decision making, and in informing future targeted analyses. The purpose of this paper is to use morphometry to further understand neuropathology in pediatric nonfatal drowning and make causal inferences regarding the pathophysiology of this disorder. This necessitates the use of robust structural neuro image analysis methods.

Voxel-based morphometry (VBM) is a quantitative, group-wise structural image analysis technique capable of detecting even subtle, consistent pathology across subjects (Ashburner and Friston, 2000). VBM methods have been applied to numerous neurological disorders and have successfully identified structural changes otherwise difficult to visually perceive. To date, they have not been implemented in pediatric nonfatal drowning. In the present study, we have acquired high-resolution T1-weighted MRI data in 11 children with chronic ABI and 11 age- and gender-matched neurotypical control children. We have utilized recently optimized, whole-brain VBM methods to define and quantify consistent structural pathology from nonfatal drowning among pediatric patients.

2. Materials and methods

2.1. Subjects

22 subjects were studied: 11 children with chronic ABI from nonfatal drowning, and 11 age- and gender-matched neurotypical controls. All ABI patients were medically stable, greater than six months post injury, with no contraindications to MRI, and with normal sleep–wake cycles (children were studied during sleep). The ABI cohort's range in age at injury (1.4–4.8 years) reflects the highest-risk population for accidental drowning. All ABI subjects displayed consistent, substantial motor impairments, as assessed through their ability for autonomous and purposeful movement, mobility, and speech production. Cognitive abilities appeared to vary, but were difficult to assess due to the motor impairments. All participants' parent(s) consented to the study's protocol approved by the University of Texas Health Science Center at San Antonio's Institutional Review Board.

2.2. Image Acquisition

MRI data were obtained on a 3T Siemens TIM-Trio (Siemens Medical Solutions, Erlangen, Germany), using a standard 12-channel head coil as a radiofrequency receiver and the integrated circularly polarized body coil as the radiofrequency transmitter. T1-weighted images were acquired during mildly sedated sleep (1–2 mg/kg Diphenhydramine HCl) using the MPRAGE pulse sequence with TR/TE = 2200/2.72 ms, flip angle = 13°, TI = 766 ms, volumes = 208, and 0.8 mm isotropic voxel size.

2.3. Visual inspection

Acquired images were visually inspected per subject for artifacts, non-related pathology, and/or evidence of motion. Three ABI and two control data sets showed excessive motion. Two of the ABI subjects were successfully rescanned, ultimately yielding high-quality data sets in 10 ABI and 9 control participants. ABI pathology ranged from mild ventricular enlargement, to moderate ventricular enlargement with mild basal ganglia atrophy and mild cortical thinning, to severe ventricular enlargement with severe basal ganglia atrophy and diffuse cortical thinning. See Table 1 for subject data.

2.4. Voxel-based morphometry

2.4.1. Gray matter VBM

T1 structural images were denoised using Matlab's MRI Denoising package (Optimized Nonlocal Means filter with Rician option activated) (Coupé et al., 2008, 2010). FreeSurfer was used to obtain brain-extracted images and masks following processing with *autorecon1*