Journal of the International Neuropsychological Society (2008), **14**, 656–659.

doi:10.1017/S1355617708080879

NEUROBEHAVIORAL GRAND ROUNDS—INTRODUCTION

Does near drowning in ice water prevent anoxic induced brain injury?

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Abstract

Cold water near-drowning is often thought to be neuroprotective in individuals with anoxia of a longer duration than that usually required to produce irreversible neurologic damage. There is a paucity of data in adults with cold water near-drowning that assess neuropsychological outcomes. Information regarding long-term effects of near cold water near-drowning on neuropathology, neuropsychological and neurobehavioral outcomes are uncommon. This paper provides an introduction to two cases of cold water near-drowning reported in this issue of JINS by Sameulson and colleagues and provides background information for interpretation of the findings of these cases in the context of outcomes following anoxia. (*JINS*, 2008, *14*, 656–659.)

Keywords: Near cold water drowning, Hypothermia, Anoxia, Neuropsychological outcomes

INTRODUCTION

The incidence of cardiac arrest with anoxia and cerebral ischemia occurs in more than 400,000 cases per year in the United States, of which more than 80% of these patients are likely to have poor neurological outcomes (Geocadin et al., 2006; Zheng et al., 2001). Recent improvements in emergency and critical care medicine have resulted in approximately 200,000 cardiac resuscitations per year of which over 70,000 patients survive but constitute only 1% of those admitted to brain injury rehabilitation centers (Bachman & Katz, 1997). Anoxia and ischemia can occur because of cardiac or respiratory arrest, open heart surgery, attempted hanging, complications of anesthesia, and near drowning.

Some brain regions are more vulnerable to the effects of anoxia/ischemia, particularly structures at the end of the vascular supply, with high metabolic rates (Brierley & Graham, 1984), and/or proximity to structures that contain excitatory amino acids such as glutamate (Martin et al., 1994; Siesjo et al., 1989). Vulnerable brain regions include the neocortex, hippocampus, basal ganglia, cerebellum, primary visual cortex, frontal regions, and thalamus (Chalela et al., 2001). Anoxic brain injury results in focal and diffuse neuropathologic lesions and atrophy (Bachevalier & Meunier, 1996; Caine & Watson, 2000; Gale et al., 1999; Hopkins et al., 1995b) including lesions in the hippocampus (Manns et al., 2003a; Manns et al., 2003b), basal ganglia, cerebellum (Mascalchi et al., 1996), subcortical and periventricular white matter lesions (Parkinson et al., 2002) and atrophy of the corpus callosum (Porter et al., 2002). Generalized brain volume loss leading to ventricular enlargement and sulcal widening (Caine & Watson, 2000) and hippocampal atrophy are also common (Hopkins et al., 1995b; Press et al., 1989). A review of anoxic brain injury ($N = 90$) found that 44% of individuals had cortical edema or atrophy, 33% had cerebellar lesions, 22% had basal ganglia lesions, 21% had hippocampal atrophy, and 3% had thalamic lesions (Caine & Watson, 2000).

Neurological and Neuropsychological Sequelae

Poor neurological outcomes after brain injury include death, coma, vegetative state, severe neurologic disability (Jennett

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& Bond, 1975), cognitive sequelae, and development of new psychiatric disorders (Bachevalier & Meunier, 1996; Caine & Watson, 2000). Neuropsychological deficits after anoxia or ischemia are heterogeneous and include agnosia (Farah, 1990), impaired memory (Hopkins et al., 2004; Manns et al., 2003a; Zola-Morgan et al., 1986), executive dysfunction (Hopkins et al., 1995a; Lezak, 1995), impaired visual-spatial skills (Barat et al., 1989), generalized cognitive impairments (Wilson, 1996), and motor disturbances (Lishman, 1998). Psychological and behavioral changes following anoxic brain injury often include euphoria, irritability, emotional volatility, depression, and anxiety (Bahrke & Schukitt-Hale, 1993; Li et al., 2000).

Mechanisms of Brain Injury

Anoxia or ischemia causes a pathophysiological cascade that leads to neuronal damage and death (for reviews of the mechanisms see Biagas, 1999; Johnston et al., 2002). Mechanisms of anoxic induced neuronal injury include: (1) decreased ATP production without decreasing ATP utilization, resulting in energy depletion, ionic pump failure, K+ outflow, and inflow of $Ca^{2}+$ (Lutz & Nilsson, 1994); (2) lactic acidosis caused by anaerobic metabolism (Siesjo, 1981); (3) excitotoxic damage caused by excessive glutamate release leading to increased neuronal firing, calcium influx, and neuronal death (Johnston et al., 2002); (4) increased calcium influx and intracellular accumulation of calcium due to ionic pump failure (Schurr et al., 1990); (5) the formation of oxygen radicals during reperfusion or reoxygenation (Biagas, 1999); (6) nitric oxide synthase leads to impaired neurotransmission, protein synthesis, and membrane peroxidation (Biagas, 1999); and (7) anoxia or ischemia also results in neuronal necrosis and/or apoptosis or programmed cell death (Beilharz et al., 1995; Steller, 1995).

Therapeutic Hypothermia

Recent research has generated considerable hope for better recovery following anoxia and ischemia using a variety of treatments. One such treatment is therapeutic hypothermia, which has shown improved neurological outcomes in 1 out of every 6 patients after cardiac arrest and cardiopulmonary resuscitation (Bernard et al., 2002; The Hypothermia after Cardiac Arrest Study Group, 2002). In principle a reduction in brain metabolic demands lead to decreased oxygen requirements and therefore reduced vulnerability to the neural effects of anoxia/ischemia. Animal models show that hypothermia inhibits multiple steps in the reperfusion phase of anoxic injury, including ATP consumption (Erecinska et al., 2003), reduced neuronal depolarization (Sick et al., 1999), decreased extra cellular glutamate concentrations (Busto et al., 1989), and decreased free radical production (Globus et al., 1995). A meta-analysis of 3 randomized controlled clinical trails in humans evaluated therapeutic hypothermia compared to normothermia found that therapeutic hypothermia was associated with good neurologic outcomes [relative risk of 1.68 (95% CI 1.29–2.07)] (Holzer et al., 2005). The data mentioned earlier raise questions as to what if any role accidental hypothermia caused by cold-water immersion may play in preventing or reducing neuropsychological and psychiatric sequelae following near drowning.

Cold Water Near-Drowning

Cold water near-drowning is often believed to be neuroprotective in individuals with anoxia of a longer duration than that usually required to produce irreversible neurologic damage (Chochinov et al., 1998). Such neuroprotection is attributed to low core body temperatures, which reduce cerebral metabolic oxygen requirements and the mammalian dive reflex, which is believed to enhance the delivery of limited available oxygen stores to the brain (Chochinov et al., 1998). Most studies to date that assess outcome following cold water near-drowning have been conducted in children. A review of near-drowning and ice-water submersion in pediatric patients (13 less than 19 years of age) found 15 patients had a good outcome and 2 patients had a "fair to good outcome", but outcome was not defined and neuropsychological tests were not administered to these patients (Orlowski, 1987). There are few cases of near-drowning with cold-water submersion with poor outcomes reported in the literature (Orlowski, 1987). Orlowski suggests that cases with poor outcome are probably not reported whereas cases with good outcome are more commonly reported, resulting in a bias of good outcomes in the literature (Orlowski, 1987). One case of note, is that of R.D. who at 2.5 years of age was submerged in frigid water for 66 minutes with reportedly "good neurologic recovery" (Bolte et al., 1988). However, a neuropsychological evaluation 13 years later in this same individual found broad neurodevelopmental compromise, impaired memory, and executive function, despite a normal brain imaging (Hughes et al., 2002).

There is a paucity of data in adults with cold water near-drowning that assess outcome and only one study assessed neuropsychological function (Huckabee et al., 1996). The two cases of cold water near-drowning reported in this issue of JINS by Samuelson and colleagues assessed short term (a few days to months) and long-term (1.5 to 3.5 years) neuropsychological outcomes. Both cases had neuropsychological impairments that persisted over time. The neuropsychological findings of these two individuals with anoxic brain injury following cold water near-drowning are similar to those reported after anoxia from other etiologies (Bachevalier & Meunier, 1996; Caine & Watson, 2000; Hopkins et al., 2004; Manns et al., 2003a; Zola-Morgan et al., 1986). Further, these two individuals had symptoms of depression and behavioral changes. The rate of mood disorders after anoxic brain injury varies from 24% to 60% of cases, which is significantly higher than the prevalence rate in the general population (2% to 9% major depression and 3% generalized anxiety), and the 12% rate observed in medical populations.

https://doi.org/10.1017/S1355617708080879 Published online by Cambridge University Press

Case 1 had a normal brain MRI scan 1.5 years after the accident, a finding that is similar to that reported by Orlowski (1987). However, brain imaging findings in near-drowning survivors are heterogeneous with abnormalities ranging from hemorrhageic infarctions to global atrophy (Fitch et al., 1985). Similarly, brain MRI findings in anoxic patients who were not near-drowning accidents include lesions in gray (e.g., basal ganglia, hippocampus, etc) and white matter, and global and focal atrophy (Bachevalier & Meunier, 1996; Caine & Watson, 2000; Hopkins et al., 2004; Manns et al., 2003a; Zola-Morgan et al., 1986). Whereas braining imaging was normal by radiologic report in Case 1, quantitative neuroimaging was not carried out (Bachevalier & Meunier, 1996; Caine & Watson, 2000; Gale et al., 1999; Hopkins et al., 1995b). Nonspecific brain damage may result in general volume reduction manifested by reduced gyral volume, increased sulcal space, passive increase in ventricular volume (i.e., hydrocephalus *ex vacuo*), increase in whole brain cerebral spinal fluid (CSF; Graham et al., 2002), and structural atrophy (e.g. hippocampus, basal ganglia, etc.). These changes may not be apparent visually but can be readily documented using quantitative MR analyses (Bigler, 2001). Thus, quantitative neuroimaging may detect important neuropathological changes in these cases that otherwise may not be detected.

The accidental hypothermia in these two cases likely contributed to preservation of life, but was not entirely neuroprotective, because both individuals had long-term neuropsychological and behavioral changes. The neuropsychological and neurobehavioral changes are similar to that observed after anoxia because of other etiologies. It is unclear if the accidental hypothermia reduced the extent and severity of the neuropsycholgoical and behavioral changes in these two cases, but it is certainly possible given the long duration of anoxia experienced by these two individuals. Research on the long-term effects of anoxia with and without cold water near-drowning on neuropathology, neuropsychological, and neurobehavioral outcomes is needed to better elucidate the effects of and possible benefits of accidental hypothermia.

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