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SYMPOSIUM

Neuropsychological and neuropathological effects of anoxic or ischemic induced brain injury

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INTRODUCTION

In recent years there has been extensive research in neuropsychological sequelae of a variety of etiologies, including traumatic brain injury, dementia, stroke, Parkinson's disease, schizophrenia, and cardiac surgery. With the exception of stroke and cardiac surgery, significantly fewer studies have been published regarding neuropsychological outcome in adults with disorders associated with anoxia or ischemia. Outcomes research in anoxic or ischemic disorders in pediatric patient populations are even more limited.

Previous research on the effects of anoxia and ischemia on brain and behavior has emphasized focal abnormalities in the medial temporal lobe and the associated memory deficits (Zola-Morgan et al., 1986). This work has formed the backbone of our understanding of the behavioral function of the medical temporal lobe/diencephalic memory systems. However, these focal lesions are the exceptions and not the rule (Caine & Watson, 2000). Emergency and critical care medicine has improved survival resulting in many patients with less focal injuries and frequently more severe deficits due to etiologies, such as acute respiratory distress syndrome. This symposium explores neuropsychological outcomes in a variety of disorders with concomitant anoxia or ischemia in pediatric and adult populations, covering a variety of etiologies including acute respiratory distress syndrome, obstructive sleep apnea, pediatric stroke, and outcome in very low birth weight infants.

PREVALENCE AND ITS IMPLICATIONS

Recent improvements in emergency and critical care medicine have resulted in approximately 200,000 cardiac resuscitations/year of which over 70,000 patients survive (Bachman & Katz, 1997). In addition to cardiac or respiratory arrest, a variety of disorders such as asthma, cardiac disease or surgery, carbon monoxide poisoning, attempted hanging, complications of anesthesia, near downing, obstructive sleep apnea, chronic obstructive pulmonary disease, stroke, and acute respiratory distress syndrome result in anoxia or ischemia. The prevalence of these disorders varies. For example, acute respiratory distress syndrome affects more than 150,000 adults per year in the United States (Rubenfeld, 2003), 55,000 children/year are born with very low birth weight (Gislason & Benediktsdottir, 1995; Young et al., 1997), and the prevalence of obstructive sleep apnea is 2 to 4% from preschool to mid-adulthood (Martin et al., 2002). The combined prevalence of all anoxic/ischemic disorders suggests that if neuropsychological sequelae are common, this could present an important public health problem and the incidence of neuropsychological morbidity must be better understood.

UNDERLYING MECHANISMS

Ischemia is defined as insufficient blood delivery due to interruption or reduction of blood delivery to the brain (i.e., cardiac arrest or stroke), anoxia is total absence of oxygen delivery to tissues (e.g., due to decreased blood oxygen levels or decreased perfusion), hypoxia is reduction of oxygen supply to the tissues (e.g., decreased blood oxygen levels, or problems with tissue oxygen utilization) below physiologic levels despite adequate perfusion of the tissue by blood, and hypoxemia is below normal oxygen content in arterial blood due to deficient oxygenation of the blood usually resulting in hypoxia (Kuroiwa & Okeda, 1994). There are at least four primary ways to decrease oxygen delivery to the tissues including: (1) inadequate arterial oxygen tension; (2) inadequate circulating hemoglobin concentration;

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(3) inadequate blood flow; and (4) cytopathic hypoxia due to impaired production of adenosine triphosphate (ATP) despite adequate availability of oxygen in the cells (Fink, 1998). The brain is the most complex organ in the body and is continually active resulting in high energy consumption. Under normoxic conditions approximately 95% of brain ATP is produced aerobically (Lutz & Nilsson, 1994). In anoxia or ischemia decreased ATP production without a concomitant decrease in utilization result in energy deficiency/failure setting off a cascade of interconnected biochemical events that ultimately results in neuronal death.

Over the last decade both *in vivo* and *in vitro* models have elucidated the mechanisms by which anoxia or ischemia damage the brain. For reviews of the mechanisms see Biagas (1999), Johnston et al. (2002), and Kuroiwa and Okeda (1994). The mechanisms of 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 due to anaerobic metabolism (Siesjo, 1981); (3) excitotoxic damage from excess release of glutamate 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, xanthine oxidase catalyzes xanthine to uric acid resulting in superoxide (oxygen radicals), which impairs cell proliferation, gene expression and disrupts membrane function (Biagas, 1999); (6) nitric oxide synthase (NOS) expressed in inflammatory cells (i.e., macrophages) leading to impaired neurotransmission, protein synthesis, and membrane peroxidation (Biagas, 1999). Thus, anoxia or ischemia causes a pathophysiological cascade that leads to neuronal damage and death.

Anoxia or ischemia also results in necrosis and/or apoptosis. Necrosis occurs due to edema and rupture of the cell sending the intracellular contents into the extra cellular space, resulting in the influx of inflammatory cells and vascular disruption (Biagas, 1999). Apoptosis is programmed cell death with associated cell shrinkage, DNA fragmentation, cellular changes and appearance of apoptotic bodies, secondary inflammation and fibrosis (Steller, 1995). Neurons in the anoxic–ischemic region die from necrosis, neurons in the penumbra (e.g., bordering areas) die from necrosis and apoptosis, and distant neurons may initially survive and then may undergo delayed apoptotic cell death (Beilharz et al., 1995).

VARIABILITY OF DAMAGE

Regional brain oxygen utilization is not homogeneous. Some brain regions are potentially more vulnerable to the effects of anoxia/ischemia, particularly structures at the end of the vascular supply, which have high metabolic rates (Brierley & Graham, 1984), and/or proximity to structures with high levels of excitatory amino acids such as glutamate (Martin et al., 1994; Siesjo et al., 1989). More vulnerable brain regions include the neocortex, hippocampus, basal ganglia, cerebellar Purkinje cells, primary visual cortex, frontal regions, and thalamus (Chalela et al., 2001). Different brain regions may develop cellular injury at different times. For example, basal ganglia and cortex damage occurs in the first few hours post anoxia/ischemia, whereas hippocampal damage may not be apparent for several days to weeks (Kuroiwa & Okeda, 1994). Anoxia may result in diffuse brain injury with global atrophy (Bachevalier & Meunier, 1996; Caine & Watson, 2000) or more focal damage, such as hippocampal atrophy (Hopkins et al., 2004; Manns et al., 2003; Zola-Morgan et al., 1986). Other brain structures that are vulnerable to anoxia/ischemia injury include the basal ganglia, and cerebellum (Armengol, 2000). White matter damage may also occur with lesions in the cerebellar white matter (Mascalchi et al., 1996), subcortical and periventricular white matter lesions (Parkinson et al., 2002), and corpus callosum (Porter et al., 2002).

NEUROPSYCHOLOGICAL SEQUELAE

Not surprisingly, given the heterogenous damage, neuropsychological deficits following anoxia or ischemia are variable and include apperceptive agnosia (Farah, 1990), impaired memory (Hopkins et al., 2004; Manns et al., 2003; Zola-Morgan et al., 1986), executive function (Hopkins et al., 1995; Lezak, 1995), visual–spatial skills (Findley et al., 1986) and generalized cognitive abilities (Wilson, 1996). Motor disturbances also are reported including problems with posture, gait, involuntary movements, as well as Parkinsonian symptoms, and limb apraxia (Lishman, 1998). Affective morbidity includes depression (Gale et al., 1999), anxiety (Bruno et al., 1993), personality changes, and emotional lability (Chapel & Husain, 1978).

Perinatal anoxia, stroke and obstructive sleep apnea in children are associated with neuropsychological morbidity including decreased intellectual function (Gottfried, 1973), impaired sensory abilities, attention, and memory in one study (Robertson & Finer, 1993) and impaired memory, perceptual–motor skills, and executive function in another study (Maneru et al., 2001). Morbidity following very low birth weight and its associated complications such as anoxia due to respiratory distress, include cognitive impairments, sensory deficits, poor academic achievement, memory and attention deficits, and behavior disorders which may persist into adulthood (Gadian et al., 2000; Maneru et al., 2003).

In summary, neuropsychological outcome following anoxic or ischemic events is a relatively new and important area for neuropsychological investigation and previous studies have identified significant neuropsychological deficits. Recent advances in empirical neuropsychological techniques and functional imaging will increase our understanding of the effects of anoxia and ischemia on the brain and improve our ability to assess more subtle impairments.

SYNOPSIS

The long-term effects of hypoxia and ischemia on neuropathology and neuropsychological outcome are increasingly the focus of current research. The papers in this *JINS* 2004 Symposium provide new information regarding the patterns of neuropsychological impairments, affect, and functional outcome in adults and children. Current data suggest that both lesion location and size are important in determining the extent and severity of neuropsychological deficits. For example, memory impairments may depend on whether damage is restricted to the hippocampus (Hopkins et al., 2004; Zola-Morgan et al., 1986), basal forebrain (Diamond et al., 1997; Myer et al., 2002), or whether the damage includes other brain areas (Bachevalier & Meunier, 1996; Caine & Watson, 2000).

Acute respiratory distress syndrome is characterized by lung injury and hypoxemia and is associated with high mortality rates, and survivors exhibit significant neuropsychological and functional morbidity. The contribution of Hopkins et al. assesses neuropsychological and functional outcome in adult patients with acute respiratory distress syndrome. They prospectively followed survivors of acute respiratory distress syndrome and assessed the relationships between depression, anxiety, decreased quality of life, and cognitive function. Survivors of acute respiratory distress syndrome had significant cognitive impairments, depression and anxiety and low quality of life 1 year after hospital discharge. The low quality of life was related to depression and anxiety but not with cognitive sequelae.

Pediatric Populations

Three of the papers in this Symposium are devoted to the effects of anoxia/ischemia in pediatric populations. Advances in neonatal care have resulted in the survival of increased numbers of children with very low birth weight ($<$1500 g; 3 lb 5 oz). These children are at risk for neonatal complications including intraventricular hemorrhage, periventricular leukomalacia, birth hypoxia, and chronic lung disease that are associated with cognitive sequelae (Frisk & Whyte, 1994; Hopkins-Golightly et al., 2003; Landry et al., 1993; Perlman, 2001), and sometimes with learning disabilities and behavioral disorders (Whitfield et al., 1997). The contribution of Taylor and colleagues assessed long-term (mean age 16 years) cognitive outcome of children with very low birth weight and the relationships between cognitive impairments and severity of chronic lung disease (duration of neonatal oxygen requirement) and neonatal periventricular pathology (ultrasound findings). The findings indicate the children born with very low birth weights have long-term impairments in visual–motor skills, spatial memory, and executive function. Predictors of outcome included lower weight for gestational age and longer duration of oxygen treatment, suggesting that infants who were more severely ill had worse outcome than infants that were less ill. The findings suggest that early cognitive morbidity persists into adolescence and early adulthood, indicating that early brain insults result in long-term cognitive and behavioral morbidity.

Similar to the finding of Taylor and colleagues, Max and colleagues' assessment of attention at age 12 and 13 years in children with stroke lesions acquired before or after 1 year of age found that earlier onset of brain injury has greater effects on attention than later brain injury. Children with younger age at lesion acquisition had greater attentional problems than children who were older at the time of stroke. The children with stroke lesions had significantly worse attention compared to normal controls. Larger lesions and lesions in the alerting and sensory-orienting networks (parietal lobes, temporo–parietal junction, frontal eye-fields, and thalamus) were associated with worse attentional function. These findings provide additional support to the mounting evidence that early age at acquisition of diffuse and focal brain injuries are associated with worse long-term neuropsychological outcome than injuries acquired later in childhood.

Neuropsychological morbidity is well documented in adults with obstructive sleep apnea. Adults with obstructive sleep apnea have impaired attention, memory, executive function, and spatial abilities (Kales et al., 1985), that correlate with severity of the nocturnal hypoxemia (Bedard et al., 1991). Research on the neuropsychological effects of obstructive sleep apnea in children is limited. The contribution of Beebe et al. assesses neuropsychological morbidity in school-aged children with obstructive sleep apnea compared to healthy children. They assessed neuropsychological outcome and its relationship to sleep and hypoxia using polysomnography and parent-reported sleep problems using a standardized sleep questionnaire. The findings suggest that neuropsychological morbidity including, attention, executive function, impulse control, and behavioral and emotional regulation are associated with the degree of sleep abnormality and likely with hypoxia in school-aged children with obstructive sleep apnea.

Conclusions

Individuals with anoxic/ischemic brain injuries are at significant risk of developing diffuse and/or focal brain injury and concomitant neuropsychological and functional impairments, both in childhood and adulthood. A multifaceted approach that integrates basic science, structural and functional neuroimaging, neuropsychological assessment, and measures of functional outcome are needed to further characterize the effects of anoxic/ischemic brain injury. In order to develop treatments and improve rehabilitation, additional research is needed regarding mechanisms of injury and outcomes following anoxic/ischemic related disorders.

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