Plasma Biomarkers of Oxidative Stress in Neonatal Brain Injury

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KEYWORDS

• Oxidative stress • Newborn infant • Brain damage • Plasma biomarkers
• Lipid peroxidation • Inflammation • Hypoxia-ischemia

KEY POINTS

- Pathogenesis of perinatal encephalopathy is quite complex. An important role for oxidative stress is now recognized.
- Prostanoids and non–protein bound iron represent specific plasma oxidative biomarkers reflecting oxidative stress injury to neuronal cells.
- Sensitive and specific biomarkers of oxidative stress can be used in premature and term infants for the early detection and follow-up of brain injury.

BACKGROUND

The preterm and term brain is particularly vulnerable to the insult of oxidative stress (OS) because rapidly growing tissues are especially sensitive to the harmful effects of free radicals (FRs).[1,2] OS causes endothelial cell damage, hemostatic abnormalities, inflammatory reactions, astrocyte dysfunction, *N*-methyl-D-aspartate (NMDA) receptor impairment, and synaptosome structural damage.[3–6] According to current knowledge, the pathophysiology of brain injury almost always involves multiple factors including hemodynamic, metabolic, nutritional, toxic, and infectious mechanisms, acting in the antenatal or postnatal period. The combination of these factors often triggers neuronal death processes.[4] Perinatal hypoxia-ischemia[7] and the so-called "encephalopathy of prematurity" encompassing intraventricular hemorrhage (IVH) and periventricular leukomalacia are major contributors to neonatal brain injury. Chronic placental inflammation and acute fetal and neonatal inflammation also increase the risk of brain injury.[8] Complex disturbance on the infant's subsequent brain development also plays an important role.[9]

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The pathogenesis of perinatal brain damage is complex with multiple contributory pathways and mechanisms of injury.[10] Efforts to understand and prevent neonatal brain injury are worthwhile because of the huge number of infants involved and the enormous cost to society.

OS plays a pivotal role in the pathogenesis of brain injury, being the final common pathway for multiple converging events. OS may result from many different pathways including glutamate release and NMDA receptor activation leading to excitotoxic processes; mitochondrial dysfunction; activation of enzymes, such as nitric oxide synthase (NOS); phagocyte activation; arachidonic acid cascade; Fenton reaction driven by the release of non–protein bound iron (NPBI); and deficiency of the antioxidant system of the immature brain.[11,12]

OS occurs at birth in all newborns as a consequence of the hyperoxic challenge that occurs with the transition from the hypoxic intrauterine environment to extrauterine life. It happens when the production of FRs exceeds the capacity of antioxidant defenses and is primarily caused by a disturbance in the delicate balance between the production of FRs and the biologic system's ability to readily detoxify the FRs or to repair the resulting damage.[13] Hypoxia-ischemia is a main event inducing an overproduction of FRs.[14] Chronic placental inflammation, acute fetal inflammation, and neonatal inflammation interact in contributing oxidative risk and/or directly damaging the developing brain.[4] Some FRs can even act as second messengers: at low levels, they are signaling molecules, and at high levels, they can damage organelles, particularly the mitochondria. Oxidative damage and the associated mitochondrial dysfunction may result in energy depletion, accumulation of cytotoxic mediators, and cell death.[15]

The discovery and validation of specific OS biomarkers of neonatal brain injury represents a key step in the evolution of neonatal neuroprotection and is based on the measurement of a single or a panel of biomarkers in biologic fluids and tissues reflecting OS injury to neuronal cells. Clinicians do not currently have access to biomarkers for early diagnosis or intervention in neonates with brain injury. Thus there is a need to develop specific OS biomarkers to enable caregivers to make an early prediction of newborns at high risk, to start preventative neuroprotective strategies, and to monitor the progression of the disease. This article examines potential reliable and specific plasma OS biomarkers that can be used in premature and term infants for the early detection and follow-up of the most common neonatal brain injuries, such as hypoxic-ischemic encephalopathy (HIE), IVH, and periventricular leukomalacia.

PLASMA BIOMARKERS OF OXIDATIVE STRESS

The quantification of OS is based on the measurement of specific biomarkers in biologic fluids and tissues, which reflect induced oxidative damage to lipids, proteins, and DNA or an increased risk for injury to macromolecules. Several biomarkers have been proposed for OS detection, but only a small number of them can be considered truly specific and reliable for brain injury; these include prostanoids and NPBI.[11,16,17] Biomarkers can be considered as indicators of a disease process, but they can also give information about the worsening and progression of the process. A reliable biomarker should be biologically plausible, with a high sensitivity and specificity, and should be measured with a reproducible and standardized methodology.

The measurement of OS level in vivo is known to be difficult because FRs usually have a short half-life. Furthermore, some tests to measure FRs suffer from problems related to low specificity and sensitivity. The discovery of more stable compounds has led to the possibility of more reliable biomarkers of neonatal brain injury.