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Invited critical review

Neonatal hypoxic ischemic encephalopathy-related biomarkers in serum and cerebrospinal fluid

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ABSTRACT

Neonatal hypoxic ischemic encephalopathy (HIE) is a common disease caused by perinatal asphyxia, a major cause of neonatal death, neurological behavior, and long-term disability. Currently, the diagnosis and prognosis of neonatal HIE are based on nervous system clinical manifestations, imaging and electrophysiological examination. These take time and late diagnosis allows brain injury to occur in newborns, so that infants of many brain injury missed the best treatment time, left with varying degrees of neurological sequelae. The use of biomarkers to monitor brain injury and evaluate neuroprotective effects might allow the early intervention and treatment of neonatal HIE to reduce mortality rates. This study reviewed the mechanism of neonatal hypoxic ischemic encephalopathy in relation to numerous brain-related biomarkers including NSE, S-100β, GFAP, UCH-L1, Tau protein, miRNA, LDH, and CK-BB. In early diagnosis of neonatal HIE, S-100β and activin A seems to be better biomarkers. Biomarkers with the greatest potential to predict long-term neurologic handicap of neonates with HIE are GFAP and UCH-L1 and when combined with other markers or brain imaging can increase the detection rate of HIE. Tau protein is a unique biological component of nervous tissues, and might have value for neonatal HIE diagnosis. Combination of more than two biological markers should be a future research direction.

Contents

Abbreviations: HIE, Neonatal hypoxic ischemic encephalopathy; MIR, magnetic resonance imaging; CSF, Cerebrospinal fluid; ATP, Adenosine triphosphate; NSE, Neuron specific enolase; MBP, Myelin basic protein; FAP, Glial fibrillary acidic protein; UCH-L1, Ubiquitin carboxyl-terminal hydrolase; BDNF, Brain-derived neurotrophic factor; miRNA, MicroRNA; MMP-9, Matrix metalloproteinase-9; ICAM-1, intercellular adhesion molecular-1; sLCAM-1, Soluble intercellular adhesion molecule 1; VEGF, Vascular endothelial growth factor; SOD, Superoxide dismutase; MDA, Malondialdehyde; Hs-CRP, High-sensitivity C-reactive protein; IL, interleukin; TNF-α, Tumor necrosis factor-α; LDH, Lactic dehydrogenase; CK-BB, Creatine kinase BB.

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1. Introduction

Neonatal hypoxic ischemic encephalopathy (HIE) is a neonatal brain injury caused by perinatal asphyxia and is a major cause of neonatal death, cerebral palsy and mental retardation [1,2]. According to estimates, of the approximately 130 million births worldwide each year, four million infants will suffer from birth asphyxia, and of these, one million will die and a similar number will develop serious and long-term sequelae including neurodevelopmental disorders [3]. In China, the incidence rate of neonatal asphyxia is 1.14–11.7%, and the incidence of HIE in full-term live birth infants is 1–2/1000 of affected newborns. Approximately 15–20% of affected newborns will succumb within the neonatal period, and an additional 25–30% will develop severe and permanent neurological handicaps [4], including cerebral palsy, seizures, visual defects, mental retardation, cognitive impairment and epilepsy [5]. Serious harm to a child's physical and mental health causes great mental and economic burden to the family and society. Currently, the early diagnosis of neonatal HIE in the clinic depends on observing clinical symptoms and signs using a combination of computer tomography (CT), magnetic resonance imaging (MRI), ultrasound and electroencephalogram (EEG). However, these examinations have different limitations and effectiveness. Biomarkers in the blood circulation are bio-chemical factors released by specific tissues or organs, and their expression levels reflect a specific physiological or pathological state of tissues and organs. The accurate detection of body fluid biomarkers in neonatal HIE is important and will allow early interventions to reduce neonatal mortality, morbidity and degree of disability. In addition, biomarker evaluation will be useful for the evaluation of neonatal HIE therapeutic measures such as mild hypothermia therapy, stem cell activity factor, neural nutrition factor, and neuroprotective drugs. With the rapid development of biomedicine, biomarkers associated with neonatal HIE have been reported; however, there has been comparatively less research in neonatal HIE than in adult HIE and the data has not been assessed together. Therefore, this study retrospectively summarized neonatal HIE research related to biomarkers to provide important information to help doctors understand, verify and apply these biomarkers to gradually establish an efficient, accurate and convenient biomarker for the diagnosis and evaluation of neonatal HIE.

2. Pathogenetic mechanisms of HIE

Brain oxygen consumption accounts for 20–25% of the human body and is very sensitive to hypoxia. Neonatal HIE cerebral injury develops in two phases: The first or “primary insult” dominated the brain tissue energy metabolism disorder and the second or “reperfusion phase” dominated the histopathological changes of ischemia/reperfusion. The mechanism of neonatal HIE brain injury is not completely understood, it might be related to formation of free radicals, effect of lipid peroxidation, intervention of inflammatory factors, effect of excitatory amino acid toxicity, water channel proteins out of control, abnormal calcium ion channels and neuronal apoptosis. They affect each other and reinforce each other, forming a multiple cascade chain, eventually leading to neuronal apoptosis or death, nerve fiber degeneration and disintegration of the brain tissue injury [6–10]. Histopathological studies have identified characteristic neonatal HIE brain pathological features including nerve cell degeneration and necrosis, periventricular leukomalacia, cerebral edema, cerebral infarction, periventricular cyst like changes, intracranial hemorrhage and cerebellar injury. In the pathological process of cerebral hypoxia ischemia, various products produced by brain tissues enter the cerebrospinal fluid and might be used as blood biomarkers; therefore, monitoring these biomarkers or products might help the clinical understanding of HIE.

3. The necessity of testing the biological markers in neonatal HIE

The clinical diagnosis of neonatal HIE and disease severity assessment mainly rely on the Sarnat score, brain CT scans, MRI, ultrasound diagnosis and EEG detection methods. Because of the influence of the progressive disease process and other factors, the Sarnat score is subjective, and other tests have certain limitations and effectiveness. After neonatal HIE onset, there is a time difference in the range of 24 h between biochemical metabolism changes, tissue morphological changes and pathological changes in the brain. Neuroimaging studies suggest the appearance of nervous system damage can take up to 72 h [11]. Therefore, the clinical diagnosis of HIE by CT detection is often greater than 72 h after neonatal HIE insult. Although MRI can observe brain pathological changes hours after neonatal brain injury, but the early minor brain injury and its injury range is limited, and neonatal disease is dying at this time, imaging detection has certain difficulties. Amplitude integrated EEG can detect early changes associated with brain injury, however, interference from hypothermic environments can reduce the prediction of HIE prognosis and it cannot determine the time of injury [12]. Therefore, the early monitoring of serum or cerebrospinal fluid of neonatal HIE related biomarkers is particularly important. A biomarker is the product of specific tissues and organs, and after the onset (minutes or hours) of neonatal HIE, damaged brain