Magnetic Resonance Imaging and Magnetic Resonance Spectroscopy in Neonatal Hypoxic-Ischemic Encephalopathy: A review article

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Abstract

Background: Hypoxic Ischemic Encephalopathy is a subcategory of neonatal encephalopathy defined as a heterogeneous, clinically distinct syndrome characterized by disturbed neurological function, abnormal muscle tone and respiratory problems in the neonatal period in term infant, presented by a decreased level of consciousness, convulsions, decreased alertness, and often accompanied by difficulty with initiating and maintaining respiration. MRI plays an increasing important role for imaging the neonatal brain and follow up of neonates with HII. MR spectroscopy allows immediate analyses of the metabolites in the neonatal brain and also serves important role in assessment of neurological outcome and prognosis. The utility of proton MR spectroscopy could detect brain ischemic injuries in neonates with HII earlier than T2- or T1- weighted MR sequences. Diffusion-weighted imaging has the highest sensitivity for early detection of brain injury in neonates with HII. Findings seen at diffusion-weighted imaging mostly peak at 3–5 days after the insult of brain injury and then gradually normalize.

Conclusions: MR spectroscopy is an accurate, sensitive and non-invasive method for early detection of perinatal ischemic brain injuries**.**

Keywords: Magnetic resonance imaging; Magnetic resonance spectroscopy; Neonatal hypoxic ischemic encephalopathy .

DOI: 10.21608/svuijm.2020.42497.1000

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Received: 10 September,2020.

Revised: 20 September, 2020.

Accepted: 30 September,2020.

Published: 30 September, 2023

Cite this article as: Barakat Mohammed Mahmoud, Mohammad Tharwat Mahmoud Solyman , Mohammad Zaki Ali , Khaled Fawzy Zaki (2024). Magnetic Resonance Imaging and Magnetic Resonance Spectroscopy in Neonatal Hypoxic-Ischemic Encephalopathy: A review article. *SVU-International Journal of Medical Sciences*. Vol.7, Issue 1, pp: 8-16.

Introduction

Perinatal hypoxia-ischemia is one of the most important causes of infant morbidity and mortality worldwide primarily in developed countries. HIE is a brain injury secondary to lacking blood flow to the newborn brain occurring because of a HI incident during the antenatal, natal or post-natal period **(Martinello et al., 2017).**

Neonatal encephalopathy can be the result of widely variable conditions. Birth asphyxia and hypoxic-ischemic (anoxic) encephalopathy are responsible for furthermost of the cases **(Melhem et al., 2002).** Ultrasound, Head computed tomography, and conventional magnetic resonance imaging (MRI) are useful to diagnose brain injury but cannot tell the degree of white matter damage **(Al-Macki et al., 2009).**

Embryonic brain development

In embryogenesis, there is a movement of undifferentiated embryonic cells to definite sites and which results in conversion of the embryo into a three-layered structure. The anterior part of this structure develops the endoderm, the middle portion progresses into the mesoderm, and the posterior division gives the ectoderm. The latter layer will deliver the central nervous system (**Cheong et al., 2009; Hayes et al., 2016**).

The closure of neural tube progresses in an anterior to the posterior pattern. The anterior portion swells into three vesicles: 1. Forebrain 2. Midbrain and 3. Hindbrain (**Hayes et al.,2016**).

Neural stem cells will later give the cerebral ventricles. Once neurons are developed, they migrate to their designated place following an inside-out pattern (**Cheong et al. 2009, Hayes et al. 2016**).

Causes of HII

Diminished cerebral blood may be produced by fetal factors as feto-maternal hemorrhage or maternal factors as impaired maternal oxygenation as in asthma and pulmonary embolism **(Bonthius and Perlman, 2007**).Postnatal hypoxia may have caused by hyaline membrane disease, sever pneumonia, or congenital heart anomalies. The fetal vascular and cardiac compromise will cause impaired brain circulation, loss of cerebral auto-regulation, and neuronal cell death with subsequent gliosis (**Shalak and Perlman, 2004; Chao et al., 2006; de Vries and Cowan, 2009).**

Stages of cerebral injury

The dangerousness of hypoxic ischemic encephalopathy depends on the period and extent of neonatal brain injury. Pathological events happen in a cascade manner in two stages: primary and secondary energy failure. In the primary stage, healing process begins in the first 60 minutes after the acute insult of the brain injury. In the latent phase (in between 1 to 6 hours), oxidative metabolism, inflammation, and continuation of the activated apoptotic cascades ensues **(Bennet et**

al., 2006). Depletion of phosphate reserves, and liberation of excitatory neurotransmitters and free radicals occurs in the second energy failure phase about six to 48 h after a hypoxic-ischemic brain injury **(Laptook, 2009).**

Clinical Manifestations of hypoxic-ischemic encephalopathy

The HIE neonate displays low Apgar scores (bradycardia, decreased effort and level of awareness, abnormal coloration, hypotonia, poor respiration and lethargy) at time of birth. Metabolic acidosis identified in umbilical arterial cord blood (acidemia). Neonates may develop apnea and convulsions within the first 24 hours of life with abnormal electroencephalographic findings in EEG **(Shalak and Perlman, 2004).**

Imaging of neonatal HIE

A) Ultrasound

Transcranial sonography is noninvasive, effortless and costless. In the thalami, putamena, globi pallidi and periventricular white matter; hyper echoic areas may be appreciated. Effaced sulci from brain edema and marked attenuated cerebral ventricles may also be present (**Clements et al., 2006**). Ultrasound is not full optimal for assessment of HII as a result of its operator dependency, reduced specificity and sensitivity. US can't identify cortical and subcortical watershed zone injuries. MR imaging is the modality of choice in diagnosis of HIE (**Clements et al., 2006).**

B) Computed tomography

CT brain is less sensitive in assessment perinatal HIE as neonatal brain contain excess water and high protein in CSF, both results in less differentiation and haziness of subcortical white matter, also the exposure to radiation has many disadvantages **(Witte-Meyer et al., 2006).**

C) Magnetic resonance imaging

Nearly most neonatal MRI brain examinations are done by using 1.5-T systems. The newborn brain contains high water and low protein so that it exhibits long T1 and T2 relaxation times. To increase cortico-medullary differentiation on T1 and T2 –weighted MRI, repetition time must be increased. The standard TR on T1-weighted MRI sequences is better to be elevated up to (800–850) msec. The standard TR on T2-weighted MRI sequences should be 9000–10,000 msec **(Jones et al., 2004).**

D) Protocol for MRI evaluation of neonatal hypoxic- ischemic encephalopathy

Axial T1-weighted MRI sequence, is ultimate for revealing of white matter myelination , ischemic lesion and subacute bleeding in basal ganglia , thalami and posterior limbs of the internal capsules **(Fig.1**) . Neonates with perinatal hypoxia are usually examined by proton MRS on three echo times 35, 144 and 288 msec , intermediate echo time (144 msec) is mostly used , the region of interest placed on basal ganglia and thalami for identifying lactate concentrations , and

elevated lactate-to-creatine ratio **(Robertson et al.,1999),** and diminished concentrations of NAA, elevated lactate levels in basal ganglia and thalami affects the prognosis of disease and primary outcome**.** The radiologist must do rapid revision for MRI brain sequences immediately after the study, to avoid unnecessary retransforming of diseased neonate from neonatal care unite (**Boichot et al., 2006).**

MRI Findings in Full-Term Neonates

Axial T1WI may display lesions of bright signal 3 days after HII (first three days after brain injury). Axial T2WI shows lesions of bright signal 6-10 after HII, bright signal seen specifically in ventrolateral thalami and basal ganglia **(Barkovich et al., 1995).** The posterior limb of the internal capsule shows loss of its normal bright signal; loss of this bright signal indicates poor prognosis and mostly abnormal outcome (**Rutherford et al., 1998).**

Axial T1WI, Axial T2WI and FLAIR may assess HII with low sensitivity, FLAIR can detect early sever lesions displayed as bright signal. DWI is very sensitive in detection of early lesions in first 5 days, displayed as bright signal, and most of these lesions become normal gradually later on (**Rutherford et al., 2004).**

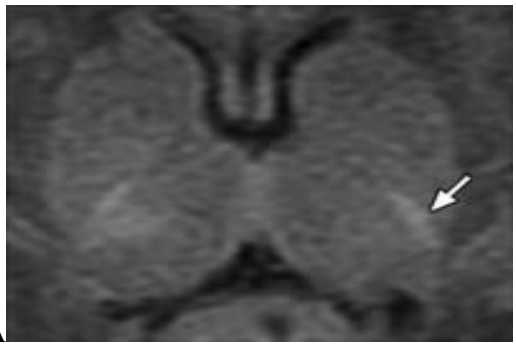
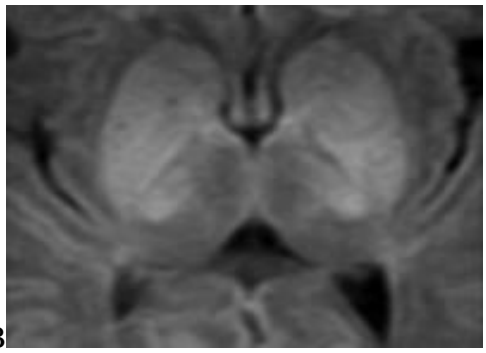
A  B 

Fig.1. (A) MRI examination; Axial T1W1 shows normal preserved bright signal of posterior limbs of both internal capsules. **(B)** MRI examination; Axial T1W1 in neonate with HIE shows loss of normal bright signal of posterior limbs internal capsules with bright signal of both ventrolateral thalami and putamen (**Robertson et al. 1999**).

Recent MRI techniques in the assessment of hypoxic-ischemic encephalopathy

I- Diffusion tensor imaging

The diffusion of free water molecules in the white matter is uneven in all directions of three-dimensional space (anisotropy). It is changed by macro and microstructural elements. The intra-axonal organization has extreme influence on diffusion anisotropy; other features include the thickness; individual fiber diameter and gradation of myelination also has effect on it. The changeability in the orientation of all white matter tracts in an imaging voxel affects the degree of anisotropy assigned to that voxel (**Provenzale et al., 2007).**

MR imaging sensitized to the water motion in the direction of the field gradient. This gradient pulse configuration is frequently known as diffusion weighting. Water diffusion is affected by tissue macro and microstructure **(Melhem et al., 2002).**

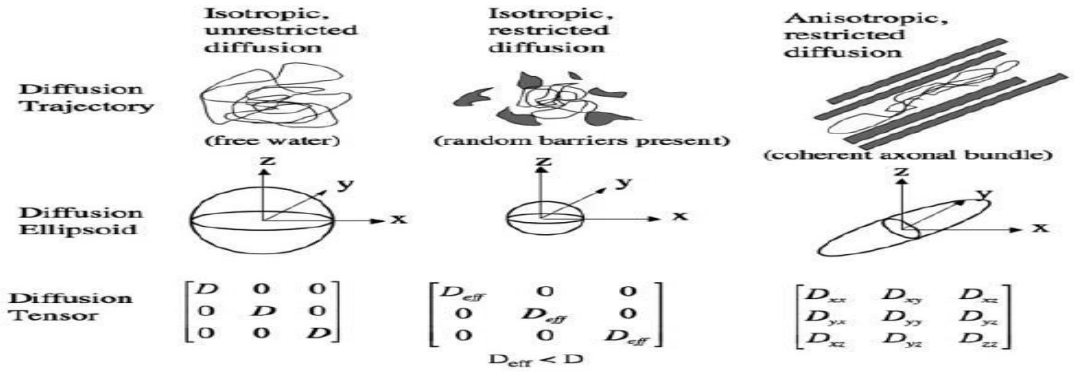


Fig.2. Diagram displaying the diffusion ellipsoids and tensors for isotropic non restricted diffusion, isotropic restricted diffusion, and anisotropic restricted diffusion (**Mukherjee et al. 2008).**

II- Magnetic resonance spectroscopy

Brain metabolites as NAA increase significantly within first 3 months, then gradually and slowly increase **(Robertson and Wyatt 2004)** (**Fig.3**).

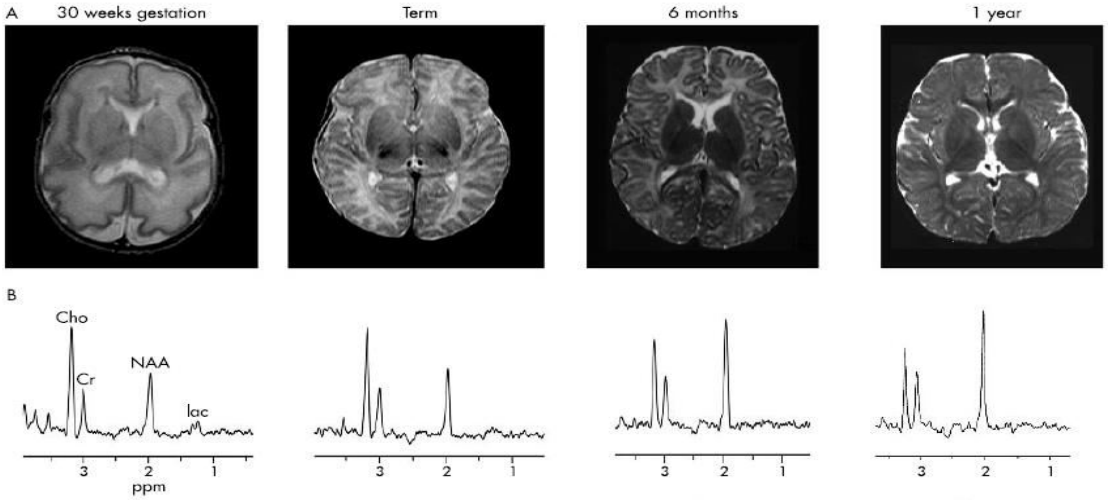


Fig.3. Age-related MRS changes. A) Axial T2 WI; The images display development of gyri and sulci with increased brain volume. (B) Series of proton MRS shows gradual increase in NAA and decrease in lactate concentrations **(Robertson and Wyatt2004).**

Normally, the neonatal brain has a negligible concentration of lactate, due to rapid brain development and maturation. Yet significant amounts of lactate could be detected in patient with HIE (**Fig.4**) (**Barkovich et al. 2006**). Patients with HII, anaerobic oxidation causes increased lactate

concentrations it has direct relationship with severity of disease , also lactate level assessment by MRS is used in follow up and monitoring of patients undertaking cooling therapy **(Barkovich et al. 2006**).

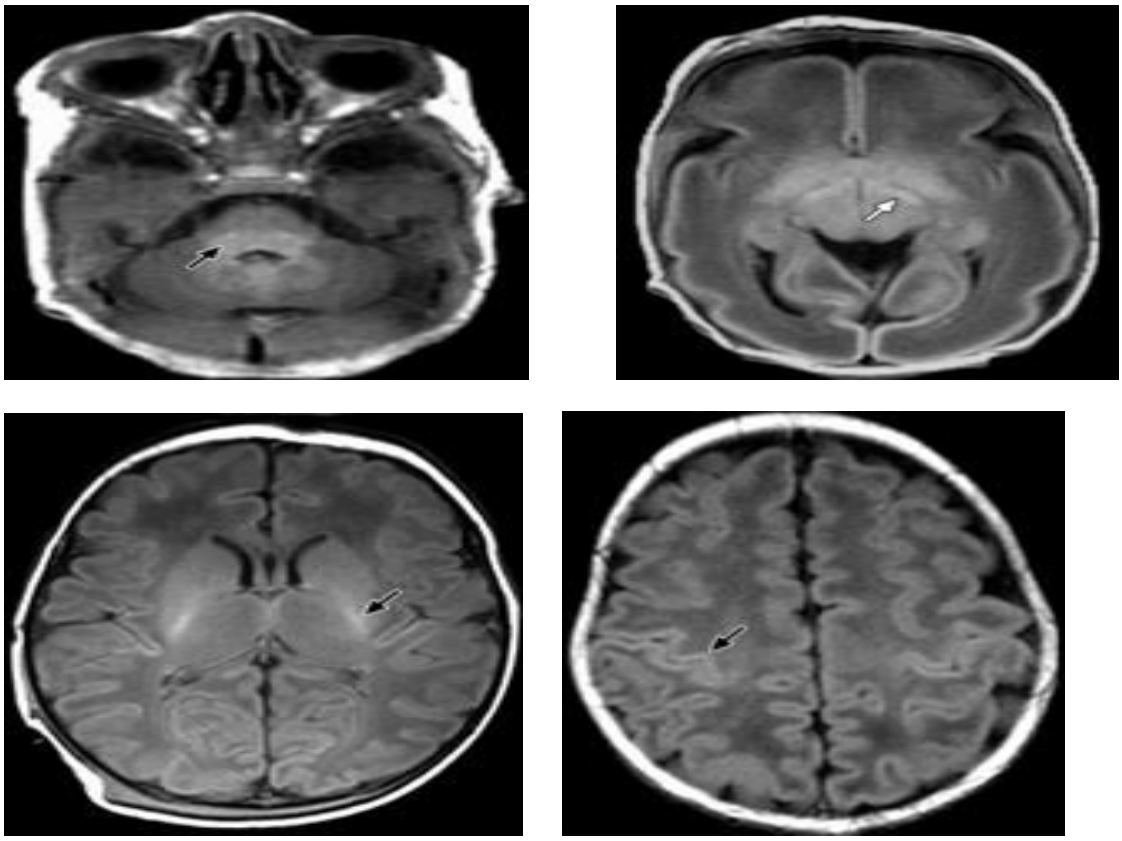


Fig.4. Brain development and early myelination patterns . (A, B) Axial T1WI MRI shows bright signal at dorsun of brain stem (A) and subthalami (B) (28 weeks gestation). (C, D) Axial T1WI shows bright signal in posterior limb internal capsule (C) and prrirolandic cortex (D) (38 weeks gestation) ***(*Counsell et al. 2002).**

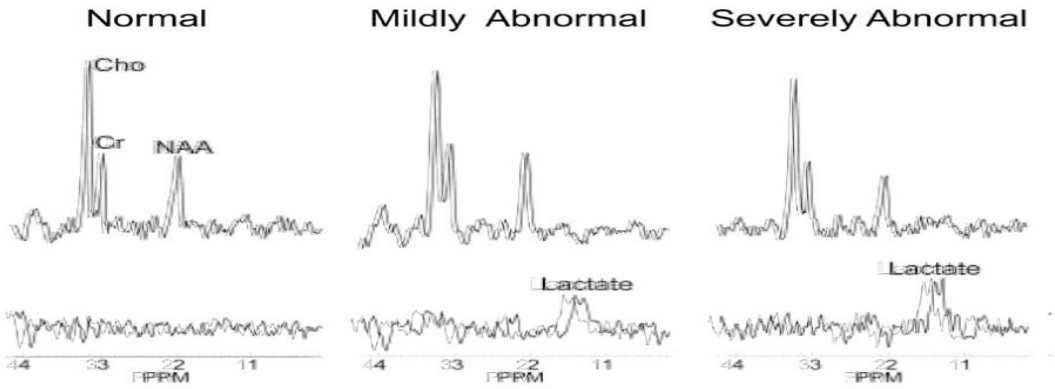


Fig.5. Metabolic profile of neonates with variable grades of HII, displaying significant increase in concentration of lactate directly related to severity of disease and decrease in NAA in lactate levels and related decrease in NAA indirectly related to severity of disease **(Barkovich et al. 2006).**

Conclusions

MR spectroscopy is an accurate, sensitive and non-invasive method for early detection of perinatal ischemic brain injuries. However, the specificity of this maneuver is very low, especially if used in the prediction of poor outcome

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