Review Article

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Neuroimaging in neonatal encephalopathy

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ABSTRACT

Neonatal encephalopathy (NE) is a significant problem and is associated with high morbidity and mortality. NE can result from diverse etiologies. Identifying the etiology of NE can guide us in giving appropriate treatment. Magnetic resonance imaging (MRI) is the most common modality of neuroimaging used in evaluation of NE. Conventional MRI sequences along with advanced MRI techniques such as magnetic resonance spectroscopy and diffusion weighted imaging are useful in identifying the etiology of NE. This review elaborates the role of MRI in various etiologies of NE.

Keywords: Neonatal encephalopathy, Etiology, Hypoxic ischemic encephalopathy, Magnetic resonance imaging, Diffusion weighted imaging

INTRODUCTION

Neonatal encephalopathy (NE) is a clinically defined syndrome of disturbed neurologic function in the earliest days of life in an infant born at or beyond 35 weeks of gestation, manifested by a subnormal level of consciousness or seizures, and often accompanied by difficulty with initiating and maintaining respiration and depression of tone and reflexes.¹

The incidence of NE from the published literature varies between 2.5 to 8.5 per 1000 live births. ²⁻⁴ NE can be caused by various etiologies such as hypoxic ischemic encephalopathy (HIE), genetic disorders, metabolic disorders, perinatal infections, neonatal stroke and thrombophilia (Figure 1).

Clinical evaluation alone cannot provide adequate information regarding etiology, diagnosis and prognosis. Magnetic resonance imaging (MRI) is the neuroimaging modality of choice in evaluating NE. MRI especially with advanced MRI techniques such as magnetic resonance spectroscopy (MRS) and diffusion weighted imaging (DWI) plays an essential role in determining the etiology,

extent of neuronal injury and also in predicting the outcome. Even though neurosonogram is considered as the first line imaging for evaluation of neonatal brain, because of its easy availability and portability, MRI is considered as the neuroimaging of choice because of greater sensitivity and specificity, also because of its ability to perform functional imaging of brain.⁵

This paper is a review of role of MRI in neonatal encephalopathy in identifying various etiologies of NE, with importance of advanced MRI techniques such as MRS and DWI.

HYPOXIC ISCHEMIC ENCEPHALOPATHY

HIE is the most important cause of neonatal mortality and morbidity with long term neurological sequelae. HIE is considered as a subset of neonatal encephalopathy.

The incidence of HIE varies from 1.3 to 1.7 per 1000 live births.^{3,4} The pattern of brain injury in HIE depends on the severity, duration and recurrence of hypoxic ischemic event which can lead to involvement of basal ganglia, thalami and/or cerebral cortex.⁶

The brain injury pattern differs according to the type of hypoxic ischemic event, whether it is severe total hypoxia or prolonged partial hypoxia. The term "severe total hypoxia" refers to sudden total loss of oxygenation, which is seen in cases of placental abruption. The term "prolonged partial hypoxia" refers to a more sustained, but incomplete, loss of oxygenation, such as that seen in prolonged difficult labour with prolonged decelerations, repetitive late decelerations, and decreased heart rate.

Even though brain injury pattern depends on type of hypoxic ischemic event, some infants may have features of both types of injury. MRI findings in these two types of hypoxic ischemic events are given in Table 1. Miller et al reported two patterns of brain injury in MRI done for babies with NE, watershed predominant injury pattern was seen in 45% of cohorts and basal ganglia/thalamus predominant pattern was less common and seen in 25% cohorts. 8

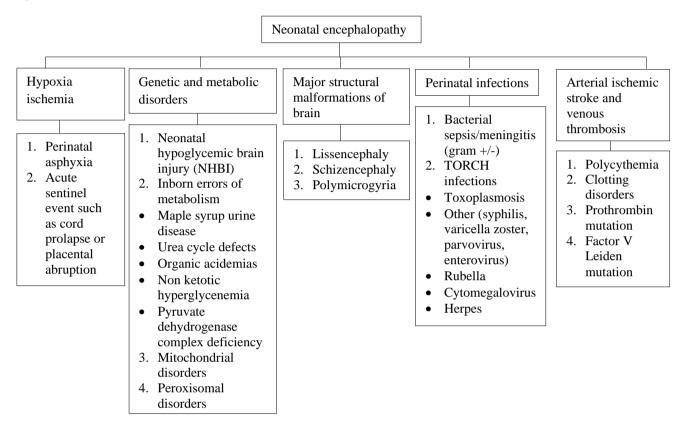


Figure 1: Various etiologies of neonatal encephalopathy.

Table 1: MRI findings in two types of hypoxic ischemic events.

Severe total hypoxia (Figure 2)	Partial prolonged hypoxia (Figure 3)
Increased signal intensity of basal ganglia on T1 weighted images	Marked cortical signal changes
Increased signal intensity in the thalamus on T1-weighted images	Three patterns of hypo perfusion injury seen are
Absence of the normal increased signal intensity in the posterior limb of the internal capsule on T1 weighted images "absent posterior limb sign"	Periventricular leukomalacia – hypo perfusion of fetal circulation, mostly seen in preterm
Diffusion restriction in the affected areas, seen as hyperintense lesions in DWI with corresponding hypointense lesions in apparent diffusion co-efficient (ADC) mapping	Bilaterally symmetric changes are located at the watershed zones between the anterior–middle cerebral artery territories and the middle–posterior cerebral artery territories
MR spectroscopy findings such as increased choline relative to creatine, decreased N-acetylasparatate (NAA) and presence of lactate peak	"Deep watershed ischemia," - typically seen in the centrum semiovale at an intermediate location between the lateral ventricle and the brain cortex.

Sie et al reported three patterns of hypoxic-ischemic brain damage after prenatal, perinatal or postnatal asphyxia. In the first pattern, signal abnormalities were predominantly located in periventricular white matter (PVL), in the second pattern lesions were predominantly located in the basal ganglia or thalamus or both (BGTL), and the third pattern consisted of a multicystic encephalopathy (MCE), with multiple large cavities in white matter associated with

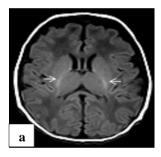
variable degree of cortical, basal ganglia or thalamic damage.⁹

METABOLIC ENCEPHALOPATHY AND INBORN ERRORS OF METABOLISM

Metabolic disorders should be considered as the cause of NE, if there is no clear intrapartum event, persistent lactic acidosis and/or hypoglycaemia.⁵

Neonatal hypoglycemic brain injury (NHBI)

Most common metabolic encephalopathy encountered in neonatal intensive care unit (NICU) is NHBI. The spectrum of cerebral injury associated with hypoglycaemia is wide and includes, white matter injury including parenchymal haemorrhage and ischemic stroke, cortical neuronal injury, and sometimes signal change in the basal ganglia (mainly the globus pallidus) and thalami 4–15. Vulnerability of the posterior parietal and occipital lobe white matter and cortex has been well reported in MRI studies (Figure 4), but the exact reason why these areas are specifically involved is not known. ¹⁰



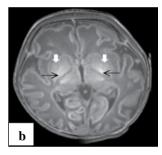
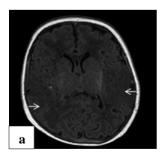


Figure 2: HIE—severe total (a) axial T1 weighted image of a day 5 old term normal neonate (arrow) showing bilateral hyperintense posterior limb of internal capsulead (b) axial T1 weighted image of a day 6 old term neonate suffered severe total hypoxia (black arrow) showing bilateral hypointense posterior limb of internal capsule and (bold white arrows) hyperintense basal ganglia.



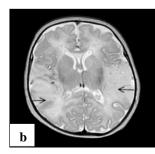


Figure 3: HIE-partial prolonged (a) axial T1 weighted image of a day 6 old term neonate showing (white arrows) large area of hypointense lesion involving bilateral parietal lobes, and (b) axial T2 weighted image of the same neonate showing (black arrows) large are of hyperintense lesion involving bilateral parietal lobes with loss of sulci gyri differentiation.

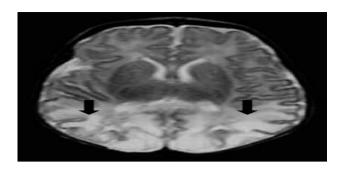


Figure 4: Hypoglycemic brain injury-axial T2 weighted image (black arrows) showing large area of hyperintense lesion involving bilateral parieto occipital lobes.

Millichap in his study of 35 term infants with symptomatic hypoglycemia reported that MRI revealed white matter abnormalities in 94% of infants, severe in 43%, predominantly posterior in location in 29%, and hemorrhagic in 30%. Cortical abnormalities occurred in 51% infants, basal ganglia/thalamic lesions in 40%, and abnormalities of the posterior limb of the internal capsule in 11%. Middle cerebral artery infarctions were present in 3 infants. Patterns of injury were not correlated with severity or duration of hypoglycaemia. 11

Wong et al reported that selective posterior white matter and pulvinar edema were most predictive of clinical hypoglycemia, and a watershed pattern of injury was seen more often in severe hypoglycaemia. ¹²

Inborn errors of metabolism (IEM)

Even though IEM are considered rare, they produce a significant clinical impact and constitute a diagnostic challenge to clinicians. Accurate diagnosis is necessary treatment and parental counselling, and also useful for prenatal counselling and antenatal diagnosis in subsequent pregnancies.

Maple syrup urine disease

Classical maple syrup urine disease (MSUD) is caused by deficiency of branched-chain ketoacid dehydrogenase (BCKDH), a mitochondrial enzyme in the degradation pathway of the branched-chain amino acids (BCAAs; leucine, isoleucine, and valine) and their ketoacid derivatives (BCKAs). Acute elevations of leucine and alpha-ketoisocaproic acid (aKIC) cause metabolic encephalopathy and life-threatening brain edema, whereas prolonged imbalances of circulating amino acids may have more subtle and lasting effects on brain structure and function.¹³

Early diagnosis is essential for the reversal of MSUD encephalopathy and delayed treatment can lead to death. The proposed mechanism of brain damage in patients with MSUD is accumulation of BCAA in the brain inhibits the activity of pyruvate dehydrogenase and α -ketoglutarate

dehydrogenase, disrupting the citric acid cycle and consequently the synthesis of amino acids, causing intramyelinic edema. MSUD patients have shown signs of both diffuse edema and intense local edema during the acute phase of the disease. DWI is an MRI technique that can identify cytotoxic or intramyelinic edema.

DWI is the best choice for detecting MSUD encephalopathy in neonates. Both diffuse cerebral edema and intense localized edema, called MSUD edemas have been found in neonates with MSUD encephalopathy. MSUD edemas mainly involve the cerebellar white matter, brainstem, globus pallidus, internal capsule, and thalamus and typically occur in myelinated areas of brain in normal full-term neonates (Figure 5). ¹⁴

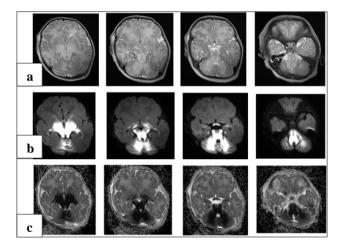


Figure 5: Maple syrup urine disease (a) axial T2 weighted image of a 21 day old neonate showing hyperintense signals in cerebellar white matter, cerebral peduncles and dorsal brainstem, (b) DWI of the same neonate showing hyperintense signals in the above mentioned areas and (c) ADC mapping of the DWI showing hypointense signals indicating there is diffusion restriction because of intramyelinic edema.

Urea cycle defects

In urea cycle disorder, different parts of brain have different sensitivities to damage because hyperammonemic episodes. The age at which hyperammonemia occurs, as well as the duration affects brain MRI findings and neurological sequelae. Mild hyperammonemia and/or hyperammonemia of short duration causes less damage, affects only the most sensitive areas and results in limited or no long-term neurological sequelae. More severe and prolonged episodes of hyperammonemia cause more widespread neurological damage, affect areas more resistant and have more severe neurological sequelae. MRI abnormalities reveal that there is differential distribution of brain involvement.

The most important factor in differentiating the severity of neurological sequelae were the presence or absence of restricted diffusion. The observed trend in distribution as the severity of neurological sequelae increased was the peri-insular region first, extending into the frontal, parietal, temporal and, finally, the occipital lobes. Restricted diffusion in the basal ganglia and the thalami has been reported, as the severity of hyperammonemia increased.

MRS also demonstrates the presence of elevated glutamate/glutamine in urea cycle disorders. 15

Organic acidemias

Organic acidemias are an important group of autosomal recessive inborn errors of metabolism. These errors are caused by defects in the intermediary metabolic pathways of carbohydrates, amino acids, and fatty acid oxidation, leading to the accumulation of organic acids in tissues and the subsequent excretion of these acids in urine.

Neuroimaging findings in organic acidemias are nonspecific. DWI depicts early parenchymal changes and enables characterization of different types of parenchymal edema—mainly cytotoxic (i.e. with low apparent diffusion coefficient [ADC] values) and vasogenic (i.e. with increased ADC values) edema. MRS is a powerful adjunct used to study various brain metabolites. ¹⁶

Non ketotic hyperglycinemia

Non ketotic hyperglycinemia (NKH) is an autosomal recessive inborn error of metabolism due to a defect in the glycine cleavage system. It is characterized by the accumulation of large amounts of glycine in plasma and CSF. The elevated glycine levels result in the devastating neurological manifestations of the disease including hypotonia, myoclonus, seizures, poor feeding, and respiratory depression.

The characteristic MRI findings of NKH include increased T2 signal and restricted diffusion confined to the white matter tracts that are normally expected to be myelinated at a given age. At birth, when most patients present, these comprise the corticospinal tracts, including the posterior limbs of the internal capsules, dorsal pons, and cerebellar white matter. The restricted diffusion observed is postulated to be secondary to the accumulation of fluid between the layers of the myelin lamellae.

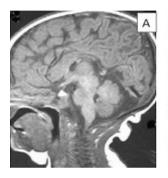
MR spectroscopy shows elevated glycine levels in the brain of patients with NKH.¹⁷

Pyruvate dehydrogenase complex deficiency

Pyruvate dehydrogenase (PDH) deficiency is a common cause of primary congenital lactic acidosis. The PDH enzyme complex is a key intra mitochondrial complex that catalyzes the oxidative decarboxylation of pyruvate to acetyl-CoA, thereby controlling the flow of substrates from the glycolytic pathway to the citric acid cycle.

Defects in the E1 alpha subunit gene (PDHA1; EC 1.2.4.1) on Xp21.3 account for most cases of PDH deficiency.¹⁸

MRI in neonates with PDH deficiency shows severe decrease in white matter volume, dilated ventricles with ventricular septations, or parenchymal cysts and partial to complete agenesis of the corpus callosum (Figure 6). The findings of markedly asymmetric white matter involvement and parenchymal cysts in MRI of a term neonate are more likely to be observed in PDH deficiency than in preterm periventricular leukomalacia or hypoxic ischemic injury.



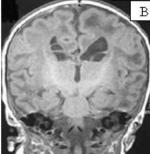


Figure 6: Pyruvate dehydrogenase complex deficiency (A) axial T1 weighted image on a day 7 old neonate showing decrease in white matter with partial agenesis of corpus callosum, and (B) coronal T1 weighted image showing ventricular dilatation with parenchymal cysts.

Ventricular enlargement in PDH deficiency is probably the result of severe white matter volume loss. The observed small size of pons and corpus callosum may be due to developmental loss of cerebral white matter. These structural defects in PDH deficiency are due to a prenatal destructive process resulting from a metabolic defect of selected cells. MR spectroscopy of basal ganglia reveals lactate peak in PDH complex deficiency.¹⁹

Mitochondrial disorders

The term "mitochondrial cytopathy" is used clinically and refers to the group of inherited heterogeneous disorders due to the dysfunctional mitochondrial respiratory chain, manifesting in the central nervous system plus or minus other organs.²⁰

Focal, bilateral, symmetric brain lesions involving basal ganglia and periaqueductal gray matter are typical of Leigh syndrome (sub-acute necrotizing encephalomyelopathy). Patients with MELAS have a characteristic imaging pattern, stroke in nonvascular territories especially infarct in the parieto-occipital region, which may be unilateral or bilateral.

Cerebral atrophy is a common, but nonspecific finding in mitochondrial disease that may occur in multiple mitochondrial subgroups. Cerebellar atrophy might be the primary neuroimaging feature in some patients with mitochondrial disorders, particularly in infants. Cerebral white matter involvement or leukodystrophy is commonly seen in childhood onset mitochondrial disorders. Several of the mitochondrial disorders present with widespread leukodystrophy. Another common radiological finding is that of "delayed myelination".²¹

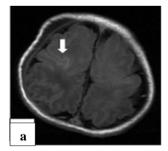
MRS has been shown to detect abnormal accumulation of lactate in brain parenchyma and CSF in patients with mitochondrial disorders. MRS provides a non-invasive tool for the diagnosis of mitochondrial diseases, especially in children with nonspecific findings on MRI, normal appearing MRI or a normal blood lactate/pyruvate ratio.²²

Peroxisomal disorders

Peroxisomes are cellular organelles responsible for the oxidative catabolism of very long chain fatty acids, the decomposition of hydrogen peroxide, and the biosynthesis of phospholipid molecules, which serve as the precursors to myelin production in the central nervous system.²³

Disorders of peroxisomal function can arise in two ways, either by absence of a specific peroxisomal enzyme or by a failure to form normal peroxisomes, resulting in generalized or multiple deficiencies of peroxisomal enzymes.²⁴

The second category is called peroxisome biogenesis disorders (PBD), mutations in peroxisome biogenesis factor (PEX) genes results in PBD. The spectrum includes Zellweger syndrome (ZS), neonatal adrenoleukodystrophy (NALD), infantile Refsum disease and rhizomelic chondrodysplasia punctata with Zellweger syndrome representing the most severe end of the spectrum. Neuroimaging findings in Zellweger syndrome, the prototype PBD are hypomyelination of the white matter and are believed to be related to the destabilizing effect of VLCFA on myelin, and decreased N-acetyl asparatate (NAA) in proton MRS (Figure 7).



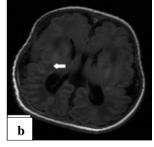
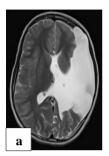


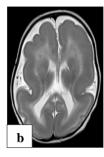
Figure 7: Peroxisome biogenesis disorder–Zellweger syndrome (a) axial T1 weighted image showing (white arrow) polymicrogyria in perirolandic cortex and (b) same patient with polymicrogyria in perisylvian region with white matter abnormality.

NALD shows severe white matter abnormalities in MRI, due to almost complete absence of myelin, and are usually more severe in NALD than in ZS.²⁵

MAJOR STRUCTURAL MALFORMATIONS OF BRAIN

Neonates born with major structural malformations (Figure 8) like lissencephaly, schizencephaly and polymicrogyria can present with NE.





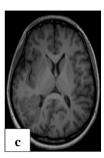


Figure 8: Major structural malformations of brain (a) schizencephaly – axial T2 weighted image showing absent septum pellucidum with a large grey matter lined cleft in cerebral cortex, (b) lissencephaly – axial T2 weighted image showing reduced gyration with shallow sylvian fissure, cerebral cortical thickening and subcortical band heterotopia, and (c) polymicrogyria – axial T1 weighted image showing increased gyration in perisylvian area, perirolandic cortex and posterior interhemisphere.

Lissencephaly ("smooth brain", LIS) is a malformation of cortical development associated with deficient neuronal migration and abnormal formation of cerebral convolutions or gyri. The LIS spectrum includes agyria, pachygyria, and subcortical band heterotopia.²⁶

Schizencephaly or developmental porencephaly, as it has been termed by some authors - is an uncommon disorder of neuronal migration or neuronal proliferation, usually presenting in childhood with partial seizures, hemiparesis and it also rarely present in neonates with microcephaly, seizures and neonatal encephalopathy.²⁷

Polymicrogyria results from a developmental disorder or injury that occurs toward the end of the period of neuronal migration and the early phase of cortical organization. Polymicrogyria most commonly seen in the bilateral perisylvian area. Perisylvian polymicrogyria (both unilateral and bilateral) has been found in several chromosomal aneuploidy syndromes, most prominently with deletion of the chromosome 22q11.2 in DiGeorge syndrome.²⁸

PERINATAL INFECTIONS

Bacterial sepsis/meningitis

Bacterial infections manifest in the form of meningitis, cerebritis, ventriculitis, epidural abscess, subdural empyema, and cerebral abscess. Meningitis is the most common form of bacterial infection of CNS in children. The causative organism varies by age group. In the

neonate, group B Streptococcus, Escherichia coli, Staphylococcus sp., Listeria monocytogenes and Pseudomonas sp., are the most common pathogens. Bacterial meningitis usually produces variable signs and symptoms such as low grade fever, bulging fontanel, poor feeding, lethargy, vomiting, seizures, coma and neonatal encephalopathy.²⁹

MRI may be normal during early stage of uncomplicated meningitis, CSF demonstrating abnormal white blood cell count is diagnostic. After intravenous contrast administration, meningeal enhancement may be seen, but this is a nonspecific finding and may also be seen in, for example, leptomeningeal carcinomatosis, and post lumbar puncture or in children with intracranial hypotension related to over shunting.

MRI is most sensitive to complications of meningitis include adjacent vasogenic or cytotoxic brain edema, focal ischemic injury, hydrocephalus and subdural, epidural or parenchymal abscesses and ventriculitis. Infarctions best identified on DWI, vasculitis and other vascular complications like focal stenosis, irregularities of intracranial arteries and dural sinus thrombosis are best identified using MR angiography and perfusion weighted imaging (PWI). PWI may show focal regions of hypoperfusion.³⁰

TORCH infections

Infections of the fetal nervous system differ from those of older children and adults in that they act on the developing nervous system. The manifestations and outcomes of these infections differ depending upon the age of the fetus at the time of infection and to a lesser extent upon the virulence of the infecting agent.

Toxoplasmosis

In utero infection with *Toxoplasma gondii* it is the second most common congenital infection after cytomegalovirus (CMV). Transplancental infection rates increases during progressing pregnancy from less than 20% in the first trimester to more than 60% in the third trimester. The incidence of fetal infection inversely correlates with severity of fetal damage at different pregnancy stages. MRI may reveal a diffuse inflammatory infiltration of the meninges or a diffuse inflammation of the brain. Hydrocephalus is most often present and is caused by an ependymitis occluding the aqueduct. Severe disease may produce porencephaly or hydranencephaly. Calcifications are common and they are usually seen in the basal ganglia, periventricular region, cerebral cortex and subcortical white matter.

Cytomegalovirus

It most commonly encountered TORCH infection with incidence rates between 30,000 and 40,000 cases per year in the United States. Congenital CMV is the most common

cause for infectious hearing loss. The timing of infection during pregnancy correlates with the severity of findings on imaging. Early infections around 16-18 weeks of gestation result in lissencephaly, whereas later infections around 18–24 weeks of gestation may cause polymicrogyria. Finally, later infection may result in an anatomically, normal appearing brain. Additional neuroimaging findings in congenital CMV infection include ventriculomegaly, abnormal white matter signal intensity, which is particularly located in the temporal lobes and represents delayed or deficient myelination, cysts in the anterior portion of the temporal lobes, intracranial calcifications and cerebellar hypoplasia.

Rubella

It is caused by Toga virus and it shows a predilection for the central nervous system. Neuroimaging findings in the setting of congenital infection may include the presence of subcortical hypodensities on computerised tomography and corresponding to areas of T2 hyperintensity on MRI and the presence of periventricular and basal ganglia calcifications. Cerebellar hypoplasia and neuronal migration anomalies have also been reported.

Herpes virus

Most of the herpes virus (HSV) infections in neonates are not strictly congenital, but occur in the perinatal/neonatal period and result from exposure to maternal HSV type 2 genital lesions at the time of vaginal birth. Infections due to HSV-2 strain produce greater morbidity than HSV-1 strain. HSV infection in adults preferentially involves frontal and temporal lobes, but in neonates it affects the deep and periventricular white matter. MRI is the most sensitive modality for the detection of HSV in the CNS. DWI has been reported to be more sensitive than T2 or FLAIR imaging. HSV infections of the CNS typically show a pattern of cortical restricted diffusion.

Other viruses like *Parvovirus B19* and *Varicella* produce lesions in brain similar to HSV.

Congenital syphilis

Here, the most common neuroimaging findings are leptomeningeal enhancement, hydrocephalus and infarction.³¹

ARTERIAL ISCHEMIC STROKE AND VENOUS THROMBOSIS

Focal clonic seizures are the most common presentation of neonatal stroke. 4% cases of neonatal stroke are due to asphyxia. Blood clotting disorders like polycythemia, factor V Leiden mutation, prothrombin mutations may also cause neonatal stroke.

Areas of arterial ischemic stroke appear as hyperintense lesion in T2 weighted images in the corresponding arterial

territory. MR angiography and MR venography used to identify the vascular occlusion (Figure 9).³²

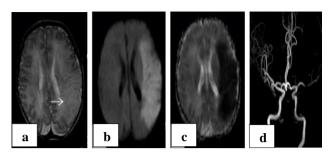


Figure 9: Neonatal stroke (a) axial T2 weighted image in a day 4 old neonate showing (white arrow) hyperintense lesion involving left middle cerebral artery (MCA) territory, (b) DWI showing hyperintense lesion in the above said area, (c) ADC mapping showing hypointense lesion corresponding to the DWI suggestive of diffusion restriction because of cytotoxic edema, and (d) magnetic resonance angiogram showing occlusion and decreased blood flow in left MCA.

CONCLUSION

Neuroimaging has been made as an indispensable thing in neonatal management, because of advances in neonatal intensive care leading to improved survival than before. Early diagnosis and evaluation is more important in case of neonatal encephalopathy, which is necessary for successful treatment and improving the outcome. Moreover, in view of emergence of successful therapeutic interventions like therapeutic hypothermia for HIE, early and appropriate diagnosis is much more important.

MRI can provide valuable information regarding the presence and extent of brain injury. MRI along with advanced techniques such as MRS, MRA and DWI useful for attaining the specific diagnosis of the etiology of neonatal encephalopathy. However MR images can overlap between different etiologies, correlation with clinical history and physical examination is more important. Sometimes combination of conditions like presence of HIE with infections or HIE with trauma, may pose diagnostic challenges.

The scope of neuroimaging in NE will expand in future with the advancement of newer imaging techniques in MRI.

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