MR Imaging for diagnostic of metabolic encephalopathy

Poster No.: C-2142
Congress: ECR 2014
Type: Educational Exhibit
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Keywords: Foetal imaging, Head and neck, MR-Spectroscopy, MR-Diffusion/Perfusion, MR-Functional imaging, Diagnostic procedure, Imaging sequences, Metabolic disorders, Seizure disorders
DOI: 10.1594/ecr2014/C-2142

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Learning objectives

The purpose of our study was to review the use of MR techniques to determine the type of metabolic encephalopathy, to describe MR imaging finding and to become familiar with major causes of metabolic encephalopathy.

Background

We report a retrospective study that evaluates 51 cases with metabolic encephalopathy, seen from January 2009 to March 2013. All patients undergo cerebral MR imaging.

Clinical presentation was characterized by varied neurological manifestations ranging from a simple partial seizures (n = 20), mental retardation (n = 6), confusion (n = 9), deep impaired sensitivity in anemic patients (n = 11) and Wilson's disease (n=5).

Findings and procedure details

The diagnoses obtained were as follows: 24 cases of leukodystrophy [Neonatal Adrenoleukodystrophy (NALD)(n = 2), Fahr's syndrome (n = 2), MELAS syndrome (n = 2), Krabbe Disease (n = 1), Pelizaeus-Merzbacher disease (PMD ) (n = 1)]; 5 cases of Wilson's disease; 3 cases of ketoacidosis disorder; 3 cases of hepatic encephalopathy with hyperammonemia; 2 cases of uremic encephalopathy, 11 cases of pernicious anemia and 3 cases of central pontine myelinolysis.

Introduction

The term encephalopathy refers to a clinical scenario of diffuse brain dysfunction, commonly due to a systemic, metabolic, or toxic derangement. Often the clinical evaluation is unsatisfactory in this scenario and imaging plays an important role in the diagnosis, assessment of treatment response, and prognostication of the disorder. Hence, it is important for radiologists to be familiar with the imaging features of some relatively frequently acquired metabolic encephalopathies encountered in the hospital setting.

Metabolic encephalopathy and inborn errors of metabolism
Inborn errors of metabolism, though individually rare, are collectively of considerable clinical impact and pose a diagnostic challenge to the clinicians. Accurate diagnosis is important for prenatal counseling and for antenatal diagnosis in subsequent pregnancies.

MRI is the most sensitive imaging technique for the evaluation of metabolic encephalopathy and inborn errors of metabolism. In addition, by using MRI, maturation of the developing brain can be estimated by signal intensity changes of myelination in the white matter. There is, however, substantial overlap in the pattern of imaging appearances of metabolic diseases as a group:

I. Diseases affecting Initially the white matter

1) Disease affecting initially the periventricular white matter
   - Metachromatic leukodystrophy
   - Krabbe disease
   - X-linked adrenoleukodystrophy
   - Childhood ataxia with diffuse central nervous system hypomyelination (vanishing white matter disease)

2) Disease initially affecting the subcortical white matter
   - Vander Knaap Disease
   - Pelizaeus-Merzbacher Disease
   - Cockayne Syndrome
   - Mitochondrial Diseases

II. Diseases affecting initially the gray matter
   - Juvenile Huntington disease
   - Creatine Deficiency Syndromes

III. Diseases affecting the gray matter and white matter

1) Canavan disease

2) Alexander disease

3) Peroxisomal diseases
   - Zellweger Syndrome
   - Refsum Disease

4) Wilson disease
5) Mitochondrial diseases

- MELAS
- Family Mitochondrial Encephalopathy with macrocephaly, Cardiomyopathy, and Complex I Deficiency
- Kearns-Sayre Syndrome
- Disorders Causing Leigh’s Syndrome

6) Molybdenum cofactor deficiency

7) GM1 and GM2 (Tay-Sachs and Sandhoff Diseases) Gangliosidose

**Neonatal Adrenoleukodystrophy:**

*Metabolic features*

Typical laboratory findings include increased plasma pipecolic, phytanic acid and very long-chain fatty acid levels and lead to the correct diagnosis despite the non-specific clinical presentation.

*Clinical features*

These children do not have dysmorphic features or skeletal abnormalities but involvement of the central nervous system is already apparent at birth by the presence of severe hypotonia, hearing loss, retinal degeneration and seizures.

*Imaging (Figures: 1, 2)*

Imaging findings are compatible with dys- and/or demyelination within the cerebellar and cerebral white matter. Signs of a neuronal migration disorder may also be conspicuous. The presence of contrast uptake in the involved areas described on CT images suggests an active, perhaps inflammatory process, similar to that seen within the active inflammation zone in X-linked adrenoleukodystrophy.

**MELAS syndrome**

*Metabolic features*
MELAS (mitochondrial encephalopathy with lactic acidosis and stroke-like episodes) is one of many mitochondrial disorders and is therefore inherited only from the mother (no mitochondria are passed on from the father, and they have their own DNA).

**Clinical features**

Clinical presentation is characterised by: stroke like episodes, encephalopathy, seizures, dementia, lactic acidosis, muscle weakness, deafness.

**Imaging (Figure 3)**

- chronic infarcts
  - involving multiple vascular territories
  - may be either symmetrical or asymmetrical
  - parieto-occipital and parieto-temporal most common
  - acute infarcts
  - swollen gyri with increased T2 signal
  - may enhance
  - subcortical white matter involved
  - increased signal on DWI (T2 shine through) with little if any change on ADC: thought to represent vasogenic rather than cytotoxic oedema.
  - MR spectroscopy: may demonstrate elevated lactate.

**Krabbe Disease**

**Metabolic features**

Krabbe disease (also known as globoid cell leukodystrophy) is an autosomal recessive leukodystrophy.

There are at least two recognised forms which include:

- infantile form: rapidly progressive usual onset < 2 years of age
- late onset / adult form: more slowly progressive
There is deficiency of the lysosomal enzyme galactocerebrosidase (GALC) which is a component in myelin metabolic turnover. This has been mapped to chromosome 14q.

Clinical features

Early-onset Krabbe disease:

- Changing muscle tone from floppy to rigid (decreasebrate posturing)
- Hearing loss that leads to deafness
- Failure to thrive
- Feeding difficulties
- Irritability and sensitivity to loud sounds
- Severe seizures (may begin at a very early age)
- Unexplained fevers
- Vision loss that leads to blindness
- Vomiting

Late-onset Krabbe disease:

- Vision problems may appear first, followed by walking difficulties and rigid muscles. Symptoms vary from person to person. Other symptoms may occur

Imaging

CT

- May show hyper dense areas symmetrically involving the thalami, cerebellum, caudate nuclei, posterior limbs of the internal capsule, and brainstem. Changes may also extend into the centrum semiovale / corona radiata region.

MRI (Figure 4)

- **T2**: may show high signal involving periventricular white matter centrum semiovale, periventricular white matter, and deep gray matter. Subcortical U fibre involvement may be spared until late in the course of the disease.
- **T1 C+ (GAD)**: no contrast enhancement in these areas.

Pelizaeus-Merzbacher disease

Metabolic features
Pelizaeus Merzbacher disease (PMD) is an X-linked leukodystrophy which is characterized by an arrest in myelin development. It occurs from a derangement in the proteolipidprotein (PLP1) gene locus at Xq22. This can be either a mutation, deletion or duplication (commonest).

Traditionally divided into 2 sub types

- classic
- connatal: rarer and more severe

**Clinical features**

Patients may present with

- pendular eye movements
- hypotonia
- pyramidal disease

**Imaging**

**CT**

- Non specific and may show hypo attenuating white matter with progressive white matter atrophy.

**MRI (Figure 5)**

- The lack of myelination is often seen as high T1 signal regions typically involving internal capsule, proximal corona radiata and the optic radiation and with near complete absence of expected low T2 signal in supra-tentorial region. Abnormal signal can either be diffuse or patchy. If there is patchy involvement, a characteristic tigroid appearance may be seen.
- MR may also show cortical sulcal prominence.
- **MR spectroscopy**: affected areas often show a reduction in the NAA peak.

**Wilson’s disease**

**Metabolic features**

**Wilson disease** also known as **hepatolenticular degeneration** is a rare autosomal recessive disorder of copper metabolism, affecting multiple organ systems.
It is a disorder that results from abnormal ceruloplasmin metabolism; a result of a variety of mutations in the ATP7B gene. Total body copper is elevated with deposition and resultant damage to a variety of organs, e.g. liver and brain.

**Clinical features**

Clinical presentation is varied and includes:

- weakening of hands and dysarthria: often the earliest symptoms
- dystonia
- pseudo-parkinsonian and cerebellar symptoms
- psychiatric symptoms

Kayser-Fleischer rings are seen in the cornea, and are a characteristic feature

**Imaging**

Neuroimaging features may vary depending on whether the disease is treated or untreated.

The basal ganglia are the most frequently affected site.

**CT**

- May demonstrate atrophic changes in the basal ganglial, cortical and cerebellar regions.

**MRI (Figure 6)**

Hyperintensity in *lentiform nuclei* and mesencephalic regions on T1 have been described as most common initial MR abnormality.

T2 hyperintensity is also seen typically involving:

- basal ganglia: putamen, globus pallidus, caudate nucleus
- thalamus: ventrolateral aspect

There may be T2 hyperintensity in the outer rim of the deep gray matter, and/or T1 hyperintensity in cases of copper toxicosis.

Axial T2 MR at midbrain level can show a "face of the giant panda sign", a characteristic of Wilson disease.

Diffusion restriction may be seen early in the course of the disease.
MRI appearances in metabolic encephalopathies
due to systemic diseases

**Hypoxic ischaemic encephalopathy**

Hypoxic-ischaemia cerebral injury occurs at any age, although the aetiology is significantly different:

- older children: drowning and asphyxiation remain common causes.
- adults: more often a result of cardiac arrest or cerebrovascular disease, with secondary hypoxemia

**Clinical features**

Patients typically present to hospital following an acute event (near-drowning, asphyxia, cardiac / respirator arrest). They are usually intubated and have a history of prolonged resuscitation.

**Imaging**

Severe global hypoxic-ischemic primarily affects the gray matter structures:

- basal ganglia
- thalami
- cerebral cortex (in particular the sensorimotor and visual cortices, although involvement is often diffuse)
- cerebellum
- hippocampi

**MRI (Figures: 7 and 8)**

- **Diffusion-weighted MR imaging** is the earliest imaging modality to become positive, usually within the first few hours after a hypoxic-ischemic event due to early **cytotoxic edema**. During the first 24 hours, there may be restricted diffusion in the cerebellar hemispheres, **basal ganglia**, or cerebral cortex (in particular, the perirolandic and occipital cortices). The thalami, brainstem or hippocampi may also be involved. Diffusion-weighted imaging abnormalities usually pseudo-normalize by the end of the 1st week.
- **T1 hyperintensities** signaling cortical laminar necrosis become evident after two weeks. This hyperintense signal does not represent hemorrhage, it’s believed to be caused by the accumulation of denatured proteins in dying cells. This hyperintensity can be seen also within a few days on FLAIR.
**Hepatic encephalopathy**

Hepatic encephalopathy (HE) refers to a spectrum of neuropsychiatric abnormalities occurring in patients with liver dysfunction. The clinical spectrum can rarely manifest in individuals without who have portal-systemic bypass without any associated intrinsic hepatocellular disease. Due to this reason is also sometimes subgrouped under the broader term portosystemic encephalopathy.

**Pathology**

The condition can be acute or chronic.

- It can occur in the setting of acute fulminant hepatic failure, or as a more chronic process in patients with hepatocellular dysfunction that leads to portosystemic shunting.
- In the majority of patients, a superimposed precipitating cause rather than worsening of hepatocellular function can be identified (particularly in acute situations).

**Imaging (Figure 9)**

The classic MR imaging abnormalities include

- T1 - classically shows high signal intensity in the globus pallidum +/- subthalamic region, and midbrain which is thought to be a reflection of increased tissue concentrations of manganese
- T2 - may also show diffuse cortical oedema and hyperintensity with sparing of the perirolandic and occipital regions
- MR spectroscopy - may show an elevated glutamine/glutamate peak coupled with decreased myo-inositol and choline signals on proton MR spectroscopy.

**Central pontine myelinolysis**

Central pontine myelinolysis (CPM) (also known as osmotic demyelination) refers to acute demyelination of the white matter tracts traversing the pons. It seen in the setting of osmotic changes, typically with the rapid correction of hyponatraemia. Despite the name extrapontine structures can also be affected: basal ganglia, midbrain and subcortical white matter.

**Clinical features**

The initial description of CPM by Adams et al in 1959 was entirely in a population of chronic alcoholics, and certainly this scenario is common. Since then it has been
increasingly recognised in other patient groups, but usually in the setting of rapidly corrected electrolyte disturbance:

- chronic alcoholics
- chronically debilitated patients
- transplant recipients

Clinically CPM presents in a biphasic pattern. The first phase is usually attributable not to the demyelination but rather to the inciting electrolyte abnormality, with patients being acutely encephalopathic. Following rapid reversal of this abnormality the patient transiently improves before progressing onto the classic CPM features 2 - 3 days later. These consist of:

- spastic quadriparesis
- pseudobulbar palsy
  - changes in levels of consciousness
  - coma or death

**Imaging (Figure 10)**

The earliest change is seen on DWI with restriction in the lower pons. This is seen within 24 hours of the onset of quadriplegia. This same region demonstrates eventual high T2 signal and later low T1 signal. The T1 and T2 changes may take up to two weeks to develop. This region has a classic trident shaped appearance. Occasionally gadolinium enhancement is also demonstrated, just as in the acute phase of an multiple sclerosis (MS) plaque. The peripheral fibers (ventrolateral longitudinal fibers) as well as the periventricular and sub pial regions are typically spared.

Signal characteristics of affected region includes

- **T1** - mildly or moderately hypointense
- **T2** - hyperintense, sparing the periphery and corticospinal tracts
- **PD** - hyperintense
- **FLAIR** - hyperintense
- **DWI** - hyperintense
- **ADC** - signal low or signal loss
- **T1 C+ (Gd)** - no enhancement

**Posterior reversible encephalopathy syndrome**

Posterior reversible encephalopathy syndrome (PRES) is a neurotoxic state that occurs secondary to the inability of posterior circulation to auto-regulate in response to acute changes in blood pressure. Hyperperfusion with resultant disruption of the blood brain barrier results in vasogenic oedema, but no infarction, most commonly in the parieto-occipital regions.
**Causes**

- Severe hypertension
  - Post partum
  - eclampsia / preeclampsia
  - acute glomerulonephritis
- Haemolytic uraemic syndrome
- Thrombocytopaenic thromboic purpura
- Systemic lupus erythromatosis
- Drug toxicity
  - Cisplatin
  - Interferon
  - Erythropoietin
  - Tacrolimus
  - Cyclosporin
  - Azathioprine

**Imaging**

**MRI (Figure 11)**

- **T1** - hypo intense in affected region(s)
- **C+ (Gd)** - patchy variable enhancement
- **T2** - hyperintense in affected region(s)
- **DWI** - usually normal
- **ADC** - signal increased in affected regions due to increased diffusion
- **GRE** - may show hypointense signal in cases of haemorrhage.

**Images for this section:**
**Fig. 1:** MRI in adrenoleukodystrophy. 09 months old, first-degree consanguinity, epilepsy, delayed motor acquisitions. T2 and FLAIR and diffusion MRI showing hyperintensities which involve parieto occipital white matter, the splenium of the corpus callosum and posterior arms of the internal capsules. This hyper signal is bilateral and symmetrical.
Fig. 2: MRI in adrenoleukodystrophy. 5 years old, epilepsy with spastic paraparesis. Coronal T2-weighted image and the axial FLAIR image showing hyperintense lesions of the peri ventricular white matter with involvement of the corpus callosum in its middle portion.

Fig. 3: MRI in MELAS syndrome. * 05 months old, epilepsy, hypertension + diabetes * coronal T2-weighted and FLAIR-weighted images reveal hyperintensity involving the Right occipital peri ventricular white matter. * MR spectroscopy revealed increased lactate in the occipital lobes.
**Fig. 4:** MRI in KRABBE disease. *3 y.o, epilepsy* *FLAIR hyperintensity noted in the posterior parietal white matter, extending to the posterior semi oval center with hypointensities involving the thalamus and corpus callosum.

**Fig. 5:** MRI in PELIZAEUS MERZBACHER's disease. *3 year.old, psychomotor retardation and epilepsy* *T2-weighted image and diffusion axial image showing the high-intensity signal throughout the cerebral white matter* *The spectroscopic imaging shows a peak of NAA and a decrease of choline.*
Fig. 6: MRI in Wilson’s disease. * 10 year old, brother died by Wilson's disease, chronic liver disease * T1-weighted sagittal image and T2-weighted axial images showing bilateral, symmetric hyperintensities in the putamina, thalami, posterior limbs of internal capsules, midbrain, and pons. Appearance suggestive of Wilson's disease.
**Fig. 7:** MRI in cortical laminar necrosis. * 2 year old, operated for cerebral empyema, with late postoperative awakening. * Cerebral MRI showing an area of infarction involving the left hemispheric cortex with lenticular reached and surrounding oedema. The hyperdensity of the cortex indicating cortical laminar necrosis.
Fig. 8: MRI in cortical laminar necrosis. * 12 year old child who presented for an episode of hypoglycemia. * Sagittal T1-weighted image shows cortical linear hyperintensities in the left frontal lobe. * The same abnormal signal is observable on the axial T2 weighted and coronal FLAIR weighted images.

Fig. 9: MRI in hepatic encephalopathy. Axial and sagittal T1-weighted images demonstrate bilaterally symmetrical pallidal hyperintensity.
**Fig. 10:** MRI in central pontine myelinolysis. * A 43 year old, chronic alcoholic. * Sagittal T1, coronal T2 weighted images reveal hyperintensity involving the central pons. * Axial contrast enhanced T1 showing a nonhomogenous enhancement of the pontine lesion.

**Fig. 11:** MRI in posterior reversible encephalopathy syndrome. Axial T2-weighted image and axial fluid-attenuated inversion recovery image illustrating bilateral, symmetrical parieto-occipital hyperintensities involving the cortices and subcortical white matter.
Conclusion

Metabolic encephalopathies may be diagnosed by a systematic assessment of the imaging patterns and signal abnormalities in the brain. However, correlation of typical imaging features with clinical and laboratory data is necessary for accurate assessment.

Personal information

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