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A Study on MR Neuroimaging in Children with Inborn Metabolic Errors

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Abstract

In neonatal disorders affecting the central nervous system, metabolic disorders are rare, but they account for a significant number of cases. Neonatal inborn errors of metabolism (IEM) are often characterized by nonspecific systemic symptoms that mimic more common acute neonatal disorders, such as sepsis, severe heart failure, and hypoxic-ischemic encephalopathy. Sepsis and cardiomyopathy may also complicate certain IEMs in the neonatal period. For long-term neurological impairments and death to be prevented, early diagnosis is imperative. Although neuroimaging findings are rarely specific, they can play a critical role in suggesting the correct diagnosis, limiting the differential diagnosis, and thereby allowing early initiation of metabolic and genetic laboratory investigations. As a newborn may present with an IEM before newborn screening results are available, neuroimaging may be particularly helpful in distinguishing metabolic disorders from other more common causes of neonatal encephalopathy, allowing for early diagnosis and treatment of IEMs based on imaging patterns. It is possible to evaluate IEMs using magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy (^{1}H-MRS). In this article, we will examine scenarios where MRI and ^{1}H-MRS suggest or diagnose IEMs, or, alternatively, refute them.

Keywords: MRI, MRS, Magnetic, Resonance, Spectroscopy

Introduction

IEM are a group of disorders caused by a defect or defects in the functioning of one or more intermediate metabolic pathways, either caused by a deficiency of enzymes, transporters, chaperones, or transcription factors. It is essential to make a prompt diagnosis to guide treatment and reduce the risk of morbidity and death [1]. Individually, IEMs are rare, but the estimated global prevalence ranges from 1 in 800 to 2500 live births. Amino acid, lysosomal storage, organic acid, mitochondrial, fatty acid, carbohydrate metabolism, peroxisomal, and urea cycle disorders are the most prevalent disorders [2].

The use of neuroimaging in diagnosis and treatment monitoring is important. It is common for IEMs to present during the neonatal or early infantile period. A newborn metabolic screen does not capture all IEMs, false positives and false negatives can occur, and genetic testing may not detect all pathogenic mutations. A newborn screen can sometimes be performed before the results of an imaging test are available, and if the results are positive and properly interpreted, an early intervention can be made. Patients with IEMs are more likely to receive their initial imaging at smaller community hospitals, so it is important that all radiologists who interpret neuroimaging are familiar with findings that may suggest an IEM so that patients can be promptly plugged into the appropriate therapeutic algorithm or transferred to a specialty center [3-5].

Among the over 1000 IEMs currently known, covering more than a minority would be impossible. The purpose of this review is to clarify the role of MRI and ^{1}H-MRS in the evaluation of IEMs. This paper discusses MRI and ^{1}H-MRS patterns that indicate, confirm, or refute a diagnosis in both specific and nonspecific clinical situations.

Clinical Scenarios Suggestive of IEM and General Classification

Symptoms of IEM in neonates are often nonspecific (e.g., encephalopathy, metabolic acidosis, hypoglycemia, cardiac or liver disorders) and can be confused with hypoxic ischemic encephalopathy (HIE), sepsis, and congenital heart disease. In addition to IEMs, patients may also suffer from cardiac disease, sepsis, or hypoglycemia [6-8].

However, certain clinical scenarios may suggest IEM, and would warrant an MRI and MRS as soon as feasible. This is usually associated with a history of normal birth/delivery and a period of symptom-free interval, followed by an unexplained clinical decline, especially for disorders resulting from toxic metabolites. The presence of multisystemic abnormalities, intellectual disabilities, seizures under 6 months of age, prolonged instability, or progression of symptoms are also important clinical clues (in contrast, HIE stabilizes by 2–3 weeks) [9]. An IEM may also be suspected if there is a history of metabolic diseases in the family, consanguinity, multiple miscarriages, and/or unexplained neonatal deaths. There are three main categories of IEMs based on clinical manifestations:

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Intoxication disorder

Disorders of amino acid metabolism: maple syrup urine disease, nonketotic hyperglycinemia (NKH), phenylketonuria, etc.

Disorders associated with organic acids: isovaleric acidemia, glutaric aciduria type I, L-2-hydroxyglutaric aciduria, methylmalonic acidemia, multiple carboxylase deficiency, propionic acidemia, etc.

Disorders of the urea cycle: Deficiency of enzymes that convert ammonia to urea. The most common disorder is ornithine transcarbamylase deficiency [10, 11].

Disorders of biosynthesis and breakdown of complex molecules

Some of these disorders can manifest in the neonatal period (Zellweger syndrome, neonatal adrenoleukodystrophy (ALD)), mannosidosis, Fabry disease, fucosidosis, Gaucher disease, Krabbe disease (globoid leukodystrophy), metachromatic leukodystrophy (MLD), mucolipidosis, mucopolysaccharidosis (MPS), Niemann pick diseases, neuronal ceroid lipofuscinosis, sialic acid disorders, GM1 gangliosidosis (Tay-Sachs disease and Sandhoff disease), etc. [12].

Energy production disorders and other disorders

Fatty acid oxidation disorders, Primary lactic acidosis disorders like Kearns–Sayre syndrome, Leigh syndrome, leukoencephalopathy with brainstem and spinal cord involvement and high lactate, mitochondrial encephalopathy, lactic acidosis, and others like Molybdenum cofactor deficiency and sulfite oxidase deficiency [13, 14].

Other disorders include Canavan disease, Alexander disease, MLD (lysosomal storage disorder), and ALD (peroxisomal disorder), Sjögren-Larsson syndrome (SLS), metal metabolism disorder like Menke's Disease, Pantothenate kinase associated neurodegeneration (PANK), and Wilson's disease. Glycosylation disorders like Aicardi-Goutières syndrome, creatine deficiency syndromes, galactosemia, muscular dystrophy-dystroglycanopathy [15-17].

Importance of MRI and MRS in IEM Diagnosis

MRI

CNS MRI provides excellent soft tissue contrast and exceptional multiplanar anatomic detail, making it the imaging modality of choice. In contrast to computed tomography (CT) and ultrasound, multiple sequences are used to detect altered tissue properties in disease [18]. In acute episodes of encephalopathy, MRI sequences such as diffusion-weighted imaging (DWI) can help characterize edema. Although MRI protocols are best tailored to the suspected disorder and clinical question, in general, the following sequences are recommended: T1 weighted imaging (T1WI), T2 weighted imaging (T2WI), T2 fluid attenuated inversion recovery (FLAIR) (age > 1 year) or proton density (PD) (age < 1 year), DWI or diffusion tensor imaging (DTI), susceptibility weighted imaging (SWI with preferably with phase assessment capability), arterial spin labeling (ASL) perfusion, and for leukodystrophies, magnetization transfer T1WI [2, 19].

There are many factors that influence neuroimaging manifestations within and among IEMs, ranging from normal to diffuse, severe CNS disease, depending on factors such as type/severity of pathway defects, amount of toxic byproduct accumulation (if present), brain maturation at the time of insult, duration of injury, compensatory mechanisms, and timing of imaging [20]. Furthermore, certain anatomic structures are specifically vulnerable to energy failure and toxic substrates.

IEMs should be considered and MRS should be included in the exam when encountering the following symptoms of symmetrical brain disease:

✓ This is uncharacteristic of mimics, such as HIE (e.g., involvement of the basal ganglia with thalamic sparing) and infection.

✓ Brainstem and/or cerebellum involvement isolated or preferential.

✓ Different types of brain lesions (e.g., reduced and facilitated diffusion).

✓ Neonates with chronic lesions and/or volume loss.

✓ Progressive atrophy.

✓ Malformations with acquired brain lesions.

^{1}H-MRS

As a result of ^{1}H-MRS, Dr. M. Lai and his colleagues were able to gain insight into the metabolic status of the brain at the time of imaging, which can reveal diagnostic or suggestive metabolic profiles or mechanisms related to certain IEMs [21].

It is possible to evaluate IEMs using single voxel spectroscopy (SVS), point resolved spectroscopy (PRESS), short echo times (TE) of 35 ms, repetition times (TR) of 1500 ms, 128 signal averages, and if possible, longer TE acquisitions (144 ms for 1.5T and 288 ms for 3T). Voxel placement (2 × 2 × 2 cm default) depends on the appearance of a brain or suspected disorder [22]. It is common to examine the cerebral deep gray nuclei and optionally the midline parietal gray matter or parietal white matter. Lesions that are chronic or inactive, necrotic, hemorrhagic, or substantially calcific should be avoided.

The ratios of metabolites change with age, with the most dramatic changes occurring during the first three months of life [23]. Understanding normal age-related metabolite ratios is crucial for accurate interpretation. The major metabolites include N-acetylaspartate (NAA at 2.0

ppm, neuronal metabolite and biomarker for viable neurons or assessment of parenchymal damage); creatine (Cr at 3.0 and 3.9 ppm, includes free creatine and phosphocreatine, marker of energetic reserve); choline (Cho at 3.2 ppm, marker of cellular proliferation from increased membrane turnover and/or inflammation); myo-inositol (mI at 3.5 ppm, glial metabolite, osmolyte, and marker of gliosis and/or neuroinflammation); lactate (Lac at 1.3 ppm, reflects anaerobic glycolysis); lipid/macromolecules (Lip MM at 0.9 and 1.3 ppm from -CH3 and -CH2 groups, respectively); and glutamate (Glu at 2–2.5 ppm, excitatory neurotransmitter) and glutamine (Gln at 2 – 2.5 and 3.6 – 3.9 ppm, osmolyte and hyperammonia detoxifier).

IEMs can sometimes be diagnosed with ^{1}H-MRS, particularly intoxication disorders (e.g., amino acid metabolism, urea cycle disorders, organic acid disorders) as well as biosynthesis and breakdown disorders (e.g., lysosomal and peroxisomal disorders). Spectroscopy shows characteristic peaks and/or peak patterns when these disorders cause accumulation of certain molecules in the brain [24]. When lactate is sought to support a diagnosis of primary-IEM-related mitochondrial dysfunction, its presence in normal appearing brain tissue is more suggestive of systemic disease than lactate in focal lesions with reduced diffusion, which may simply reflect local anaerobic metabolism associated with the lesion itself. Pre-term infants may have a small amount of lactate due to underactivity of pyruvate dehydrogenase, but term infants should have little or no lactate [25].

MR can also be useful in evaluating leukoencephalopathies, which often present with diffuse white matter signal changes. Among leukodystrophies characterized by demyelination, ALD, MLD, and Krabbe disease, Cho levels may be elevated, mI levels may be elevated, NAA levels may be decreased, and Lac levels may be high [26]. Metabolites may also decrease leukodystrophies such as megalencephalic leukoencephalopathy with subcortical cysts (van der Knaap disease) or vanishing white matter disease.

Clinical Context of MRI and/or 1H-MRS Suggestive of IEMs

Urea cycle disorders (UCDs) are caused by defects in the conversion of ammonia to urea, resulting in an accumulation of ammonia and glutamine (Gln). Gln is osmotically active, causing diffuse edema in the cerebral cortex and subcortical white matter at high concentrations. MR findings of UCD-related hyperammonemia include peri-rolandic, peri-insular, and basal ganglia edema, often sparing the thalami, which helps distinguish it from HIE.

In times of hyperammonemia, MRS shows elevated Glu/Gln peaks, and a lactate doublet at 1.3 ppm when mitochondrial function fails to meet metabolic demand. At 1.5T, Glu/Gln resonances overlap, but at 3T they are more distinct due to chemical shift dispersion; the peak centered at 2.4 corresponds more to glutamine [27]. A commonly overlooked glx peak is produced by alpha protons at 3.75 ppm. Chronic hyperammonemia usually results in reduced MI and Cho, which can strongly suggest an underlying UCD.

A primary lactic acidosis disorder may exhibit focal edema in the deep gray nuclei, the periaqueductal areas, white matter, and/or cerebellar peduncles in the early stages. As the disease progresses, more diffuse brain involvement may be observed. An increased lactate doublet on MRS at 1.3 ppm is nonspecific but may indicate mitochondrial encephalopathy or a problem with energy production [28]. Other IEMs such as organic acid and amino acid disorders may also have increased lactic acid levels. In areas of normal brain, lac can be elevated on MRS, suggesting underlying IEM.

On MRI, the most well-known and recognized pattern is Leigh syndrome, with symmetric deep grey nuclei and/or brainstem involvement. There are many genetic variants that can cause Leigh syndrome, either in nuclear DNA or mitochondrial DNA.

Leukoencephalopathy with brainstem and spinal cord involvement with lactate elevation (LBSL), due to a defect in mitochondrial enzyme aspartyl-tRNA synthetase, is another entity, which may present with suggestive imaging findings of extensive white matter involvement concentrated in the brainstem (corticospinal, ascending sensory, pontocerebellar, On MRS, the cerebellum (corticospinal tracts, dorsal columns, and trigeminal nerve fibers) and cerebral white matter are variable (corticospinal tracts, corpus callosum, and other cerebral white matter are typically spared) and Lac is elevated [29].

There may also be suggestive imaging features with mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), with patients experiencing non-vascular territorial metabolic strokes. In a similar way to MELAS, POLG-related mitochondrial disorders cause nonterritorial cortical/subcortical edema/injury; however, perirolandic parenchyma and thalami are more commonly affected.

Molybdenum cofactor deficiency (MCD) and sulfite oxidase deficiency (SOD) affect sulfur-containing amino acids and electron transport chains. Clinically and on neuroimaging, they may appear to be indistinguishable from HIE and mitochondrial diseases. MCD/SOD is associated with caudate head involvement (usually spared in HIE), thalamic sparing (often involved in HIE), and chronic lesions in neonates like necrotic/hemorrhagic basal ganglia lesions (often asymmetric), progressive encephalopathy, facial dysmorphism, intractable seizures, high urinary sulfite levels, and decreased uric acid levels. Unlike HIE, cytotoxic edema may occur in the striatum and/or cortex/subcortical cerebral white matter without preference for border zone arterial territories. The MRS can demonstrate accumulation of taurine (3.2–3.4 ppm), S-sulocysteine (3.6 ppm) and cysteine (2.9 - 3 ppm) as well as elevated Glu/Gln (sulfites inhibit glutamate dehydrogenase), Lac, and NAA. Due to its osmolytic properties, Cho tends to be elevated rather than reduced in acute HIE [30].

Basal ganglia disease because of biotin-thiamine exposure: SLC19A3 gene mutations cause multifocal progressive lesions of deep gray in the brain (basal ganglia > thalami) that progress to encephalomalacia, gliosis, and necrosis. The cerebral cortex, white matter, brainstem, and cerebellum are less commonly affected. There is a possibility that MRS will show pyruvate.

Lipid metabolism disorders include carnitine palmitoyl transferase (CPT) disorders, which may cause lipid elevations on MRS despite normal neuroimaging, mild brain changes, or nonspecific MRI abnormalities.

Disorders of metal metabolism

Copper metabolism disorders, including Menke's disease and Wilson's disease, may have suggestive MR imaging findings. In Menke's disease, the Circle of Willis arterial elongation and tortuosity are nearly universal; white matter changes include transient vasogenic temporal white matter edema, vermian hypoplasia, progressive atrophy, and subdural fluid collections. Detecting these neuroimaging manifestations in young patients is particularly important, since Menke's disease's characteristic kinky hair may not be clinically evident until a few months after diagnosis. In Wilson's disease, brain MRI findings are age-dependent; most are normal under 10 years of age, hepatic-disease-related T1 hyperintensity may be present in the globus pallidus ± striatum and/or upper brainstem at mean age 11 years, and T2 hyperintensity may be present at mean age 13 years involving the following regions in descending order of prevalence: putamen (sometimes with central hypointensity), globus pallidus, caudate, thalamus, brainstem.

In PANK, there is an accumulation of brain iron that results in a highly suggestive MRI pattern called the eye-of-the-tiger sign, which is characterized by hypointensity in the globus pallidus and a central hypointensity on T2WI, which indicates iron accumulation with necrosis. An extrapyramidal movement disorder develops clinically.

MRI and/or ^{1}H-MRS Diagnostic Based on Disease Pattern

In maple syrup urine disease (MSUD), the branched-chain amino acids (BCAAs) valine, isoleucine, and leucine are not properly decarboxylated. The accumulation of metabolites in urine produces an odor like maple syrup. There is marked diffusion restriction along myelinated white matter of the cerebrum, cerebellum, and brain stem as a characteristic MRI finding. The H MRS shows a characteristic broadened peak complex at 0.9 ppm that inverts at intermediate TE due to branched chain amino acids and ketoacids. Additionally, to short TE, a longer echo time MRS can eliminate the overlapping peaks of lipid at 0.9 ppm. There may also be a lactate peak (anaerobic glycolysis) and a decreased NAA/Cr ratio.

Glycine encephalopathy or NKH: NKH results in reduced diffusion in myelinated white matter tracts due to intramyelinic edema and vacuolization (usually involving the internal capsules, brainstem, and cerebellar white matter), with less involvement than MSUD [31]. There is usually hypo genesis of the corpus callosum and hypoplasia of the cerebellar vermis as well. Due to its longer T2 decay, ^{1}H-MRS reveals an elevated glycine peak at 3.55 ppm, which can be distinguished from the normal mI peak with intermediate or long echo MRS.

It is usually diagnosed at newborn screening for phenylketonuria (PKU). The lack of phenylalanine dehydroxylase in PKU can result in elevated phenylalanine levels in the brain, with phenylalanine peaks at 7.37 ppm on MRS. The white matter of the periventricular region and the subcortical area may show increased T2 signals on MRI.

In GA-I, lysine, hydroxylysine, and tryptophan catabolism is disrupted, resulting in poorly developed operculums, widened Sylvian fissures, frontotemporal CSF spaces, large cavum septi pellucidi, and lesions of the basal ganglia on MRI. It is possible for supratentorial subdural hematomas to develop over time because of cerebral atrophy. The syndrome should be distinguished from glutaric aciduria type II, which occurs when proteins and fats cannot be broken down for energy and manifests as underdeveloped frontotemporal lobes, enlarged sylvian fissures, delayed myelination, and hypoplasia of the corpus callosum [31].

The mitochondrial enzyme gene L2HGDH is mutated in L-2-hydroxyglutaric aciduria (L2HGA) causing an accumulation of L-2-hydroxyglutaric acid. The MRI is usually found to show a centropedal pattern of brain involvement with edema within the frontal and subcortical white matter, which gradually becomes confluent while sparing the brainstem. It usually affects the dentate nucleus and basal ganglia, but not the thalami. Unlike L2HGA, Kearns-Sayre syndrome shows centrifugal white matter involvement and typically displays calcifications. During L2HGA, MRS may reveal decreased NAA and increased mI.

MRI features of MPS include enlarged perivascular spaces, cerebral white matter hyperintensity on T2/FLAIR, and ventriculomegaly. An imaging study of the spine shows multiple dysostoses. When mucopolysaccharides accumulate in the brain, MRS can demonstrate elevated Cho (gliosis and demyelination).

The MRS shows a broadened peak that represents mannose-rich oligosaccharides that can resolve following bone marrow transplantation. The MRI shows hypomyelination and leukodystrophy.

A broadened peak at 3.8 - 3.9 ppm may be observed in MRS in cases of fucosidosis resulting from carbohydrate-containing macromolecules, such as mannosidosis. An additional peak at 1.2 ppm, which inverts at intermediate echo time, attributable to fructose, makes the diagnosis. Hypomyelination of the globus pallidus with T1 and T2 shortening, T2 prolongation in the internal medullary lamina of the globus pallidus, and callosal thinning are characteristic MRI abnormalities.

The Salla disease results in an increase of N-acetyl neuraminic acid due to a defect in sialic acid transport. An elevated peak of the N-acetyl methyl group at 2.0 ppm on MRS may be mistaken for NAA [2, 6]. It is rare and most prevalent in Scandinavians, with limited or slow myelination, cerebral subcortical white matter involvement sparing deep white matter, accelerated iron deposition most prominent in the globus pallidus, thinning of the corpus callosum, and variable cerebellar atrophy.

The X-linked ALD occurs when long-chain fatty acids are not properly oxidized, resulting in their accumulation. It is most common for lesions to begin in the callosal splenium and spread to the forceps major, the projectional fibers, and the auditory and visual pathways of the brain; however, in a minority of cases, they can begin in the callosal genu and extend into the forceps minor. With active demyelination and inflammation, laminated zones of signal alteration are characteristic, with decreased diffusion and post-contrast enhancement. X-ALD has been added to newborn screen testing for presymptomatic MR screening; these scans should be examined carefully for signs of early/mild chang-

es with particular attention paid to the corpus callosum. According to consensus guidelines, boys with X-ALD should undergo serial MRIs. During MRS, NAA is reduced, and Cho and mI are elevated, finding that can improve after successful stem cell transplantation.

Canavan disease: A spartoacylase, which catalyzes the hydrolysis of NAA, is deficient in this disease, resulting in the accumulation of NAA. Macrocephaly is typically present but not universal. On MRI, diffuse spongiform changes are present involving the white matter, thalami and globi pallidi but sparing the caudate nuclei and putamina. During the active phase of disease, there is reduced diffusion in the involved white matter. There is a significant increase in NAA peak at 2.01 ppm in the 1H MR spectrum, which is pathognomonic [3].

Alexander disease: Alexander disease is an astrocytopathy, which like Canavan disease, may present as a macrocephalic leukodystrophy. The predominance of frontal disease, striatal involvement, thalamic sparing, post-contrast enhancement, and lack of restricted diffusion usually distinguish Alexander disease from Canavan disease. In contrast to Canavan disease, MRS generally shows elevated inositol levels and reduced NAA levels.

Pyruvate dehydrogenase complex (PDHc) deficiency causes lactate accumulation and impaired pyruvate to acetyl-coA conversion. In MRS, Lac and Pyruvate levels are elevated at 2.37. A PDHc deficiency is associated with two phenotypes: (1) prenatal onset characterized by destructive changes and brain malformations; and (2) postnatal onset energy failure with Leigh disease.

In patients with succinate dehydrogenase (SDH) deficiency, the respiratory chain cannot oxidize succinate to fumarate and electrons to the Krebs cycle cannot reach the respiratory chain. Lac levels rise significantly, and a succinate peak is detected at 2.4 ppm in white matter patients with SDH deficiency. The white matter of the brain is affected (excluding the U-fibers and corpus callosum outer fibers), as well as the cortico-spinal tracts, the middle cerebellar peduncles, the spinal cord, and specific regions of the thalamus [2].

CDG-1a: CDGs are genetically heterogeneous autosomal disorders caused by abnormal glycosylation of N-linked oligosaccharides. CDG-1a is a neurodegenerative disorder with selective hindbrain involvement and a variable clinical presentation. MR findings include diffuse cerebellar volume loss and diffuse cerebellar T2/FLAIR hyperintense signals. In addition, the cerebellum and pons, as well as the supratentorial white matter, show progressive volume loss. There is a decrease in NAA/Cr ratios and an increase in mI because of MRS.

Toxic-induced metabolic disturbances may produce MRI findings like those found with IEMs. There is a possibility that carbon monoxide, heroin, and MDMA can cause bilateral globi pallidi infarctions, which are also seen in disorders such as methylmalonic acidemia and PDHc deficiency. Like Leigh disease, Wernicke encephalopathy (thiamine vitamin B1 deficiency) can cause changes in the thalami, putamina, tectal plate, and periaqueductal gray matter; however, involvement of the hypothalamus and mamillary body favors Wernicke encephalopathy. Due to destruction of myelin and edema caused by extrapontine osmotic myelinolysis (rapid correction of hyponatremia), symmetric thalamic and basal ganglia abnormalities can occur [31]. Infantile spasms treated with Vigabatrin (GABA inhibitor) can result in hyperintense T2 signals and restricted diffusion in the thalami, globus pallidus, anterior commissure fibers, central tegmental tracts, dentate nucleus, and cerebral peduncles. In some cases, these findings can be confused with IEMs, but they can be differentiated by looking at the clinical history and the pattern of involvement (Table 1).

Conclusions

Diagnostic evaluation of IEMs requires neuroimaging. Rarely, radiological and/or clinical phenotyping can identify a specific entity, allowing for single gene testing. A radiological phenotyping of IEMs may indicate a specific disease category, prompting an analysis of a particular gene panel. The phenotype of metabolic profiling is often nonspecific but can allow whole exome sequencing. A whole genome sequencing, chromosomal microarray, or other work-up may be necessary to further evaluate the results.

As a result of their often nonspecific clinical and imaging presentations, IEMs are a heterogeneous group of disorders that can be difficult to diagnose. However, many of them have characteristic neuroimaging and MRS patterns. The paper reviews and clarifies the role of MRI and ^{1}H-MRS in evaluating IEMs and focuses on scenarios where they are suggestive of or diagnostic for them.

Table 1: Inborn errors of metabolism with unique MRS and MRI profiles that can be suggestive or diagnostic.

Disorder	Classification	Defect + metabolic consequence	Key MRS metabolite (ppm) or MRI feature
MSUD*	Amino aciduria	Defect in branched-chain keto-acid dehydrogenase enzyme ➔ ↑ branched chain amino acids and ketoacids (BCAAs, BCKAs)	↑ BCAAs + BCKAs (0.9) Intramyelinic edema involving cerebrum, cerebellum, brainstem
NKH*	Amino aciduria	Defective mitochondrial enzyme involved in glycine cleavage ➔ ↑ glycine	↑ Glycine (3.5) Intramyelinic edema, Hypogenesis corpus callosum, vermian hypoplasia
PKU*	Amino aciduria	Phenylalanine hydroxylase deficiency	↑ Phenylalanine (7.37) periventricular and subcortical white matter (WM) abnormalities
Glutaric aciduria type I (GA-I)*	Organic aciduria	Enzyme deficiency altering lysine, hydroxylysine, tryptophan metabolism➔ ↑ glutaric acid, hypoglycemia	Poorly formed operculum, widened sylvian fissures and frontotemporal subarachnoid spaces, basal ganglia (BG) lesions
L2HGA*	Organic aciduria	Mitochondrial enzyme L2HGDH mutation➔ ↑ L-2-hydroxyglutaric acid	Initial frontal and subcortical WM, with later confluent WM and BG abnormality. Dentate nuclei lesions
Methylmalonic acidemia (MMA)	Organic aciduria	Defect in methylmalonyl-coenzyme A mutase➔ ↑ methylmalonic acid, glycine, ammonia	Cerebral WM and globus pallidus lesions
Propionic acidemia	Organic aciduria	Defect in propionyl-coenzyme A carboxylase	↑ propionic acid, glycine cerebral WM and striatum lesions

UCD	UCD	Deficiency in detoxification of ammonia to urea➔ ↑ ammonia, glutamine	↑ Glu ± ↓ mI and Cho cortical and subcortical lesions usually sparing thalamus
α-Mannosidosis*	Lysosomal	Deficiency of α-mannosidase	Mannose-rich oligosaccharides (3.5–3.9) hypomyelination leukodystrophy (LD)
Fucosidosis*	Lysosomal	Deficiency of α-L-fucosidase needed to metabolize fucose-containing compounds	Carbohydrate-containing macromolecules (3.8–3.9) fructose (1.2 doublet); inverts at intermediate echo time hypomyelination, thalamic and GP T2 hypointensity
Globoid cell leukodystrophy (Krabbe disease)	Lysosomal	Galactocerebroside β-galactosidase deficiency ➔ globoid cell accumulation	Thalamic T2 hypointensity Centrifugal gradient LD, tigroid WM pattern, cranial nerve enhancement, optic nerve enlargement
MLD	Lysosomal	Decreased arylsulfatase A enzyme activity ➔ metachromatic sulfatide deposits	Centrifugal gradient LD, tigroid WM pattern, cranial nerve enhancement
MPS*	Lysosomal	Deficiencies in lysosomal hydrolases responsible for metabolizing mucopolysaccharides (a.k.a. glycosaminoglycans)	Mucopolysaccharides (3.6–3.7) ↑ Cho enlarged perivascular spaces, ventriculomegaly, WM lesions, dysostosis multiplex, CVJ stenosis
Salla disease*	Lysosomal	Defect in sialic acid transport ➔ N-acetyl neuraminic acid	↑ N-acetyl neuraminic acid (2) Diffuse WM abnormality
Tay-Sachs and Sandhoff (GM-2 gangliosidosis)	Lysosomal	Reduced beta-hexosaminidase enzyme➔ ↑ GM2-ganglioside accumulation	Sandhoff (N-acetylhexosamine metabolite at 2.1) thalamic T2 hypointensity striatum T2 hyperintensity
X-ALD*	Peroxisomal	Inability to oxidize long-chain fatty acids (VLCFA) into short-chain fatty acids ➔ accumulation of long-chain fatty acids	Peri-trigonal T2 hyperintensity and restricted diffusion-posteroanterior & centrifugal gradient
Zellweger syndrome*	Peroxisomal	Decreased dihydroxyacetone phosphate acyl transferase (DHAP-AT) activity. Peroxisomal function crucial to neuronal migration	Lipids (0.87, 1.27) peri-sylvian polymicrogyria, germinolytic cysts
Biotin-thiamine responsive basal ganglia disease	Thiamine metabolism	Mutation in SCL19A3 gene encoding a thiamine transporter	Leigh-like phenotype Pyruvate (2.37)
Leigh disease (subacute necrotizing encephalopathy)	Mitochondrial	Multiple mutations in mitochondrial or nuclear DNA	↑ Lac (1.33) pattern of symmetric basal ganglia or brain-stem abnormalities
Leukoencephalopathy with brainstem and spinal cord involvement (LBSL)	Mitochondrial	Mitochondrial aspartyl-tRNA synthetase deficiency	↑ Lac (1.33), mI, Cho, ↓ NAA diffuse cerebral volume loss, involvement of brain and spine
MELAS and POLG-related mitochondrial disorders	Mitochondrial	Mutations in mitochondrial DNA	↑ Lac (1.33) Non-territorial and basal ganglia "stroke-like" lesions Peri-rolandic parenchyma and thalami preferentially affected in POLG-related disorders
PDHc deficiency*	Mitochondrial	Impaired pyruvate to acetyl-coA conversion and lactate accumulation	Impaired pyruvate to acetyl-coA conversion and lactate accumulation
MCD and SOD	Amino aciduria/ Electron transport chain	Defect in amino acid metabolism, involved in electron transport chain	↑ taurine (3.2–3.4), ↑ S-sulocysteine (3.6), ↑ cysteine (2.9–3), ↑ Glx,↑ Lac, ↑ Cho, ↓ NAA. Caudate head involved, thalamic sparing
SDH deficiency*	Mitochondrial	Absent/insufficient oxidation of succinate ➔ fumarate and electron delivery to the respiratory chain	Succinate (2.4), ↑ Lac (1.33) leigh disease pattern
Alexander disease*	Leukodystrophy (Macrocephalic)	Astrocytopathy resulting in defect in myelin deposition	Frontal predominant WM disease and striatum involvement, enhancement, ↑ mI and sI
Canavan disease*	Leukodystrophy (Macrocephalic)	Inability to metabolize N-acetyl asparate (NAA) into asparate and acetate	↑↑ NAA diffuse WM and thalamic lesions sparing striatum
Menke's disease	Metal metab-olism	Copper metabolism defect	Circle of Willis tortuosity and elongation universal, ± WM changes, vermian hypoplasia, atrophy, subdural collections
PANK	Metal metab-olism	Neurodegeneration with brain iron accumulation	"Eye-of-the-tiger" sign - peripheral and central globus pallidus T2 hypointensity
Wilson's disease	Metal metab-olism	Copper metabolism defect	T1 hyperintensity in globus pallidus ± striatum and/or upper brainstem (11 years) T2 hyperintensity in putamen, globus pallidus, caudate, thalamus, brainstem (13 years)
Aicardi–Goutières syndrome	Miscellaneous	Defect in genes involved in nucleotide metabolism and/or sensing	Classic triad: calcifications, WM disease, atrophy various other features correlate with genotype
CPT	Miscellaneous	Disorder of lipid metabolism	↑↑ Lipid
Creatine deficiency disorders*	Miscellaneous	Disorders of biosynthesis and transport of creatine	Reduced or absent Cr (3) MRI may be normal
Galactosemia*	Miscellaneous	Deficiency of galactose-1-phosphate enzyme ➔ ↑galac-tose-1-phosphate and galactitol	Galactitol (3.7): doublet at short TE, peak inversion at intermediate TE; ↓ mI
Congenital disorder of glycosylation Type 1a (CDG-1a)	Miscellaneous	Mutation in gene encoding PMM2 ➔ abnormal glycosylation of N-linked oligosaccharides	Marked cerebellar volume loss with diffuse cerebellar T2 hyperintensity. Progressive volume loss of pons, cerebellum, and supratentorial WM. ↓ NAA/Cr ratio, ↑mI
Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies)*	Miscellaneous	Reduced glycosylation of alpha-dystroglycan	Extensive malformations of cortical developmental (i.e., cobblestone lissencephaly, kinked z-shaped brainstem, midline pontine clefting)

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Conflict of Interest

None.

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