An approach to MRI of metabolic disorders in children

Approche IRM des maladies métaboliques de l’enfant

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Abstract

Inborn errors of metabolism are a difficult group of disorders for the neuroradiologist, as there are few good clinical or neuroradiological criteria for differentiating them. In this review, a technique of diagnosis by pattern recognition, supplemented by metabolic data from proton MR spectroscopy and microstructural data, as assessed by diffusion weighted images, is presented. Proper use of these neuroimaging tools can be very useful for separating these disorders into more manageable groups, and sometimes allows a specific diagnosis to be made.

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The pattern approach to metabolic disease

Inborn errors of metabolism are a difficult group of disorders for the physician. Many such disorders exist and they are classified in many different ways (e.g. by biochemical characteristics, by clinical characteristics, or by cellular organelle affected). They can present at nearly any age, and their clinical signs and symptoms are almost invariably nonspecific in separating one disorder from another. These disorders can be particularly confusing to the neuroradiologist. The imaging appearance of many disorders overlaps and, often, varies with the stage and the variant of the disease. The white matter is very commonly involved, sometimes primarily (a true leukodystrophy) or sometimes secondarily due to Wallerian degeneration. Involvement of the basal nuclei (the thalami and basal ganglia) may be...
the result of gray matter or white matter injury (about half of the basal nuclei is composed of white matter). In the end stage, all disorders look much the same, with atrophy of the cerebral cortex and basal ganglia, reduced volume of hyperintense white matter, and shrunken basal ganglia. Therefore, it is important to image the patient early in the course of the disease, when the pattern of injury may be more characteristic.

Use of a systematic approach based on the pattern of brain involvement can be useful in the analysis of neurometabolic disorders by imaging [9,72,81]. van der Knaap and Valk have computerized pattern recognition. To accomplish this, they created a database that was subsequently used to develop a computer-assisted pattern recognition program [81]. A large amount of information was entered into the database. To start, they recorded the involvement of the cerebral cortex, subcortical U fibers (arcuate fibers), deep white matter, and periventricular white matter in each cerebral lobe. Next, they assessed the presence or absence of involvement of the internal capsule (anterior and posterior limb), external capsule, caudate nucleus, putamen, globus pallidus, thalamus, corpus callosum (rostrum, genu, body, and splenium), cerebellar cortex, cerebellar white matter, cerebellar dentate nuclei, cerebellar peduncles, hilus of the dentate nucleus, midbrain, pons, and medulla. Subsequently, they analyzed which areas were predominantly involved (i.e. supratentorial or infratentorial, cerebral lobe, subcortical or deep or periventricular white matter), degree of left-right asymmetry, extension of the lesions (small or large, isolated or confluent), appearance (swelling, atrophy, cystic degeneration), signal intensity, homogeneity, and demarcation from surrounding brain (sharp, vague, or mixed). Finally, they listed extra characteristics such as calcium, hemorrhage, contrast enhancement, enlargement of subarachnoid spaces, presence of absence of cerebellar atrophy, and myelinization (normal, delayed, absent). This data were recorded for nearly 1500 patients with known diagnoses and entered into their database. With the database available, diagnosis of new patients is greatly facilitated. The results of the imaging analysis of each new patient is entered into their database and analyzed. With some patients, they get an exact (or nearly exact) match and the diagnosis is established. If a precise diagnosis cannot be made, the patient may be put into a group in which several diagnoses remain possible; entering the patient into this smaller group limits the number of potential diagnoses and reduces the amount of biochemical and genetic testing that must be performed. Sometimes, the data do not match any known syndromes, but matches one or more previously entered unknowns; a result such as this may be the first step in the proposal of a new syndrome.

In this manuscript, a less sophisticated, but nonetheless systematic, approach to the analysis of these disorders, based upon the pattern of brain involvement on magnetic resonance (MR) images, will be presented. Disorders with similar patterns can sometimes be differentiated on the basis of their microstructure, which can be tested by diffusion weighted imaging, or their biochemical signatures, which can be grossly identified by proton MR spectroscopy (MRS). This approach does not replace a thorough biochemical and genetic work-up, but it is a good starting point in the analysis of these disorders.

White matter versus gray matter

The first important decision is whether the disease involves primarily gray matter, primarily white matter, or both gray and white matter. In general, disorders that primarily affect cortical gray matter will show cortical thinning and prominent cortical sulci. The cerebral white matter will often have an abnormal appearance in these patients, as Wallerian degeneration of axons causes diminished white matter volume and mild to moderate hyperintensity on FLAIR and T2 weighted images. This white matter appearance can often be differentiated from that of primary white matter disorders if the study is performed early in the course of the disease, as the affected white matter will often be edematous and, therefore, brighter and more voluminous (causing compressed, smaller sulci) than the white matter that has undergone Wallerian degeneration. Those disorders primarily affecting deep gray matter will show FLAIR hyperintensity and prolonged T1 and T2 relaxation times on MR imaging in the involved structures acutely and may show short T2 relaxation times in a more chronic stage, especially in the cerebral cortex. Disorders primarily affecting white matter cause marked signal abnormality before any volume loss is apparent. The white matter disorders sometimes have an inflammatory component in the early stages that causes edema, with accompanying mass effect, upon adjacent structures [46]. Moreover, many white matter disorders, such as adrenoleukodystrophy (ALD) and fibrinoid leukodystrophy (Alexander disease) start locally and advance over time to involve adjacent areas. White matter diseases can result in devastation of the involved areas, with necrosis and cavitation of the affected regions and subsequent ex vacuo dilatation of the ventricles, whereas the abnormal white matter in gray matter disorders appears less severely damaged. Finally, the clinical presentation of patients with cortical gray matter disorders (seizures, dementia in early stages) differs from that of deep gray matter disorders (chorea, athetosis, dystonia) and both differ from the presentation of white matter disorders (spasticity, hypertreflexia, ataxia); clinical information is often very useful to get started on the right track.

Gray matter disorders

Once a disorder is identified as being primarily of gray matter, the next step is to determine whether the cerebral cortex or the deep gray matter nuclei are primarily involved. This is most easily determined by examining the deep gray nuclei to look for abnormal signal intensity on T2 weighted or FLAIR images. For confirmation of cortical involvement, a specific search for sulcal enlargement, cortical thinning, and abnormal signal intensity of the cortex may be helpful. If only deep gray matter is involved, the identification of the specific structures that are affected and the signal intensity of the affected structures is crucial. Involvement of the striatum (caudate and putamen) is seen in mitochondrial disorders (primarily Leigh syndrome, mitochondrial
encephalopathy with lactic acidosis and stroke-like symptoms (MELAS), and the glutaric acidurias), propionic acidemia, Wilson’s disease, juvenile Huntington’s disease, molybdenum co-factor deficiency, asphyxia, and hypoglycemia (Table 1). Many of these disorders often have associated white matter or cortical injury. If involvement is restricted to the globus pallidus, and consists of T2 shortening or T2 shortening with central T2 prolongation (Fig. 1), the diagnosis of pantothenate kinase associated neuropathy (formerly called Hallervorden-Spatz disease) can be made with some confidence [27,28]. If isolated globus pallidus involvement shows T2 prolongation, succinate semialdehyde dehydrogenase deficiency, methylmalonic acidemia, guanidinoacetate methyltransferase (GAMT) deficiency (a creatine synthesis disorder), isovaleric acidemia, pyruvate dehydrogenase deficiency (due to mutation of the dihydrolipoamide acetyltransferase (E2) component), carbon monoxide poisoning, or the chronic phase of kernicterus should be considered [9,79] (Table 2). If T2 or FLAIR hyperintensity of the globus pallidus is seen in association with subcortical white matter demyelination and involvement of the cerebellar dentate nuclei, L-2-hydroxyglutaric aciduria (Fig. 2) and Kearns-Sayre syndrome should be considered. If associated atrophy of the dorsal brain stem and cerebellar dentate nuclei is seen, consider dentatorubral and pallidolysian atrophy [29,43]. If T1 hyperintensity of the globi pallidi is seen associated with normal T2 signal, consider chronic hepatic disease. If T1 hyperintensity is seen associated with T2 hyperintensity, consider acute hyperbilirubinemia of infancy [25,42,53], systemic lupus erythematosus [38,52], and hemolytic-uremic syndrome [26,61]; the latter is most likely if there is associated edema involving the external and extreme capsules and the claustrum (Fig. 3) [26]. T2 hyperintensity of the globus pallidus associated with T2 prolongation of the insula and perirlandic cortex should suggest a diagnosis of urea cycle disorders [66,68].

If the pattern of the imaging study indicates that the metabolic disorder is primarily one of cortical involvement (cortical thinning with enlarged cortical sulci), consideration should be given to such disorders as the neuronal cer-

<table>
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<tr>
<th>Table 1</th>
<th>Disorders causing T2 or FLAIR hyperintensity of the corpus striatum</th>
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<tbody>
<tr>
<td>Leigh syndrome</td>
<td>Juvenile Huntington disease</td>
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<td>Wilson disease</td>
<td>Glutaric aciduria type I</td>
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<tr>
<td>Propionic academia</td>
<td>Molybdenum co-factor deficiency</td>
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<tr>
<th>Table 2</th>
<th>Disorders causing T2 or FLAIR hyperintensity of the globi pallidi</th>
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<tbody>
<tr>
<td>Methylmalonic academia</td>
<td>Succinic semialdehyde dehydrogenase deficiency</td>
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<tr>
<td>Urea cycle disorders</td>
<td>GAMT deficiency</td>
</tr>
<tr>
<td>Pyruvate dehydrogenase (E2) deficiency</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Hemolytic-uremic syndrome</td>
<td>Bilirubin toxicity</td>
</tr>
<tr>
<td>Isovaleric academia</td>
<td>Cyanide and carbon monoxide intoxication</td>
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Figure 1  
Pantothenate kinase associated neuropathy (formerly called Hallervorden-Spatz disease). On this axial SE 2500/70 image, both globi pallidi (black arrows) are abnormally hypointense with central hyperintensity, a very characteristic appearance.

Figure 2  
L-2-Hydroxyglutaric aciduria. Coronal FSE 3000/100 image shows hyperintensity of the globi pallidi (white arrows) and of the subcortical white matter with sparing of the periventricular white matter.
oid lipofuscinoses, the mucolipidoses, glycogen storage diseases, or GM1 gangliosidosis [9,79].

White matter disorders

White matter disorders can be segregated based on three factors: whether white matter never myelinates completely (hypomyelination) or whether myelin forms and is subsequently destroyed (demyelination); whether myelin destruction is in the periventricular, deep or subcortical white matter; and what part of the white matter (specific gyrus or lobe) is affected.

The pattern of a lack of myelination, or hypomyelination, is seen in very few disorders. It is most commonly found in Pelizaeus–Merzbacher disease, a disorder that affects the PLP1 gene that codes for the production of proteolipid protein, one of the major structural proteins of myelin [82,83]. The appearance of the brain in this disorder is that of a normal, much more immature brain. For example, the MRI of a 5-year-old child with this disorder might be mistaken for that of a 5-month-old infant (Fig. 4). Similar appearances can be seen in disorders of trichothiodystrophy with photosensitivity [12,54], in patients with the 18q-syndrome (deletion of a large portion of the long arm of chromosome 18) [39,41], and in patients with Sala disease (a disorder of sialic acid transport) [40,62]. If there is a question about the diagnosis of Pelizaeus–Merzbacher disease, proton MRS may help, as it shows and elevated NAA peak [67].

If myelin develops but is subsequently damaged, the brain should be analyzed to determine whether the region primarily affected is the deep white matter or the subcortical white matter. If the subcortical white matter is involved, it should be carefully analyzed to see if the subcortical U fibers are affected. If so, an attempt should be made to find out whether the patient has macrocephaly. Bilateral, symmetrical, frontal white matter involvement involving the U fibers in a macrocephalic patient is quite specific for Alexander disease, particularly if it extends posteriorly to involve the caudate heads [76] (Fig. 5) (Table 3). Bilateral, diffuse and symmetric, peripheral white matter involvement without macrocephaly should raise suspicion for organic acidurias or early Kearns–Sayre syndrome (Fig. 6) [4,9]. Diffuse white matter abnormality involving the subcortical U fibers and associated with subcortical cysts suggests megalencephalic leukoencephalopathy with subcortical cysts (MLC, Fig. 7) [70,74,75].

If early myelin injury is restricted to primarily deep white matter, the thalami should be specifically analyzed. High attenuation on CT or short T1 (hyperintensity) or T2

Table 3 Leukodystrophies with early involvement of subcortical white matter

<table>
<thead>
<tr>
<th>Alexander disease</th>
<th>Kearns-Sayre syndrome</th>
<th>Megalencephalic leukoencephalopathy with subcortical cysts</th>
<th>Galactosemia</th>
<th>Mitochondrial disorders</th>
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hypointensity) on MR bilaterally in the thalami strongly suggests globoid cell leukodystrophy (Krabbe disease) or GM2 gangliosidosis [9,33,34,47] (Table 4). If the thalami are normal, the brain stem should be evaluated for involvement of specific tracts, particularly the corticospinal tracts. If specific tracts (the corticospinal tracts, in particular) are involved, peroxisomal disorders such as X-linked ALD should be strongly considered [3]. If not, consideration should be given to metachromatic leukodystrophy, cerebellar ataxia with cerebral hypomyelination (vanishing white matter disease), phenylketonuria (PLU), Lowe syndrome (oculocerebrorenal syndrome), mucolipidosis type IV, merosin deficient congenital muscular dystrophies, and, in the proper clinical setting, damage from radiation or chemotherapy [9,79]. Among these, vanishing white matter disease should be considered if the clinical history is one of periodic acute worsening after trauma or infection and

**Figure 5** Alexander disease. Axial SE 2500/70 image shows abnormal hyperintensity of the frontal white matter (white arrows) including the subcortical fibers. The heads of the caudate nuclei (c) and the anterior putamina are also affected. Bilateral, symmetrical, frontal white matter involvement involving the U fibers in a macrocephalic patient is quite specific for Alexander disease, particularly if it extends posteriorly to involve the caudate heads.

**Figure 6** Kearns-Sayre syndrome. Coronal FLAIR image shows bilateral symmetric areas of hyperintensity in the subcortical posterior frontal lobes. At this stage in the disease, no abnormality is yet seen in the globi pallidi.

**Figure 7** Megalencephalic leukoencephalopathy with subcortical cysts. Parasagittal SE 600/15 image in a 2-year-old shows a nearly complete lack of myelin that involves the subcortical, deep, and periventricular white matter of the cerebral hemispheres. A subcortical cyst (white arrows) is seen in the anterior temporal lobe which is one of the more common locations, along with the parietal lobe.

**Table 4** Leukodystrophies with early involvement of deep white matter and sparing of subcortical white matter

<table>
<thead>
<tr>
<th>Leucodystrophies with atteinte précoce de la substance blanche profonde et épargnant la substance blanche sous-corticale</th>
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<tbody>
<tr>
<td><strong>Krabbe disease</strong> (globoid cell leukodystrophy)</td>
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<tr>
<td><strong>Metachromatic leukodystrophy</strong></td>
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<tr>
<td><strong>GM2 gangliosidoses</strong></td>
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<tr>
<td><strong>Childhood ataxia with CNS hypomyelination (vanishing white matter disease)</strong></td>
</tr>
<tr>
<td><strong>Lowe syndrome (oculocerebrorenal syndrome)</strong></td>
</tr>
<tr>
<td><strong>Mucolipidosis type IV</strong></td>
</tr>
<tr>
<td><strong>Merosin deficient congenital muscular dystrophy</strong></td>
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<tr>
<td><strong>Damage from radiation or chemotherapy</strong></td>
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if areas of cystic degeneration (seen as hypointense on FLAIR images, Fig. 8) develop in the hemispheric white matter [58,73]. Lowe syndrome should be suspected in many small cysts are seen in the affected white matter, particularly in the periventricular region [19,59]. If the dorsal brain stem, internal capsules, cerebral peduncles, and cerebellar white matter are affected in a newborn, maple syrup urine disease should be considered; this diagnosis can be confirmed by the finding of reduced diffusion on diffusion weighted images and the presence of a broad peak from branched chain keto acids at 0.9 ppm on proton MRS (see the later section of uses of MRS) [18,31].

Nonspecific white matter patterns include those with involvement of both superficial and deep white matter, those with unilateral involvement, those with diffuse involvement, and those with bilateral asymmetric involvement of white matter. Included under this heading are the congenital muscular dystrophies with neurologic impairment [1,8,37,77], collagen vascular diseases, such as systemic lupus erythematosus (which tend to involve the white matter bilaterally and asymmetrically), and demyelinating diseases, such as multiple sclerosis and acute disseminated encephalomyelitis (which affect the white matter bilaterally and asymmetrically and may affect deep cerebral nuclei) [13,35]. End stage white matter disease of any cause results in diffuse (superficial and deep), bilateral white matter damage that is completely nonspecific.

Disorders affecting gray and white matter

Disorders involving both gray and white matter can be divided into those involving only the cerebral cortex and those involving deep gray matter (with or without cortical involvement). Those disorders involving only cortical gray matter can be subdivided depending on whether the patient has normal long bones and spinal column. If the bones are normal, the cortex should be analyzed for areas of cortical dysplasia. If cortical dysplasia is present in addition to a lack of myelination, the differential diagnosis includes the generalized peroxisom disorders [15,24], congenital cytomegalovirus disease [6,14,63], and congenital muscular dystrophies with cerebral involvement (these disorders will typically have pontine hypoplasia and cerebellar dysplasia, as well [8]). If no cortical dysplasia is present, differential considerations include Alpers disease and Menkes disease, both of which cause considerable brain destruction [4]. If the bones are abnormal, the differential includes primarily storage diseases, such as the mucopolysaccharidoses and lipid storage disorders [10,11,36,48].

If deep gray matter is involved, differential diagnosis is dependent upon which nuclei are primarily involved (Table 1). If the thalami are involved, differential considerations include Krabbe disease and the GM1 and GM2 gangliosidoses, which have high attenuation on CT and short T1 and T2 relaxations times (hyperintense on T1 weighted images and hypointense on T2 weighted images) on MR (Fig. 9), and neonatal profound asphyxia, which typically involves the ventrolateral thalami along with posterior putamina and perirlandic cortex [2,5,7]. Krabbe disease is distinguished from the others by the presence of abnormal T2 hyperintensity along the corticospinal tracts (Fig. 9c). Another consideration is autosomal dominant acute necrotizing encephalitis [49,50], particularly if T2 hyperintensity is also seen in the dorsal brain stem. Thalami may also be affected in mitochondrial disorders, Wilson disease, and Canavan disease; typically other deep gray matter nuclei will be affected, as well (putamina in mitochondrial disorders and Wilson disease, globi pallidi in Canavan disease). Globus pallidus involvement in association with diffuse white matter disease including the subcortical, deep, and periventricular regions suggests a diagnosis of Canavan disease [17] (Fig. 10) (Table 5). Association with subcortical white matter and sparing of periventricular white matter suggests a later phase of Kearns-Sayre syndrome (globi pallidi are spared in early phases) or L-2-hydroxyglutaric aciduria; the latter will often show involvement of the cerebellar dentate nuclei [20]. Diffuse white matter involvement sparing the subcortical white matter during the early stages of the disease suggests methylmalonic acidemia, maple syrup urine disease, carbon monoxide toxicity, or cyanide toxicity. Maple syrup urine disease typically has involvement of the corticospinal tracts in the centrum semiovale, internal capsules, cerebral peduncles, dorsal pons, and cerebellar white matter, reduced diffusivity in the affected regions, and a characteristic peak at 0.9 ppm on proton MRS (see below) [16,18,31]. Carbon monoxide and cyanide toxicity typically involve

**Figure 8** Cérébelle avec ataxie nerveux system hypomyélinisation (vanishing white matter disease). Axial FLAIR image in a 5-year-old child shows abnormal hyperintensity of the cerebral white matter. In addition, there are areas of cavitation of the white matter (arrows), seen as isointensity to cerebrospinal fluid. In the proper clinical setting, these areas of cavitation are diagnostic of vanishing white matter disease.

**Figure 8** Ataxie cérébelleuse avec hypomélinisation du système nerveux central (vanishing white matter disease). Image axiale FLAIR chez un enfant de cinq ans. Aspect hyperintense de la substance blanche. Il existe aussi des aires de cavitation de la substance blanche iso-intenses au liquide céphalorachidien (flèche). Ces cavitations sont spécifiques de la maladie dans un cadre clinique adéquat.
the cerebral cortex and striatum and, sometimes, the cerebellum [32,51,55,56]. Primary striatal (putamen and caudate) involvement suggests Leigh syndrome, MELAS, propionic acidemia, glutaric aciduria type I (glutaryl CoA dehydrogenase deficiency) (Table 6), molybdenum cofactor deficiency, isolated sulfite oxidase deficiency, hypomyelination with atrophy of the basal ganglia and cerebellum, toxic exposure, later infantile or childhood profound hypoxic-ischemic injury, or childhood hypoglycemia. Regions of involvement in Leigh syndrome vary with the underlying molecular cause of the disorder, although no consistently reproducible genotype-phenotype associations have been identified. In MELAS, cortical lesions are seen more commonly than basal ganglia lesions, and are usually present when the basal ganglia are involved. Two important features that differentiate the cortical lesions from those of ischemic infarcts are the locations (they do not correspond to vascular terri-

**Figure 9**  Globoid cell leukodystrophy (Krabbe disease). A. Axial noncontrast CT scan shows abnormally increased attenuation (arrows) of the thalami. B. Axial spoiled gradient echo 35/7 image shows abnormal hyperintensity (arrows) of the thalami. C. Axial SE 3000/120 image shows abnormally hypointense thalami and abnormal hyperintensity (arrows) of the posterior limbs of the internal capsules.

**Figure 9**  Leucodystrophie à cellules globoïdes (maladie de Krabbe). A. Tomodensitométrie cérébrale sans injection de contraste : aspect hyperdense des thalamus (flèches). B. Image axiale écho de gradient 35/7 : aspect hyperintense des thalamus (flèches). C. Image axiale SE 3000/120 : les thalamus et le bras postérieur des capsules internes (flèches) sont hyperintenses.

**Table 5**  Leukodystrophies with globus pallidus involvement

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<thead>
<tr>
<th>Tableau 5</th>
<th>Leukodystrophies avec atteinte des pallidums</th>
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<tr>
<td>Canavan disease</td>
<td>Methylnalonic academia</td>
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<tr>
<td>Kearns Sayre syndrome</td>
<td>L-2-Hydroxyglutaric aciduria</td>
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<tr>
<td>Maple syrup urine disease</td>
<td>Carbon monoxide poisoning</td>
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<td>Cyanide toxicity</td>
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**Table 6**  Leukodystrophies with striatal (caudate and putaminal) involvement

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<th>Tableau 6</th>
<th>Leukodystrophies avec atteinte de noyaux gris centraux (noyaux caudés et putamén)</th>
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<tbody>
<tr>
<td>Leigh syndrome</td>
<td>MELAS</td>
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<tr>
<td>Other mitochondrial leukoencephalopathies</td>
<td>Propionic academia</td>
</tr>
<tr>
<td>Glutaric acidemia type I</td>
<td>Isolated sulfite oxidase deficiency</td>
</tr>
<tr>
<td>Late infantile/childhood profound hypoxic-ischemic injury</td>
<td>Childhood hypoglycemia</td>
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**Figure 10**  Canavan disease in a 10-month-old infant. Axial SE 3000/120 image shows diffuse white matter hyperintensity, including the subcortical, deep, and periventricular white matter. Abnormal hyperintensity is also seen in the globi pallidi (arrows) and anterior and lateral thalami.

**Figure 10**  Maladie de Canavan chez un enfant de dix mois. Image axiale SE 3000/120. Aspect hyper-intence de la substance blanche de façon diffuse, avec atteinte de la substance blanche sous corticale, profonde et périventriculaire. Les pallidums (flèches), les parties antérieure et latérale des thalamus sont aussi affectées.
Glutaric aciduria type I (glutaryl-CoA dehydrogenase deficiency) and the common association of premature senescent calcifications in the globi pallidi [80]. Glutaric aciduria type I is typically associated with enlarged subarachnoid spaces, particularly in the anterior sylvian fissures (Fig. 11a), and central white matter T2 hyperintensity (Fig. 11b). Isolated sulfite oxidase deficiency is rapidly progressive and causes multicystic encephalomalacia of the cerebral white matter (Fig. 12). Cockayne disease will show calcification of the striatum, as well as characteristic facies and other aspects of the syndrome.

Proper analysis of the MR scans using this pattern system can facilitate the work-up of patients with inborn errors of metabolism.

**When is spectroscopy helpful?**

Proton MRS can be extremely useful adjunct in making the diagnosis of an inborn error of metabolism. In some cases, the spectroscopy serves as an adjunct, to help verify a diagnosis already suspected by the use of pattern recognition. For example, the pattern of brain involvement in neonatal maple syrup urine disease is very specific. Edema (FLAIR and T2 hyperintensity) is present in the dorsal brain stem, the cerebellar white matter, the internal capsules and cerebral corticospinal tracts, and the globi pallidi (Fig. 13) [16]. Proton MRS helps to confirm the findings when it shows a characteristic broad peak centered at 0.9 ppm (Fig. 13) that represents branched chain amino acids and ketoacids [31]. Similarly, Canavan disease has a characteristic pattern of diffuse white matter edema, involving peri-cortical areas and the subcortical white matter. Figure 11. Glutaric aciduria type I (glutaryl-CoA dehydrogenase deficiency). Axial SE 2500/70 image at the level of the pons and middle cranial fosse shows large extraparenchymal CSF collections (white arrows in a) that represent the anterior portions of enlarged sylvian fissures. Note also abnormal hyperintensity in the central tegmental tracts (small arrows in a). Axial SE 2500/70 image at the level of the basal ganglia shows abnormal T2 hyperintensity in the putamina (arrows), globi pallidi, and deep frontal white matter (large arrowheads).

**Figure 11** Acidurie glutarique de type I (déficit en glutaryl-CoA déshydrogénase). Images axiales SE 2500/70. Collections liquidiennes extracérébrales (a, flèches blanches) en rapport avec un élargissement des fissures sylviennes. Il existe aussi une atteinte des faisceaux postérieur du tegmentum (a, petites flèches). Aspect hyperintense des putamens (b, flèches), des pallidums, et de la substance blanche frontale (b, têtes de flèches).

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**When is spectroscopy helpful?**

Proton MRS can be extremely useful adjunct in making the diagnosis of an inborn error of metabolism. In some cases, the spectroscopy serves as an adjunct, to help verify a diagnosis already suspected by the use of pattern recognition. For example, the pattern of brain involvement in neonatal maple syrup urine disease is very specific. Edema (FLAIR and T2 hyperintensity) is present in the dorsal brain stem, the cerebellar white matter, the internal capsules and cerebral corticospinal tracts, and the globi pallidi (Fig. 13) [16]. Proton MRS helps to confirm the findings when it shows a characteristic broad peak centered at 0.9 ppm (Fig. 13) that represents branched chain amino acids and ketoacids [31]. Similarly, Canavan disease has a characteristic pattern of diffuse white matter edema, involving peri-cortical areas and the subcortical white matter. Figure 11. Glutaric aciduria type I (glutaryl-CoA dehydrogenase deficiency). Axial SE 2500/70 image at the level of the pons and middle cranial fosse shows large extraparenchymal CSF collections (white arrows in a) that represent the anterior portions of enlarged sylvian fissures. Note also abnormal hyperintensity in the central tegmental tracts (small arrows in a). Axial SE 2500/70 image at the level of the basal ganglia shows abnormal T2 hyperintensity in the putamina (arrows), globi pallidi, and deep frontal white matter (large arrowheads).

**Figure 11** Acidurie glutarique de type I (déficit en glutaryl-CoA déshydrogénase). Images axiales SE 2500/70. Collections liquidiennes extracérébrales (a, flèches blanches) en rapport avec un élargissement des fissures sylviennes. Il existe aussi une atteinte des faisceaux postérieur du tegmentum (a, petites flèches). Aspect hyperintense des putamens (b, flèches), des pallidums, et de la substance blanche frontale (b, têtes de flèches).
Figure 13  Maple syrup urine disease in a 2-week-old infant: value of proton spectroscopy and diffusion weighted imaging. A–C. Axial SE 3000/120 images show abnormal hyperintensity in the dorsal pons, middle cerebellar peduncles, and cerebellar white matter in 13a; in the globi pallidi (g) and posterior limbs of the internal capsules (black arrows) in 13b; and along the corticospinal tracts in the cerebral hemispheres (black arrows) in 13c. D–E. Axial calculated diffusivity images show reduced diffusion (hypointensity) in the globi pallidi (white arrows in 13d), internal capsules and thalami (black arrows in 13d) and corticospinal tracts in the cerebral hemispheres (black arrows in 13e). F. Proton MRS (TE = 26 ms) shows a large peak at 0.9 ppm that represents branched chain ketoacids (BCKA). This peak is characteristic of maple syrup urine disease. The spectrum is otherwise normal for age.

Figure 13  Maladie des urines d’érable chez un nouveau-né de deux semaines. Valeur de la spectroscopie de protons et de l’imagerie de diffusion. A–C. Images axiales SE 3000/120 : Aspect hyperintense de la partie dorsale de la protubérance, des pédoncules cérébelleux moyens, de la substance blanche du cervelet (13 a), des pallidums (g, 13 b), du bras postérieur des capsules internes (flèches noires, 13b), du faisceau corticospinal des hémisphères cérébraux (flèches noires, 13c). D–E. ADC images : restriction de la diffusion (aspect hypo-intense) au niveau des pallidum (flèches blanches, 13d), des capsules internes, des thalami (flèches noires, 13d), et du faisceau cortiospinal des hémisphères cérébraux (flèches noires, 13e). F. Spectroscopie de protons (TE 26 ms) : il existe un pic large à 0,9 ppm qui représente les aminoacides branchés. Ce pic est caractéristique de la maladie. Par ailleurs le spectre est normal pour l’âge.
ventricular, deep, and subcortical white matter, in addition to bilateral globus pallidus and sometimes thalamic involvement [17,69]. Proton MRS helps to confirm this by showing a very large NAA peak at 2.01 ppm.

In some disorders, MRS is essential for making the diagnosis. The clinical features and MRI imaging pattern of patients with nonketotic hyperglycinemia, for example, is nonspecific. Proton MRS, however, shows an elevated glycinic peak at 3.55 ppm (Fig. 14) on both long and short echo spectra. Using a short echo time, one might confuse the peak with that of myo-inositol, but if the peak persists at long echo times such as 270 or 288 ms, it represents glycinic and strongly suggests the diagnosis. In creative deficiency syndromes, MRS is the most important technique in making the diagnosis. Creative deficiency syndromes include disorders due to defects in synthesis (GAMT deficiency [60,65] and arginine:glycine amidotransferase (AGAT) deficiency [30]) and defects in the transport of creatine across the blood-brain barrier (X-linked creatine transporter defect) [21,57]. Patients with GAMT deficiency often have abnormal hyperintensity of the globi pallidi on FLAIR and T2 weighted images, but patients with AGAT deficiency and creatine transporter defects can only be detected by appreciated the low or absent creatine peak on proton MRS of the brain (Fig. 15). As oral creatine supplementation leads to striking improvements in neurological exam and intellectual development [64], detection of this disorder with MRS is extremely important.

Proton MRS can also be important in assessing response to therapy of metabolic disorders. Response to oral creatine supplementation by following brain creatine levels with MRS has already been discussed in the previous paragraph. Proton MRS also allows monitoring of the brain phenylalanine levels in patients with PLU, although it requires the use of a very short echo time (20 ms or less), because of the short T2 relaxation time of the phenyl protons, and a large field of view because cerebral phenylalanine level is typically very low (less than 1 mmol/l). The resonances of the phenyl protons are visualized in a single peak at 7.36 ppm; this peak has a large enough amplitude that it can be quantified. Direct analysis of the brain is important because phenylalanine levels in the brain do not correlate closely with those in the blood [44,45].

In some disorders, proton MRS can aid in making a diagnosis and instituting therapy before clinical signs and symptoms develop. An excellent example of this is X-linked ALD. In this disorder, the central issue is whether a boy carrying the biochemical/genetic defect should undergo a hematopoietic stem cell transplantation, a form of treatment reserved for the rapidly progressive cerebral disease (and not for the later-onset variant known as adrenomyeloneuropathy). If bone marrow transplantation is performed early in the course of the rapidly progressive disease, it may prevent further deterioration or even lead to improvement [22,23,84]. However, the therapy is not recommended for asymptomatic children, as the morbidity and mortality associated with transplantation is high and more than 50% will never develop the serious form of ALD. Waiting until the child has rapidly advancing or severe cerebral involvement is not recommended, either, as the procedure may lead to acceleration of the disease [22,23,84]. Proton MRS provides important information in this regard, as it shows abnormalities before the MR imaging study becomes abnormal in some children [71] and in normal appearing white matter peripheral to the regions of T2 prolongation and enhancement; this area of abnormal MRS may represent Zone C. Indeed, it is suggested that reduction in the NAA/choline ratio to below 5.0 is predictive of disease progression within the next 2-3 years [22]. Therefore, proton MRS should be performed in all individuals with ALD, particularly those with stable MR imaging exams and in siblings (of patients with ALD) who are known to have the ALD mutation but are as yet asymptomatic.

**When is diffusion weighted imaging helpful?**

The literature concerning the utility of diffusion weighted imaging in metabolic disorders is rather confusing, probably because the timing of the study plays an important factor. For example, diffusion weighted imaging early in the course of metachromatic leukodystrophy or globoid cell leukodystrophy shows reduced diffusion in the affected white matter, while in later phases, diffusivity in increased [78]. However, some types of myelinopathy (myelin vacuolization [78]) result in a marked decrease in diffusivity. For example, in neonatal onset maple syrup urine disease, all myelinated parts of the brain show up to an 80% reduction in diffusivity, resulting in markedly increased signal intensity on diffusion weighted images and markedly decreased signal intensity on diffusivity images (also called apparent diffusion coefficient images, Fig. 14d, e) [18]. Several other disorders show similar findings of markedly reduced diffusion in the acute state, including nonketotic hyperglycinemia, Kearns-Sayre syndrome, and Canavan disease. It is important to remember, however, that after the acute stage of encephalopathy, myelin will break down and diffusivity will increase.

**Confounding factors**

The approach described in this manuscript will often work well in allowing the neuroradiologist to limit the differential diagnosis to a list of disorders of reasonable length. However, the approach is not perfect and will not always allow a diagnosis to be made. The approach is complicated by several confounding factors. The first of these is the fact that many metabolic disorders have a different appearance on imaging studies when imaged at different stages of the disease (therefore, this approach is most useful in the early stages of the disease). Another potential source of error is that some disorders are diagnosed biochemically while others are diagnosed genetically. Atypical imaging patterns can be seen in disorders diagnosed biochemically because many diseases that manifest the same serum/urine biochemistry actually have different underlying genetic and neurochemical defects. Disorders diagnosed genetically may appear heterogeneously because different mutations of the gene may result in abnormalities of different pathways (different parts of proteins may participate in different chemical pathways). Nonetheless, this systematic approach will allow the user to get close to the diagnosis much of the time.
Figure 14  Nonketotic hyperglycinemia in a 10-day-old neonate. A. Axial SE 3000/120 image shows abnormal hyperintensity of the basal ganglia. B. Proton MRS (TE = 288 ms) through the basal ganglia shows an abnormal peak (gl) at 3.5 ppm representing a large amount of glycine in the brain.

Figure 15  Creatine deficiency due to GAMT deficiency. a. Proton MR spectrum from the patient’s basal ganglia region shows only two peaks, choline (Ch) and N-acetylaspartate (NAA). Compare with 15b. b. Proton MR spectrum (TE = 288 ms) from an age matched control shows the presence of three major peaks, choline (Ch), creatine (Cr), and NAA.
Conclusion

Although inborn errors of metabolism are a very difficult group of diseases to comprehend, the use of a practical methodological approach helps in the differentiation of the various disorders. Through this approach, the imager can start to differentiate the various disorders and simplify the job of the neurologist or geneticist trying to make the proper diagnosis.

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