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Congenital Genetic Inborn Errors of Metabolism Presenting as an Adult or Persisting Into Adulthood: Neuroimaging in the More Common or Recognizable Disorders

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Numerous congenital-genetic inborn errors of metabolism (CIEMs) have been identified and characterized in detail within recent decades, with promising therapeutic options. Neuroimaging is becoming increasingly utilized in earlier stages of CIEMs, and even in asymptomatic relatives of patients with a CIEM, so as to monitor disease progress and treatment response. This review attempts to summarize in a concise fashion the neuroimaging findings of various CIEMs that may present in adulthood, as well as those that may persist into adulthood, whether because of beneficial therapy or a delay in diagnosis. Notably, some of these disorders have neuroimaging findings that differ from their classic infantile or earlychildhood forms, whereas others are identical to their early pediatric forms. The focus of this review is their appearance on routine magnetic resonance imaging sequences, with some basic attention to the findings of such CIEMs on specialized neuroimaging, based on recent or preliminary research. The general classes of disorders covered in this complex review are: peroxisomal disorders (adrenoleukodystrophy), lysosomal storage disorders (including metachromatic leukodystrophy, Krabbe or globoid cell leukodystrophy, Fabry, Niemann-Pick, GM1, GM2, Gaucher, mucopolysaccharidoses, and Salla diseases), mitochondrial disorders (including mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes, myoclonic epilepsy with ragged red fibers, Leigh disease, and Kearns-Sayre syndrome), urea cycle disorders, several organic acidemias (including phenylketonuria, maple syrup urine disease, 3-hydroxy-3-methylglutaryl colyase deficiency, glutaric acidurias, methylmalonic academia, proprionic academia, 3-methylglucatonic aciduria, and 2-hydroxyglutaric acidurias), cytoskeletal or transporter molecule defects (including Alexander or fibrinoid leukodystrophy, proteolipid protein-1 defect or Pelizaeus Merzbacher, Wilson, and Huntington diseases), and several neurodegenerative disorders of brain iron accumulation. Additionally, an arbitrary "miscellaneous" category of 5 recognizable disorders that may present in or persist into adulthood is summarized, which include megalencephalic leukoencephalopathy with subcortical cysts (megancephalic leukoencephalopathy with subcortical cysts or van der Knaap disease), polymerase-III gene defect ("4H syndrome"), childhood ataxia with central nervous system hypomyelination ("vanishing white matter disease"), striopallidodentate calcinosis ("Fahr disease"), and Cockayne syndrome.
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Introduction

With advances in molecular biology over the last few decades, several congenital-genetic inborn errors of metabolism (CIEMs) have been identified and characterized in detail. The therapeutic options for these disorders have also shown vast improvement in variety and success. These

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advances have been accompanied by advances in imaging sciences, giving us a better understanding of these disorders and enabling us to diagnose, monitor disease progress, and treatment response using imaging tools.

Herein, we review the imaging findings of the inborn errors of metabolism presenting in adulthood, as well as those that may persist into adulthood as a result of improvements in disease management or delay in diagnosis. As will be evident from this review, some of these disorders have imaging findings that are significantly different from the findings in their classic early-onset phenotypes, whereas others follow the pediatric forms on neuroimaging. A better understanding of these typical or atypical imaging findings is essential to avoid errors or delays in diagnosis.

This review does not constitute a comprehensive index of CIEMs, as it does not include all the inborn errors of metabolism that have been described to cause neurologic derangement; particularly, this review does not include the multitude of disorders that are almost always fatal in childhood. Rather, it focuses on those disorders that have been well described either to occur in adulthood or to persist into adulthood, and have a characteristic and recognizable imaging appearance; to a lesser degree, it focuses on those disorders in which imaging may play a role in monitoring disease progress and treatment response (Table 1).

X-Linked Adrenoleukodystrophy

Adrenoleukodystrophy (ALD) is well recognized in the literature as a leukoencephalopathy with a myriad of presentations. The average age at onset for the childhood form is 7.1 years.[1] Onset in adulthood has been described to occur in 28%-45%.[1,2] The frequency of hemizygotes in the United States has been stated to be as high as 1 in 42,000 persons.[2]

The mechanism by which the ABCD1 gene mutation causes demyelination is unclear. It has been proposed that the ABCD1 gene may code for an adenosine triphosphate (ATP)-binding membrane transporter involved in transporting very long chain fatty acids (VLCFA) into the peroxisome.[3] Failure of this transport mechanism, leading to accumulation of VLCFA in the cells, as well as an immunologic reaction to the gangliosides and phospholipids abnormally acylated by the VLCFAs, is a putative mechanism.[2]

The clinical presentation and imaging manifestations of the adult-onset form of ALD are often different from the childhood form. It can present with cognitive impairment, motor symptoms, visual abnormalities, auditory tract symptoms as well as psychiatric manifestations. The classic childhood form consists of involvement of the splenium of the corpus callosum and parieto-occipital white matter (WM) in approximately 80% of patients.[4] Among all age groups, this pattern constitutes 66%, followed by the frontal pattern in approximately 15.5%.[4] A severity scoring system (the "Loes" score) has been utilized in numerous publications.[4]

The imaging patterns in adult onset have been classified by Kumar et al[5] into 4 categories. In the group of 119 male patients, abnormal findings in brain imaging were seen in 54 (45%). Out of these 54 patients, 32 (27%) of the symptomatic adult men with abnormal magnetic resonance imaging (MRI) findings had the cerebral lobar form of ALD, which is closest in appearance to the childhood form, and T2-weighted images (T2WI) or fluid-attenuated inversion recovery (FLAIR) images showed bilateral parieto-occipital WM and corticospinal involvement (Fig. 1). In 6 (5%) patients, the WM involvement was more extensive and did not have the parieto-occipital predominance that is typical of childhood ALD. This subtype also had atrophy in the cerebral cortex, subcortical regions, and brainstem, unlike the childhood form. Of the patients, 16 (13%) had only long tract involvement, with abnormal signal in the corticospinal tracts, extending from the internal capsule downward into the medulla. That subset can mimic adult-onset Krabbe disease and amyotrophic lateral sclerosis.[6] Whether in the adult onset or childhood form, active demyelination (the "edge") may have either reduced diffusion on diffusion-weighted imaging (DWI) or enhancement on postcontrast T1-weighted images (T1WI); however, the DWI findings typically precede the enhancement. Most importantly, 55% of symptomatic men who test positive for the disease have a normal-appearing brain MRI.[5] Additionally, atypical adult-onset presentations have been described, including frontal lobe predominance[7] and spinocerebellar involvement.[8] Additionally, the anecdotal experience of these authors is that asymptomatic siblings with the genetic defect may appear entirely normal, have focal, but symmetric WM disease, or have abnormal findings such as within the periventricular WM or within the internal capsules, which may be quite subtle (Fig. 2).

There has been some interest in implementing MRI-based techniques to monitor disease progression and treatment response in patients with ALD who undergo hematopoietic stem cell transplantation (HSCT), but most of this data are based on the childhood form of ALD. The "Loes score" has shown utility in that patients with lower scores before HSCT have better outcomes, and proton MR spectroscopy (MRS) could be useful in monitoring disease progression and therapeutic response.[4,9-11] Diffusion tensor imaging (DTI) has also been utilized, where changes in mean diffusivity (MD) within the optic radiations have been shown to correlate with changes in neurologic function after HSCT.[12] There has also been interest in using perfusion MRI, as areas of cerebral blood volume normalization suggest arrest of disease progression, whereas regions of decreasing cerebral blood volume precede worsening contrast-enhancing foci.[13]

Lysosomal Storage Disorders: Lipid Metabolism Disorders: Sphingolipidosis

Metachromatic Leukodystrophy

The most common genetic defect in metachromatic leukodystrophy (MLD) is the ARSA gene (mapped to chromosome 22q), with an overall incidence of the defect estimated to be approximately 1:40,000-1:160,000.[14,15] Several variants have been described, all of which have deficient activity of