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REVIEW

Inborn errors of metabolism for the diagnostic radiologist

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Abstract Inherited metabolic disorders are becoming more important with the increasing availability of diagnostic methods and therapies for these conditions. The radiologist has become an important link in making the diagnosis or collaborating with the specialist centre to diagnose these disorders and monitor effects of therapy. The modes of presentation, disease-specific groups, classic radiological features and investigations are explored in this article to try and give the general radiologist some crucial background knowledge. The following presentations are covered: acute intoxication, hypoglycaemia, developmental delay and storage features. Specific groups of disorders covered are the abnormalities of intermediary metabolism, disorders of fatty acid oxidation and ketogenesis, mitochondrial disorders, lysosomal storage disorders, and, briefly, other groups such as peroxisomal disorders, disorders of glycosylation, and creatine synthesis disorders. New advances and the demands for monitoring are also briefly explored.

Keywords Inborn errors of metabolism · Radiology · Children

Introduction

Inherited metabolic disorders are a collective name for rare genetically inherited disorders with a chemical imbalance generally causing the pathology. The basic principle as described by Garrod [1] is that a genetic defect will cause abnormality of an enzyme. The main function of an enzyme is to degrade chemical substances, and disruption of this function will cause disease either due to deficiency ahead of the block or toxic effects due to accumulation of substances before the block. Although this is not entirely true for all of the disorders it does help in understanding some of the principles of these disorders. Individually these disorders are rare with a common incidence of about 1 in 50,000, but collectively their incidence will be around 1 in 1,000 depending on which disorders are included. As these are multisystem disorders there is great overlap between different medical specialties. One of the landmarks of these disorders is that they involve more than one system and are more likely to cause unexpected findings. These disorders were traditionally paediatric diseases, but with longer survival and the recognition of attenuated variants they have become disorders from cradle to grave.

There is increasing demand for the radiologist to be aware of rare disorders due to the fact that routine radiography is becoming an increasingly important tool for diagnosis. The increase in knowledge regarding the mechanism, progression and diagnosis of rare diseases has led to development of new therapies. These therapies demand early diagnosis, but have also created a demand for some objective measures of efficacy of treatment. Advances in the development of new radiological techniques have made procedures such as MRI and CT more applicable and are being used early as investigative tools. This creates a situation where the radiologist becomes an important collaborator in diagnosing rare inherited metabolic disorders and some basic knowledge of the conditions and the appropriate investigations is crucial. Good communication between the radiologist and a specialist centre for these conditions is important and centres for these disorders

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are within reach of most parts of the world or relationships can be established via electronic links.

There are different ways of trying to deal with the great number of rare inherited metabolic disorders, but a combined approach with some overlap is used in this article. The disorders and the radiological implications are discussed using the following main classifications: mode of presentation, and specific disease groups with some classic or unusual radiological features.

Mode of presentation

The clinical information provided with a request for radiological investigation will be crucial in many of these disorders as some relatively common patterns have been established. The classic patterns are the picture of acute intoxication, i.e. a patient who was previously well becomes acutely and inappropriately ill. Disorders causing these patterns generally fall into the following categories: disorders of amino acid metabolism, disorders of fatty acid oxidation, and mitochondrial disease. The toxic metabolites accumulating are ammonia, organic acids and abnormal intermediary products, and this combined with energy deficiency causes the classic clinical features. These disorders are usually triggered by infection, change in diet, fasting, vaccinations or surgical procedures. General radiological features are bilateral changes in the basal ganglia plus other features more specific to the group.

The next typical presentation is in association with hypoglycaemia not associated with multiorgan failure and disorders causing this are disorders of fatty acid oxidation, glycogen storage disorders, ketogenesis defects, and disorders of gluconeogenesis. Hyperinsulinism will also cause hypoglycaemia and the association with hyperammonaemia in the absence of multiorgan failure would suggest a diagnosis of hyperinsulinism hyperammonaemia (HIHA), a disorder of glutamate overactivity. Many inborn errors of metabolism will cause multiorgan failure, and hypoglycaemia will be a feature of organ dysfunction. The conditions commonly causing this picture are galactosaemia, tyrosinaemia, mitochondrial disorders and some of the organic acidaemias. The characteristic radiological feature is involvement of the occipital and parietal cortex.

The next classic presentation is developmental delay. Typically this is global developmental delay (i.e. all aspects are delayed) and the presence of regression/loss of skills increases the probability. Developmental delay associated with other system involvement also increases the probability. The spectrum for this group is wide as attenuated forms of the intoxication group will present with developmental delay. Conditions that are typically associated with developmental delay are organic acidaemias, urea cycle disorders, amino acid disorders, mitochondrial disorders and lysosomal storage disorders, but potentially any of the groups can present in this way if untreated. Due to screening programmes, developmental delay due to phenylketonuria is hardly seen in the developed world, but should not be forgotten where there are no screening programmes in place. The usual radiological features are frontotemporal atrophy and a mixture of grey or white matter involvement depending on the underlying condition.

The next common presentation is accumulation of abnormal storage material with a usually slowly progressive clinical picture. As the storage material tends to accumulate in a variety of tissues, multisystem involvement is usually apparent. These patients tend to have increase in liver and spleen size with associated bone, eye and brain disease. The usual conditions causing these disorders are lysosomal storage disorders, with the disorders of oligosaccharide metabolism causing more severe and earlier onset disease, and the mucopolysaccharidoses and sphingolipidoses the later onset disorders. The typical radiological features are dysostosis multiplex and white-matter disease.

Specific disease groups

Disorders of amino acid metabolism

There are many different subgroups; I attempt to cover a broad base with specific reference to radiological features.

Phenylketonuria Phenylketonuria is a defect of the enzyme phenylalanine hydroxylase, which causes an increase in phenylalanine concentrations in the blood and central nervous system. Most countries have screening programmes to detect this disorder and treatment should ideally be started before 21 days of age. Diagnosis is dependent on finding elevated levels of phenylalanine and deficient levels of tyrosine. The mainstay of therapy is a phenylalanine-restricted diet and supplementation with additional amino acids to prevent any deficiencies due to protein restriction. The patients are also susceptible to deficiencies of vitamin B_{12} and trace elements if these are not supplemented. Untreated, this condition causes severe neurodevelopment delay, microcephaly and fair complexion. Poor compliance, especially in the first 8 years of life, is associated with loss of IQ points and mild learning difficulties. Diet for life is the current recommendation by most experts in developed countries, but the effects of discontinued diet in adulthood are controversial. MR spectroscopy studies show white-matter changes or dysmyelination in adult patients off diet with reversal of these changes after return to diet [2]. Decrease in bone mineral density is also reported.

Tyrosinaemia type 1 Tyrosinaemia type 1 is a deficiency of the enzyme fumarylacetoacetase, which causes acute liver failure in the neonate and, if untreated, renal tubulopathy, rickets, growth failure, neurological crises, cirrhosis and ultimately hepatocellular carcinoma and renal failure. Diagnosis is by looking at urine organic acids and finding the metabolite succinyl acetone, and elevated levels of tyrosine in the blood. Treatment is with nitisinone and a tyrosine-restricted diet with supplemented amino acids and trace elements to prevent deficiencies. Long-term monitoring is needed, and routine MR imaging is combined with chemical markers to diagnose possible malignant change at an early stage. Very early treatment seems to be protective for malignancy at this stage of knowledge [3]. Radiological features are those of rickets, enlarged hyperechoic kidneys, and nephrocalcinosis. MRI shows white-matter signal difference in the perirolandic area, and the posterior limbs of internal capsules show higher signal compared to the rest of the white matter. MR spectroscopy reveals two separate prominent peaks spread between 3.4 and 3.9 ppm. These peaks could represent the CH and CH_2 aliphatic protons of the tyrosine molecule [4]. Although not reported in children, decreased bone density has been observed in our adult population affected by this condition and the cause is likely to be multifactorial.

Alkaptonuria Alkaptonuria is a deficiency of the enzyme homogentisate 1,2-dioxygenase and is diagnosed by finding increased homogentisic acid in the urine when testing for urinary organic acids. Urine left to stand will become black in colour. Clinical trials are in progress that are assessing the value of low-dose nitisinone in these patients. The common radiological features are joint space narrowing that may progress to bony ankylosis, calcifications, osteophytosis, and reactive sclerosis of the articular surfaces [5]. This disorder can also cause aortic calcification, which may be an incidental finding on routine imaging [6].

Homocystinuria Homocystinuria can be caused by different enzymatic defects, either alone or in combination with methylmalonic aciduria. For ease of understanding, the classic form of homocystinuria is described here while methylmalonic aciduria is described in a different section. Combined disorders will have features of both and are very rare. Homocystinuria is caused by a defect of cystathionine β-synthase and can be fully responsive to pyridoxine supplementation. Non-responsive patients will need to be treated with a methionine-restricted diet or betaine to keep the levels of homocysteine low. High levels of homocysteine are associated with vascular stroke in typical vascular territorial areas, but at unexpected ages. Measurement of levels of homocysteine in plasma (very unstable and should be sent to the laboratory quickly) and urine (much more stable) will usually confirm the diagnosis. The radiological feature is arterial stroke in a young patient [7]; patients develop marfanoid habitus and so elongated long bones and kyphoscoliosis are common. Osteoporosis is also found, similar to other disorders in this group [8].

Sulphite oxidase deficiency and molybdenum cofactor deficiency Sulphite oxidase deficiency and molybdenum cofactor deficiency can be considered together as they share common clinical features and a common metabolic pathway. Measuring urate (uric acid) in blood and urine is a useful screening test. Diagnosis is achieved by measuring purines in urine; hypoxanthine is elevated in molybdenum cofactor deficiency and normal in sulphite oxidase deficiency. Further diagnostic tests are increased sulphite in urine or, more reliably, increased sulphocysteine in plasma. Radiological features are severe, and include early-onset white-matter atrophy and cystic changes as well as cortical, brainstem, thalamic and basal ganglia signal-intensity abnormalities [9]. This can sometimes be confused with the clinical presentation of hypoxic ischaemic encephalopathy [10]. There is no available effective therapy.

Maple syrup urine disease Maple syrup urine disease (MSUD) is caused by deficiency of the branched-chain α-ketoacid dehydrogenase complex (BCKDH), which is a multienzyme complex involved in degradation of branched-chain amino acids. Different clinical forms have been described with presentations from early acute neonatal to chronic intermittent forms being diagnosed in adolescents. Diagnosis is made by a positive DNPH test (dinitrophenylhydrazine solution reacts with 2-oxoacids to turn the solution cloudy), increased branched-chain keto- and hydroxyacids in the urine and elevation of alloisoleucine, which is diagnostic for all variants. Treatment is by a special leucine-restricted diet and supplementation of valine and isoleucine to promote catabolism during acute decompensation. Haemofiltration is sometimes needed for severe forms in addition to dietary manipulation.

Radiological features are generally similar for all variants, with dysmyelination a common features while patients are well [11]. In the acute neonatal phase MRI shows abnormal white matter in the cerebellum, dorsal brainstem, thalami, posterior limbs of internal capsules, and corona radiata [12]. MR spectroscopy shows the presence of abnormal branched-chain amino acids and branched-chain alpha-ketoacids at 0.9 ppm as well as an elevated lactate peak at 1.33 ppm [13].

Organic acidurias

Organic acidurias, also sometimes referred to as organic acidaemias, are a group of disorders with characteristic

accumulation of carboxylic acids in the urine. These conditions are diagnosed by analysing urine for organic acids and looking for the characteristic acylcarnitine profiles in plasma samples. Enzyme analysis in fibroblasts or molecular analysis are usually the confirmatory investigations required. Treatment is generally the same for most conditions with the mainstay being protein restriction, carnitine supplementation, and treating acute decompensation with a combination of high-energy fluids and drugs to remove toxic metabolites. Toxic metabolites are removed by sodium benzoate and sodium phenyl butyrate or acetate. It is currently believed that ammonia and glutamine are the toxic metabolites that cause most of the pathology. These treatment regimes are commonly referred to as emergency regimes and all patients should be aggressively treated early as failure to do this will necessitate the need for haemofiltration or dialysis.

Individual conditions are discussed below, highlighting radiological features and differences in management where appropriate.

Glutaric aciduria type 1 Glutaric aciduria type 1 is a defect of the enzyme glutaryl-CoA dehydrogenase that is crucial for degradation of lysine and tryptophane. It has recently been proven that a lysine-restricted diet is the treatment of choice in combination with general treatment for organic acidaemias. It seems that trapping of metabolites inside the brain may be the major cause of the pathology [14]. Radiological features are frontotemporal atrophy, wide cerebrospinal spaces anterior to the temporal lobe and wide sylvian fissures. Bilateral frontoparietal subdural haematomas that may lead to hydrocephalus needing shunting have been described and this is particularly important in the differential diagnosis of non-accidental head injury. Changes in the basal ganglia are also seen after acute decompensation and are very similar to the changes seen in other organic acidurias and mitochondrial disorders, but the widening of the opercula seem to be characteristic of this condition [15].

L-2-Hydroxyglutaric aciduria L-2-Hydroxyglutaric aciduria is a disorder clinically very different from glutaric aciduria type 1, with the only common features being macrocephaly and accumulation of lysine. This condition is slowly progressive, causing progressive ataxia, seizures and developmental delay, and does not have acute episodes of decompensation. Diagnosis is via the methods discussed above. Therapy is supportive only, there being no benefit from diet or carnitine [16]. Radiological features are cerebellar tract involvement, subcortical white-matter changes, brainstem and cerebellar atrophy, and signal changes in the putamen and dentate nuclei [17].

D-2-Hydroxyglutaric aciduria D-2-Hydroxyglutaric aciduria is another disorder in this group with different features and unknown aetiology. Again, this will be diagnosed by the same investigations, and both mild and severe phenotypes have been described as well as a combined disorder of D-2- and L-2-hydroxyglutaric aciduria. Clinical presentation is usually with developmental delay, cortical blindness and epileptic encephalopathy in the severe neonatal form, or developmental delay and hypotonia in the milder variant [18].

Reported radiological features are enlargement of the lateral ventricles with occipital more than frontal increase, subependymal cysts, delayed maturation and, later, multifocal white matter abnormalities [19]. Subdural haemorrhage has been described in one case [20]. Bilateral periventricular lesions in the parietooccipital white matter [21] are also recorded. Spondyloenchondromatosis is a rare skeletal dysplasia with multiple enchondromata in the metaphyses of the long bones and dysplastic vertebral bodies has been associated with this condition [22, 23].

Glutaric aciduria type 2 Glutaric aciduria type 2 is not an organic aciduria but rather a combined disorder of fatty acid oxidation and metabolism of branched-chain amino acids, but is mentioned here due to overlap of terminology. The correct term for this condition is multiple acyl-CoA dehydrogenase deficiency, and two forms have been described, namely a severe neonatal-onset form and a mild adult-onset form usually responsive to riboflavin therapy. The biochemical abnormalities in the urine (increased dicarboxylic acids, glutaric and ethylmalonic acid) were the reason why it was named with the preceding disorders. This condition is associated with facial dysmorphism, cardiomyopathy, epilepsy, hypoglycaemia, and progressive encephalopathy. Treatment is with a low-fat, low-protein and high-carbohydrate diet, and the emergency regime during times of stress and riboflavin in those who respond.

Radiological features are renal cystic changes that are present before birth on routine antenatal US imaging [24]. Cardiomegaly may be noticed on routine chest radiography and echogenic changes in the liver, spleen and kidney may be present. Features of acute hypoglycaemia may be present on MR imaging as well as a leukodystrophy. Other reported features are cystic changes in the putamen and periventricular areas, as well as agenesis of the cerebellar vermis [25]. Proton spectroscopy reveals an elevated choline/creatine ratio in the frontal lobe that improves on treatment. This together with a decreased NAA/Cr ratio is consistent with a demyelinating process [26].

Isovaleric aciduria, propionic aciduria and methylmalonic aciduria Isovaleric aciduria, propionic aciduria and methylmalonic aciduria are common organic acidurias and are diagnosed by using the general techniques and treated using general principles. Isovaleric acidaemia responds to glycine

supplementation, methylmalonic aciduria may respond to vitamin B_{12} supplementation and a rare response of propionic acidaemia to biotin has been reported.

Radiological features are initially mild attenuation of white matter and this may be due to initial neonatal presentation associated with hyperammonaemia. This is followed by widening of fissures and sulci, mild atrophy and delayed myelination. Basal ganglia changes are usually bilateral and involve the globus pallidus [27].

The biochemical defects and the therapy are likely to cause severe bone demineralization and are likely to become increasingly important the longer these patients survive.

Disorders of fatty acid oxidation

Disorders of fatty acid oxidation are usually associated with hypoglycaemia and are diagnosed by looking at urine organic acids and characteristic acylcarnitine profiles. The mainstay of therapy is the use of emergency high-energy regimes, low-fat diets and carnitine supplementation in some of these disorders. Carnitine supplementation is usually reserved for patients with significant clinical symptoms and proven carnitine deficiency. Only those with radiological features will be mentioned and most of these conditions will cause severe hypoglycaemia with the classic neuroimaging features in the occipital lobes. Many conditions are associated with cardiomyopathy, so an enlarged heart on routine chest radiography may be seen. Some of these conditions may cause hyperammonaemia and features of this are discussed under the urea cycle disorders. Long-chain defects seem to be more severe and affect more body systems, and may be associated with rhabdomyolysis.

The commonest disorder is *medium-chain acyl-CoA dehydrogenase (MCAD) deficiency*, which can be detected on newborn screening programmes; it presents with hypoglycaemia and an acute encephalopathy in older individuals. *Long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency* presents with a combination of hypoglycaemia, cardiomyopathy, hypotonia, liver dysfunction and retinopathy and has been associated with mothers with HELLP syndrome in late pregnancy and acute fatty liver of pregnancy. *Very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency* has a similar clinical picture to LCHAD with some patients with milder disease described.

Other conditions in this group are *carnitine transporter deficiency* that presents with cardiomyopathy, liver disease and muscle weakness, *carnitine palmitoyltransferase 1 deficiency* with a similar picture without cardiomyopathy but with renal tubular acidosis and associated renal cysts or altered echo pattern on US. High fasting levels of triglycerides may be an indicator of this disorder when seen with other features. *Carnitine palmitoyltransferase 2 deficiency* is usually an adult-onset disease with myopathy, cardiomyopathy, liver disease and episodes of rhabdomyolysis, but the neonatal form is more severe and usually associated with abnormalities of the liver and kidney.

Disorders of ketogenesis and ketolysis

These conditions are diagnosed by analysing urine organic acids and acylcarnitine profiles. Hypoglycaemia is a common feature and hyperammonaemia may also be a feature.

Hydroxymethylglutaryl coenzyme A (HMG-CoA) lyase deficiency is a disorder of ketogenesis and leucine oxidation presenting with hypoglycaemia, metabolic acidosis, hyperammonaemia and liver disease. Therapy is with a low-fat, low-protein diet, carnitine supplementation and an emergency regime with high carbohydrate content during decompensation. Radiological features on MRI are multiple coalescent lesions in the periventricular white matter and arcuate fibres. This is most noticeable in the frontal and periatrial regions were slightly hyperintense subcortical white matter is superimposed together with involvement of the dentate and caudate nuclei. A picture suggesting a leukodystrophy has been observed in some of our patients. Spectroscopy shows decrease in *N*-acetylaspartate, increase in choline and *myo*-inositol, a pathological lactate peak at 1.33 ppm, and a prominent peak at 2.42 ppm [28].

HMG-CoA synthase deficiency presents with hypoketotic hypoglycaemia and management is similar to that for fatty acid oxidation defects; no specific radiological features have been described.

3-Ketothiolase deficiency is a disorder of ketolysis that may present with episodes of ketosis/acidosis vomiting and coma. This may be associated with hyperammonaemia and relatively high blood sugar. Neurological disease is reported and is associated with high T2 signal in the posterolateral aspect of the putamen and delayed myelination [29].

Urea cycle defects

These are among the commonest disorders and are due to a few different enzyme defects. These disorders usually present in the neonatal period with acute crisis after a period of lethargy and associated respiratory alkalosis. They are diagnosed by analysing the serum amino acids, noting the presence or absence of orotic acid in the urine, and excluding secondary causes of hyperammonaemia. The mainstay of treatment is acute detoxification at times of crisis by haemofiltration, dialysis or ammonia scavenger drugs such as sodium benzoate, sodium phenyl butyrate or acetate, supported by high-calorie solutions and protein restriction combined with supplementation of deficient

amino acids. Chronic management depends on a protein-restricted diet, amino acid (arginine or citrulline) supplementation, vitamin and trace element supplementation and use of maintenance ammonia scavenger drugs.

Radiological features of the acute crisis overlap among different conditions; neonatal cranial US may demonstrate cerebral oedema, hyperechoic white matter and abnormal cortical folding [30]. Decreased bone density is likely to be a long-term consequence of these disorders. Hypoplasia of the corpus callosum and cerebral atrophy are relatively common findings in many metabolic disorders and also reported in this group of conditions.

Ornithine transcarbamylase (OTC) deficiency/ornithine carbamoyltransferase (OCT) deficiency is an X-linked condition in which males are severely affected and is usually present in the neonatal period; death usually occurs in the first year of life. Biochemical diagnosis is made following identification of low citrulline level in plasma and very high orotic acid in urine. An attenuated form presents in affected females and can present at any age with peaks in infancy, adolescence and during or shortly after pregnancy precipitated by episodes of catabolism. It may present as an acute encephalopathy, developmental delay, protein aversion, stroke or hemiplegia at any age.

The described radiological features are a consequence of cerebral oedema and energy deficiency in the basal ganglia; cystic changes and calcification are seen at the grey–white matter junction especially in frontal, parietal, hippocampal and insular regions in all long-term survivors of hyperammonaemia crises.

Carbamylphosphate synthase 1 (CPS 1) deficiency is another severe, often fatal urea cycle disorder with classically low citrulline levels in plasma but normal orotic acid concentrations in urine. Treatment is by general principles and some late-onset forms have been described. Radiological features reported in three patients were bilateral changes in the lentiform nuclei and the perirolandic and insular cortices [31].

N-Acetylglutamate synthase (NAGS) deficiency is very similar to CPS 1 deficiency and diagnosis is confirmed by molecular analysis. Specific therapy with *N*-carbamylglutamate is available.

Arginase deficiency (argininaemia), in common with the other disorders, presents with mild hyperammonaemia, but clinical presentation is usually with spastic diplegia that may be progressive. Diagnosis is achieved by finding very high levels of arginine in plasma. Radiological features are mild cerebellar and cerebral atrophy and lesions in the posterior putamen and insular cortex bilaterally. MR spectroscopy demonstrates an elevated choline/creatine ratio and an abnormal peak at 3.8 ppm [32].

Argininosuccinate lyase deficiency (argininosuccinic aciduria) is a milder condition if the neonatal episode is treated successfully. Later onset forms present with developmental delay, protein aversion or an acute crisis during episodes of catabolism or stress. Patients tend to develop hepatic and neurological disease even if well controlled. Proton spectroscopy shows a guanidinoacetate peak suggesting creatine deficiency that recovers on therapy; this feature should make the radiologist aware that abnormalities in this peak are not limited to disorders of creatine metabolism [33].

Argininosuccinate synthase deficiency (citrulinaemia type 1) represents a milder form with the elevated levels of citrulline in plasma being the diagnostic feature. General management is associated with acceptable outcome if treated early and aggressively. Reported radiological features are frontoparietal ulegyria with relative sparing of the mediotemporal gyri and occipital lobes, microcavities, and subcortical areas of necrosis. Cerebral atrophy and mild ventricular dilation are also seen [34].

Mitochondrial aspartate glutamate carrier (citrin) deficiency (citrulinaemia type 2) is a condition causing adult-onset encephalopathy with elevated levels of ammonia and citrulline thought to occur only in patients from Asia, but now also reported in other ethnic groups and younger patients. Treatment is by liver transplantation for those with proven neurological involvement. Imaging shows cirrhotic changes in the liver and bilateral symmetrical signal abnormalities in the insular cortex and cingulate gyrus. Spectroscopy shows elevation of the glutamine plus glutamate peaks at 2.1–2.5 ppm and 3.7–3.9 ppm. The radiological features in children with this condition have not been described but they present with unconjugated hyperbilirubinaemia and an aversion to sweet and carbohydrate-rich food and liquids [35].

Mitochondrial disease

Mitochondrial disease is the collective term for a wide variety of very different conditions. The initial classic picture of conditions inherited via maternal transmission, associated with lactic acidosis and imaging changes in the basal ganglia has now been replaced by a vast number of overlapping conditions with every possible type of inheritance pattern, with or without lactic acidosis, and a great variety of radiological features. Disorders of mitochondrial assembly and repair are also becoming more important, but only some conditions are mentioned here. Notwithstanding this, no great therapeutic advances have been made in these conditions and non-evidence-based vitamin cocktails are still frequently used with no consensus on their use.

Molecular techniques are becoming more important diagnostic tools, but the mainstay is still by combination of clinical features, results of muscle biopsy, fibroblast culture, and radiological imaging combined with some surrogate markers.

Leigh syndrome is the collective term for classic lactic acidaemia with onset usually before the age of 2 years (although the condition has been described at all ages) associated with bilateral fluctuating hypodensities in the basal ganglia. The putamen seems to be involved in most cases, with or without volume loss, and bilateral changes in the globus pallidus, caudate nuclei and thalamus are reported. Cerebral atrophy seems common with some associated occipitoparietal white matter changes [36]. A lactate peak at 1.33 ppm is generally present.

Myoclonic epilepsy lactic acidosis and stroke-like episodes (MELAS) is associated with short stature, diabetes and maternal inheritance pattern, and can present at any age, but it is the stroke-like episodes that usually bring them to radiography. Cerebral infarctions are usually not related to specific vascular territories. On follow-up only mild atrophy may be evident or calcification/cyst formation of the basal ganglia. Changes are not restricted to the brain with changes of the spinal column also reported. Individual case reports suggest that early intervention with intravenous arginine solution may potentially limit the extent of stroke.

Myoclonic epilepsy with ragged red fibres (MERRF) has similar radiological features but tends to have neuropathy and progressive dementia as clinical features.

Kearns-Sayre syndrome (KSS) is usually described in older patients with chronic progressive external ophthalmoplegia, retinopathy, deafness and cardiac involvement. Radiological features are bilateral hyperdensity in the deep grey matter, cerebellum and subcortical white matter [37]. A doublet at 1.33 ppm is seen on spectroscopy correlating with a lactate peak [38].

Pearson syndrome is commonly regarded as the early-onset form of KSS with very similar radiological features but with added pancreatic insufficiency, sideroblastic anaemia due to bone marrow dysfunction, and renal tubular leak causing early-onset failure to thrive combined with neurological disease. Treatment consists of correcting electrolyte disturbances caused by tubular dysfunction, regular blood transfusion if needed, and iron chelation therapy. Echogenic changes are found in the pancreas and kidneys of these children on US from personal experience but have not been reported in the literature.

Myoneurogastrointestinal encephalopathy (MNGIE) is a disorder of thymidine metabolism that can be diagnosed by looking at thymidine products in the urine or screening for the thymidine phosphorylase gene. The presence of gastric dysmotility, sensorimotor neuropathy and a leukodystrophy picture should be investigated for this disorder [39].

Leber hereditary optic neuroretinopathy (Leber amaurosis) is a maternally inherited form of X-linked blindness, usually in young males. It is a mitochondrial defect causing multifactorial disease; it is poorly understood.

Neurodegeneration, ataxia, retinitis pigmentosa (NARP) is another mitochondrial inherited disorder with similar clinical and radiological features to the other mentioned disorders.

Alpers syndrome is historically described as a disorder of mitochondrial dysfunction where intractable epilepsy is followed by liver failure, especially if precipitated by valproate therapy. It has now been established as a defect in the polymerase gamma gene as well as mitochondrial depletion defects. It is now recognized that liver disease may precede the encephalopathy, which is associated with the typical grey and white matter changes of mitochondrial disease [40].

Lysosomal storage disorders

Lysosomal storage disorders are a group of about 45 disorders presenting at all ages with multisystem involvement. New therapies have been developed for these disorders and this makes early diagnosis crucial; many patients will have some form of radiological investigation. The screening tests for these disorders are urine samples looking for abnormal oligosaccharides or mucopolysaccharides (MPS), also called glycosaminoglycans (GAGS). Specific white-cell enzymes have to be measured for some of these disorders and dialogue with a specialist laboratory is crucial when the diagnosis is suspected. Typically, hepatosplenomegaly is combined with facial dysmorphism and bone disease. The bone disease is either dysostosis multiplex or the destructive bone disease as seen in Gaucher disease. Dysostosis multiplex is the combination of vertebral body beak formation, J-shaped sella, flat broad ribs, hypoplasia of the odontoid peg, proximal pointing of metacarpals, shallow acetabula and poorly formed pelvic ala. Changes in the hands resulting in early formation of claw hands and carpal tunnel syndrome in childhood and a history of non-immune hydrops is very suggestive of these disorders. Other common radiological features are cystic changes in the corpus callosum, centrum semiovale, peritrigonal white matter and pericallosal region [41].

Enzyme replacement therapy is available for MPS-I, MPS-II, MPS-VI, Pompe, Gaucher and Fabry disease, with the likelihood of therapy for MPS-III, MPS-IV, alpha mannosidosis, metachromatic leukodystrophy and Niemann Pick type B and C in the not too distant future. There is also demand for monitoring therapies by radiological techniques such as calculation of liver volume, bone disease burden, pulmonary involvement and progression of neurological disease. The use of liver volumes is encouraged in the monitoring of patients with lysosomal storage disorders on enzyme replacement or substrate deprivation therapy. Liver volumes can be measured by US, CT or MRI depending on local availability [42]. In Gaucher disease determining the

effect on bone at the onset of therapy and monitoring progress is an important marker of response to therapy. Guidelines have been developed in many parts of the world to incorporate regular MRI imaging of bone. In the UK it has been accepted that if children have no bone MRI changes at the onset of therapy they are unlikely to develop, and routine imaging is not advised. If bone involvement is present at the onset, this is monitored at 2-yearly intervals and improvement has been reported [43–48]. Neither the current therapies nor bone marrow transplantation offer a cure for bone disease associated with these conditions and routine skeletal radiography has a role in planning corrective or preventative surgery.

Common procedures that are planned in some of these patients are lower limb stapling or osteotomies, shelving procedures, hip joint replacement, and corrective surgery of the spine. The cervical spine in particular is closely monitored in patients with MPS-IV and VI. At present there are no good imaging techniques to follow response to therapy in important joints such as the hip and shoulder and these need to be developed.

High-resolution CT of the chest is particularly useful to establish pulmonary involvement in Niemann Pick A and B and in future may become an important monitoring tool. MRI and MR spectroscopy of the brain are more widely available and may become important tools in monitoring some of these new therapies; experience in this area is expanding rapidly [49–51].

MPS-I has three distinctive forms with the early-onset severe form treated with early bone marrow transplantation and the attenuated forms with enzyme replacement therapy and supportive measures. *MPS-II* is an X-linked condition mainly affecting boys. Some have neurological disease while others have near-normal intellect. *MPS-III* is caused by four different enzymes, but differentiation is only important for prenatal testing. These children tend to have mainly neurological disease, but abnormalities of the hips similar to Perthes disease associated with hyperactivity and mild hepatomegaly should alert the clinicians to the diagnosis, especially as the dysmorphology can be subtle. *MPS-IV (Morquio)* has classic skeletal changes, but no neurological disease; short stature is very pronounced. *MPS-VI (Maroteaux-Lamy)* is clinically indistinguishable from MPS-IV except that corneal clouding is more prominent.

Alpha mannosidosis is similar to the other conditions but deafness and mild mental retardation are very common findings. There are frequent infections, particularly of bone. This is one of the oligosaccharidoses (as is sialidosis types 1 and 2) that was previously called mucolipidosis type 1. Type 2 can be quite variable with dysostosis multiplex; type 1 is usually associated with progressive myoclonic seizures. *Mucolipidosis type II (I-cell disease)* is a severe disorder with early-onset disease very similar to MPS-I, but at a younger age with cardiac involvement, gingival hypertrophy, craniosynostosis and hydrocephalus [52]. No therapy is available and death at a young age is common.

Sphingolipidoses comprise variable disorders presenting with neurological disease, either centrally or peripherally, due to accumulation of sphingolipids.

Niemann-Pick type A and B is the same disorder but at two ends of a spectrum. Type A is the early-onset disease with hepatosplenomegaly, cherry red spot, and pulmonary infiltrates, thickening of interlobular septa and patchy areas of ground glass opacity on CT [53]. Death occurs before age 5 years. Type B has similar features, but onset is in early adulthood. Imaging confirms hepatosplenomegaly. Because of increased lipid concentrations, early intimal interstitial thickening should be demonstrable but is not yet reported.

Niemann Pick type C is a disorder of cholesterol trafficking and is not in the same category as the above-mentioned. The clinical picture is very variable with early neonatal conjugated hyperbilirubinaemia or liver failure that usually recovers and is then followed in later life by progressive neurological disease. Treatment by substrate deprivation may be possible in the future. Radiological features are cerebral and cerebellar atrophy and high-signal white matter changes in the posterior white matter [54]. Proton spectroscopy shows a significantly decreased NAA/Cr ratio in the frontal and parietal cortex, centrum semiovale and caudate nucleus, and an increased Cho/Cr ratio in the frontal cortex and centrum semiovale [36, 55].

Gaucher disease has three clinical phenotypes: severe neurological disease and early onset is type 2, the intermediate form with neurological disease is type 3, and the commonest is type 1 that mostly affects the reticuloendothelial system. Radiography is used to determine the burden of disease on bone and to measure organ volumes for monitoring [45].

Fabry disease is mainly a disease of vascular endothelium initially, followed by chemical deposition in kidney, eye, heart and central nervous system. This diagnosis should be considered when stroke occurs in a young patient and is associated with nonspecific white matter lesions predominantly located in the frontal, parietal lobes and posterior thalamus involvement also called the pulvinar sign [56]. Cardiomegaly due to cardiomyopathy may be noted on routine chest radiography or other chest imaging. Renal US demonstrates decreased cortical thickness, cystic changes and increased echogenicity.

Krabbe disease (globoid cell leukodystrophy) is a disorder of central and peripheral nervous tissue. Early bone marrow transplantation (before 8 weeks of age) or intrauterine bone marrow transplantation may improve the outcome of this devastating condition. The radiological features are bilateral increased density in the thalami extending into the centrum semiovale combined with demyelination of the brainstem and cerebellum [57].

Metachromatic leukodystrophy is the commonest leukodystrophy and is frequently associated with peripheral neuropathy. Diagnosis is achieved by measurement of aryl sulphatase A and correcting for a common pseudodeficiency in the population. It can present at any age and bone marrow transplantation is offered if diagnosed in the presymptomatic phase. In the late infantile form demyelination is more prominent in the occipital lobes and the direction of demyelination seems to be dorsofrontal. Non-enhancing demyelination of the periventricular white matter with sparing of the subcortical U fibres, leopard skin pattern of demyelination or tigroid pattern in the centrum semiovale, involvement of the corpus callosum, internal capsule and corticospinal tracts are frequent manifestations [58]. Spectroscopy reveals marked decreased choline and NAA in the white and grey matter and elevated lactate in demyelinated areas; in contrast to other leukodystrophies there is a generalized increase in *myo*-inositol in the white matter [59].

Pompe disease (acid maltase deficiency) is a lysosomal storage disorder causing cardiomyopathy in the infantile form and myopathy and respiratory failure in the late-onset form. Hypertrophic cardiomyopathy may be noted on cardiac MRI [60]. No other radiological features are currently reported but white matter lesions in the brain have been reported in adults at recent scientific meetings; however, this may be incidental and does not seem to be disease causing.

Others

It would be impossible to cover all the inborn errors in this review, but the following are mentioned briefly. Peroxysomal disorders are generally severe disorders causing either central nervous system disease or skeletal dysplasia. They are diagnosed by measuring levels of very-long-chain fatty acids in plasma and the commonest conditions belonging to this group are X-linked adrenoleukodystrophy (a leukodystrophy picture combined with adrenal dysfunction in boys) and Zellweger disease (long-bone stippling is seen within the first few weeks of life associated with severe hypotonia).

Creatine synthesis defects have been described and as they respond to creatine supplementation they are important to diagnose. They are usually found with normal MR imaging and low levels of creatine on spectroscopy. A few words of caution are appropriate. First, many conditions can have secondary creatinine deficiency; second, not all creatine disorders have decreased creatine levels on MR spectroscopy and when these conditions are suspected a urine sample looking for the metabolites is more reliable and will pick up most of these new conditions [61].

Congenital disorders of glycosylation, which are diagnosed by looking for abnormal glycoproteins or lipid-laden oligosaccharides, are multisystem disorders with neuronal migrational abnormalities and cerebellar atrophy associated with cystic changes in kidneys or exostoses of long bones.

Conclusion

Individually rare but collectively common means that there is increasing demand for more knowledge on these rare disorders, especially as new therapies are emerging. To diagnose these conditions it is important that the diagnostic radiologist has at least some source of reference and it is hoped that this review is at least an attempt to fill part of this gap.

Conflict of interest The author is a medical advisor for some of the companies developing and marketing ultra-orphan drugs, is an invited speaker at some of their conferences, and has received travel grants and honoraria from them.

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