Inherited metabolic disorders (IMDs) are individually rare, but owing to their large number, they are collectively relatively common. Advances in diagnostic technology, particularly the rise of tandem mass spectroscopy and next generation DNA sequencing, have enhanced our ability to diagnose these disorders rapidly and accurately. Well-recognized disorders are being diagnosed with increasing frequency in patients of all ages; in addition, the total number of individual disorders is expanding in line with improved diagnostic techniques.

The expression of inherited metabolic diseases, as for any other disorders, is developmentally dependent. Thus, the manifestations in neonates, young children, older children, teenagers and adults may vary considerably both in terms of the extent of disease within one or more systems and the precise nature of its expression. Because these disorders are often multisystem, they frequently mimic other more common disorders and may be easily overlooked. It is important not to miss such diagnoses. In the case of young children, an overlooked diagnosis in an index case means that parents do not have the opportunity to make informed family-planning decisions. Moreover, where disease-modifying therapies are available, which is increasingly the case, they are most likely to be effective early in the course of the illness, and delayed diagnosis will lessen the effectiveness of such interventions.

Stroke
Inherited metabolic disorders may cause or mimic stroke through a variety of mechanisms (Table 1).

**Table 1: Metabolic disorders associated with strokes or stroke-like episodes**

<table>
<thead>
<tr>
<th>Disorder</th>
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<tr>
<td>Mitochondrial (oxidative phosphorylation) disorders, CoQ10</td>
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<tr>
<td>Congenital disorders of glycosylation (PMM2-CDG)</td>
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<tr>
<td>Urea Cycle disorders</td>
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<td>Lysosomal disorders – Fabry</td>
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<td>Amino acidopathies – Homocystinuria, MTHFR deficiency</td>
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<tr>
<td>Organic acidemias – Propionic, Methylmalonic, Isovaleric acidemia</td>
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<td>Fatty acid oxidation defects - MCAD</td>
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<td>“Metal” disorders – Menkes, Mb cofactor/sulfite oxidase</td>
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<tr>
<td>Purine nucleoside phosphorylase deficiency</td>
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<tr>
<td>Vanishing white matter disease</td>
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<tr>
<td>Progeria</td>
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[Modified from Nyhan WL, Kolker S, Hoffmann GF. Work-up of the Patient with Acute Neurological or Psychiatric Manifestations. Chapter 18 (pp119-240 in Hoffmann GF, Zschocke J, Nyhan WL (Editors) Inherited Metabolic Diseases. A Clinical Approach. 2/e Heidelberg: Springer 2017]

Several inherited metabolic diseases may impair the coagulation cascade leading to true ischemic or hemorrhagic stroke. This is the case for homocystinuria and associated disorders and, in particular, in the congenital disorders of glycosylation. Stroke may be mimicked by disorders which alter membrane structure and potentials, leading to subtle or subclinical seizures that may imitate stroke. This may be the case in congenital disorders of glycosylation, certain channelopathies or small molecule diseases. The vascular structure may be altered as can occur with disorders such as Menkes disease or Fabry disease and finally, there may be changes in the intra and intercellular metabolic milieu, which lead to focal or multifocal neuronal dysfunction which, if focal or multifocal may mimic an ischemic or hemorrhagic stroke.

Amongst the disorders that may manifest in this fashion are other the oxidative phosphorylation disorders sometimes known as mitochondrial diseases (archetypally, MELAS), forms of inherited coenzyme Q 10 deficiency, the congenital disorders of glycosylation, (particularly phosphomannomutase-2 deficiency), lysosomal disorders (particularly Fabry disease) and amino disorders (particularly homocystinuria and...
methylenetetrahydrofolate reductase deficiency. Disorders of the urea cycle\(^1\), organic acidemias (particularly propionic, methylmalonic and isovaleric acidemia), fatty acid oxidation defects (particularly medium chain acyl-CoA dehydrogenase deficiency) and so-called “metal” disorders including Menkes disease and molybdenum cofactor deficiency may also produce strokes or stroke-episodes. Less commonly, purine nucleoside phosphorylase deficiency or vanishing white matter disease may produce focal deficits reminiscent of stroke and finally, children with progeria have accelerated atherosclerosis and may experience true strokes early in life.

The congenital disorders of glycosylation provide an excellent example of disorders which can produce both strokes and stroke-like episodes.

Pearl and Krasnewich\(^6\) described three children with phosphomannutase-2 deficiency in 2001 who presented with focal deficits but who had no ischemia or infarction on imaging. These children had electrographic seizures or intermittent epileptiform activity on EEG and showed clinical and electrographic improvement with antiseizure medications. One of these children showed evidence of transient edema.

Ishikawa, et al\(^2\) described a child with phosphomannutase-2 deficiency who first presented with right hemiparesis at 5.2 years of age, attributable to ischemic stroke. He subsequently exhibited right upper extremity clonic seizures which were controlled with midazolam. Laboratory investigation showed thrombocytopenia with a platelet count of 37. The child recovered over several months but also had episodes of recurrent hemiparesis lasting fewer than 12 hours without change on the MRI. Some of these episodes represented partial seizures with or without a Todd paresis, but in other cases, there was transient focal edema followed by necrosis. It is clear from the reports in the literature that all of these mechanisms may operate at different times in any individual\(^7\). Thus, appropriate investigation is mandatory with each presentation to ensure that the correct diagnosis is made and appropriate treatment administered.

Childhood ataxia with central hypomyelination, also known a vanishing white matter disease may present with sudden episodes of neurologic dysfunction\(^8\)\(^-\)\(^10\). Classically, this disorder, which results from mutations in any one of five genes in coding subunits of eukaryotic translation initiation factor 2B, will present with slowly-progressive ataxia in the first five years of life. Patients may have tremor, dysarthria and seizures which may be focal and which may be associated with Todd paresis. In the most dramatic cases, patients have episodes of coma, which may occur spontaneously, may be precipitated by minor trauma, fever or even fright. The MR imaging of the brain shows symmetric diffuse signal hyperintensity in the white matter with progressive rarefaction of the white matter over time with relative cortical preservation. Most patients succumb to the illness in the second decade of life.

**Immune-mediated Disorders**

Several groups of inherited metabolic disease may mimic immune-mediated disorders\(^11\) (Table 2.). Perhaps most prominent amongst these are a group recently categorized as the interferonopathies. Perhaps better recognized are specific subgroups of mitochondrial diseases, lysosomal and peroxisomal disorders and some other recently-recognized leukodystrophies\(^12\).
Table 2: Inherited metabolic diseases mimicking multiple sclerosis and related disorders.

Type 1 interferonopathies (Aicardi-Goutieres syndrome spectrum)

Mitochondrial cytopathies
- LHON, MELAS/MERRF, Leigh disease, POLG-related disease, Optic atrophy type 1, PDH deficiency

Lysosomal disorders
- Krabbe disease; Metachromatice Leukodystrophy; Fabry disease, Niemann-Pick disease, type C, Chediak-Higashi disease

Peroxisomal disorders
- X-linked adrenoleukodystrophy and adrenomyeloneuropathy

Other inherited metabolic diseases
- Urea cycle disorders, Adult polyglucosan body disease, Acute intermittent porphyria, Cobalamin and folate disorders, biotinidase deficiency, cerebrotendinous xanthomatosis

Non-metabolic leukodystrophies
- Alexander disease, ADLD, LBSL, HDLS, CADASIL/CARASIL, CIC-2 chloride channel deficiency
- leukoencephalopathy, X-linked CMT disease

[Modified from references 12 and 13]

Crow and colleagues have recently reviewed the role of type 1 interferon in white matter disease 13. In such cases, exogenous viral infection, or endogenous sources of nucleic acid such as mutations affecting ribonuclease genes, leading to an increased concentration in nucleic acid ligands, altered composition of nucleic acid ligands, increased sensitivity or enhanced signaling to interferon 1, or impaired negative signaling may induce type 1 interferon expression. This in turn leads to immune activation manifest as chronic lymphocytic pleocytosis in the cerebral spinal fluid associated with brain injury causing white matter changes, calcification most likely in the basal ganglia, and in many cases, cutaneous manifestations such as lupus pernio.

The classic type 1 interferonopathy is Aicardi-Goutieres syndrome 14. These authors first described eight children from five families in 1984. The children presented with progressive regression, spasticity, dystonia, acquired microcephaly and early death. Children typically had hepatomegaly and thrombocytopenia in the neonatal period, and later developed chilblain-like skin lesions. Imaging showed basal ganglia calcification and cerebrospinal fluid analysis shows a chronic lymphocytic pleocytosis. Subsequently, interferon levels and neopterin were found to be elevated in the cerebrospinal fluid completing a picture which mimicked congenital viral infection. A more recent study has found that the imaging appearance of the Aicardi-Goutieres syndrome overlaps substantially with that of infection by cytomegalovirus and Rubella, and, in very young children, may also be mimicked by mitochondrial disease, megalencephalic leukoencephalopathy with temporal cysts and vanishing white matter disease 15.

The Aicardi-Goutieres spectrum ranges from classical Aicardi-Goutieres syndrome through later-onset presentations with isolated-skin disease, bilateral striatal necrosis, progressive spastic paraparesis with normal neuroimaging, idiopathic intracranial calcification and the Singleton-Merton syndrome characterized by periodontitis, aortic calcification, glaucoma and contractures. There are also some patients who have mutations in the relevant genes but have complete nonpenetrance 14.

Amongst the mitochondrial disorders, many can produce prominent white matter disease which may be mistaken for multiple sclerosis and related disorders and in some cases, particularly those associated with specific mutations causing Leber hereditary optic neuropathy (LHON), can produce inflammatory changes in the cerebrospinal fluid 16.

Lysosomal and peroxisomal disorders may produce white matter changes, which although typically symmetric, may present in patchy fashion and potentially be confused with multiple sclerosis. It should also be noted that end-stage multiple sclerosis tends to produce bilateral and more or less symmetrical lesions which may overlap with those seen in lysosomal and peroxisomal disorders. Amongst the other leukodystrophies not included in this category are Alexander disease which typically involves periventricular regions and astrocytes around the CSF pathways which may mimic neuromyelitis optica, particularly in juvenile presentations and megalencephalic leukoencephalopathy with subcortical cysts, which as mentioned above, may have an appearance similar to congenital infection, particularly in early-onset cases.
Summary
There are many inherited metabolic diseases which may mimic stroke or stroke-like episodes as well as immune-mediated disorders. The most important factor in diagnosing these disorders is awareness of their existence, and ensuring that they are considered in a broad differential diagnosis of these presentations. Neuroimaging is essential to such diagnoses and particularly, in the case of the immune-mediated mimics, may be diagnostic in its own right\textsuperscript{11,17}. Specific approaches to diagnosis depend on the precise disease in question. Where possible, measurement of biomarkers reflecting the functional effects of a mutation is important in complementing the diagnosis, but in some cases the only confirmatory diagnostic test is DNA sequencing. As next generation sequencing becomes less expensive, and as computer-processing costs and algorithms improve, DNA diagnostics alone are becoming increasingly reliable. None of these tools, however, are meaningful unless interpreted in the light of a systematic history and examination.

References