# Identifying inherited metabolic disorders presenting with developmental delay: what not to miss

James E Davison


## Abstract

Inherited metabolic disorders (IMDs) can interrupt the normal progression of brain development and ongoing function, and consequently IMDs frequently present with abnormalities of neurodevelopment. Many IMDs have disease-modifying treatments available, and early recognition and diagnosis can improve long-term outcomes. However, while neurodevelopmental disorders are estimated to affect up to 17% of children, only a small percentage (less than 0.5%) of these are due to an IMD. The careful evaluation of a child with a developmental disorder, focussing on specific features identified via the clinical history and examination, can help identify those children who have "red flag" features that indicate a specific focus on testing for an IMD is important, and will guide which specific biochemical testing is needed. Neurodevelopmental regression, childhood dementia, and recurrent acute encephalopathy are suggestive of an IMD. Specific abnormalities of neurology including refractory seizures and movement disorders, and examination features including organomegaly and various ophthalmic features, can also direct investigations to identify an IMD. Early discussion with professionals with expertise in the metabolic/neurometabolic disorders will ensure the relevant testing is selected to identify key diagnoses and permit access to treatment.


**Keywords** biochemical testing; childhood dementia; developmental regression; inherited metabolic disorder; neurodevelopmental disorder

## Neurodevelopmental disorders

The acquisition of standard developmental milestones relies on the normal early development and maturation of the brain, starting from early brain formation and neuronal migration events *in utero*, the formation and pruning of synaptic connections between neurons, progressive myelination of axons, and the synthesis of neurotransmitters and development of cell surface receptors, all relying on the normal biochemical and metabolic functioning of neuronal and glial cells.

***James E Davison*** ***BMedSci(Pharm) MBChB(Hons) PhD FRCPCH,*** *Consultant in Paediatric Metabolic Medicine, Metabolic Medicine, Great Ormond Street Hospital NHS Foundation Trust, London, UK.*
*Conflicts of interest: none declared.*

Inherited metabolic disorders (IMDs) can interrupt the normal progression of brain development and ongoing function, and consequently IMDs frequently present with abnormalities of neurodevelopment.

Disorders of neurodevelopment encompass a wide range of diagnoses, with varying patterns of developmental abnormality affecting the different domains of development, variously including motor, communication, vision, hearing, cognitive and social development. Global developmental delay (GDD) has impacts across all domains; neurodiverse conditions include autistic spectrum disorders and attention deficit hyperactivity disorder; intellectual and learning disabilities impact predominantly on the cognitive domains.

Neurodevelopmental disorders are estimated to affect up to 17% of children, although only a small percentage (less than 0.5%) of these are due to an IMD. The careful evaluation of a child with a developmental disorder focussing on specific features identified via the clinical history and examination, can help identify those children who have "red flag" features that indicate a specific focus on testing for an IMD is important, and will guide which specific biochemical testing is needed.[1]

The identification of the cause of a child's neurodevelopmental disorder is important for many reasons, including the increasing availability of specific disease-modifying treatments, being able to inform tailored clinical monitoring, facilitating accurate cascade family testing, and wider genetic counselling for family. A specific diagnosis also allows closure of the "diagnostic odyssey", avoiding unnecessary further medical tests.

There are over 100 treatable IMDs, and earlier diagnosis and treatment can often improve the long-term prognosis.[2] While newborn screening programmes can identify some IMDs, current programmes only test for a small subsection of this group of conditions; in the UK the current newborn screening blood spot testing only identifies 7 IMDs.

## How do IMDs affect neurodevelopment?

Normal metabolic pathways rely on enzymes to catalyse each chemical reaction. The majority of IMDs are caused by the deficiency of one of these specific enzymes, and result in the accumulation of the substrate of the reaction, the generation of other toxic products, and the deficiency of the product of the enzyme reaction. This conceptual model of an IMD helps explain how IMDs can affect normal developmental processes and also informs the biochemical testing that aims to identify patterns in metabolites, looking for increased concentrations of substrates and decreased concentrations of products, to pinpoint the metabolic defect.

Some IMDs affect normal brain development and function by the accumulation of a toxic metabolite. This is seen acutely in IMDs such as the urea cycle disorders associated with a high level of ammonia that is directly neuro-toxic and results in acute encephalopathy, or in non-ketotic hyperglycinaemia (NKH, glycine encephalopathy) where high concentrations of glycine trigger a severe infantile epileptic encephalopathy. There can also be a chronic toxic effect, for example in disorders such as phenylketonuria associated with accumulation of phenylketones that results in a chronic encephalopathy with progressive acquired microcephaly.

Other IMDs result in abnormal brain function due to the deficiency of a specific metabolite. This is seen in the creatine synthesis defects where the brain is deficient in creatine, which is required for cells to be able to effectively utilise adenosine triphosphate (ATP) in energy metabolism. IMDs that result in hypoglycaemia in disorders of glucose generation or transport result in brain deficiency of glucose with the associated impact on normal brain function. Other IMDs have a direct impact in the synthesis of neurotransmitters, and so impact on neuronal communication and function, often resulting in movement disorders.

Neurodegeneration, the progressive destruction of normal brain cells and tissue, is also a feature of some IMDs, characterised clinically by neuroregression and often progressive childhood dementia.[3] This is seen in the lysosomal diseases, where the lack of a specific lysosomal enzyme or system leads to the abnormal accumulation and storage of large macromolecules within the lysosome, which then impacts on the normal function of the lysosomal-endosomal trafficking systems within the cell, and can trigger neuroinflammatory processes. Neurodegeneration is also a feature of the peroxisomal disorders and mitochondrial defects.

The mitochondrial disorders can result in abnormalities of neurodevelopment manifesting in a plethora of ways, including with neuroregression, eye movement and functional abnormalities, ptosis, and movement disorders. Mitochondrial disorders affect the ability of cells to generate ATP for normal energetic function and impact via the many other metabolic and cellular functions of mitochondria.

Early brain formation and structural integrity can also be affected by certain IMDs that are associated with brain structural abnormalities. This is seen in some of the congenital disorders of glycosylation that impact on complex extracellular receptor signalling processes, as well as in disorders of sterol synthesis such as Smith Lemli Opitz syndrome.

## Requesting the right tests for identifying IMDs

### Biochemical metabolic testing

The identification of an IMD relies on biochemical profiles seeking characteristic metabolite patterns, looking for increased concentrations of substrates and decreased concentrations of products to pinpoint the metabolic defect. This can be undertaken in blood, dried blood spot, urine and cerebrospinal fluid samples. In some instances, assays that directly measure enzyme function are used, for example measurement of biotinidase enzyme activity, or the function of specific lysosomal enzymes in leucocytes or plasma. Enzymes may not be expressed in all tissues of the body, and thus enzyme testing may require specific tissue sampling, for example liver or muscle biopsies.

It is important that the correct tests are undertaken depending on the clinical scenario so that treatable disorders can quickly be identified, and so that important diagnoses are not overlooked by inadvertent omission of the relevant tests. Discussion with a specialist in metabolic disorders can help ensure appropriate test selection.

Table 1 summarises the main metabolic biochemical testing that is indicated depending on the specific "red flag" signs and symptoms identified.

**Key targeted metabolic tests depending on phenotypic red flags**

| Category | Test | Phenotypic "red flag" | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Developmental regression/ development plateau | Acute encephalopathy | Stroke-like episodes | Seizures | Protein aversion | Movement disorder | Hypertonia | Hypotonia | Organomegaly | Dysmorphic/Coarse facial/skeletal |
| Basic biochemistry | Ammonia | ✓ | ✓ | | | | | | | | |
| | Glucose | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | |
| | Lactate | | | | | | | | | | |
| | Blood gas, anion gap | | | | | | | | | | |
| | Ketones | | | | | | | | | | |
| | Renal, liver function | | | | | | | | | | |
| | Vitamin B12 | | | | | | | | | | |
| | Urate | | | | | | | | | | |
| | CK | ✓ | | | | | | | ✓ | | |

Table 1 (*continued*)

| Category | Test | Phenotypic "red flag" | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Developmental regression/ development plateau** | **Acute encephalopathy** | **Stroke-like episodes** | **Seizures** | **Protein aversion** | **Movement disorder** | **Hypertonia** | **Hypotonia** | **Organomegaly** | **Dysmorphic/Coarse facial/skeletal** |
| Intermediary metabolism | Total homocysteine<br>Plasma amino acids<br>Acylcarnitine profile<br>Urine organic acids<br>Biotinidase activity | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | |
| Creatine synthesis | Creatine, guanidinoacetate | ✓ | | | ✓ | | | ✓ | | | |
| Storage disorders | Urine glycosaminoglycans | ✓ | | | | | ✓ | | | ✓ | ✓ |
| | Urine sialic acid | ✓ | | | | | | | | ✓ | ✓ |
| | Urine oligosaccharides<br>Lysosomal enzymology (panels depending on presentation)<br>Blood film histopathology for vacuolated lymphocytes<br>Palmitoyl phosphocholineserine (PPCS), Oxysterols | | | | | | | | | | |
| | Pompe enzyme (bloodspot/ leucocyte) | | | | | | | | ✓ | | |
| Peroxisomal | Very long chain fatty acids (VLCFA) | ✓ | | | ✓ | | | ✓ | | ✓ | |
| Sterol synthesis | Sterols (7 dehydrocholesterol) | ✓ | | | | | | | | | ✓ |
| Purine and pyrimidine | Urine and plasma purine & pyrimidine | ✓ | | | ✓ | | | | | | |
| Glycosylation defects | Transferrin electrophoresis | ✓ | | ✓ | ✓ | | | | | | |
| Metals | Copper, caeruloplasmin | | | | ✓ | | ✓ | | | | |
| | Urine sulphite | | | | ✓ | | | | | | |
| | Urine amino adipic semialdehyde (AASA) | | | | | | | | | | |

(*continued on next page*)

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|---|---|---|---|---|---|---|---|---|---|---|
| | | Developmental regression/ development plateau | Acute encephalopathy | Stroke-like episodes | Seizures | Protein aversion | Movement disorder | Hypertonia | Hypotonia | Organomegaly | Dysmorphic/Coarse facial/skeletal |
| Cerebrospinal fluid studies | Amino acids | | (✓) | | ✓ | | ✓ | | | | |
| | Glucose, lactate | | | | | | | | | | |
| | Neurotransmitters | | | | | | | | | | |
| | Pterins | | | | | | | | | | |
| | 5-methyl tetrahydrofolate | | | | | | | | | | |
| | Pyridoxal phosphate | | | | | | | | | | |

The tests suggested in this table are not exhaustive, and discussion with a metabolic specialist is recommended to guide planning targeted testing depending on the clinical scenario.

**Table 1**

### Genetic testing

Molecular genetic testing is also needed in the diagnosis of an IMD. Historically this would be done after biochemical testing had identified either a specific IMD or was suggestive of a category of IMD conditions. Increasingly, broad genetic testing may be done as a first line investigation and may identify specific gene variants suggestive of an IMD, which then requires evaluation via biochemical means. Variants of uncertain significance specifically require further biochemical testing to help determine the relevance of the variants.

The early use of chromosomal microarray testing is recommended in many guidelines as a first line test for children with global developmental delay, intellectual disability, autistic spectrum disorders, and other neurodevelopmental disorders with additional features suggestive of a syndromic disorder. Fragile X testing should also be considered in children with suggestive clinical features.[1]

Molecular genetic testing for IMDs may include targeted single-gene analysis if a specific biochemical diagnosis has already been reached or may include testing for a panel of genes if biochemical testing is suggestive of a group of conditions but has not narrowed this down to a single defect. A broad panel of genes associated with IMD may be tested if there is clinical suspicion for an IMD but without specific data from biochemical testing to indicate more focused testing.

## Red flag features suggestive of an IMD

While developmental disorders are very common in childhood only a small fraction of these will be due to an IMD. The diagnostic yield of testing for IMDs is significantly increased if this is focused on children who have specific "red flags" to suggest an IMD is more likely, i.e. those with "developmental delay plus …".[1]

### History

A careful history should be obtained of the child's developmental trajectory, as well as assessment for any additional features. This should include background information from the wider family history, and assessment of pregnancy and perinatal events.

The pattern of development problems, including which developmental domains are affected, is needed to hone specific investigations. A history of developmental *regression* is a definite red flag for a potential underlying IMD, as this implies there is a process causing ongoing damage to the central nervous system, manifesting in loss of previously acquired developmental skills. The association of regression with intercurrent illness episodes can suggest specific metabolic stress or energy depletion that may indicate there is a mitochondrial disorder or other disorder of metabolism affecting energy metabolism. Progressive decline in neurologic function and cognition akin to a childhood dementia process suggests there is a significant and serious disorder that requires urgent evaluation.[3]

Episodes of *acute encephalopathy*, especially if recurrent, suggests the accumulation of a toxic metabolite affecting global brain function. Such episodes can be triggered by intercurrent illness, or excess protein intake, and should mandate biochemical testing during an acute episode to identify the potential toxin (e.g. ammonia, leucine) as well as the further biochemical tests

to identify the specific aetiology (e.g. plasma amino acids and urine organic acids to identify urea cycle disorders and organic acidurias). Patients with IMDs affecting protein metabolism such as the urea cycle disorders will often demonstrate *dietary aversion to consumption of protein*, and review of the dietary history can identify this.

Review of the pregnancy is important in noting any abnormalities identified on routine mid-trimester ultrasound scans; a history of increased foetal movements can sometimes suggest *in utero* seizure activity as seen in non-ketotic hyperglycinaemia (glycine encephalopathy).

The history within the wider family of other potentially affected children who have either unexplained recurrent illness/encephalopathy episodes, or unexplained death, or a known specific disorder, is important given that most IMDs are autosomal recessive and therefore have a significant recurrence risk. Evaluation of parental consanguinity is important in understanding the genetic context, although it should be noted that recessive disorders also present in children born to non-consanguineous parents.

### Neurological features

**Stroke-like episodes:** the occurrence of stroke-like episodes, especially if these do not follow typical vascular territories, can suggest a "metabolic stroke", and can suggest a disorder affecting energy metabolism (mitochondrial disorders, organic acidurias). Thrombotic strokes (which would follow vascular territories) are a feature of the IMDs associated with high homocysteine levels (e.g. homocystinuria) and are a feature of some congenital disorders of glycosylation.

**Movement disorders:** the presence of a movement disorder needs careful evaluation by a paediatric neurologist and most often some neuroimaging. IMD directly affecting neurotransmitter biochemistry, including neurotransmitter synthesis defects, as well as those IMD affecting cofactors of these pathways, should be investigated. Abnormalities of the basal ganglia are a frequent feature in IMD, as the basal ganglia have an apparent vulnerability to energy depletion. Bilateral/symmetric abnormalities of the basal ganglia can be seen in several classes of IMD, notably glutaric aciduria type 1, mitochondrial (Leigh-like) disorders, and some of the biotin/thiamine responsive disorders.

**Seizures/epileptic encephalopathy:** epileptic seizure disorders, especially where seizures are hard to control, can occur in IMDs. Some of these disorders are highly responsive to specific metabolic cofactors or vitamin treatments, and early identification can improve long term outcomes. This includes disorders of vitamin B6 (pyridoxal phosphate) metabolism, and uridine-responsive seizures seen in CAD deficiency (a pyrimidine pathway defect identified by the presence of anisopoikilocytosis and raised red cell distribution width (RDW) with anaemia on the full blood count in a child with drug-resistant epilepsy).

**Hypotonia:** an infant with significantly decreased muscle tone (hypotonia) warrants careful evaluation for myopathies, disorders of neuromuscular junction function, and peripheral neuropathy. Important IMD associated with myopathies include Pompe disease (glycogen storage disease type II), carnitine cycle defects, and the fatty acid oxidation defects. Significant hypotonia is also seen in infants with peroxisomal biogenesis defects (the Zellweger spectrum disorders).

**Psychiatric:** psychiatric manifestations of IMDs can represent a version of toxin-accumulation induced acute encephalopathy; some of the later-presenting urea cycle disorders with chronically elevated ammonia can present in this manner, including postpartum psychosis in females with OTC deficiency. Psychiatric manifestations are also seen in some patients with Wilson disease affecting normal copper metabolism.

### Examination

**General appearance/"dysmorphic" features:** some IMDs can have specific impacts on the general appearance. The lysosomal diseases, notably the mucopolysaccharidoses (MPS), are associated with progressive storage of macromolecules within soft tissues of the face leading to the characteristic so-called "coarse" facial features. The MPS disorders also affect the hair which is often profuse and thick. Sparse, friable hair is seen in Menkes disease. Examination of the skin can also yield diagnostic clues, including a history of ichthyosis in certain sterol pathway (cholesterol synthesis) disorders. Angiokeratoma are a feature in some lysosomal diseases including Fabry and fucosidosis. Some IMD have a distinctive odour due to the volatile organic acids that accumulate in the urine (e.g. maple syrup urine disease) and may sometimes be detected.

Skeletal features may also be detected and may be incidentally observed on radiological investigations obtained for other reasons, such as the detection of broad ribs or vertebral anomalies identified on a chest radiograph undertaken due to suspected chest infection. The detection of aspects of "dysostosis multiplex" via skeletal imaging, including spinal gibbus or vertebral defects, is suggestive of a lysosomal disorder, while peroxisomal defects can cause a range of skeletal pathology including epiphyseal stippling, or rhizomelic shortening of specific bones.

**Head size:** along with routine measurement of height and weight attainment compared to the standard growth chart, evaluation of head growth is an important indicator for children with neurodevelopmental disorders. Relative macrocephaly is seen in a range of inherited metabolic disorders, especially if there is also abnormal white matter features seen on MR imaging. Progressive microcephaly is seen in a number of IMDs, indicating failure of normal brain growth. Examples are given in Table 2.

**Organomegaly:** the identification of organ enlargement can suggest there is a progressive accumulation ("storage") of unmetabolized substrate. Hepatomegaly, splenomegaly and nephromegaly detected clinically or radiologically can be indicative of the lysosomal diseases, or the glycogen storage disorders (associated with hypoglycaemia), especially if detected in combination with neurodevelopmental abnormalities and other multisystem manifestations. Table 3 provides examples of IMDs that can be associated with patterns of organomegaly.

**Eye features:** careful examination of the eyes can reveal a wide range of features that could help pinpoint a specific diagnosis. This includes abnormalities of the extraocular muscle function

**IMD associated with abnormal head size**

| Macrocephaly | | Microcephaly |
|---|---|---|
| **Leukodystrophies** | **Other white matter abnormalities** | |
| Alexander disease *(GFAP genetics)* | Glutaric aciduria type 1 (*Urine organic acids, acylcarnitine profile)* | Sulphite oxidase deficiency/Molybdenum cofactor deficiency *(Urate, urine sulphocysteine)* |
| Canavan disease *(Urine organic acids)* | Hexoaminidase A deficiency (Tay Sachs) *(Lysosomal enzymology)* | Branched chain ketoacid dehydrogenase kinase deficiency *(Plasma and CSF amino acids)* |
| L-2-hydroxyglutaric aciduria *(Urine organic acids, acylcarnitine profile)* | Infantile lysosomal storage disorders *(Lysosomal enzymology)* | Maternal phenylketonuria (fetus affected) |
| Megalencephalic leukoencephalopathy with cysts *(MLC1 genetics)* | Mucopolysaccharidoses *(Urine glycosaminoglycans)* | Untreated phenylketonuria *(Plasma amino acids)* |
| | | Serine synthesis disorders *(Plasma ± CSF amino acids (fasted))* |

Key diagnostic tests indicated in *italics*.

**Table 2**

**Hepato (spleno) megaly metabolic differential diagnosis**

| IMD category | Example disorders |
|---|---|
| Lysosomal diseases | Gaucher<br>Mucopolysaccharidoses<br>Niemann Pick C<br>Oligosaccharidoses |
| Glycogen storage disorders | Hepatic forms e.g. GSD I, GSD III<br>Pompe disease |
| Other glucose/fructose pathway disorders | Fanconi Bickel |
| Congenital disorders of glycosylation | MPI-CDG |
| Amino acids transport | Lysinuric protein intolerance |
| Polyol pathway disorders | Transaldolase deficiency |
| Peroxisomal | Zellweger spectrum |
| Disorders resulting in chronic liver disease | |
| Disorders with acute liver disease | Fatty acid oxidation, organic acidurias, galactosaemia |

**Table 3**

leading to ophthalmoplegia, the occurrence of ptosis, through to pathology affecting any structural part of the eye from the anterior cornea through to retinal and optic nerve abnormalities. The detection of a "cherry red spot" on fundoscopy is highly suggestive of a small group of lysosomal diseases. Table 4 gives examples of these disorders and investigations, with further detail previously published.[4]

## Multisystem involvement

One of the hallmarks of the IMD is the tendency for multiple body systems, organs and tissues to be affected. The detection of multisystem disease in conjunction with a developmental disorder therefore warrants careful evaluation for IMDs including lysosomal, mitochondrial, peroxisomal, sterol or glycosylation defects. A specific diagnostic challenge is that children with a multisystem IMD may encounter multiple different clinical specialities each addressing individual system problems, and it is only when the "dots are joined up" and the bigger picture of a multisystem disorder is recognised that the likely diagnosis of an IMD becomes apparent.

## Brain imaging features

The advance in brain magnetic resonance imaging often provides precise potential differential diagnoses for a child with a

**Examples of ophthalmic abnormalities suggestive of IMDs (see [4])**

| Ophthalmic finding | Example metabolic differentials | Extra-ocular features | Key investigations |
|---|---|---|---|
| Ptosis | Pompe disease | Hypotonia, hypertrophic cardiomyopathy | CK, Pompe enzyme test |
| | Mitochondrial | Multisystem | DNA, lactate, general metabolic |
| Ophthalmoplegia | Niemann Pick C (vertical supranuclear gaze palsy) | Regression organomegaly | Palmitoyl phosphocholineserine, genetic |
| | Mitochondrial | Multisystem | DNA (including mitochondrial DNA) |
| Corneal clouding | Mucopolysaccharidosis | Dysmorphic features, dysostosis multiplex | Urine glycosaminoglycans |
| Ectopia lentis (lens dislocation)_ | Homocystinuria | Marfanoid habitus, thromboembolic event | Plasma amino acids, total homocysteine |

**Table 4** (*continued*)

| Ophthalmic finding | Example metabolic differentials | Extra-ocular features | Key investigations |
|---|---|---|---|
| Neonatal cataract | Galactosaemias | Liver dysfunction | Galactose-1-phosphate uridyl transferase (Gal-1-Put), Galactose-1-phosphate. |
| Childhood cataract | Wilson disease | Neurologic and hepatology presentations | Copper, caeruloplasmin |
| Retinitis pigmentosa | Congenital disorders of glycosylation | Multisystem | Transferrin electrophoresis |
| | Cobalamin C defect | Haematological, multisystem | Urine organic acids, plasma amino acids, acylcarnitine profile |
| | Peroxisomal defects | Hypotonia, hepatology | Very long chain fatty acids |
| Cherry red spot | Lysosomal disorders: GM1, GM2 gangliosidoses | Regression, multisystem | Lysosomal enzymology |
| Optic atrophy | Biotinidase deficiency | Seizures, skin rash | Biotinidase activity, lactate, urine organic acids |
| | Neuronal ceroid lipofuscinoses | | Genetics, specific lysosomal enzymology |

**Table 4**

neurodevelopmental disorder.[5] A child with a specific white matter disease process including the leukodystrophies, or abnormalities of the basal ganglia will require tailored further metabolic biochemical and genetic investigation. Functional imaging modalities including magnetic resonance spectroscopy may also lead to the identification of specific brain metabolite abnormalities suggestive of an IMD, including the creatine deficiency disorders.

## Conclusion

Identifying inherited metabolic disorders presenting with developmental delay is important in allowing access to disease-modifying treatments. While most children with neurodevelopmental disorders do not have an IMD, the systematic identification of salient "red flag" features in the clinical history, examination and first line investigations can indicate which children will benefit from evaluation with targeted metabolic biochemical and/or genetic testing. Early discussion with professionals with expertise in the metabolic/neurometabolic disorders will ensure the relevant testing is selected to identify key diagnoses, and permit access to current and emerging therapeutic options. ◆

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## Practice points

- It is important to consider IMD in children with neurodevelopmental conditions as many are treatable
- The recognition of "red flag features" in children with neurodevelopmental disorders can help identify those who may have an IMD. Features such as worsening symptoms during acute illness, seizures or movement disorders, eye signs or organomegaly should prompt thorough investigation
- With advances in genetic testing and neuroimaging a diagnosis may be reached or suggested as part of a thorough and methodical investigation pathway
- Selection of appropriate biochemical tests should be guided by the clinical phenotype, and early discussion with an IMD expert can be helpful