Inborn Errors of Metabolism in Adults: A Diagnostic Approach to Neurological and Psychiatric Presentations

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Late-onset forms of IEM presenting initially in adulthood are often unrecognised, so that their exact prevalence is unknown [1]. Most often they have psychiatric or neurological manifestations, including atypical psychosis or depression, unexplained coma, peripheral neuropathy, cerebellar ataxia, spastic paraparesis, dementia, movement disorders and epilepsy [2][3][4][5].
Physicians caring for adult patients with IEM are also involved in the management of those with early onset forms who reach adulthood. The transfer of such patients from paediatric to adult care raises a number of medical, dietetic and social concerns.
A further important issue is the diagnosis of adult patients who had their first clinical signs in childhood but for whom the diagnosis was missed, either because IEM were not considered or because the disease or its mild clinical form had not been described at that time.

2.1 Differences Between Paediatric and Adult Phenotypes

Adults' physicians who want to specialise in IEM are faced with the fact that, with the exception of several review articles, most if not all existing books and diagnostic algorithms refer to paediatric forms of these diseases. Late-onset forms of IEM tend to display attenuated phenotypes, which in some instances are associated with one or more clinical manifestations that differ from the classic clinical picture described in children. ◘ Table 2.1 gives some examples of differences between childhood and adult onset presentations. Although the limited information available about adult forms of IEM makes the specialty new and quite exploratory, the diagnostic approach in adults is facilitated by the fact that the nervous system is already mature. Therefore, clinical presentations are more homogeneous than in children, in whom clinical signs usually differ depending on their stage of maturation (▶ Chapter 1).

2.2 General Approach to IEM in Adulthood

As stated above, adult-onset presentations of IEM are essentially neurological or psychiatric. The typical situation is that of a patient with an unexplained and bizarre neurological or psychiatric problem in whom the usual aetiologies have been excluded by appropriate tests. The diagnostic approach in such a situation is always based on the two questions of when to suspect an IEM and, when an IEM is suspected, what type of metabolic investigations must be performed [6].

Some general clinical features are highly suggestive of an IEM: when clinical signs or symptoms are fluctuating, especially when triggered by fasting, exercise, fever, catabolic circumstances or post-partum; when clinical signs suggest a diffuse disease including neurological signs plus systemic signs (eye or skin problems, organomegaly etc.) or involvement of different parts of the nervous system (optic nerves and cerebellum; leukoencephalopathy and polyneuropathy).

In addition, some clinical signs are highly suggestive of a particular IEM or of a particular group of IEM. Some of these 'red flags' are listed in ◘ Table 2.2.

Unfortunately, in many circumstances, highly specific signs or symptoms are lacking and the presentation is that of a less specific neurological or psychiatric disorder (epilepsy, cognitive decline, psychiatric signs). In such situations, the diagnostic approach is based on the type of clinical signs, their clinical course (acute, acute-relapsing, with diurnal variations, progressive, static), brain MRI findings, eye findings and electroneuromyography. Some matching between clinical, imaging, ophthalmological and electrophysiological findings and IEM is shown in the text and tables below.

Metabolic diseases involving the nervous system can be divided into five main categories, all of which display some similarities in clinical presentation, diagnostic methods and treatment strategies.

2.2.1 Disorders of Energy Metabolism

Disorders of energy metabolism include respiratory chain disorders (that can be primary or secondary, as can occur in organic acidurias), pyruvate dehydrogenase deficiency, Krebs cycle deficiencies, GLUT1 deficiency, β-oxidation defects and disorders involving co-factors such as ETF deficiency, vitamin E deficiency, biotinidase deficiency, biotin-responsive basal ganglia disease, creatine deficiency syndromes and coenzyme Q synthesis defects. Acute manifestations are often triggered by infections and encompass Leigh syndrome, acute optic neuropathy, acute cerebellar ataxia, pseudo-strokes or status epilepticus. Chronic presentations often involve muscles, cerebellum, basal ganglia (parkinsonism, dystonia), cortex (epilepsy, myoclonus) or the peripheral nervous system (axonal polyneuropathy). In adults, the brain white matter is less involved and spastic paraparesis is uncommon.

2.2.2 Disorders of Lipid Metabolism

Disorders of lipid metabolism include sphingolipidoses (Krabbe disease, metachromatic leukodystrophy, Niemann Pick A and B, Fabry disease and Gaucher disease), peroxisomal disorders (adrenomyeloneuropathy, Refsum disease, disorders of pristanic acid metabolism, peroxisome biogenesis disorders), sterols disorders (cerebrotendinous xanthomatosis, Niemann-Pick C, spastic paraplegia type 5 and Tangier disease) and the newly described group of metabolic diseases affecting the synthesis and remodelling of phospholipids (mutations in *PLA2G6*, *DDHD1*, *DDHD2*, *NTE*, *CYP2U1*, *ABHD12*) and sphingolipids (mutations in *FA2H*, *GBA2*, *B4GALNT1*) [7][8] (▶ Chapter 34, ▶ Chapter 38, ▶ Chapter 40). Given the great proportion of lipids in the nervous system, these diseases can produce almost all kinds of symptoms but spastic paraparesis is very common. Leukodystrophy and demyelinating polyneuropathy are hallmarks of disorders interfering with myelin formation or maintenance. A past history

Table 2.1 Phenotypic differences between childhood-onset and adult-onset forms of inborn errors of metabolism

Disease	Classic presentation in childhood	Adult-onset forms
AGAT deficiency	Psychomotor delay, severe language impairment, failure to thrive and autistic-type behaviour	Mild mental retardation with myopathy
AMACR deficiency	Neonatal cholestasis, mental retardation, retinitis pigmentosa	Recurrent encephalopathy, epilepsy, psychiatric disorders, polyneuropathy
α-Mannosidosis	Mental retardation, deafness, upper airways infections, dysmorphic features	Episodes of psychosis, confusion, cerebellar ataxia, posterior leukoencephalopathy
Biotinidase deficiency	Muscular hypotonia, lethargy, grand mal and myoclonic seizures, ataxia, stridor, skin lesions	Bilateral optic atrophy, spastic paraparesis, motor neuropathy
Cerebral glucose transporter (GLUT1) deficiency	Epilepsy, psychomotor delay, dystonia, ataxia, acquired microcephaly	Isolated seizures, exercise-induced dystonia, lethargy triggered by fasting, dystonic tremor
Cobalamin C disease	Progressive encephalopathy, abnormal movements, epilepsy, comas, multisystem pathology (renal failure, hepatic dysfunction, cardiomyopathy), retinopathy, macrocytosis	Psychiatric problems, confusion, subacute myelopathy, peripheral neuropathy, thromboembolic events. MRI: normal or leukoencephalopathy, macrocytic anaemia is rare
Coenzyme Q10 deficiency	Leigh syndrome, myoglobinuria, encephalopathy	Cerebellar ataxia, myopathy
Cerebrotendinous xanthomatosis	Mental retardation, chronic diarrhoea, epilepsy, juvenile cataract, neonatal cholestasis	Tendon xanthomas, cerebellar ataxia, spastic paraparesis, dementia, psychiatric signs
Cystathionine β-synthase deficiency	Mental retardation, marfanoid habitus, epilepsy, autism, lens dislocation, scoliosis	Strokes (internal carotid dissection), deep vein thrombosis, psychiatric disorders
Fatty acid β-oxidation defects	Non-ketotic hypoglycaemia, cardiomyopathy, liver disease, rhabdomyolysis, peripheral neuropathy, retinitis pigmentosa (LCHAD)	Encephalopathy (MCAD), rhabdomyolysis, proximal myopathy
Fabry disease	Crises of acroparaesthesia	Strokes, vertigo, cardiomyopathy, hearing loss, proteinuria
GAMT deficiency	Epilepsy, movement disorders, mental retardation, behavioural problems	Isolated myopathy
Glutaric aciduria type 1	Encephalopathy or movement disorders with bilateral lesions of basal ganglia, dystonia predominates	Leukoencephalopathy with subependymal nodules, spastic paraparesis, cephalalgia, dysexecutive syndrome, peripheral neuropathy
Glycogenosis type IV (glycogen branching enzyme deficiency)	Neuromuscular form, combined hepatic and myopathic form	Polyglucosan body disease: spastic paraparesis, peripheral neuropathy, leukoencephalopathy with spinal cord atrophy
GM1 gangliosidosis	Dysmorphic features, organomegaly, macular cherry red spot, progressive spasticity, seizures, decerebrate posturing	Generalised dystonia, parkinsonism, dysarthria, kyphoscoliosis, vertebral and hip dysplasia. MRI: high signal of posterior putamen
GM2 gangliosidosis	Motor weakness, visual loss, progressive spasticity, macular cherry red spot, epilepsy	Psychosis, lower motor neuron disease, cerebellar ataxia, dystonia, sensory neuronopathy
Krabbe disease	Progressive encephalopathy, hyperaesthesia, tonic spasms, signs of peripheral neuropathy, blindness, loss of bulbar function, seizures	Spastic paraparesis with or without peripheral neuropathy, specific leukoencephalopathy involving cortico-spinal tracts
Lesch-Nyhan syndrome	Severe generalised dystonia, cognitive disability and self-injurious behaviour	Isolated dystonia, mild cognitive or behavioural problems
L-2-Hydroxyglutaric aciduria	Seizures, progressive ataxia, spasticity, mental retardation, progressive macrocephaly, leukoencephalopathy with cerebellar atrophy	Epilepsy, progressive dystonia and parkinsonism, leukoencephalopathy involving the subcortical white matter, malignant brain tumours
MERRF	Myoclonic epilepsy, generalised epilepsy, cerebellar ataxia	Cerebellar ataxia, hearing loss, peripheral neuropathy, lipomatosis

Table 2.1 (continued)

Disease	Classic presentation in childhood	Adult-onset forms
Metachromatic leukodystrophy	Progressive gait problems, hypotonia, peripheral neuropathy, spasticity in all four limbs, optic atrophy, cerebellar ataxia	Psychiatric form: »psychosis-like features (mimics schizophrenia), cognitive decline« Motor form: »spastic paraparesis, cerebellar ataxia, dystonia, demyelinating polyneuropathy«
3-Methylglutaconyl-CoA hydratase deficiency	Mental retardation or motor delay, movement disorders, febrile seizures	Ataxia, dementia, optic atrophy, spasticity, leukoencephalopathy
Maple syrup urine disease	Coma, failure to thrive	Episodes of vomiting, lethargy, ataxia triggered by fever
MTHFR deficiency	Progressive encephalopathy with apnoea, epilepsy, microcephaly	Psychiatric disorders, spastic paraparesis, thromboembolic events, polyneuropathy
Neurotransmitter defects (dopamine synthesis)	Seizures, mental retardation, oculogyric crises, abnormal movements	Focal or generalised dopa-responsive dystonia or parkinsonism
Niemann-Pick disease type C	Liver disease, hypotonia, psychomotor delay, epilepsy, spasticity, ataxia, cataplexy, vertical supranuclear gaze palsy	Psychosis, cognitive decline, cerebellar ataxia, vertical supranuclear gaze palsy, dystonia, isolated splenomegaly
Non ketotic hyperglycinemia	Epilepsy with suppression bursts, encephalopathy	Paroxysmal choreic movement disorders, confusion triggered by fever, mental retardation with aggressive behaviour
PDH deficiency	Lactic acidosis, corpus callosum agenesis, Leigh syndrome, polyneuropathy	Episodic ataxia triggered by fever, optic neuropathy, MRI can be normal
Peroxisome biogenesis defects	Mental retardation, liver disease, deafness, cerebral malformations, dysmorphic features (high forehead, epicanthic folds), skeletal abnormalities, retinopathy, cataracts, seizures	Various combinations of peripheral neuropathy, cerebellar ataxia, deafness, retinitis pigmentosa, leukoencephalopathy
Phenylketonuria (untreated)	Mental retardation, autistic behaviour, seizures, movement disorders	Spastic paraparesis, optic atrophy, dementia, parkinsonism
***POLG* mutations**	Severe encephalopathy with intractable epilepsy and hepatic failure	Ptosis, ophtalmoplegia, sensory neuronopathy, cerebellar ataxia
Thiamine transporter (*SLC19A3*) mutations	Biotin responsive basal ganglia disease (encephalopathy, coma, epilepsy, generalised dystonia)	Wernicke-like encephalopathy
Serine deficiency	Mental retardation, epilepsy, microcephaly	Polyneuropathy
Sialidosis type 1	Dysmorphic features, mental retardation, progressive encephalopathy	Action and stimulus-sensitive myoclonus, cerebellar ataxia
SSADH deficiency	Epileptic encephalopathy	Behavioural/psychiatric disorders, isolated seizures
Urea cycle disorders	Coma, failure to thrive	Nausea, vomiting, cephalalgia, confusion, psychiatric disorders, ataxia, stroke-like episodes, coma
Wilson disease	Hepatic failure	Psychiatric signs, tremor, parkinsonism, dystonia, dysarthria

Treatable disorders are shown in **boldface type**

Table 2.2 Examples of syndromes or signs with very high diagnostic value (see also ▶ Chapter 1)

Syndromes	Metabolic pathways involved
Neurological	
Recurrent coma of unknown cause	Urea cycle disorders (mainly)
Dopa-responsive dystonia	Monoamine synthesis defects
Acute or subacute myelopathy	Homocysteine remethylation defects
Exercise-induced paroxysmal dyskinesia	GLUT1 deficiency
Brain MRI	
Abnormally high signal of basal ganglia on T_2-weighted sequences (Leigh syndrome)	Energy metabolism defects (pyruvate dehydrogenase, respiratory chain, coenzyme Q10)
Abnormally low signal of basal ganglia on T_2-weighted sequences	Neurodegeneration with brain iron accumulation
Abnormally high signal of basal ganglia on T_1-weighted sequences	Disorders of manganese metabolism, porto-systemic shunts
Stroke-like episodes	Energy metabolism defects (mitochondrial DNA mutations, *POLG* mutations)
Ophthalmological	
Supranuclear gaze palsy	Lysosomal diseases (Gaucher, Niemann Pick C)
Bilateral optic neuropathy	Energy metabolism defects (pyruvate dehydrogenase, respiratory chain, organic acidurias), *PLA2G6* mutations
Macular cherry red spot	Sialidosis
Cataract	Cerebrotendinous xanthomatosis, *GBA2* mutations
Retinitis pigmentosa	Energy metabolism defects (respiratory chain), peroxisomal disorders, Sjögren Larsson syndrome, *NTE* mutations, *DDHD1* mutations
Cutaneous	
Progressive dysmorphia	Lysosomal diseases
Angiokeratoma	Lysosomal diseases
Xanthomata (Achilles tendons)	Cerebrotendinous xanthomatosis
Ichthyosis	Sjögren Larsson syndrome, Refsum disease, *ELOVL4* mutations
Visceral	
Splenomegaly	Lysosomal diseases, Tangier disease
Venous and arterial thrombosis	Hyperhomocystinemia
Gout, nephrolithiasis, tophi	Purine salvage (Lesch-Nyhan syndrome)
Past history of neonatal cholestasis	Sterols metabolism (Niemann-Pick C, hereditary spastic paresis type SPG5, cerebrotendinous xanthomatosis, alpha-methyl-acyl-CoA racemase deficiency), citrin deficiency

of prolonged neonatal jaundice is suggestive of disorders of sterols metabolism (▶ Chapter 1 ▶ Section 1.3.1). Splenomegaly is highly suggestive of Niemann-Pick B and C, Gaucher disease and Tangier disease.

2.2.3 Intoxication Syndromes

These include porphyrias, urea cycle defects, organic acidurias, aminoacidopathies and homocysteine remethylation defects. The occurrence of acute symptoms that accompany the metabolic crisis can be very characteristic. However, in mild adult forms, symptoms can be progressive giving rise to leukoencephalopathies, epilepsy, psychiatric disorders or spastic paraparesis.

2.2.4 Disorders of Neurotransmitter Metabolism

Disorders of neurotransmitter metabolism are mostly represented by defects in the synthesis of serotonin and dopamine. Clinical signs are related to dopamine deficiency (dystonia, parkinsonism, oculogyric crisis), noradrenergic deficiency (ptosis, myosis, hypotension) or serotonin deficiency (sleep disturbance, dysthermia, behavioural disturbance). Dopa-responsive dystonia or parkinsonism is highly suggestive. Diurnal fluctuations of symptoms are also characteristic, with improvement in the morning and worsening during the day. Diagnosis of these disorders relies on analysis of neurotransmitter metabolism in the CSF.

2.2.5 Metal Storage Disorders

Metal storage disorders include Wilson disease (interfering with copper metabolism), the group of NBIA (neurodegeneration with brain iron accumulation such as neuroferritinopathy, aceruloplasminaemia, *PANK2*-associated neurodegeneration and *PLA2G6* mutations) interfering, even if only partially, with iron metabolism and a recently identified disorder of manganese metabolism. The hallmark of these diseases is the metal deposits that occur in the basal ganglia and that are visible on brain MRI (▶ Chapter 1 ▶ Section 1.5.2). The main presentations are movement disorders because of the primary involvement of the basal ganglia. Treatments, when they exist, are mainly based on metal chelators.

2.3 Specific Approaches to Neurometabolic Presentations in Adults

The clinical diagnostic strategies are illustrated in the Sections below, starting from the main neurological and psychiatric syndromes seen in adults with IEM. For each syndrome, the signs (clinical or radiological) indicative of an IEM and the approach leading to the specific metabolic investigations are discussed (see also ▶ Chapter 1 ▶ Section 1.5.1).

Table 2.3 Diagnostic approach to metabolic causes of encephalopathy, strokes or pseudo-strokes (see also ▶ Chapter 1 ▶ Section 1.4.1)

Diseases	Encephalopathy/coma	Strokes or pseudostrokes
Energy metabolism disorders		
Respiratory chain disorders (MELAS and others)	+	+
Thiamine transporter (*SLC19A3*) mutations, PDH deficiency	+	
MCAD deficiency	+	
Intoxication syndromes		
Urea cycle disorders	+	+
Homocysteine RD	+	+
CBS deficiency		+
Acute intermittent porphyrias	+	
Lysinuric protein intolerance	+	
MSUD	+	
Non ketotic hyperglycinemia	+	
Lipid metabolism/storage		
AMACR deficiency	+	+
Fabry disease		+
Pompe disease		+

AMACR, α-methyl-acyl-CoA racemase; *CBS*, cystathionine-β-synthase; *MCAD*, medium-chain acyl-CoA dehydrogenase; *MELAS*, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; *MSUD*, maple syrup urine disease; *RD*, remethylation defects.
Treatable disorders are shown in **boldface type**

2.3.1 Encephalopathies/Comas

In a patient with an unexplained encephalopathy or coma, certain features are highly suggestive of an IEM, firstly when the encephalopathy is triggered by an external factor (surgery, fasting, exercise, high protein intake, new medication) and secondly when specific brain lesions are present on brain MRI [5] (▶ see also Chapter 1 ▶ Section 1.4.1).

Two main groups of IEM are responsible for encephalopathies in adults: intoxication syndromes and energy metabolism defects (Table 2.3). In the first group MRI is usually normal or shows nonspecific features (brain oedema, generalised leukoencephalopathy), whereas in the second group MRI is often abnormal, showing bilateral lesions of basal ganglia (Leigh syndrome) or stroke-like lesions.

In addition, some clinical signs suggest specific diagnoses. Encephalopathies in the context of urea cycle disorders, organic aciduria and aminoacidopathies are usually associated with gastrointestinal symptoms such as nausea or vomiting. Porphyria crises are associated with abdominal pain, acute neuropathy or hyponatraemia. Homocysteine remethylation defects cause acute or subacute myelopathy and are often preceded by psychiatric symptoms lasting for months or years.

Fatty acid oxidation disorders usually cause muscular symptoms; however, patients with MCAD deficiency can

present with isolated encephalopathies starting in adolescence or adulthood with normal MRI.

Lastly, α-methyl-acyl-CoA racemase (AMACR) deficiency can cause a very severe relapsing encephalopathy. Patients with this disease often have characteristic MRI findings including abnormal signals of the thalami and brain stem, with cortical lesions mimicking infectious encephalitis or pseudostrokes (▶ Chapter 40).

2.3.2 Strokes and Pseudostrokes

Some IEM cause ischaemic strokes in adulthood (see also ▶ Chapter 1 ▶ Section 1.4.1). This is the case in Fabry disease and homocystinurias. In the former, strokes typically involve small arteries of the vertebrobasilar system, leading to acute deafness, vertigo, diplopia, hemiplegia. In homocystinurias (cystathionine β-synthase deficiency) or homocysteine remethylation defects, thrombosis or dissection or large vessels (carotid arteries) is observed. Ischaemic brain lesions have also been reported in patients with Pompe disease. In addition, acute focal neurological signs mimicking strokes (pseudo-strokes) are very evocative of mitochondrial diseases, especially mitochondrial DNA mutations (MELAS, MERRF, NARP) and can also be seen in patients with urea cycle disorders and AMACR deficiency. These pseudo-strokes differ from real strokes in that they do not correspond to usual arterial territories and are often associated with signs of encephalopathy, including cephalalgia, confusion and epileptic seizures. A good way to distinguish pseudostrokes from true ischaemic strokes is diffusion imaging: the diffusion coefficient is typically normal or increased in the former and decreased in the latter.

2.3.3 Movement Disorders

In patients with movement disorders, an IEM should be suspected in several situations: (1) when a patient displays several types of abnormal movements (example dystonia + parkinsonism); (2) when movement disorders are associated with other neurological signs (epilepsy, dementia, etc.); (3) when dystonia involves the orofacial region; (4) when bilateral lesions of the basal ganglia are observed on brain MRI; and (5) when paroxysmal movement disorders are triggered by fasting and exercise [9] (◘ Table 2.1 and ◘ Table 2.2).

Generally, a particular movement disorder can be seen in many different IEM, and conversely, a given IEM can present with different abnormal movements. As a consequence, the classic phenomenological diagnostic approach to movement disorders (i.e. dystonia, parkinsonism, chorea, myoclonus) is less applicable to the diagnosis of IEM. As in the case of acute encephalopathies, brain MRI can help the diagnostic approach. A T2 hypersignal of the basal ganglia suggests an energy metabolism disorder (see above) whereas a T2 hyposignal of the pallidum suggests NBIA [10] (◘ Table 2.5). Diffuse T2-hypersignal involving thalami, brain stem and cerebellar peduncles are suggestive of Wilson disease.

When MRI is normal, the diagnostic approach can be based on the course of the disease. Dystonia or parkinsonism with diurnal fluctuations suggests a neurotransmitter metabolism defect. Paroxysmal dystonia triggered by exercise is highly suggestive of GLUT1 deficiency but can also be observed in PDH deficiency. In addition, paroxysmal dyskinesias (not triggered by exercise) have been observed in several IEM, including Wilson disease and neurotransmitter metabolism defects.

2.3.4 Peripheral Neuropathies

Peripheral neuropathies in the context of IEM are often labelled 'Charcot-Marie-Tooth disease'. These types of neuropathy are characterised by long-standing chronic, predominantly motor, distal and symmetrical polyneuropathy with claw toes, diffuse, and severe homogeneous electrical abnormalities. IEM should be suspected in such patients if the neuropathy is associated with other incongruous neurological signs (leukoencephalopathy, ataxia, pyramidal signs, psychiatric or visual signs) or with systemic disease (skin problems, xanthomas, splenomegaly, cataract). In some cases, peripheral neuropathies may be acute or relapsing, and may involve multiple nerves (mononeuropathy, multiplex), motor neurons or dorsal root ganglia [11] (◘ Table 2.6).

Two main groups of metabolic diseases give rise to peripheral neuropathies: lipid storage disorders and energy metabolism defects. In lipid storage disorders, both the peripheral and central myelin can be involved, leading to a leukoencephalopathy seen on brain MRI. In contrast, defects of energy metabolism are mostly responsible for axonal peripheral neuropathies and are usually associated with other signs of energy metabolism defects (cerebellar ataxia in the case of respiratory chain disorders). Many exceptions to this schematic view exist, however. MNGIE (mitochondrial neurogastrointestinal encephalomyopathy) syndrome caused by thymidine phosphorylase deficiency (▶ Chapter 35) is typically responsible for a demyelinating polyneuropathy. Some lipid storage disorders, such as cerebrotendinous xanthomatosis (▶ Chapter 33), adrenomyeloneuropathy and other peroxisomal diseases, may cause polyneuropathies that can be axonal, demyelinating or both. Metabolic neuropathies may also present as autosomal dominant diseases such as the hereditary sensory and autonomic neuropathy type 1 (HSAN1) related to mutations in the gene encoding serine palmitoyltransferase and leading to toxic accumulation of abnormal sphingolipids [12] (▶ Chapter 38) and mutations in the α-N-acetyl-glucosaminidase (*NAGLU*) gene associated with a late-onset painful sensory neuropathy [13]. Acute polyneuropathies mimicking Guillain-Barré syndrome can be observed in acute attacks of porphyria and in pyruvate dehydrogenase deficiency, acute exacerbations of Refsum disease or untreated tyrosinaemia type 1. Painful peripheral neuropathy involving small fibres is reminiscent of Fabry disease, Tangier disease, GM2 gangliosidosis and porphyria. Motor neuron involvement mimicking spinal muscular atrophy is characteristic of late-onset Tay-

Table 2.4 Diagnostic approach to metabolic causes of movement disorders

Disease	Parkinsonism	Dystonia	Chorea	Myoclonus	Paroxysmal dystonia
Energy metabolism disorders					
Respiratory chain disorders	+	+	+	+	
Adenylate cyclase (*ADCY5*)		+	+	+	+
PDH deficiency	+	+	+		+
GLUT1 deficiency		+	+		+
BBGD (*SLC19A3*)		+			
Vitamin E deficiency		+			
Lipid metabolism disorders					
Cerebrotendinous xanthomatosis	+		+		
Niemann-Pick type C	+	+	+	+	
GM1 gangliosidosis	+	+			
GM2 gangliosidosis	+	+	+		
Gaucher disease	+	+		+	
CYP2U1 mutations (SPG56)		+			
FA2H mutations (SPG35)		+			
B4GALNT1 mutations (SPG26)		+			
Intoxication syndromes					
Phenylketonuria	+				
Homocystinuria	+	+	+		
L-2-Hydroxyglutaric aciduria	+	+			
Neurotransmitter metabolism defects					
GTP cyclohydrolase-1 deficiency	+	+			+
Tyrosine hydroxylase deficiency	+	+			
Dopamine transporter deficiency	+	+			
PTP synthase deficiency		+			+
Sepiapterin reductase deficiency	+	+			
Non-ketotic hyperglycinaemia			+		
Metal storage disorders					
Wilson disease	+	+	+		+
Aceruloplasminaemia	+	+	+		
Panthotenate kinase deficiency	+	+	+		
Neuroferritinopathy	+	+	+		
Manganese metabolism disorder (*SLC30A10*)	+	+			
PLA2G6 mutations	+	+			
Others					
Ceroid-lipofuscinosis	+	+		+	
Lesch-Nyhan disease		+	+		
Sialidosis				+	

BBGD, biotin-responsive basal ganglia disease; *PDH*, pyruvate dehydrogenase; *PTP*, 6-pyruvoyl-tetrahydropterin. Treatable disorders are shown in **boldface type**

Table 2.5 Diagnostic approach to metabolic causes of basal ganglia lesions on brain MRI

Diseases	Pallidum	Thalamus	Putamen	Brain stem nuclei	Dentate nuclei
Energy metabolism disorders					
Respiratory chain disorders	+	+	+	+	+
BBGD (*SLC19A3*)			+	+	
PDH deficiency	+	+	+	+	+
Co-enzyme Q10 deficiency			+	+	
Mitochondrial thiamine pyrophosphate transporter (*SLC25A19*)			+		
CoA synthase deficiency (COASY)	+	+	+		
Lipid storage disorders					
Cerebrotendinous xanthomatosis	+				+
AMACR deficiency		+		+	
GM1 gangliosidosis			+		
Fabry disease		+			
Intoxication syndromes					
Methylmalonic/propionic aciduria	+				
SSADH deficiency	+				+
Urea cycle disorders	+				+
Glutaric aciduria type 1			+		
Metal storage disorders					
Wilson disease	+	+	+	+	+
Aceruloplasminaemia	+	+	+	+	+
Neuroferritinopathy	+		+	+	+
PANK2 mutations	+				
PLA2G6 mutations	+			+	
FA2H mutations (SPG35)	+				
Manganese metabolism disorder (*SLC30A10*)	+		+		+

AMACR, α-methylacyl coenzyme A racemase; *BBGD*, biotin-responsive basal ganglia disease; *SSADH*, succinic semialdehyde dehydrogenase deficiency. Treatable disorders are shown in **boldface type**

Sachs disease. Lastly, involvement of dorsal root ganglia is highly suggestive of *POLG* mutations (mtDNA polymerase γ). In summary, the type of metabolic investigations is mainly based on the type of the peripheral neuropathy (demyelinating versus axonal), its topography and course and on brain MRI results.

2.3.5 Leukoencephalopathies

The first step in the diagnostic approach of leukoencephalopathies is to search for acquired, potentially treatable causes. These causes are numerous and include inflammatory, infectious, metabolic, neoplastic, paraneoplastic, toxic or vascular diseases. In metabolic leukoencephalopathies, lesions are usually bilateral and symmetrical involving specific white matter tracts (pyramidal tracts, cerebellar peduncles, U-fibres, etc.). Furthermore, the existence of an associated polyneuropathy is highly suggestive of an IEM [14][15][16].

Table 2.6 Diagnostic approach to metabolic causes of peripheral nervous system

Diseases	Demyelinating	Axonal	Motor neurone involvement	Small fibres	Dorsal root ganglion	Acute	Mononeuropathy multiplex
Energy metabolism disorders							
Respiratory chain disorders		+			+		
MNGIE	+						
PDH deficiency		+				+	
Vitamin E deficiency		+			+		
β-Oxidation defects (LCHAD, TFP)		+			+		
Biotinidase deficiency			+			+	
Lipid storage/oligosaccharidoses							
Cerebrotendinous xanthomatosis	+	+					
GM2 gangliosidosis			+	+			
Fabry disease				+			
Metachromatic leukodystrophy	+						
Krabbe disease	+	+					
Adrenoleukodystrophy/adrenomyeloneuropathy	+	+					
Refsum disease	+					+	+
ABHD12 mutations (PHARC)	+						
AMACR deficiency	+	+					
Peroxisome biogenesis defects	+	+					
Tangier disease				+		+	+
β-Mannosidosis	+						
Serine palmitoyltransferase mutations (HSAN1)		+	+	+			
PLA2G6 mutations		+					
CYP2U1 mutations (SPG56)		+					
GBA2 mutations (SPG46)		+					
B4GALNT1 mutations (SPG26)		+					
NTE mutations (SPG39)		+					
Presynaptic choline transporter (*SLC5A7*)		+					
Others							
Serine deficiency		+					
Homocysteine RD	+	+			+		
APBD		+	+				
Acute porphyrias		+		+		+	+
CDG syndromes		+					
Tyrosinaemia type 1						+	

AMACR, α-methylacyl coenzyme A racemase; *APBD*, adult polyglucosan body disease; *CDG*, congenital disorders of glycosylation; *HSAN1*, dominant hereditary sensory and autonomic neuropathy; *LCHAD*, long-chain 3-hydroxyl-CoA dehydrogenase; *PDH*, pyruvate dehydrogenase; *MNGIE*, mitochondrial neurogastro intestinal encephalomyopathy; *RD*, remethylation defects; *TFP*, trifunctional protein.
Treatable disorders are shown in **boldface type**

Table 2.7 Diagnostic approach to metabolic causes of leukoencephalopathies

Diseases	Periventricular	Pyramidal tracts	Cerebellum	Spinal cord	Juxtacortical	Brain stem	Corpus callosum
Lipid storage							
Metachromatic leukodystrophy	+						+
Adrenoleukodystrophy		+					+
Krabbe disease		+					+
Cerebrotendinous xanthomatosis	+	+	+			+	+
Refsum disease	+						
AMACR deficiency						+	
Peroxisome biogenesis disorder	+	+				+	
α-Mannosidosis	+						
Niemann-Pick C	+						
Intoxication syndromes							
Homocysteine RD	+			+	+		
Phenylketonuria	+						+
Glutaric aciduria type 1	+				+		
L-2-Hydroxyglutaric aciduria					+		
3-methylglutaconyl-CoA hydratase deficiency					+		
Disorders of energy metabolism							
Respiratory chain	+	+	+		+	+	+
APBD	+	+	+	+		+	
MNGIE	+				+		
DARS2 mutations	+	+	+	+		+	
Others							
Wilson disease			+			+	

AMACR, α-methylacyl coenzyme A racemase; *APBD*, adult polyglucosan body disease; *MNGIE*, mitochondrial neurogastrointestinal encephalomyopathy.
Treatable disorders are shown in **boldface type**

The diagnostic approach to genetic leukoencephalopathies should be guided by the clinical examination, the MRI aspect and electroneuromyographic studies (see also ▶ Chapter 1 ▶ Section 1.5.2). Some IEM are responsible for a specific pattern of leukoencephalopathy (Table 2.7). In general, two main groups of IEM are responsible for leukoencephalopathies: lipid storage disorders and aminoacidopathies/organic acidurias. In the first group, brain abnormalities are usually restricted to specific tracts within the deep brain white matter and the cortico-spinal tracts, cerebellar peduncles, corpus callosum and optic radiations, while U-fibres (juxtacortical fibres) are relatively spared. Furthermore, involvement of the peripheral nerves (polyneuropathy) is usually present (see paragraph »Polyneuropathies«). In contrast, aminoacidopathies and organic acidurias involve the peripheral nerves only exceptionally (one exception being homocysteine remethylation defects), and brain abnormalities usually extend to U-fibres.

2.3.6 Epilepsy

Although epilepsy is a frequent presentation of IEM in neonates and children, several IEM may also manifest in adults with onset of epileptic seizures, but these are usually observed as part of a larger clinical spectrum.

In a patient with epilepsy, several clinical, radiological or electrophysiological features suggest an IEM: (1) the form of epilepsy does not match with any classic epileptic syndrome, i.e. atypical electroclinical presentation, mixture of generalised and partial epileptic manifestations (e.g. association of myoclonus and partial seizures); (2) progressive myoclonic epilepsy; (3) association with other neurological impairments (cerebellar, pyramidal, etc.), with unexplained mental retardation, or with other organ disorders; (4) seizures that are related to the times of eating (fasting, protein rich meal); (5) inefficacy of or worsening with classic antiepileptic drugs; (6) unexplained status epilepticus; (7) abnormalities on proton magnetic resonance spectroscopy, e.g. creatine deficiency or increased lactate; (8) slowing of the background activity on the EEG, photo-paroxysmal responses during the photic intermittent stimulation at low frequencies (1-6 Hz) [17].

The three main groups of IEM presenting with epilepsy in adults are disorders of energy metabolism, intoxications and LSD (Table 2.8). Myoclonic epilepsy suggests lysosomal disorders or certain respiratory chain disorders (MERRF syndrome). Partial motor or occipital seizures are frequent in respiratory chain disorders together with slow waves predominating in posterior brain regions. Tonic-clonic seizures are often observed in intoxications but are not really specific.

Table 2.8 Diagnostic approach to metabolic causes of epilepsy

Diseases	Generalised or focal epilepsy	Progressive myoclonic epilepsy
Energy metabolism disorders		
Respiratory chain disorders (MERRF, MELAS, NARP, *POLG* and others)	+	+
GAMT deficiency	+	
GLUT1 deficiency	+	+
***SLC19A3* mutations**	+	
Lipid metabolism/storage		
Cerebrotendinous xanthomatosis	+	
Niemann-Pick C	+	+
Gaucher type 3	+	+
Ceroid lipofuscinosis	+	+
LIMP2 deficiency	+	+
Sialidosis	+	+
Lafora disease	+	+
Intoxication syndromes		
Homocysteine RD	+	
L-2-Hydroxyglutaric aciduria	+	
SSADH deficiency	+	
Acute intermittent porphyrias	+	
Others		
Hyperinsulinism-hyperammonaemia	+	+

GAMT, guanidinoacetate N methyl transferase; *LIMP2*, lysosomal integral membrane protein type 2; *MELAS*, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke; *MERRF*, myoclonic epilepsy with ragged red fibers; *NARP*, neuropathy, ataxia, and retinitis pigmentosa; *RD*, remethylation defects; SSADH, succinate semialdehyde dehydrogenase. Treatable disorders are shown in **boldface type**

2.3.7 Psychiatric Disorders

IEM frequently present with psychiatric diseases in adolescents or adults. Retrospective analysis of patients with various IEM shows that psychiatric signs may remain isolated for years before more specific organic involvement becomes obvious. Since psychiatrists' awareness of these rare disorders is low, IEM presenting with a pure psychiatric illness are often missed. In most cases, treatments are more effective at the 'psychiatric stage' of the disease, before the development of irreversible neurological lesions.

The diagnosis is especially difficult when psychiatric signs are initially isolated, without a family history or clinical somatic involvement. In addition, it is sometimes difficult, in a patient with physical signs, to determine whether psychiatric problems are due to the same disease or not. Furthermore, physical signs may not be evident after a simple clinical examination (as examples, leukodystrophies may be missed if a brain MRI is not performed, peripheral neuropathy, cataract or xanthomas may not be symptomatic, organomegaly is often missed clinically in an adult). It is therefore important to determine which psychiatric symptomatology points to an IEM and should lead to further investigations (Table 2.9). Diseases can be schematically classified into three groups [18][19].

Group 1 includes diseases with acute and recurrent attacks of confusion and behavioural changes, which are usually associated with physical signs (gastrointestinal signs, cephalalgia, dysautonomia, pyramidal signs, alteration of consciousness). This group corresponds mainly to intoxications (urea cycle defects, homocysteine remethylation defects and porphyrias) but also energy defects (mitochondrial diseases). Therefore, plasma ammonia, homocysteine and lactate should be measured in unexplained acute psychiatric presentations.

Group 2 is made up of diseases with isolated psychiatric signs arising in adolescence or adulthood in a previously non symptomatic patient. This group includes hyperhomocystinaemia (homocysteine remethylation defects and cystathionine β-synthase deficiency) and lipid metabolism disorders (metachromatic leukodystrophy, GM2 gangliosidosis, Nie-

Table 2.9 Diagnostic approach to metabolic causes of psychiatric disorders

Diseases	Adult-onset psychiatric disorders without mental retardation	Behavioural/psychiatric disorders with mental retardation
Energy metabolism disorders		
Respiratory chain disorders	+	+
Creatine transporter deficiency		+
Intoxication syndromes		
Urea cycle disorders	+	+
Homocysteine remethylation defects	+	+
CBS deficiency	+	+
Acute intermittent porphyrias	+	
Non ketotic hyperglycinemia		+
SSADH deficiency		+
Phenylketonuria	+	+
Lipid storage/oligosaccharidoses/MPS		
Niemann-Pick C	+	
GM2 gangliosidosis	+	
Metachromatic leukodystrophy	+	
Adrenoleukodystrophy	+	
Cerebrotendinous xanthomatosis	+	+
β-Mannosidosis		+
α-Mannosidosis	+	+
Ceroid lipofuscinoses	+	+
MPS type III (San Filippo syndrome)		+
AMACR deficiency	+	
Metal storage disorders		
Wilson disease	+	
Aceruloplasminaemia	+	
Neuroferritinopathy	+	
PANK2 mutations	+	+

AMACR, α-methyl-acyl-CoA racemase; *CBS*, cystathionine-β-synthase; *MPS*, mucopolysaccharidoses; *SSADH*, sucinate semialdehyde dehydrogenase.
Treatable disorders are shown in **boldface type**

mann-Pick type C disease, adrenoleukodystrophy and cerebrotendinous xanthomatosis). Patients in this group may initially present with recurrent psychotic attacks, chronic delusion or disorganised behaviour, which may mimic schizophrenia. It also includes behavioural and personality changes. The diagnosis is particularly difficult in this group given the relative non-specificity of psychiatric signs, especially when they remain isolated for years or decades. However, catatonias, visual hallucinations, fluctuating symptoms, mental confusion, resistance or even deterioration with treatments and associated cognitive decline constitute atypical features that suggest an IEM.

Group 3 includes patients with mild mental retardation from childhood and disorders of behaviour or personality without a definite psychiatric syndrome. This group includes chronic intoxications (homocystinurias, non ketotic hyper-

glycinaemia, succinic semialdehyde dehydrogenase deficiency), some neurotransmitter metabolism defects, (monoamine oxidase A deficiency and probably disorders of serotonin synthesis), and some miscellaneous diseases (creatine transporter deficiency, α- and β-mannosidosis, MPS III).

Given the important number of IEM presenting with chronic psychiatric symptoms, minimal investigations include brain MRI, ophthalmological examination, abdominal ultrasonography, electromyogram as well as plasma biomarkers such as homocysteine, cholestanol and oxysterols (cholestane-3β,5α,6β-triol and 7-ketocholesterol).

2.3.8 Spastic Paraparesis

Spastic paraparesis is a general term describing progressive stiffness and weakness in the lower limbs caused by pyramidal tract degeneration. This clinical situation is frequently encountered in adult neurology. The diagnostic strategy (Table 2.10) is usually limited to searching for acquired causes (spinal cord compression, inflammatory, metabolic, infectious diseases) and the so-called hereditary spastic paraplegias (HSP). To date, more than 70 forms of HSP have been identified, with various modes of inheritance [20]. HSP are clinically classified as »uncomplicated« (or »pure«) when symptoms are limited to spastic paraparesis and as »complicated« (or »syndromic«) when accompanied by other neurological or systemic signs.

However, although poorly recognised by neurologists, spastic paraparesis is also one of the many presentations of IEM in children and adults [21]. Pyramidal signs are usually included in a diffuse neurological or systemic clinical picture, but in some cases spastic paraparesis remains the only symptom for years. In a patient with spastic paraparesis some signs are suggestive of an IEM: (1) when a polyneuropathy is present on EMG; (2) when a leukoencephalopathy is present on MRI; (3) when the course is acute or subacute, with sensory ataxia suggesting subacute degeneration of the spinal cord.

Two groups of IEM give rise to spastic paraparesis: (1) disorders of lipid metabolism and (2) intoxication syndromes, including homocysteine remethylation defects. In the first group, polyneuropathy and leukoencephalopathy are often present. It should be noted that dopamine synthesis defects (guanosine-5'-triphosphate [GTP] cyclohydrolase and tyrosine hydroxylase deficiencies) can produce dystonia mimicking spastic paraparesis in the lower limbs. In such cases, treatment with levodopa is highly effective in alleviating the symptoms.The first metabolic autosomal dominant form of HSP has also been recently identified in patients with mutations in *ALDH18A1* encoding delta-1-pyrroline-5-carboxylate synthetase (P5CS) who present with hypocitrullinaemia [22]. The exploration of spastic paraparesis should therefore comprise the measurement of plasma ammonia, amino acids, homocysteine, vitamin B12, folate, very long chain fatty acids, pristanic and phytanic acids, oxysterols (27- and 25-hydroxycholesterol) and cholestanol.

Table 2.10 Diagnostic approach to metabolic causes of acute myelopathy or spastic paraparesis

Diseases	Chronic	Acute
Lipid metabolism		
Cerebrotendinous xanthomatosis	+	
CYP7B1 mutations (SPG5)	+	
Adrenoleukodystrophy	+	
Krabbe disease	+	
Peroxisomal biogenesis disorder	+	
DDHD1 mutations (SPG28)	+	
DDHD2 mutations (SPG54)	+	
CYP2U1 mutations (SPG56)	+	
NTE mutations (SPG39)	+	
FA2H mutations (SPG35)	+	
GBA2 mutations (SPG46)	+	
B4GALNT1 mutations (SPG26)	+	
PGAP1 mutations (GPI-Anchor synthesis pathway)	+	
Intoxication syndromes		
Phenylketonuria	+	
Arginase deficiency	+	+
Triple H syndrome	+	
ALDH18A1 mutations	+	
Homocysteine RD	+	+
L-2-Hydroxyglutaric aciduria	+	
Neurotransmitter metabolism defects		
GTP cyclohydrolase 1 deficiency	+	
Tyrosine hydroxylase deficiency	+	
Others		
Biotinidase deficiency		+
APBD	+	

APBD, adult polyglucosan body disease; *RD*, remethylation defects. Treatable disorders are shown in **boldface type**

2.3.9 Cerebellar Ataxia

Except for focal cerebellar lesions, the many causes of cerebellar ataxia include inflammatory diseases, paraneoplastic disorders, acquired metabolic disorders, alcohol intoxication, multiple system atrophy, and genetic diseases (Friedreich ataxia, dominant spinocerebellar ataxias etc.). Cerebellar ataxia in the context of IEM may be

Table 2.11 Diagnostic approach to metabolic causes of cerebellar ataxia

Diseases	Chronic cerebellar ataxia	Spinocerebellar ataxia	Episodic or acute ataxia	Myoclonic ataxia
Energy metabolism disorders				
Respiratory chain disorders	+	+	+	+
PDH deficiency	+		+	
Vitamin E deficiency	+	+		
Co-enzyme Q10 deficiency	+			
***SLC19A3* mutations (Wernicke-like)**			+	
Lipid metabolism/oligosacccharidoses				
Cerebrotendinous xanthomatosis	+	+		
Niemann-Pick type C	+			+
GM2 gangliosidosis	+			
Gaucher type 3	+			+
Adrenomyeloneuropathy		+		
Refsum disease	+			
NTE mutations (SPG39)	+	+		
Acyl-CoA oxidase deficiency	+			
PEX10 mutations	+			
α-Mannosidosis	+			
Sialidosis				+
Abetalipoproteinaemia	+	+		
Intoxication syndromes				
Urea cycle disorders			+	
Urocanase deficiency			+	
Mevalonate kinase deficiency	+			
Others				
Hartnup disease			+	

PDH, pyruvate dehydrogenase. Treatable disorders are shown in **boldface type**

acute, triggered by fever (PDH deficiency, respiratory chain disorders or *SLC19A3* mutations) [23], or chronic (Table 2.11). Chronic cerebellar ataxia is rarely pure. In practice, several situations are usually encountered.

- Associated polyneuropathy: the association of cerebellar ataxia with an axonal polyneuropathy suggests a disorder of energy metabolism (*POLG* mutations, NARP syndrome, PDH deficiency, etc.) or a peroxisomal disease (PEX10). Association with a demyelinating polyneuropathy suggests a neurolipidosis such as Refsum disease or cerebrotendinous xanthomatosis.
- Association with a pyramidal syndrome and a proprioceptive ataxia (so-called spinocerebellar ataxia) suggests lipid metabolism disorders (cerebrotendinous xanthomatosis or adrenomyeloneuropathy).
- Isolated cerebellar ataxia can be the only presenting sign of GM2 gangliosidosis or of Niemann-Pick disease type C.

2.3.10 Myopathy

Metabolism within muscles is very different from that of the nervous system (Table 2.12). Except for mitochondrial disorders that can affect both the muscle and the nervous system, diseases affecting the muscle usually spare the nervous system. Hallmarks of metabolic myopathies are exercise intolerance

Table 2.12 Diagnostic approach to metabolic causes of myopathies

Diseases	Permanent weakness	Exercise intolerance and/or myglobinuria	Cardiomyopathy
Glycogen storage disorders			
McArdle disease (GSD-V)		+	
Pompe disease (GSD-II)	+		+
Debranching enzyme (GSD-III)	+		
Branching enzyme (GSD-IV)	+		
Glycolysis defects		+	+
Respiratory chain disorders			
MELAS	+	+	+
MERRF	+	+	+
MNGIE	+		
PEO-Kearns Sayre	+	+	+
POLG mutations	+		
Cytochrome B deficiency		+	
Fatty acid oxidation defects			
VLCAD deficiency	+		+
ETF and ETFDH deficiencies	+	+	
TFP deficiency		+	
CPT2 deficiency		+	
Primary carnitine deficiency	+		+
Other lipids metabolism			
Lipin 1 deficiency (*LPIN1*)		+	
Barth syndrome (*TAZ*)	+		+
CHKB mutations	+		+
PNPLA2 mutations (neutral lipid storage disorder)	+		+
Others			
Cystinosis	+		
AGAT deficiency	+		
GAMT deficiency	+		
AMACR deficiency		+	

AGAT, l-Arginine glycine amidinotransferase; *AMACR*, α-methyl-acyl-CoA racemase; *CPT2*, carnitine palmitoyltransferase 2; *ETF*, electron transfer flavoprotein; *ETFDH*, electron transfer flavoprotein dehydrogenase; *GAMT*, guanidinoacetate N-methyltransferase; *MELAS*, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke; *MERRF*, myoclonic epilepsy with ragged red fibers; *MNGIE*, mitochondrial neurogastrointestinal encephalomyopathy; *PEO*, progressive external ophthalmoplegia; *TFP*, trifunctional protein; *VLCAD*, very long-chain acyl-CoA dehydrogenase.
Treatable disorders are shown in **boldface type**

(exertional cramps or fatigue) and recurrent rhabdomyolysis [24][25] (see also ▶ Chapter 1 ▶ Sections 1.4.1 and 1.6.8). However, presentations may be less specific, with progressive proximal myopathy or cardiomyopathy. Muscle histology may be suggestive of a metabolic disorder when it shows ragged red fibres, lipid droplets or high glycogen content with PAS staining. The four main groups of metabolic diseases affecting muscle are (1) mitochondrial disorders, (2) fatty acids β-oxidation defects (FAOD), (3) glycogen storage disorders (GSD), and (4) complex lipid synthesis disorders.

Mitochondrial diseases may show a wide range of manifestations including exercise intolerance with premature fatigue or myalgia out of proportion to weakness. These symptoms are frequently associated with progressive external ophthalmoplegia, which is highly suggestive of *POLG* mutations or other mtDNA deletion syndromes.

FAOD may manifest with rhabdomyolysis triggered by prolonged exercise or prolonged fasting, but progressive proximal weakness with lipid storage is also a common presentation in adults. Lipin deficiency 1 has been observed only in few adults so far (▶ Chapter 34).

Clinical presentations of muscle glycogenoses are various, ranging from exercise intolerance to isolated progressive muscle weakness. Patients with McArdle disease typically exhibit premature fatigue and contractures, frequently accompanied by muscle breakdown. A sign considered pathognomonic of this disease is the »second wind phenomenon«, which is a marked improvement in exercise tolerance about 10 minutes into aerobic exercise involving large muscle masses (jogging or cycling).

Adipocyte triglyceride lipase (ATGL) deficiency (*PNPLA2* mutations) gives neutral lipid storage with myopathy typically presenting in young adults with weakness and fatty infiltration of muscle or with cardiomyopathy. Weakness can be proximal, distal or generalized. The disease is progressive: some patients are athletic in childhood. Jordan anomaly on a blood smear is highly diagnostic (▶ Chapter 34).

2.3.11 Others

Table 2.13 and Table 2.14 summarise other important signs, including sensorial disorders and miscellaneous presentations that can be helpful in determining which investigations should be undertaken.

Table 2.13 Diagnostic approach to metabolic causes of deafness/visual problems

Diseases	Deafness	Corneal deposits	Retinitis	Macula cherry red spot	Optic nerve disorders	Cataract	Gaze palsies
Energy metabolism disorders							
Respiratory chain disorders	+		+		+	+	+
β-Oxidation defects (LCHAD, TFP)			+				
Vitamin E deficiency			+				
Biotinidase deficiency	+				+		
PDH deficiency					+		
Intoxication syndromes							
Homocysteine RD			+		+		
CBS deficiency						+	
Phenylketonuria					+		
Galactokinase deficiency						+	
Lipid storage							
Niemann-Pick C	+						+
Metachromatic leukodystrophy					+		
Adrenoleukodystrophy	+				+		
Gaucher disease							+
Fabry disease	+	+				+	
Cerebrotendinous xanthomatosis						+	
GBA2 mutations (SPG46)						+	
Sjögren-Larsson disease			+			+	
ELOVL4 mutations			+				

Table 2.13 (continued)

Diseases	Deafness	Corneal deposits	Retinitis	Macula cherry red spot	Optic nerve disorders	Cataract	Gaze palsies
DDHD1 mutations (SPG28)			+				
NTE mutations (SPG39)			+				
ABDH12 mutations (PHARC)	+		+			+	
FA2H mutations (SPG35)					+		
Acyl-CoA oxidase deficiency			+			+	
AMACR deficiency			+				
Refsum disease	+		+			+	
Peroxisome biogenesis disorder	+		+		+	+	
Mucopolysaccharidosis	+	+	+			+	
Fish eye syndrome		+					
Cystinosis		+					
α-Mannosidosis	+						
β-Mannosidosis	+						
Sialidosis type 1				+			
Metal storage disorders							
Wilson disease		+				+	
Aceruloplasminaemia			+				
PANK2 mutations			+				
PLA2G6 mutations					+		
Others							
CDG syndrome (PMM2-CDG)			+				
Ceroid lipofuscinoses			+		+		

AMACR, α-methylacyl-CoA racemase; *CBS*, cystathionine β-synthase; *CDG*, congenital disorders of glycosylation; *LCHAD*, long-chain L-3 hydroxyacyl-CoA dehydrogenase; *PDH*, pyruvate dehydrogenase; *RD*, remethylation defects; *TFP*, trifunctional protein.
Treatable disorders are shown in **boldface type**

Table 2.14 Diagnostic approach to metabolic causes of miscellaneous presentations

Diseases	Dysautonomia	Gliomas	Aseptic meningitides	Pseudotumor cerebri	Abdominal pain	Ichthyosis
Energy metabolism disorders						
Respiratory chain disorders	+		+			
MNGIE	+				+	
APBD	+					
Succinate dehydrogenase		+				
L-2-Hydroxyglutatic aciduria		+				
Intoxication syndromes						
Acute porphyrias	+				+	
Galactokinase deficiency				+		

Table 2.14 (continued)

Diseases	Dysautonomia	Gliomas	Aseptic meningitides	Pseudotumor cerebri	Abdominal pain	Ichthyosis
Lipid storage						
Fabry disease			+		+	
Sjogren-Larsson						+
ELOVL4 mutations						+
GM2 gangliosidosis	+					
Cystinosis	+			+		
Others						
CDG syndrome (ALG6-CDG)				+		

APBD, adult polyglucosan body disease; *CDG*, congenital disorders of glycosylation; *MNGIE*, mitochondrial neurogastrointestinal encephalomyopathy.
Treatable disorders are shown in **boldface type**

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