REVIEW

Inborn errors of metabolism and motor disturbances in children

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Summary Motor disturbances are very common in paediatric neurology. Often families can be reassured that these are just variants of normal development. However, abnormal movements can also be the hallmark of severe brain dysfunction of different and complex origins. This review concentrates on motor disturbances as frequent and important symptoms of inborn errors of metabolism. A structured diagnostic approach is developed taking into account age-dependent physiological developments and pathophysiological responses of gross and fine motor functions. A series of investigations are presented with the primary aim of early diagnosis of treatable conditions. The correct recognition and differentiation of movement disorders (ataxia, rigid akinetic syndrome ('parkinsonism'), dystonia, athetosis, tremor, and others), spasticity, and neuromuscular disorders, requires profound neurological expertise. A high level of suspicion and close interaction between paediatric neurologists and specialists in inborn errors of metabolism are indispensable to effectively and timely identify patients in whom motor disturbances are the presenting and/or main symptom of an inborn error.

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In memory of Professor Robert Surtees, our friend and outstanding colleague in the field of paediatric neurology and neurometabolic diseases.

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Abbreviations

CNS	central nervous system
CPK	creatine phosphokinase
CTX	cerebrotendinous xanthomatosis
GLUT-1	glucose transporter type 1
HHH	hyperammonaemia, hyperornithinaemia, homocitrullinuria
IEM	inborn error of metabolism
MERRF	myoclonic epilepsy with ragged red fibres
MSUD	maple syrup urine disease
MNGIE	myoneurogastrointestinal encephalopathy
MTP	mitochondrial trifunctional protein
NARP	neuropathy ataxia and retinitis pigmentosa
NPC	Niemann–Pick type C
PKAN	pantothenate kinase
PLA2G6	phospholipase A2G6

Introduction

Abnormal movements can refer to subtle physiological variants of normal development or can be caused by severe brain dysfunction. Furthermore, they are an almost constant feature in childhood encephalopathies whatever their origin might be. Inborn errors of metabolism (IEMs) frequently involve motor function not only because of the many anatomical regions that participate in this complex task, but also because they require perfect neurochemical interactions. The primary motor cortex (frontal lobe), and secondary motor cortices (e.g. parietal lobe) generate and transform neuronal impulses that control the execution of movement. The basal ganglia and cerebellum interact and regulate these signals that travel down the corticospinal tract through the spinal white matter to interact with interneurons and motor neurons in the spinal cord ventral horn. These ventral horn neurons send their axons through the ventral roots to individual muscle fibres. Each motor neuron in the spine is part of a functional unit called the motor unit. The motor unit is composed of the motor neuron, its axon, and the muscle fibres it innervates. Consequently, IEMs affecting motor cortex, basal ganglia, cerebellum, myelin, motor neurons, axons, muscle, or neuromuscular junctions or any of the interactions between them, can cause abnormal movements or disturbed locomotion. From a clinical point of view we can classify these motor abnormalities into movement disorders, spasticity, peripheral neuropathy, and muscle disorders. Because the last group corresponds to an extensive highly specialized field, it will not be considered in this review. As a rule, in IEMs, a combination of diverse motor signs will be present in most individual disorders (Table 1).

Movement disorders

Our understanding of paediatric movement disorders is rapidly evolving stimulated by progress in the discovery of monogenic neurogenetic disorders and consecutively the development of structured diagnostic and therapeutic approaches. In neurometabolic disorders causing abnormal movements, investigations of specific metabolites can give important clues to diagnoses in addition to the clinical presentation. A logical series of investigations should be followed with the primary aim of early diagnosis of treatable conditions. In this part we will concentrate on the main causes of ataxia, dystonia, and other movement disorders.

IEMs and ataxia

Ataxia is defined as an inability to maintain normal posture and smoothness of movements while force and sensation are intact. There are many variations in the clinical phenotype, ranging from consequences of pure cerebellar dysfunction (Poretti et al. 2008) to mixed patterns of brain involvement (extrapyramidal pathways, brainstem, and/or cerebral cortical involvement). A wide range of molecular defects have been identified, all involving the spinocerebellar pathways and without metabolic abnormalities. IEMs present a less frequent cause of ataxias and can be clinically classified following a pragmatic approach based on the clinical evolution: intermittent or episodic, stable or progressive ataxias (Prasad et al. 2005). Figure 1 proposes a diagnostic algorithm.

Intermittent/episodic ataxias

If due to a neurometabolic disorder, these are mainly diseases of intermediary metabolism. Ataxia is a frequent sign during acute/subacute decompensations of amino acids (such as MSUD disease; Holmgren et al. 1980) and organic acid and urea cycle disorders. Usually, these disorders have other neurological or extraneurological markers. By contrast, defects of energy metabolism presenting with intermittent ataxia may involve exclusively the nervous system and may be more difficult to diagnose. This is the case of respiratory chain disorders, e.g. the NARP syndrome, pyruvate dehydrogenase deficiency, and biotinidase deficiency. In NARP syndrome, isolated mental retardation may precede the appearance of episodic ataxia by years. Furthermore, once ataxia appears it tends to remain constant, with worsening during episodes of decompensation. Carbohydrate- and fever-sensitive ataxia is a feature of mild pyruvate dehydrogenase deficiency (Robinson et al. 1996). Biotinidase deficiency may also give rise to intermittent ataxia. High plasma lactate and other characteristic biochemical features of these disorders may be present only intermittently.

GLUT1 deficiency can present with intermittent ataxia as the only finding, mimicking other episodic ataxias. In this disease ataxia usually worsens before meals. Some children improve greatly with frequent carbohydrate-rich snacks and may not even need a strict ketogenic diet (Wang et al. 2005). Intermittent ataxia can also be seen in Hartnup disease; additional symptoms are pellagra-like skin changes, photic dermatitis, and psychiatric symptoms (Kleta et al. 2004). Recently a new cause of intermittent ataxia and

mental retardation due to urocanic aciduria in a patient with mutations in the urocanase gene has been described (Espinós et al. 2009).

The so-called 'episodic ataxias' may be mistaken for metabolic disorders, although they belong to the channelopathies (Jen 2008). Correct diagnosis is important, as effective treatment exists. As a rule, metabolic parameters may be normal between bouts of ataxia in inborn errors of metabolism; testing is therefore mandatory when patients are symptomatic and usually involves CSF investigations. An important non-metabolic differential diagnosis for intermittent ataxia is intoxication, especially with benzodiazepines and other centrally acting drugs. Moreover, in a child with acute ataxia it is obviously mandatory to exclude more frequent aetiologies such as infectious diseases and opsoclonus-myoclonus syndrome.

Ataxias with progressive spinocerebellar dysfunction

The best example of this group is Friedreich's ataxia. The main additional clinical symptoms are polyneuropathy and pyramidal tract lesions and cardiomyopathy. Vitamin E deficiency and abeta-/hypobetalipoproteinaemia can also result in retinopathy, neuropathy, ophthalmoplegia, progressive mental retardation, and cardiomyopathy. Ataxia with vitamin E deficiency (AVED; Mariotti et al. 2004; Marzouki et al. 2005) is caused by mutations in the gene for alpha-tocopherol transfer protein. Laboratory findings include low-to-absent serum vitamin E and high serum cholesterol, triglycerides, and beta-lipoprotein. High doses of vitamin E (400–1200 IU/day) improve the neurological function. Abetalipoproteinaemia is a rare disorder due to a dysfunction in the microsomal triglyceride transfer protein gene (*MTP*). Acanthocytosis on peripheral blood smears is a constant finding. Decreased serum LDL and VLDL and increased HDL cholesterol levels are present together with low triglyceride levels. High-dose supplementation of vitamin E has a beneficial effect on neurological symptoms (Homer et al. 2005). IOSCA (infantile-onset spinocerebellar ataxia) represents one of the most severe forms of recessive ataxias. It is characterized by progressive atrophy of the cerebellum, brainstem, and spinal cord and sensory axonal neuropathy (Table 1). It has been related to mitochondrial depletion syndromes (Hakonen et al. 2008). Cerebrotendinous xanthomatosis can also manifest as spinocerebellar ataxia (Siebner et al. 1996).

Ataxias with progressive neurological deterioration

Other disorders presenting with chronic (progressive) ataxia are Refsum disease, sphingolipidoses, L-2-hydroxyglutaric aciduria, cerebrotendinous xanthomatosis, and coenzyme Q_{10} deficiency. The degree of neurological deterioration depends on the disorder. In some cases the clinical picture may remain stable. Coenzyme Q_{10} deficiency may produce non-progressive ataxia as the only neurological manifestation. High-dose coenzyme Q_{10} supplementation is effective in some cases. Some phenotypes of GLUT-1 deficiency are characterized by chronic non-progressive ataxia, with intermittent fluctuations associated with fasting (Overweg-Plandsoen et al. 2003). The list of diseases to be included in this group is wide. Among them is also Niemann–Pick disease type C (NPC) and other neurodegenerative disorders; however, other signs of progressive neurological dysfunction as dementia usually become prominent.

Interestingly, in 4-hydroxybutyric aciduria and some forms of congenital disorders of glycosylation, ataxia may improve rather than deteriorate.

Ataxias with progressive myoclonic epilepsy

MERRF syndrome, Lafora disease, and neuronal ceroid lipofuscinoses are typical representatives of this group. Severe epilepsy is the clinical hallmark (Buccoliero et al. 2003). Ataxia and myoclonic epilepsy are also a feature of some lysosomal disorders such as the juvenile form of Gaucher disease (type 3), NPC, and sialidosis type 1.

IEMs and other movement disorders

Other than ataxia, movement disorders in children may be divided into rigid akinetic syndrome ('parkinsonism') and dyskinetic movements (dystonia, athetosis, tremor, chorea, myoclonus, tic, and stereotype) (Fernández-Alvarez 2001). Tics are very rarely related to IEMs. Important movement disorders in IEMs are dystonia, secondary parkinsonism, chorea, tremor, and myoclonus (see Fig. 2). Different movement disorders may coexist in the same patient with an IEM. In children with an IEM, movement disorders are often dystonic (Assmann et al. 2003). In general, diseases causing parkinsonism in adults, may present with dystonia in children. Some neurometabolic disorders require metabolic studies of CSF metabolites for diagnosis (Table 2; Hoffmann et al. 1998).

Rigid akinetic syndrome and IEMs

Metabolic disorders causing primarily a rigid-akinetic syndrome include: (1) neurotransmitter deficiencies

Table 1 Metabolic diseases with prominent motor disturbances

	Ataxia	MD	Spasticity	Peripheral neuropathy	Other main NRL signs	Brain MRI	Investigations
Intoxication							
Classical organic acidurias	+[a]	+[a]	(+)		MR(+)	BG and/or WM matter involvement[a]	Plasma AA, urine OA, acylcarnitines
Cerebral organic acidurias							
Glutaric aciduria type I	++	++	(+)		Macrocephaly, acute encephalopathy	Striatum involvement, F-T atrophy, leukoencephalopathy	Urine OA, acylcarnitines
L-2-hydroxyglutaric aciduria	++	+	+		Macrocephaly, MR, seizures	Leukodystrophy (U fibres), High T2 dentate and pallidum	Urine OA
MHBD deficiency	+	++	(+)		Blindness, seizures, progressive disorder	Periventricular WM and/or, BG involvement, atrophy[a]	Urine OA
Canavan disease		(+)	++		Macrocephaly, MR, optic atrophy	WM involvement with swelling, BG involvement. NAA in MRS elevated	Urine OA
Amino acid disorders							
UCD	+[a]		++ HHH/AD	++ OAT	Encephalopathy, lethargy, seizures, PS	Cortical, WM, and/or BG, stroke-like imaging[a]	Plasma ammonia, AA, urine orotic acid
Serine deficiency			++	+	Seizures, MR	Hypomyelination, atrophy	Plasma and CSF AA
Homocystinurias		+	++ (RD)	++ (RD)	MR, seizures, PS	Stroke, venous thrombosis	Plasma AA
NKH		+ (late onset)			MR, epileptic encephalopathy	WM involvement, corpus callosum dysgenesis	Plasma, urine, CSF AA
Hartnup disease	++				MR, PS		Plasma, urine AA
Energetic deficiency							
NARP syndrome	++	(+)	(+)	++	MR may precede other signs for years	Symmetrical BG lesions, cerebellar atrophy	Mitochondrial DNA study
PDH deficiency	++	+	(+)	+	MR, optic atrophy, Leigh syndrome	Corpus callosum dysgenesis, WM (cysts) and/or BG	Lactate/pyruvate ratio, PDH activity
CoQ$_{10}$ deficiency	++	+	(+)		MR, Leigh syndrome	Cerebellar atrophy, BG	CoQ$_{10}$ measurement in fibroblasts or muscle
Leigh syndrome	+	++	+	(+)	MR, cranial nerve	Symmetrical lesions of deep grey matter, cerebellum and brainstem	RC, mitochondrial/ nuclear genes
IOSCA	++	(+)	++	++	Regression about 1 year of age, epilepsy, ophthalmoplegia	Mild to severe atrophy of brainstem and upper spinal cord. T2 high intensity of cerebellar WM	RC, PEO1 gene, mitochondrial DNA quantification
MNGIE	(+)		(+)	++	Ophthalmoplegia, muscle weakness	WM involvement	Plasma and urine thymidine, TP activity
Other mitochondrial disorders	+Such as MERRF	+	+In MELAS related to stroke-like episodes	+	MR, cranial nerve, muscle involvement	Many patterns possible	RC, mitochondrial/ nuclear genes
Biotinidase deficiency	++	(+)	+	(+)	Deafness, MR	BG, cerebellum, brainstem, WM involvement[a]	Plasma lactate, AA, urine OA, biotinidase activity
LCHAD/MTP	++			++	Retinitis pigmentosa,		OA urine, acylcarnitines

Table 1 Continued

	Ataxia	MD	Spasticity	Peripheral neuropathy	Other main NRL signs	Brain MRI	Investigations
Glut-1 deficiency	+	+	+		muscle weakness Epilepsy, language difficulties, microcephaly	Atrophy, periventricular WM, ventriculomegaly[a]	CSF glucose, CSF/plasma glucose
Creatine deficiency (AGAT and GAMT)	(+)	++	+		Epilepsy, MR, autistic behaviour	Normal or slight brain atrophy. Symmetrical high signal lesions in deep grey matter structures Absent/low creatine peak in brain MRS	Guanidinoacetate, creatine, creatinine urine
Complex molecules Peroxisomal disorders							
Refsum disease	++		+	++	Deafness, retinitis pigmentosa	WM involvement	Plasma phytanic acid
X-linked ALD			++	+ (late onset)	Regression, PS	Leukoencephalopathy (usually posterior predominance)	Plasma VLCFA
Sphingolipidoses							
Gaucher type II/III	+	(+)	+	+	Ophthalmoplegia, ME, MR		Urine oligosaccharides
Krabbe			++	++	Blindness, deafness irritability	Periventricular predominance leukoencephalopathy	Beta-galactocerebrosidase activity
MLD		(+)	++	++	Regression, irritability, PS	Prominent periventricular WM changes	Arylsulfatase A activity
Gangliosidosis (GM₁, GM₂)	+	+	++	(+)	Regression, ME, PS	Hypomyelination, atrophy, thalamic changes	Enzymatic activities
Fabry				++	Paraesthesias, strokes	Multifocal WM abnormalities, White pulvinar (T1)	Alpha-galactosidase A
Mucopolysaccharidoses			+ (type III)		MR, characteristic phenotypic features	Atrophy, ventriculomegaly, multifocal WM involvement, enhanced Virchow-Robin spaces	Urine GAGs
Oligosaccharidoses							
Mannosidosis	+		+	+ (beta)	MR. ME	WM involvement, enhanced Virchow-Robin spaces	Urine oligosaccharides
Sialidosis type 1	++		++	++	MR, ME	Cerebellar atrophy, ventriculomegaly	Urine GAGs and oligosaccharides
CDG	++	(+)	(+)	+	MR	Cerebellar atrophy, pontocerebellar hypoplasia	Transferrin electrophoresis
NCL	(+)	(+)	++		Regression, ME, PS, retinitis pigmentosa	Cerebellar and brain atrophy	Enzyme and genetic studies
Neurotransmitters							
IEM of dopamine		++	(+)		Oculogyric crises	Usually normal	CSF biogenic amines

Disease				Clinical	Imaging	Diagnosis
4-Hydroxybutyric aciduria	++	+	(+)	MR, PS, epilepsy	Cerebellar atrophy, signal changes of the dentate nucleus, BG and/or WM involvement	Urine OA
Purines						
Lesch–Nyhan disease	++	++	(+)	Self-mutilation, hypotonia	Normal or cortical atrophy	Uric acid, xanthines
Metals						
Wilson disease	++	++	(+)	Dysarthria, PS	BG involvement	Copper and ceruloplasmin
PKAN deficiency	++	++	(+)	Dysarthria, retinitis pigmentosa	T1 hypointensity and central gliosis of the pallidum (eye of tiger phenomenon)	Genetic tests
PLAG6 mutations	+	++	++	It is a cause of INAD; Regression, hypotonia, nystagmus	Cerebellar atrophy with hyperintense cerebellar cortex, hypointense pallidum	Genetic tests
Hypermanganesaemia	++	++	(+)	Extrapyramidal symptoms	High T1 signal of BG	Manganese in biological fluids
Vitamin-responsive diseases						
Vitamin E deficiency	++	+	++	MR, retinopathy, ophthalmoplegia	Mostly normal, cerebellar atrophy may be present	Plasma vitamin E
Biotin-responsive BG disorder	(+)	++	+	Subacute encephalopathy, dystonia	Caudate and putamen involvement	Response to biotin
Lipid metabolism						
Niemann–Pick C	++	+	(+)	Regression, vertical ophthalmoplegia	Brain atrophy	Sphingomyelinase activity
Abetalipoproteinaemia	++	+	++	Similar to vitamine E deficiency	Cerebellar atrophy	Cholesterol, triglycerides, ApoB, blood smear
Others						
Sjögren–Larsson (FADH)	++		++	MR, seizures, retinopathy	Periventricular WM involvement, abnormal MRS	Enzyme and genetic studies
CTX (bile acid disorder)	++	+	+	MR, dementia	Leukodystrophy with posterior fossa predominance, cerebellar atrophy	Cholestanol, bile acids
MCT8 mutations	++	++	(+)	MR, hypotonia, muscle hypoplasia	Normal, brain atrophy or delayed myelination	T3, T4, TSH

a Can be present in decompensation periods only.

++, prominent feature. +, often present. +, sometimes present. AD, arginase deficiency. ADL, adrenoleukodistrophy. AGAT, arginine glycine amidinotransferase. BG, basal ganglia. CDG, congenital disorders of glycosylation. CSF, cerebrospinal fluid. CTX, cerebrotendinous xanthomatosis. FADH, fatty-aldehyde dehydrogenase. F-T, frontotemporal. GAGs, glycosaminoglycans. GAMT, guanidinoacetate methyltransferase. HHH, hyperammonaemia, hyperornithinaemia, homocitrullinuria. INAD, infantile neuroaxonal dystrophy. IOSCA, infantile-onset spinocerebellar ataxia. LCHAD, long-chain hydroxyacyl-CoA dehydrogenase. MCT8, monocarboxylate transporter type 8. ME, myoclonic epilepsy. MELAS, encephalomyopathy, lactic acidosis, stroke-like episodes. MERRF, myoclonic epilepsy with ragged red fibres. MHBD, 2-methyl-3-hydroxybutyryl-CoA dehydrogenase. MNGIE, myoneurogastrointestinal encephalopathy. MR, mental retardation. MRS, magnetic resonance spectroscopy. MTP, mitochondrial trifunctional protein. NAA, N-acetylaspartate acid. NARP, neuropathy ataxia retinitis pigmentosa. NCL, neuronal ceroid lipofuscinosis. OA, organic acids. OAT, ornithine aminotransferase. PDH, pyruvate dehydrogenase. PEO, progressive external ophthalmoplegia. PS, psychiatric symptoms. PKAN, pantothenate kinase deficiency. PLAG6, phospholipase AG6. RC, respiratory chain. RD, remethylation defects. TP, thymidine phosphorylase. UCD, urea cycle disorders. VLCFA, very long-chain fatty acids. WM, white matter.
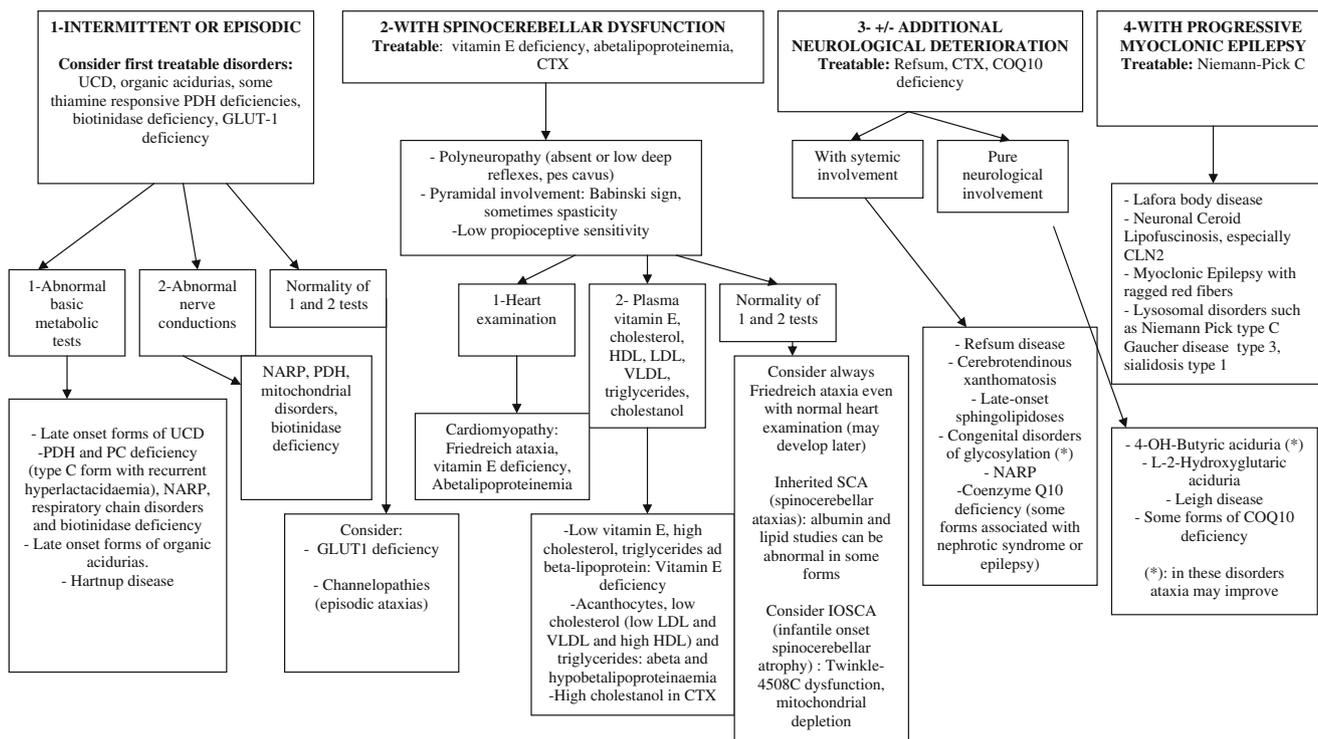
Fig. 1 Diagnostic approach for metabolic disorders with prominent ataxia

(especially early-onset forms) such as tyrosine hydroxylase, aromatic L-amino acid decarboxylase, and sepiapterin reductase deficiencies, biopterin defects with or without hyperphenylalaninaemia (Hyland et al. 2009), and the recently described mutations in the dopamine transporter gene. Contrary to the former diseases, this last disorder produces an elevated level of homovanillic acid in the CSF (Kurian et al. 2009). (2) Early-onset disorders of energy metabolism such as pyruvate carboxylase deficiency (Garcia-Cazorla et al. 2006), or some mitochondrial DNA defects (Davidzon et al. 2006). (3) Wilson disease with neurological manifestations has only exceptionally been related to early childhood, but mild neurological and neuropsychiatric disturbances are not unusual in this period of life. However, as Wilson disease is a treatable disorder, copper studies are strongly recommended from early school age. (4) Early onset rigid-akinetic syndrome has been recently associated with *PLAG6* mutations (Kurian et al. 2008).

Dystonia

Dystonia is a major symptom in many different metabolic diseases. In fact, almost all neurometabolic disorders can cause dystonia at some stage, but glutaric aciduria type I, Leigh syndrome, and other mitochondrial cytopathies are among the most frequent.

If dystonia is focal, progresses slowly, or remains isolated over time, the most likely IEMs to be considered are primary dopaminergic deficiencies such as autosomal dominantly inherited GTP cyclohydrolase deficiency (Segawa disease; Segawa et al. 2003) or late-onset forms of tyrosine hydroxylase deficiency. By contrast, if the dystonia appears abruptly, settles rapidly, is generalized and postural from the very first stages of the disease, different metabolic causes should be strongly considered. Organic acidurias such as propionic aciduria and methylmalonic aciduria can develop dystonia during acute periods of decompensation, although in general, movement disorders are not a prominent sign in these disorders (Deodato et al. 2006). In many cases, dystonia develops late in the course of the disease, with focal onset and progressive generalization, causing major disability and wheelchair dependency (e.g. homocystinuria, NPC, GAMT deficiency). In NPC, isolated dystonia may appear as the first symptom before visceral involvement takes place. Glutaric aciduria type I and late-onset forms of gangliosidoses types I and II may present as progressive dystonia also (Gouider-Khouja and Ben Youssef-Turki 2006). The distribution of dystonia may also be helpful to differentiate these disorders. For example, onset of dystonia in the lower limbs is frequent in primary dopaminergic deficiencies, whereas oromandibular dystonia is very characteristic of pantothenate kinase-associated neurodegeneration
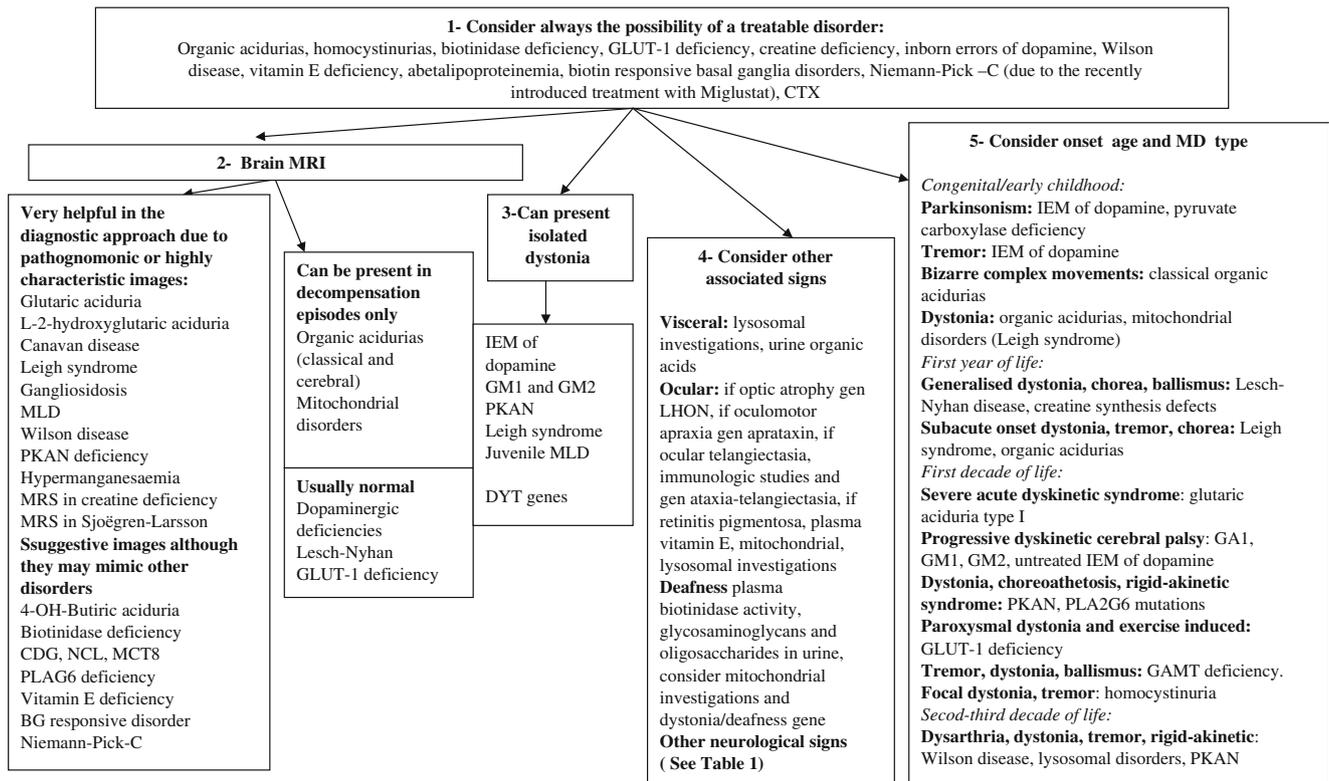
1- Consider always the possibility of a treatable disorder:
Organic acidurias, homocystinurias, biotinidase deficiency, GLUT-1 deficiency, creatine deficiency, inborn errors of dopamine, Wilson disease, vitamin E deficiency, abetalipoproteinemia, biotin responsive basal ganglia disorders, Niemann-Pick –C (due to the recently introduced treatment with Miglustat), CTX

2- Brain MRI

5- Consider onset age and MD type

Congenital/early childhood:
Parkinsonism: IEM of dopamine, pyruvate carboxylase deficiency
Tremor: IEM of dopamine
Bizarre complex movements: classical organic acidurias
Dystonia: organic acidurias, mitochondrial disorders (Leigh syndrome)
First year of life:
Generalised dystonia, chorea, ballismus: Lesch-Nyhan disease, creatine synthesis defects
Subacute onset dystonia, tremor, chorea: Leigh syndrome, organic acidurias
First decade of life:
Severe acute dyskinetic syndrome: glutaric aciduria type I
Progressive dyskinetic cerebral palsy: GA1, GM1, GM2, untreated IEM of dopamine
Dystonia, choreoathetosis, rigid-akinetic syndrome: PKAN, PLA2G6 mutations
Paroxysmal dystonia and exercise induced: GLUT-1 deficiency
Tremor, dystonia, ballismus: GAMT deficiency.
Focal dystonia, tremor: homocystinuria
Secod-third decade of life:
Dysarthria, dystonia, tremor, rigid-akinetic: Wilson disease, lysosomal disorders, PKAN

Very helpful in the diagnostic approach due to pathognomonic or highly characteristic images:
Glutaric aciduria
L-2-hydroxyglutaric aciduria
Canavan disease
Leigh syndrome
Gangliosidosis
MLD
Wilson disease
PKAN deficiency
Hypermanganesaemia
MRS in creatine deficiency
MRS in Sjoëgren-Larsson
Ssuggestive images although they may mimic other disorders
4-OH-Butiric aciduria
Biotinidase deficiency
CDG, NCL, MCT8
PLAG6 deficiency
Vitamin E deficiency
BG responsive disorder
Niemann-Pick-C

Can be present in decompensation episodes only
Organic acidurias (classical and cerebral)
Mitochondrial disorders

Usually normal
Dopaminergic deficiencies
Lesch-Nyhan
GLUT-1 deficiency

3-Can present isolated dystonia

IEM of dopamine
GM1 and GM2
PKAN
Leigh syndrome
Juvenile MLD

DYT genes

4- Consider other associated signs

Visceral: lysosomal investigations, urine organic acids
Ocular: if optic atrophy gen LHON, if oculomotor apraxia gen aprataxin, if ocular telangiectasia, immunologic studies and gen ataxia-telangiectasia, if retinitis pigmentosa, plasma vitamin E, mitochondrial, lysosomal investigations
Deafness plasma biotinidase activity, glycosaminoglycans and oligosaccharides in urine, consider mitochondrial investigations and dystonia/deafness gene
Other neurological signs (See Table 1)

Fig. 2 Diagnostic approach for metabolic disorders with prominent movement disorders (MD) other than ataxias

(PKAN). Dystonia is a typical sign in PKAN in children (usually starting at around 5–6 years of age and often preceded by psychomotor delay), whereas the adult form manifests as rigid-akinetic syndrome.

Although other signs of neurological dysfunction usually coexist, some metabolic diseases can initially present as isolated dystonia (IEM of dopamine, gangliosidoses, PKAN, Leigh syndrome, pyruvate dehydrogenase deficiency, juvenile form of metachromatic leukodystrophy). Recently, a new phenotype of GLUT1 deficiency consisting of paroxysmal exercise-induced dyskinesia has been described (Suls et al. 2008). Dystonic or choreoathetotic movements appear at a mean age of 8 years and are preceded by epileptic seizures in half of the patients. Paroxysmal exercise-induced dyskinesia is usually triggered by a prolonged walk and lasts from few seconds to a few hours. Sugar administration or rest may improve the dyskinesia. In opposition to the classical phenotype of GLUT1 deficiency described by De Vivo et al. (1991), these patients are neurologically normal between episodes and show higher only borderline low glucose CSF/plasma ratios (mean 0.52 compared with a mean of 0.33 in classical phenotypes). It is now considered the most frequent genetic disease responsible for paroxysmal exercise-induced dyskinesia. Haemolytic anaemia is another common laboratory finding in this condition. A recently described disorder that causes dystonia is hypermanganesaemia associated with hepatic cirrhosis and polycythaemia. Brain MRI is especially helpful, showing high intensity of basal ganglia in T1-weighted images, suggesting accumulation of manganese (Tuschl et al. 2008). Figure 2 is a diagnostic approach to movement disorders (other than ataxia) in IEMs.

IEM and spasticity

Spasticity is a very common clinical situation in paediatric neurology. It results from damage to upper motor neurons or to the corticospinal tracts. Abnormal

Table 2 Clinical situations requiring CSF studies in patients presenting with predominant motor disturbances

- Unexplained diskinetic cerebral palsy
- Unexplained isolated dystonia or other type of movement disorder
- Unexplained rigid-akinetic syndrome
- Paroxysmal exercise-induced dyskinesia
- Unexplained spastic paraparesis

muscle contraction gives rise to muscle stiffness interfering with voluntary movements. Symptoms may vary from mild stiffness to severe muscle spasms and include hypertonia, brisk deep tendon reflexes, pathological reflexes, clonus, and weakness. In children, most events causing such motor damage occur during late pregnancy and delivery such as prematurity, neonatal asphyxia, birth trauma or infections. The resulting manifestations are usually grouped under the general term 'cerebral palsy'. Spasticity is the most common motor symptom in IEMs, but at the same time the least specific. It is usually associated with additional neurological findings or systemic involvement. However, some disorders can start with isolated spastic paraparesis such as X-linked adrenoleukodystrophy, homocysteine remethylation defects, the hyperammonaemia-hyperornithinaemia-homocitrullinuria (HHH) syndrome, arginase deficiency, or Segawa disease. This possibility of an IEM should be considered in every child with the diagnosis of cerebral palsy but without history and MRI findings of perinatal or postnatal brain injury. In the diagnostic approach (Fig. 3) it is crucial to consider brain MRI findings. White-matter abnormalities and their main neuroradiological characteristics can be extremely helpful (Schiffmann and van der Knaap 2009) and allow diagnosis in certain cases, eliminating the need for much unnecessary metabolic and genetic testing. Other associated symptoms such as peripheral neuropathy also contribute to making a more specific differential diagnosis.

Treatable IEMs with diparesis/tetraparesis

Urea cycle disorders such as arginase deficiency can result in progressive spasticity, seizures, and mental retardation despite relatively mild hyperammonaemia. Sodium phenylbutyrate and dietary arginine restriction are effective therapeutic tools (Scaglia and Lee 2006). HHH syndrome is a disorder of ornithine transport between cytoplasm and mitochondria that causes progressive spastic diplegia and other signs of neurological dysfunction (Salvi et al. 2001). Therapeutic strategies include diet and ammonium-lowering agents.

Biotinidase deficiency may also cause progressive spastic paraparesis that improves with biotin administration (5–20 mg/day) (Ramaekers et al. 1993). Defects of homocysteine remethylation can cause demyelination of the pyramidal tracts and subacute combined degeneration of the spinal cord (Surtees 1998). It is important to measure plasma amino acids, total homocysteine and folate concentrations in every patient with isolated spasticity, as it may be the leading or only clinical sign for a long period. Patients treated
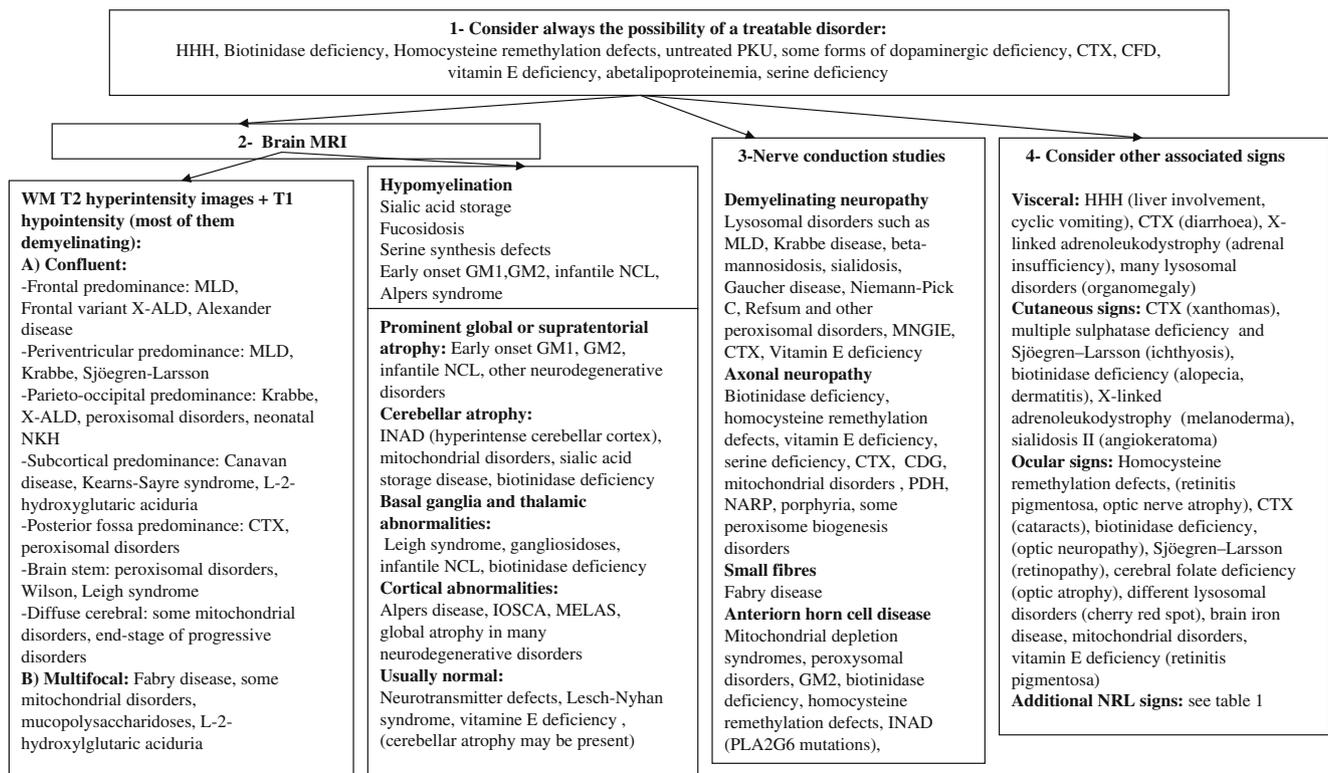

1- Consider always the possibility of a treatable disorder:
HHH, Biotinidase deficiency, Homocysteine remethylation defects, untreated PKU, some forms of dopaminergic deficiency, CTX, CFD, vitamin E deficiency, abetalipoproteinemia, serine deficiency

2- Brain MRI

WM T2 hyperintensity images + T1 hypointensity (most of them demyelinating):
A) Confluent:
-Frontal predominance: MLD, Frontal variant X-ALD, Alexander disease
-Periventricular predominance: MLD, Krabbe, Sjöegren-Larsson
-Parieto-occipital predominance: Krabbe, X-ALD, peroxisomal disorders, neonatal NKH
-Subcortical predominance: Canavan disease, Kearns-Sayre syndrome, L-2-hydroxyglutaric aciduria
-Posterior fossa predominance: CTX, peroxisomal disorders
-Brain stem: peroxisomal disorders, Wilson, Leigh syndrome
-Diffuse cerebral: some mitochondrial disorders, end-stage of progressive disorders
B) Multifocal: Fabry disease, some mitochondrial disorders, mucopolysaccharidoses, L-2-hydroxyglutaric aciduria

Hypomyelination
Sialic acid storage
Fucosidosis
Serine synthesis defects
Early onset GM1,GM2, infantile NCL, Alpers syndrome

Prominent global or supratentorial atrophy: Early onset GM1, GM2, infantile NCL, other neurodegenerative disorders
Cerebellar atrophy:
INAD (hyperintense cerebellar cortex), mitochondrial disorders, sialic acid storage disease, biotinidase deficiency
Basal ganglia and thalamic abnormalities:
Leigh syndrome, gangliosidoses, infantile NCL, biotinidase deficiency
Cortical abnormalities:
Alpers disease, IOSCA, MELAS, global atrophy in many neurodegenerative disorders
Usually normal:
Neurotransmitter defects, Lesch-Nyhan syndrome, vitamine E deficiency, (cerebellar atrophy may be present)

3-Nerve conduction studies

Demyelinating neuropathy
Lysosomal disorders such as MLD, Krabbe disease, beta-mannosidosis, sialidosis, Gaucher disease, Niemann-Pick C, Refsum and other peroxisomal disorders, MNGIE, CTX, Vitamin E deficiency
Axonal neuropathy
Biotinidase deficiency, homocysteine remethylation defects, vitamin E deficiency, serine deficiency, CTX, CDG, mitochondrial disorders, PDH, NARP, porphyria, some peroxisome biogenesis disorders
Small fibres
Fabry disease
Anteriorn horn cell disease
Mitochondrial depletion syndromes, peroxysomal disorders, GM2, biotinidase deficiency, homocysteine remethylation defects, INAD (PLA2G6 mutations),

4- Consider other associated signs

Visceral: HHH (liver involvement, cyclic vomiting), CTX (diarrhoea), X-linked adrenoleukodystrophy (adrenal insufficiency), many lysosomal disorders (organomegaly)
Cutaneous signs: CTX (xanthomas), multiple sulphatase deficiency and Sjöegren–Larsson (ichthyosis), biotinidase deficiency (alopecia, dermatitis), X-linked adrenoleukodystrophy (melanoderma), sialidosis II (angiokeratoma)
Ocular signs: Homocysteine remethylation defects, (retinitis pigmentosa, optic nerve atrophy), CTX (cataracts), biotinidase deficiency, (optic neuropathy), Sjöegren–Larsson (retinopathy), cerebral folate deficiency (optic atrophy), different lysosomal disorders (cherry red spot), brain iron disease, mitochondrial disorders, vitamin E deficiency (retinitis pigmentosa)
Additional NRL signs: see table 1

Fig. 3 Diagnostic approach for metabolic disorders with prominent spasticity

with a combination of betaine (up to 10 g/day in 3 doses), folic acid (5–10 mg/day), and hydroxycobalamin (0.5–1 mg/day orally or 1 mg i.m. monthly) from the neonatal period may develop normally (Strauss et al. 2007), whereas late-treated patients show at most a partial recovery of the neurological signs together with an improvement of cerebral myelination on MRI (Surtees et al. 1991). This combination of betaine is not as effective as it is in resolving other neurological or psychiatric symptoms related to the defect. Untreated phenylketonuria and a recently described cerebral folate deficiency syndrome (Ramaekers et al. 2005), although the latter is still not clearly defined, are other examples of treatable IEMs that may exhibit progressive spasticity without treatment. Cerebrotendinous xanthomatosis may present with progressive spasticity from the second decade of life if appropriate treatment has not been initiated during early stages of the disease (Verrips et al. 2000).

Dopamine synthesis defects, especially autosomal dominant GTP cyclohydrolase I deficiency, may exhibit pyramidal tract signs. In some cases, lower limb dystonia can mimic spastic paraparesis. Therefore, CSF studies and a trial of levodopa, should be performed in all patients with unexplained spastic paraparesis or dystonic cerebral palsy (Hyland et al. 2009). In vitamin E deficiency, spasticity may appear together with ataxia, peripheral neuropathy, and retinitis pigmentosa.

Progressive spasticity associated with additional neurologic signs, irritability, and global deterioration

This group of heterogeneous disorders usually results in complex neurological pictures, in which progressive spasticity is only one of the main features. Peripheral neuropathy and visual, auditory, and visceral involvement are frequently present. Brain MRI may reveal specific white-matter lesions (Fig. 3).

Lysosomal disorders and X-linked adrenoleukodystrophy share these characteristics and are well described elsewhere (Desnick and Schindler 2001; Moser 1997). Infantile neuroaxonal dystrophy (INAD) and related disorders are due to mutated *PLA2G6*, encoding a phospholipase. They manifest with progressive neurological regression and distended axons (spheroid bodies) in the nervous system and increased iron deposition in basal ganglia. Progressive spastic tetraparesis, extrapyramidal signs, dementia, retinitis pigmentosa, and optic atrophy are frequently present (Morgan et al. 2006). The first signs are nystagmus, hypotonia, and ataxia.

Pyramidal tract involvement is also frequent in mitochondrial disorders, but other signs and symptoms often guide the diagnostic approach (Table 1).

Some cerebral organic acidurias such as Canavan disease (high urine and brain MRS *N*-acetylaspartate) (Lyon et al. 2006) or L-2-hydroxyglutaric aciduria are examples of childhood leukodystrophies exhibiting different degrees of progressive spasticity and well-defined brain MRI patterns (Schiffmann and van der Knaap 2009).

Other signs

Other associated signs, especially cutaneous and ocular, can provide important clues to the diagnosis (Fig. 3).

IEMs presenting mainly as peripheral neuropathy

The peripheral nerves make up an intricate network that connects the brain and spinal cord to the muscles, skin, and internal organs. Peripheral neuropathies can be acute or chronic, involving large or small fibres, be demyelinating or axonal, the latter being differentiated by electrodiagnostic studies or nerve biopsy. In IEMs the peripheral nerves may affect the structure or function of myelin and axons due to metabolic pathway dysregulation or storage.

Acute polyneuropathies mimicking Guillain–Barré syndrome can be observed in acute attacks of porphyrias (Sedel et al. 2007), in patients with tyrosinaemia type I (Mitchell et al. 1990) and in pyruvate dehydrogenase deficiency (Debray et al. 2006).

Chronic axonal polyneuropathy is the most common form of peripheral neuropathy in IEMs. Many metabolic disorders may cause this form of neuropathy (Sedel et al. 2007). Treatable disorders are biotinidase deficiency, homocysteine remethylation defects, ornithine aminotransferase deficiency, vitamin E deficiency, serine deficiency, Wilson disease, and cerebrotendinous xanthomatosis (Sedel et al. 2007). Neuromyopathic forms of trifunctional protein deficiency can produce progressive polyneuropathy and limb girdle myopathy with recurrent episodes of rhabdomyolysis (Spiekerkoetter et al. 2004). Chronic sensorimotor polyneuropathy is the most common form of peripheral neuropathy associated with mitochondrial disorders. However, various other forms have been reported (Bouillot et al. 2002). NARP, SANDO (sensory ataxic neuropathy, dysarthria, and ophthalmoparesis), and MNGIE (myoneurogastrointestinal encephalopathy) are among the most common mitochondrial disorders that are associated with neuropathy. Long-chain fatty acid oxidation defects (LCHAD) present with peripheral sensorimotor polyneuropathy and pigmentary retinitis as

late complications of the disease (Saudubray et al. 1999).

Chronic demyelinating polyneuropathy is a common feature in some lysosomal diseases involving myelin metabolism (such as metachromatic leukodystrophy and Krabbe disease), peroxisomal disorders (Wanders 2004), and some mitochondrial disorders such as MNGIE due to thymidine phosphorylase gene mutations (Needham et al. 2007).

In Fabry disease, painful acroparaesthesias with dysautonomic features is a sign of small-fibre peripheral neuropathy (Lacomis et al. 2005).

Lower motor neuron disease refers to any disease involving spinal or bulbar motor neurons. Muscle weakness and atrophy, cramps, and fasciculations are the main clinical features. In children, lower motor neuron disease has been described in peroxisomal biogenesis defects (Baumgartner et al. 1998) and mitochondrial depletion syndromes, especially thymidine kinase 2 deficiency (Oskoui et al. 2006; Pons et al. 1996). Anterior horn cell disease is also one of the features of infantile neuroaxonal dystrophy (INAD), recently related to PLAG6 mutations (Kurian et al. 2008).

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