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Review article

How to detect late-onset inborn errors of metabolism in patients with movement disorders – A modern diagnostic approach☆

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ABSTRACT

We propose a modern approach to assist clinicians to recognize and diagnose inborn errors of metabolism (IEMs) in adolescents and adults that present with a movement disorder. IEMs presenting in adults are still largely unexplored. These disorders receive little attention in neurological training and daily practice, and are considered complicated by many neurologists. Adult-onset presentations of IEMs differ from childhood-onset phenotypes, which may lead to considerable diagnostic delay. The identification of adult-onset phenotypes at the earliest stage of the disease is important, since early treatment may prevent or lessen further brain damage. Our approach is based on a systematic review of all papers that concerned movement disorders due to an IEM in patients of 16 years or older. Detailed clinical phenotyping is the diagnostic cornerstone of the approach. An underlying IEM should be suspected in particular in patients with more than one movement disorder, or in patients with additional neurological, psychiatric, or systemic manifestations. As IEMs are all genetic disorders, we recommend next-generation sequencing (NGS) as the first diagnostic approach to confirm an IEM. Biochemical tests remain the first choice in acute-onset or treatable IEMs that require rapid diagnosis, or to confirm the metabolic diagnosis after NGS results. With the use of careful and systematic clinical phenotyping combined with novel diagnostic approaches such as NGS, the diagnostic yield of late-onset IEMs will increase, in particular in patients with mild or unusual phenotypes.

1. Introduction

Movement disorders can be caused by many different conditions, including genetic disorders. Inborn errors of metabolism (IEMs) are a subgroup of these genetic disorders. These are conditions in which the impairment of a biochemical pathway is intrinsic to the pathophysiology of the disorder [1]. Advances in the knowledge of the pathogenesis underlying IEMs have led to specific treatments for these disorders, including many IEMs that cause movement disorders [2]. The identification of patients with IEMs is therefore important to obtain optimal treatment results, and prevent further and irreversible damage of the brain.

IEMs are not exclusive childhood-onset disorders, but can present from the neonatal period to late adulthood with acute or chronic symptoms, frequently including movement disorders [3]. However, the identification of IEMs as the cause of neurological symptoms in adolescents and adults appears to be a largely neglected area, which leads to serious under-diagnosis [4]. The recognition of a patient with a late-onset IEM is frequently challenging, as presenting symptoms in adolescents or adults can be quite different and more subtle than in children [5]. Symptoms are not always very specific, and can overlap with symptoms of more common non-metabolic disorders [6]. One of the strategies to improve the recognition of IEMs is to focus on the presence of red flags. Unfortunately, the many different IEMs all have

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their own (rare) red flags. Another strategy is to look for phenotypic syndromic patterns, including laboratory tests and brain imaging [2], but this requires quite extensive knowledge of the disorders involved.

In 2008, Sedel et al. combined the earlier mentioned strategies, and proposed a diagnostic algorithm for IEMs in adult patients presenting with a movement disorder based on literature and expert opinion [3]. We have taken this approach further, and combine it with the advances in diagnostic techniques for IEMs, including next-generation sequencing (NGS).

This paper presents a modern diagnostic approach that includes NGS. In contrast to earlier algorithms, it is focused and based on a systematic review of the available literature on adolescent- and adult-onset presentations of IEMs with movement disorders.

2. Methods

We performed a systematic review of all papers that concerned movement disorders in adolescent- and adult-onset IEMs up to July 2019. Search terms and the PRISMA scheme can be found in Supplementary Appendix I. All papers with a confirmed diagnosis of IEM, first symptoms starting at the age of 16 years or later, and detailed description of symptoms for each patient were included. Patients with symptoms due to an IEM presenting before the age of 16 years, including epilepsy and learning problems, were excluded (Supplementary Appendix II). References were identified using PubMed, textbooks, and through relevant citations in books or papers. Only papers published in English were included. Mitochondrial disorders were included as a combined group. In this study, 97 papers were included, consisting of case reports or case series of 35 different IEMs (Supplementary Appendix II).

3. Clinical approach to patients with a movement disorder due to an inborn error of metabolism

We propose a modern diagnostic approach for adolescent and adult patients presenting with a movement disorder in whom an IEM should be considered (Fig. 1).

3.1. Step 1 – Which movement disorder is present?

The first step is to decide which movement disorder is present in a patient, for example dystonia, myoclonus, chorea, tremor, tics, parkinsonism, or ataxia. Movement disorders must be distinguished from other disorders that affect movement, such as spasticity and weakness.

3.2. Step 2 – Are there clinical clues of an inborn error of metabolism?

Clinical clues of an underlying IEM in adult patients with a movement disorder comprise three items. First, and most important, is the phenotype of the patient. Many patients have a mixed movement disorder, often in combination with accompanying neurological, psychiatric, or visceral manifestations. Second, patients can have specific triggers and acute onset of movement disorders. Finally, it is important to pay attention to the family history.

3.3. Description of the phenotype

3.3.1. Multiple movement disorders

The presentation with two or more movement disorders, especially early in the disease course, can be an important clue to an IEM. With disease progression, more movement disorders may develop, leading to complex and mixed phenotypes. The dominant movement disorder may be replaced by another movement disorder that may become dominant over time [7]. Overall, the type of dominant movement disorder is not specific for an IEM or a group of IEMs, although dystonia in patients with dopa-responsive dystonia is one of the exceptions to this. Some combinations of movement disorders have a stronger association with a specific IEM than others. For example, in pantothenate kinase-associated neurodegeneration (PKAN) there is a strong relationship between parkinsonism and dystonia.

3.3.2. Eye movement disorders

Eye movement disorders are frequent in IEMs [8], but regain little attention as patients themselves do not always complain about visual disturbances. Recognition of an eye movement disorder can help to diagnose an IEM. For example, in patients with Niemann-Pik type C multiple movement disorders are combined with a vertical supranuclear gaze palsy [7], whereas a horizontal supranuclear gaze palsy is seen in patients with Gaucher disease. Oculogyric crisis (episodes of tonic upward gaze with an inability to look downward) are also a symptom in various IEMs, especially in disorders affecting dopamine metabolism.

3.3.3. Epilepsy

Epilepsy is associated with about 40% of all IEMs [9], and the epilepsy syndromes can be divided into progressive myoclonus epilepsy and other epilepsy subtypes with or without cognitive decline [10]. The phenotype of progressive myoclonus epilepsy is characterized by action myoclonus, cerebellar ataxia, epileptic seizures, cognitive decline, and a progressive course. Several lysosomal storage disorders are associated with progressive myoclonus epilepsy, such as Gaucher disease type 3, Tay-Sachs disease, neuronal ceroid lipofuscinoses, and sialidosis type 1. It is also frequent in mitochondrial disorders, for example in myoclonic epilepsy with ragged red fibers (MERRF) [11,12]. Other epilepsy syndromes are also common, but may be clinically or neurophysiological atypical, and do not always respond well to anti-epileptic drugs. Changes in seizure frequency may be related to fasting, dietary changes, or intercurrent illnesses. Certain anti-epileptic drugs exacerbate seizures in specific mitochondrial disorders, and should be avoided [12].

3.3.4. Polyneuropathy and myopathy

Polyneuropathy in IEMs is often distal and symmetric with a chronic progressive course. Acute polyneuropathies, small fiber neuropathies, mononeuropathies, and mononeuropathy multiplex have been described as well [13]. Two main groups of IEMs are associated with polyneuropathy: lysosomal storage disorders (demyelinating neuropathy) and energy metabolism disorders (axonal neuropathy) [14]. It is important to realize that approximately 3,5% of the elderly have symptoms of polyneuropathy, usually caused by diabetes mellitus, alcohol, or neurotoxic drugs [15]. This implies that the positive predictive value of the combination of polyneuropathy and movement disorders in the diagnosis of IEMs is higher in younger compared to older patients.

Myopathy in late-onset IEMs is seen in glycogen storage disorders, fatty acid oxidation disorders, disorders of purine metabolism, and when combined with movement disorders, especially in mitochondrial disorders and coenzyme Q10 deficiency [16,17]. Hallmarks of myopathies are episodes of rhabdomyolysis, pigmenturia/myoglobinuria, exercise intolerance, fatigue, myalgia, cramps, and stiffness [18]. In patients with a mitochondrial myopathy, ptosis and ophthalmoplegia may be present as well.

3.3.5. Spastic paraparesis

IEMs may present with spastic paraparesis. Signs suggestive of an underlying IEM include the additional presence of polyneuropathy, leukoencephalopathy on brain imaging, and an acute or subacute disease course [14]. It is sometimes difficult to differentiate spasticity from a movement disorder. An important pitfall is the misdiagnosis of dystonia as spastic paraparesis, for example in patients with dopa-responsive dystonia [19]. Lysosomal storage disorders, particularly Krabbe disease and metachromatic leukodystrophy, but also cerebrotendinous xanthomatosis, and X-linked adrenoleukodystrophy, can show a combination of spastic paraparesis and movement disorders [20].

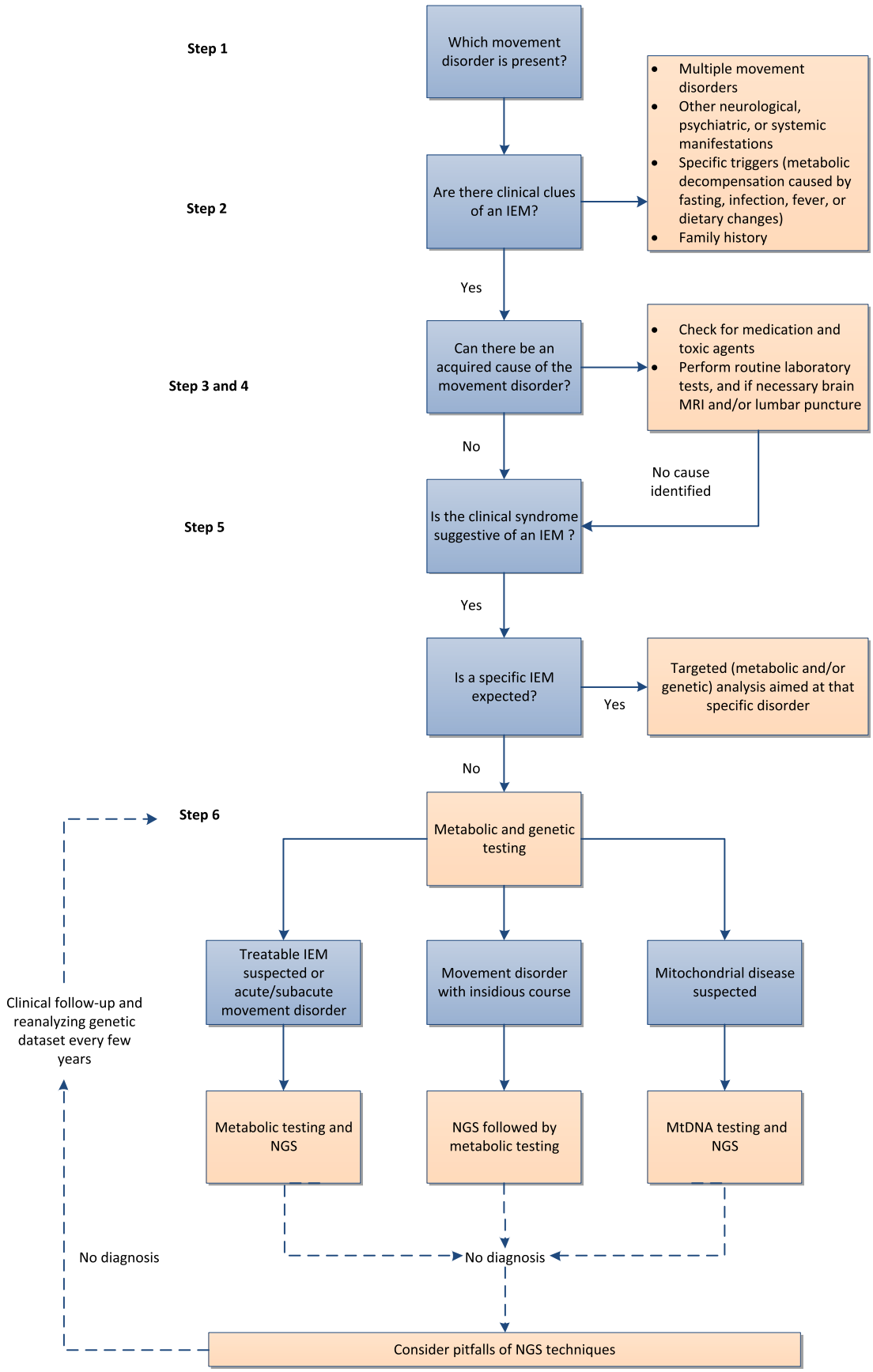

Fig. 1. Six consecutive steps to diagnose an inborn error of metabolism in patients with a movement disorder. Abbreviations: IEM, inborn error of metabolism; MtDNA, mitochondrial DNA; NGS, next-generation sequencing.

3.3.6. Stroke and stroke-like episodes

Ischemic strokes have been found in urea cycle disorders, homocystinemia, and Fabry disease [14] (which are not primarily associated with movement disorders), while stroke-like episodes are especially frequent in mitochondrial disorders, for example in mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) [21]. Unlike strokes, which cause acute neurological deficits associated with the affected arterial territory, stroke-like episodes often present with more diffuse neurological symptoms, for example encephalopathy, seizures, confusion, and headache.

3.3.7. Psychiatric symptoms and cognitive decline

In adolescents and adults, psychiatric symptoms may be the only symptom of an IEM for years [22]. Symptoms include behavioral disturbances, catatonia, psychosis, hallucinations, and depression. There is often an acute onset combined with other symptoms, such as gastrointestinal complaints, coma, and autonomic failure. Urea cycle disorders, homocysteine remethylation defects, and porphyrias are the main causes of this [22]. Movement disorders are not a prominent sign in this group of IEMs. Other IEMs are associated with chronic psychiatric symptoms, such as lysosomal storage disorders and metal storage disorders, and patients often present with a combination of psychiatric symptoms and a movement disorder. Treatment of psychiatric manifestations caused by an IEM can be difficult, and a paradoxical response to anti-psychotic drugs can serve as an important clue for IEMs [23]. Furthermore, movement disorders are often wrongly attributed to side effects of antipsychotic drugs [24].

Cognitive impairment is frequent in IEMs, including early-onset mental retardation [22], but also development of cognitive decline later in life, leading to difficulties in finishing school or problems at work [7,25].

3.3.8. Ocular disease and other systemic manifestations

Abnormalities of the eyes are frequently seen in IEMs, and may even lead to loss of vision [26]. Different parts of the eye can be involved, including cornea, lens, retina, and optic nerve. The most common form of lens involvement is cataract, such as seen in cerebrotendinous xanthomatosis. Corneal involvement is frequent in Wilson's disease: patients can show a Kayser-Fleischer ring in which copper deposits form a ring in the cornea. Retinitis pigmentosa is frequent in mitochondrial disorders, and a "cherry-red spot", is a feature of many lysosomal disorders, also in adults. Finally, optic neuropathy is seen in patients with mitochondrial disorders, pyruvate dehydrogenase deficiency, and a number of leukodystrophies [26,27].

Many other organs can be involved in IEMs. Organomegaly, and in particular hepatosplenomegaly, is a frequent symptom in patients with lysosomal storage disorders and peroxisomal disorders. Xanthomata of the Achilles tendons are a specific sign of cerebrotendinous xanthomatosis, and are easily seen during the neurological examination.

3.4. Specific triggers and acute onset of movement disorders

Patients with an underlying IEM can deteriorate fast under certain circumstances, for example during intercurrent illness, fever, state of catabolism, dietary changes, or excessive exercise. Early recognition and treatment may have a big impact on the outcome.

Presenting symptoms can consist of rhabdomyolysis, or be more aspecific, including vomiting and loss of appetite, behavioral changes and subsequently encephalopathy, seizures, and coma. Hyperammonemia, metabolic acidosis, and hypoglycemia are the most observed biochemical abnormalities in these acute presentations. One must be aware of the fact that this can occur in adults, and not only in children [28,29].

Many IEMs can present with acute movement disorders, although this is more frequent in the early-onset than in the late-onset forms. Examples include mitochondrial disorders and organic acidemias, such as glutaric aciduria type 1, in which movement disorders can be triggered by for example viral infections. This is also the case for patients with a late-onset form of biotin-thiamine-responsive basal ganglia disease, leading to a Wernicke-like encephalopathy, including ataxia, status epileticus, and eye movement abnormalities [30]. Rapid onset of symptoms is also described in adult patients with metachromatic leukodystrophy and X-linked adrenoleukodystrophy.

Paroxysmal movement disorders are also described. Exercise-induced movement disorders are frequent in patients with GLUT-1 deficiency, in which the onset of other symptoms (psychomotor retardation and epilepsy) is often earlier in life [31]. Other IEMs that can present with paroxysmal movement disorders in adolescence or adulthood are Wilson's disease, neurotransmitter disorders, and pyruvate dehydrogenase deficiency [3,14].

3.5. Family history

Consanguinity is a risk factor for genetic disorders, and therefore for IEMs. Mitochondrial disorders can be maternally inherited.

3.6. Step 3 – Can there be an acquired cause of the movement disorder?

Before considering a metabolic disorder as the cause of the movement disorder, other acquired causes must be excluded. Movement disorders are frequently medication-induced [32]. Other important toxic causes include alcohol consumption or withdrawal, and substance abuse. Supplementary Appendix II contains an overview of drugs and toxic agents that can induce or exacerbate movement disorders. It is not always possible to completely exclude an acquired movement disorder due to toxins or drugs in patients with an IEM, as exposure to drugs can occur on a background of an IEM, in particular in patients with psychiatric symptoms.

Other acquired disorders that need to be considered in the differential diagnosis of late-onset movement disorders include neurodegenerative diseases and para-infectious, autoimmune, or paraneoplastic disorders. The latter can present with a variety of symptoms, including movement disorders and psychiatric symptoms. Anti-NMDAR receptor encephalitis is the most common [33], and is important to recognize because treatment is possible [34].

3.7. Step 4 – General additional investigations

3.7.1. Laboratory tests and CSF examination

Table 1 presents an overview of general blood tests recommended in patients with a movement disorder. Organ dysfunction can cause derangements of homeostasis that leads to movement disorders, for example myoclonus or tremor in liver failure. A general blood test may also point into the direction of an underlying IEM: elevated ferritin is found in aceruloplasminemia and hemochromatosis, whereas a low ferritin can be found in neuroferritinopathy.

CSF examination can be performed if an acquired cause of the movement disorder is suspected (infection, auto-immune/paraneoplastic disorder, or prion disease), but can also help to diagnose an IEM.

Table 1
General blood tests to perform in patients with a movement disorder.

General blood tests	
Blood	White blood cell count, C-reactive protein, Hb, MCV, MCH, thrombocytes, electrolytes, iron, ferritin, transferrin, cholesterol, LDL, HDL, triglycerides, glucose, HbA1c, ALT, GT, LD, ALP, CK, bilirubin, urea, uric acid, creatinine, TSH, fT3, fT4, parathyroid hormone, vitamin B12, methylmalonic acid, folate, vitamin D, vitamin E, ammonia, copper, ceruloplasmin, lactate

3.7.2. Brain MRI

Brain MRI can be necessary to exclude an acquired cause of a movement disorder, but can also be very helpful when an IEM is suspected. Some IEMs have striking MRI abnormalities, for example abnormalities of the white matter in patients with leukodystrophies [35]. In patients with PKAN an "eye-of-the-tiger" sign can be seen, which is caused by the accumulation of iron in the globus pallidus, and in patients with Wilson's disease a "face-of-the-giant-panda" sign can be found [36]. However, many MRI abnormalities in IEMs are not very specific, including atrophy and (vascular) white matter lesions, and may overlap with other more common disorders. Moreover, little is known about MRI abnormalities in late-onset IEMs. An overview of MRI-abnormalities can be found in Table 2.

The recommended brain MRI protocol encompasses T1-weighted and T2-weighted imaging, fluid-attenuated inversion recovery (FLAIR), and susceptibility weighted imaging (SWI) to asses iron accumulation. The role of diffusion-weighted imaging (DWI) is not clear, altered diffusion may be found in some early-stage leukodystrophies or acute metabolic derangements [66]. MR spectroscopy (MRS) can be used to investigate the presence of certain metabolites in the brain, for example lactate in mitochondrial disease.

3.8. Step 5 – Is the clinical syndrome suggestive of an IEM?

The combination of a movement disorder, associated neurological, psychiatric, or systemic features, and findings during additional investigations can increase the suspicion of an underlying IEM.

Sometimes the clinical phenotype is characteristic of an IEM, for

Table 2
MRI brain abnormalities in IEMs that present with late-onset movement disorders.

Metabolic disorder	MRI abnormalities
Niemann-Pick type C	Initially normal, global atrophy and white matter lesions later in disease. Reduced midbrain-pons ratio [37].
Gaucher disease	Mild cerebral atrophy, non-specific periventricular white matter abnormalities, abnormalities of the thalami and/or the dentate nuclei [38].
Tay-Sachs disease	Lamellar cerebellar atrophy and generalized cerebral atrophy in late-onset forms [39,40].
Sandhoff disease	Cerebellar and generalized cerebral atrophy in late-onset forms [40].
GM1 gangliosidosis	Bilateral hyperintensities of caudate nucleus and posterior putamen on T2 weighted images [41].
Neuronal ceroid lipofuscinosis (Kufs disease and Parry type)	Diffuse cerebral atrophy, cerebellar atrophy, leukoencephalopathy, and thalamic T2 hypointensities [42].
Sialidosis type 1	Initially normal, atrophy (more pronounced in the cerebellum, vermis atrophy) later in disease [43].
Galactosialidosis	Initially normal, atrophy (more pronounced in the cerebellum, vermis atrophy) later in disease [44,45].
Metachromatic leukodystrophy	Bilateral symmetrical confluent areas of periventricular deep white matter abnormalities. Anterior lesions with sparing of the subcortical U fibers leading to a butterfly pattern in patients with later onset disease. Cortical and subcortical atrophy [46].
Krabbe disease	In late-onset disease parieto-occipital periventricular white matter abnormalities and posterior corpus callosum signal changes on T2 weighted images. Sparing of the subcortical U-fibers and cerebellar white matter. Sometimes isolated corticospinal tract abnormalities [47].
Cerebrotendinous xanthomatosis	Cerebral and cerebellar white matter lesions, including the dentate nuclei. Cerebral and cerebellar atrophy [48].
Polyglucosan body disease	Deep white matter lesions, often stretching out to the cervical-medullary junction. Cerebral, cerebellar, and spinal cord atrophy [49].
Wilson's disease	Abnormal T2 hyperintensity in the putamina and the deep gray nuclei. Face of the giant panda sign on axial images caused by involvement of the midbrain tegmentum. Miniature panda sign on axial T2 of the pons [50].
Pantothenate kinase-associated neurodegeneration	Eye of the tiger sign (low T2 signal in combination with a central strip of high signal) [50].
PLA2G6-related dystonia-parkinsonism	Cerebellar hypoplasia, high T2 signal in the cerebellum [50].
Ataxia with vitamin E deficiency	Cerebellar atrophy, sometimes high T2 spots in the periventricular region and the deep white matter [51].
Aceruloplasminemia	Hypointense basal ganglia, thalamus, red nucleus, occipital cortex, and dentate nuclei on T2 weighted images [50].
Hemochromatosis	SWI abnormalities of the basal ganglia, choroid plexus, anterior pituitary gland, pineal gland, and area postrema [52].
Syndrome of liver cirrhosis, dystonia and hypermanganesemia	T1 hyperintensities of the basal ganglia, sparing of the thalamus and ventral pons. White matter abnormalities and anterior pituitary involvement later in disease [53].
Neuroferritinopathy	Cystic lesions in the basal ganglia, bilateral pallidal necrosis. Hypointense basal ganglia and red nuclei on T2. Mild cortical atrophy [50].
Propionic acidemia	Delayed myelination, white matter abnormalities, cerebellar hemorrhage, and cerebral atrophy. (Paroxysmal) basal ganglia abnormalities during acute decompensation [54].
Phenylketonuria	Progressive white matter abnormalities starting in the periventricular and parieto-occipital regions, involvement of the subcortical white matter later in disease. Atrophy [55].
L-2-hydroxyglutaric aciduria	Bilateral and symmetrical leukoencephalopathy, first affecting the subcortical U fibres. The deep white matter is initially preserved. Basal ganglia abnormalities, cerebellar vermis atrophy [56].
Glutaric aciduria type 1	T2 hyperintensity and volume loss in the striatum. Isolated signal changes of the globus pallidus. White matter changes, wide CSF spaces anterior to the temporal poles and in the Sylvian fissures, transient subependymal nodules (in late-onset forms) [57].
Phosphomannomutase 2 deficiency (PMM2-CDG-1A)	Cerebellar atrophy, sometimes also supratentorial atrophy [58].
Zellweger spectrum disorders	Hypomyelination, cortical gyral abnormalities, and germinolytic cysts [59].
2-methyl acyl-CoA racemase deficiency (AMACR deficiency)	Degeneration of cerebellar afferents and efferents, including the dentatothalamic tract, with high T2 signal of the thalami, midbrain, and pons [60].
Leukoencephalopathy-dystonia-motor neuropathy syndrome	Bilateral hyperintense signals in the thalamus, butterfly-like lesions in the pons, and lesions in the occipital region [61].
X-linked adrenoleukodystrophy	Spinal cord atrophy (mainly thoracic segment) with normal brain MRI. In adults with the cerebral form: high signal on T2 weighted images in the parieto-occipital white matter, splenium, and visual and auditory pathways. Sometimes involvement of the corticospinal tract [46].
Dopa-responsive dystonia, classic Segawa	Normal [62].
Dopamine transporter deficiency syndrome	Normal [63].
Mitochondrial diseases	Depends on the specific disorder. Heterogeneous abnormalities, including white matter lesions (often symmetrical), abnormalities of the basal ganglia, focal atrophy of the cortex or cerebellum [64].
Pyruvate dehydrogenase E2 deficiency	Symmetrical T2 hypointensities in the globus pallidi [65].
Coenzyme Q10 deficiency	Normal to cerebellar atrophy [66].

example when a patient presents with a combination of movement disorders, vertical supranuclear gaze palsy, and gelastic cataplexy. This strongly points in the direction of Niemann-Pick type C. In other patients the combination of a finding during the neurological examination and a positive family history is suggestive of an IEM, for example in the case of dopa-responsive dystonia. In the latter, a diagnostic trial of levodopa can be performed to make this diagnosis more likely [67]. In other disorders, the combination of a movement disorder and abnormalities in laboratory tests or brain MRI may give the most important clue. This is the case in metal storage disorders and leukodystrophies.

Unfortunately, the clinical syndrome of many IEMs, and especially late-onset IEMs, is often not specific for a particular IEM. Although a spot diagnosis is possible in a few of the aforementioned cases, this is more difficult in many other disorders, so that further investigations are needed.

3.9. Step 6 – Metabolic testing and genetic testing

Historically, IEMs were tested only through biochemical procedures, but nowadays NGS strategies take a prominent place in the diagnostic procedures of IEMs. NGS uses massive parallel sequencing, and with these new technique the coding regions of every gene (whole exome sequening (WES)) or the whole genome (whole genome sequencing (WGS)) can be analyzed. Because IEMs are genetic disorders, they can be approached as such with regard to diagnostic procedures.

3.9.1. A specific IEM is suspected: targeted analysis

When the clinical syndrome is suggestive of a specific metabolic disorder, it is recommendable to perform a targeted analysis aimed at that specific disorder.

3.9.2. Treatable IEMs and acute or subacute movement disorders: metabolic testing and NGS

In acute or subacute movement disorders or when a treatable IEM is suspected, biochemical testing should be done first to recognize a treatable IEM as fast as possible (Table 3). This is still the fastest method to obtain test results in many laboratories. As mentioned before, hyperammonemia, metabolic acidosis, and hypoglycemia are the most frequently observed biochemical abnormalities in acute neurological deterioration caused by IEMs. They can be diagnosed with a routine blood test complemented with a blood gas, electrolytes to calculate the anion gap, and lactate. Metabolic tests in movement disorder emergencies include organic acid analysis, amino acid analysis, and acylcarnitine profiling [68].

Table 4 presents metabolic tests for treatable late-onset IEMs that can present with movement disorders.

3.9.3. Insidious course movement disorders: NGS followed by metabolic testing

In patients with an insidious course of the movement disorder, we recommend genetic testing with NGS as the first choice. If the clinical suspicion is not focused on a specific IEM, the first-tier approach is targeted-panel NGS based on specific symptoms, for example a movement disorder panel [72]. When a variant of unknown significance is found, the interpretation whether it is pathogenic or not can be difficult, as little information is available about the clinical phenotype of many late-onset IEMs. This is particularly the case for heterozygous mutations that can cause classical IEMs in adults, due to dominant negative effects of these mutations [73]. Close collaboration between neurologists and geneticists is therefore essential. In those cases, biochemical tests can be performed in addition to NGS. This can be done in a targeted approach aimed at confirming the involvement of a specific gene.

Table 3
Laboratory tests in acute movement disorders focused on IEMs (adapted from Blau et al. [68]).

Laboratory tests	
Blood	Complete blood count, C-reactive protein, electrolytes, liver and kidney function tests, blood gas, electrolytes for anion gap, lactate, glucose, ammonia, uric acid, CK, metabolite tests, acylcarnitines, amino acids
Urine	Ketones, glucose, protein, organic acids

3.9.4. Analyzing mitochondrial DNA

IEMs can also be caused by mutations in mitochondrial DNA. It is important to keep in mind that mitochondrial DNA analysis is not included in nuclear DNA based NGS panels, and needs to be requested separately. Mitochondrial DNA can be tested in peripheral blood, although the diagnostic yield is lower than DNA obtained from other tissue, such as renal cells voided in urine, or muscle [74].

3.9.5. Advantages of NGS

NGS has several advantages above biochemical testing, in particular in late-onset IEMs. First, the results of NGS are more robust than biochemical tests, where more variation exists and cut-off values are not always available. The predictive power of biochemical tests in adults may be lower than in children because the biochemical defect may be less severe, and thus can be more difficult to detect [75]. Second, with the introduction of NGS it is possible to analyze many genes simultaneously. In particular in heterogeneous conditions like IEMs, the use of NGS is efficient and has led to more and unexpected diagnoses [76]. Testing multiple genes at the same time is not only faster than consecutively testing all genes, but also cost-effective [76,77].

4. Discussion

We present a modern approach to detect and diagnose an IEM in adolescents and adults presenting with a movement disorder in the (outpatient) clinic. Detailed clinical phenotyping remains the cornerstone of this approach. However, other than in earlier presented algorithms for metabolic disorders, we approach IEMs as primary genetic disorders in which NGS is the first choice, as in the majority of genetic disorders. Only in emergencies or when a treatable IEM is suspected as the cause of the movement disorder, biochemical tests can be performed first or in parallel with NGS to get a diagnosis as fast as possible.

The distinction between a metabolic and non-metabolic genetic disorder is not always possible based on clinical grounds alone. Non-metabolic genetic disorders may also present with a combination of movement disorders and other manifestations. In clinical practice, a NGS gene panel for movement disorders that contains genes of both metabolic and non-metabolic disorders will be applied in patients with these combined phenotypes.

There are a few pitfalls when using NGS. Large structural rearrangements are missed due to technical reasons. Mutations in promoter regions, intronic regions, and repeat expansions are also not detected by exome sequencing, and mitochondrial DNA is not always tested in these exome based gene panels. Finally, when a likely pathogenic variant or a variant of unknown significance is present in a gene that could explain the phenotype, further investigations are necessary, such as targeted biochemical tests. If all these considerations are kept in mind, and still no diagnosis is found, clinical follow-up of the patient is recommended. Because new movement disorder genes are reported frequently, reanalyzing the patient's genetic dataset every few years may eventually lead to a diagnosis [78].

This review has some limitations. IEMs are rare disorders, and late-onset variants are even more rare. This means that on average limited information is available about the exact phenotype and clinical spectrum. The description of a part of the late-onset IEMs in this review is based on only a few published patients, so information about the phenotype might be incomplete, and there might be a publication bias when it comes to more severe or unusual phenotypes. Moreover, the list of late-onset IEMs that present with movement disorders may not be

Table 4
Laboratory tests in treatable late-onset IEMs that can present with movement disorders.

	Blood	Urine	CSF
Niemann-Pick type C [69]	Oxysterols, lysosphingolipids		
Gaucher disease	Chitotriosidase, Beta-D-glucosidase activity in leukocytes		
Galactosialidosis	Galactitol, Beta-galactosidase enzyme activity in leukocytes, neuraminidase activity in leukocytes	Oligosaccharides	
Metachromatic leukodystrophy	Arylsulfatase A activity in leukocytes	Sulphatides	Protein
Krabbe disease	GALC activity in leukocytes		Protein
Cerebrotendinous xanthomatosis	25-Hydroxy vitamin D, cholestanol, cholesterol	Specific bile alcohols	
Wilson's disease [70]	Copper, ceruloplasmin	Copper in 24 h urine	
Ataxia with vitamin E deficiency	Vitamin E (α-tocopherol)		
Aceruloplasminemia	Ceruloplasmin, copper, iron, ferritin		
Propionic acidemia	Propionylcarnitine, glycine, glutamine, carnitine, propionyl-CoA carboxylase activity in leukocytes	3-OH-propionic and methylcitric acids, acylcarnitines, glycine	Glutamine, glycine
Phenylketonuria (untreated)	Phenylalanine, phenylalanine/tyrosine ratio	Phenylalanine, phenylpyruvic acid	5-Hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA), phenylalanine
Glutaric aciduria type 1 [71]	Glutaric acid, 3-OH-glutaric acid, carnitine, acylcarnitines, GCDH activity in leukocytes	Glutaric acid, 3-OH-glutaric acid, carnitine, acylcarnitines	
X-linked adrenoleukodystrophy	Very long chain fatty acids (VLCFA)		
Dopa-responsive dystonia, classic Segawa disease	Phenylalanine, GTPCH1 activity (in phytohemagglutinin stimulated mononuclear blood cells)		Biopterin, neopterin, 5-Hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA)
Pyruvate dehydrogenase E2 deficiency	Lactate, pyruvate, lactate/pyruvate ratio, ketones, alanine	Ketones	
Coenzyme Q10 deficiency	Lactate, albumin, acylcarnitines, carnitine, NADH-cytochrome *c* reductase activity, succinate cytochrome *c* oxidoreductase activity	Acylcarnitines, glutaric acid, dicarboxylic acids, lactate	

complete as IEMs in adults are still overlooked. Applying our systematic approach and performing genetic testing will increase the recognition of IEMs in adult patients who present with a movement disorder, also in patients with milder or unusual phenotypes.

Over time, more and more IEMs will be included in newborn screening programs, and this will affect the prevalence of late-diagnosed disease in the long term as well. However, given the fact that IEMs can be diagnosed up to late age, this means that the impact of screening on prevalence in adults is likely to be negligible in the coming decades. What becomes more relevant is that through newborn screening more children will need follow-up as adults, for instance patients with glutaric aciduria type I with insidious onset of dystonia despite screening. Therefore adult neurologists need to be trained to take care of these patients.

To conclude, we propose a modern diagnostic approach that includes genetic testing to increase the recognition of metabolic disorders in adolescent and adult patients presenting with a movement disorder. Early recognition of IEMs is important, especially in late-onset patients because their symptoms are usually milder than in patients with early-onset disease. Therefore, patients with late-onset IEMs likely benefit most from timely treatment [79]. Furthermore, recognition and adequate classification of movement disorders is not only important because it can serve as a clue to the diagnosis of IEMs, but symptomatic treatment of the movement disorder itself can also improve quality of life [80,81].

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2021.02.029.

Ethical compliance statement

The authors confirm that the approval of an institutional review board was not necessary for this review paper. There was no human or animal research in this review study. Informed consent was not necessary.

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