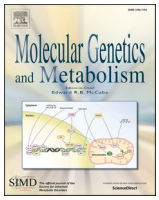
Molecular Genetics and Metabolism 145 (2025) 109084

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme



Research Paper

Clinical and biochemical footprints of inherited metabolic diseases: Ia. Movement disorders, updated

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ARTICLE INFO

Keywords:
Movement disorders
Inborn errors of metabolism
ataxia
Dystonia
Myoclonus
Parkinsonism

ABSTRACT

Movement disorders are a common manifestation of inherited metabolic diseases (IMDs), categorized into hyperkinetic movement disorders, hypokinetic-rigid syndromes, ataxia, and spasticity. We reviewed and updated the list of known metabolic disorders associated with movement disorders, identifying a total of 559 IMDs. We outlined the more common and treatable causes, sorted by the dominant movement disorder phenomenology, and provided a practical clinical approach for suspected IMDs presenting with movement disorders. This work represents an updated catalog in a series of articles aimed at creating and maintaining a comprehensive list of clinical and metabolic differential diagnoses based on system involvement.

1. Introduction

Inherited metabolic disorders (IMDs) are monogenic diseases that disrupt key biochemical processes through aberrant enzymatic activity, impaired cellular transport, or mitochondrial dysfunction. The basal ganglia, being highly metabolically active regions of the central nervous system, are particularly vulnerable to metabolic insults [1,2]. A prior study involving 38 patients with movement disorders aged 0 to 84 years (mean: 31 years) found that 9.3 % of these patients had an underlying metabolic etiology, while an IMD was identified in 22 % of the pediatric subset [3]. Consequently, IMDs causing movement disorders bridge two subspecialty areas: "movement disorders" and "inherited metabolic disorders."

With many disease-modifying therapies emerging for IMDs, early diagnosis is imperative. However, this can be challenging for treating physicians, as many of these conditions are rare or even exceptionally rare. Therefore, we are providing an update to our previously published high level overview of IMDs presenting with movement disorders [4]. Key updates include an expanded catalog of IMDs and a detailed clinical review of disorders seen more often in our practice, with specific emphasis on treatable conditions. This review offers a readily accessible list of IMDs categorized by movement disorder phenomenology.

Abbreviations: AAV, Adeno-associated virus; AMN, Adrenomyeloneuropathy; CALD, Cerebral adrenoleukodystrophy; CLN3, Ceroid lipofuscinosis type 3; cPMP, Cyclic pyranopterin monophosphate; GLUT1-DS, Glucose transporter type 1 deficiency syndrome; GTPCH1 deficiency, GTP cyclohydrolase 1 deficiency; HSCT, Hematopoietic stem cell transplantation; HHH, Hyperornithinemia-hyperammonemia-homocitrullinuria; HRS, Hypokinetic-rigid syndrome; IMD, Inborn metabolic disorder; RNAi, Interfering RNA; ICIMD, International Classification of Inherited Metabolic Disorders; LD, Lafora disease; MLD, Metachromatic leukodystrophy; MELAS, Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes; MPS, Mucopolysaccharidosis; MERRF, Myoclonic epilepsy with ragged red fibers; NBIA, Neurodegeneration with brain iron accumulation; NCL, Neuronal ceroid lipofuscinosis; NPC, Niemann-Pick type C; PKAN, Pantothenate kinase-associated neurodegeneration; LD, Progressive myoclonic epilepsy, Lafora type; PKAN, Pantothenate kinase-associate neurodegeneration; PBD, Peroxisome biogenesis disorder; EPM1, Progressive myoclonic epilepsy type 1; PDHc, Pyruvate dehydrogenase complex; PDHA1 deficiency, Pyruvate dehydrogenase E1-alpha deficiency; RCDP1, Rhizomelic Chondrodysplasia Punctata type 1; ZSD, Zellweger spectrum disorder.

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https://doi.org/10.1016/j.ymgme.2025.109084
Received 20 December 2024; Received in revised form 6 March 2025; Accepted 7 March 2025
Available online 18 March 2025

Table 1
Clinical manifestations and symptoms reported in IMDs associated with movement disorders, based on the six most frequently affected groups.

Ataxia	%	Spasticity	%	Dystonia	%
Ataxia	76.8	Spasticity	50.8	Dystonia	84.0
Cerebellar ataxia, non-progressive	7.1	Pyramidal signs	18.4	Opisthotonus	4.4
Dysmetria	4.2	Spastic paresis	7.3	Oculogyric crisis	3.9
Gait ataxia	4.0	Spastic paraparesis/ paraplegia/ tetraplegia	5.7	Action dystonia	1.7
Dysdiadochokinesis	2.8	Spasticity, limbs	3.8	Dystonic cerebral palsy	1.7
Truncal ataxia	1.4	Spastic paraparesis	3.5	Dystonic crisis	1.1

Chorea / Athetosis	%	HRS	%	Other	%
Athetosis	41.6	Parkinsonism	40.3	Movement disorder	25.2
Choreoathetosis	32.7	Hypokinesia	15.6	Gait disturbance	23.2
Chorea	21.8	Bradykinesia	14.3	Dyskinesia	14.8
Ballismus	2.0	Stiffness	10.4	Extrapyramidal movement disorder	8.4
Orofacial dyskinesia	1.0	Parkinsonism, hypokinetic features	6.5	Cerebral palsy	6.5
Orolingual/ facial dyskinesia	1.0	Hypomimia	5.2	Hyperkinesia	5.2

2. Materials and methods

The source of the information was IEMbase, the knowledge base of IMDs (http://www.iembase.org) [5]. As of August 2024, IEMbase catalogs 1956 IMDs and 4444 corresponding clinical and biochemical signs and symptoms, grouped into 22 organ and system categories: Autonomic, Cardiovascular, Dental, Dermatological, Digestive, Dysmorphic, Ear, Endocrine, Eye, Genitourinary, Hair, Hematological, Immunological, Metabolic, Muscular, Neurologic, Psychiatric, Kidney, Respiratory, Skeletal, Tumoral, and Other. The clinical symptoms associated with movement disorders (n = 559) were extracted from the Neurologic group. The nosology of IMDs [6] was reclassified according to the International Classification of Inherited Metabolic Disorders (ICIMD) [7].

We categorized the signs and symptoms of metabolic diseases presenting with movement features as follows: Ataxia, Dystonia, Chorea / Athetosis, Myoclonus, Tremor, Hypokinetic-Rigid Syndrome (HRS), Spasticity, and Other (Supplemental Table S1).

3. Results

The most commonly reported movement phenomenology was ataxia, identified in 278 out of 559 (50 %) disorders, followed by spasticity in 273 out of 559 (49 %), dystonia in 166 out of 559 (30 %), chorea and athetosis in 64 out of 559 (11 %), tremor in 53 out of 559 (9 %), hypokinetic-rigid syndrome (HRS) in 51 out of 559 (9 %), and myoclonus in 33 out of 559 (6 %). Approximately 26 % of disorders exhibited other movement phenomenologies. 47 % of disorders exhibit a single phenotype, while 54 % present with multiple movement phenotypes: 32 % have 2 phenotypes, 12 % have 3, 6 % have 4, 4 % have 5, and two disorders, GDH and SLC6A3 (0.4 %), are associated with 6 phenotypes.

In the “Ataxia” group, the most reported movement symptoms included ataxia (77 %), non-progressive cerebellar ataxia (7 %), dysmetria (4 %), and gait ataxia (4 %). In the “Spasticity” group, the predominant symptoms were spasticity (51 %), pyramidal signs (18 %), spastic paresis (7 %), spastic paraparesis/paraplegia/tetraplegia (6 %), and spasticity of the limbs (4 %). In the “Dystonia” group, the main symptoms were dystonia (84 %), opisthotonus (4 %), oculogyric crisis (4 %) and dystonic cerebral palsy (2 %). In the “Chorea and Athetosis” group, the most common symptoms were athetosis (42 %), choreoathetosis (33 %), and chorea (22 %). In the “HRS” group, the most reported symptoms were parkinsonism (40 %), hypokinesia (16 %), and bradykinesia (14 %). In the “Other” group, the most frequently reported movement symptoms were movement disorder (25 %), gait disturbance (23 %), and dyskinesia (15 %) (Table 1; also refer to Fig. 1 and Supplemental Table S1). Our updated database of IMDs presenting with

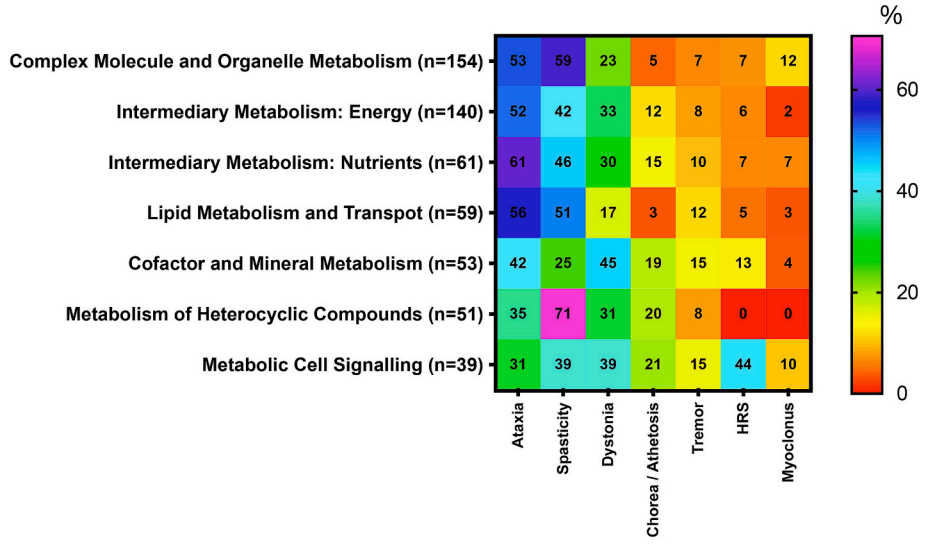

Fig. 1. Occurrence (%) of symptoms associated with 559 disorders presenting with movement phenotype in 7 categories of IMDs. The percentages for movement abnormalities were calculated using as the denominator the total number of IMDs in each category presenting with any with movement phenotype. Heat scale ranges from red (0 %) for diseases with no particular symptoms reported to violet (100 %) for diseases with particular symptoms occurring with highly frequency within the disorders group. For definition of 7 categories of movement symptoms see Supplemental Tables S1 and S2. For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Focussed differential diagnosis of inborn metabolic disorders presenting with movement disorders sorted by typical dominant movement disorder phenomenology. Emphasis is on more common or treatable conditions.

Ataxia	Dystonia	Myoclonus	Hypokinetic-rigid syndrome	Spasticity
Pyruvate dehydrogenase E1-alpha deficiency	Dopa-responsive dystonia	Neuronal ceroid lipofuscinosis	Dopa-responsive dystonia	ARG1-associated arginase 1 deficiency
Thiamine pyrophosphokinase deficiency	Glutaric aciduria type 1	Mitochondrial disorders: POLG, MELAS, MERRF	Niemann-Pick type C	SLC25A15-associated hyperornithinemia-hyperammonemia-homocitrullinuria syndrome
Ataxia with Vitamin E deficiency	Pantothenate kinase-associated neurodegeneration	Lafora disease	Neuronal ceroid lipofuscinosis	Molybdenum cofactor deficiency
Niemann-Pick disease type C	Wilson disease	Unverricht-Lundborg disease	Mucopolysaccharidosis	X-linked adrenoleukodystrophy
Maple syrup urine disease	Methylmalonic acidemia		GM1 gangliosidosis	Sandhoff disease
Succinic semialdehyde dehydrogenase deficiency	Proprionic acidemia		Tay-Sachs disease	Metachromatic leukodystrophy
Zellweger spectrum disorders	Mitochondrial disorders		Morquio syndrome	Krabbe disease
Congenital disorders of glycosylation	Lesch-Nyhan disease			
Glucose transporter 1 deficiency syndrome				

Abbreviations: POLG, polymerase gamma related disorder; MELAS, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers.

movement disorders is included in Supplemental Table S2. In addition, Table 2 lists a suggested differential diagnosis of IMDs to consider when presented with a patient experiencing movement disorder sorted by the most typical dominant movement phenotype. Below is a description of each entry.

3.1. Ataxia

Ataxia refers to the inability to perform or maintain an expected movement trajectory, manifesting as a lack of coordination. Cerebellar ataxia may clinically present with a syndrome that includes nystagmus, scanning speech, intention tremor, dysdiadochokinesia, dysmetria, and/or truncal or gait ataxia. The cerebellum is particularly sensitive to neurometabolic and neurodegenerative pathology, leading to a broad list of IMDs that may present with either intermittent ataxia, chronic or progressive ataxia, or ataxia accompanied by myoclonic epilepsy. These disorders typically manifest with a combination of ataxia, pyramidal signs, extrapyramidal symptoms, and/or cognitive concerns, although pure cerebellar presentations are also possible [8].

Pyruvate dehydrogenase E1-alpha (*PDHA1*) deficiency is one cause of primary pyruvate dehydrogenase complex deficiency. Patients with this condition present with a Leigh-like syndrome: intermittent ataxia, dystonia, microcephaly, hypotonia, and epilepsy. Neuroimaging may reveal asymmetric ventriculomegaly and corpus callosum dysgenesis; structural brain abnormalities are an atypical feature among treatable IMDs and its finding may delay diagnosis if a high degree of clinical suspicion is not maintained [9]. Ataxia is often precipitated by metabolic stressors such as fever. The standard therapy for this treatable form of Leigh disease includes the ketogenic diet, as patients do not metabolize carbohydrates effectively, and early initiation of the diet can improve developmental outcomes [10]. The pyruvate dehydrogenase complex requires thiamine as a cofactor, and so other variants leading to deficiency in its active form, thiamine phosphate, can present with a similar phenotype [11]. This may be caused by thiamine pyrophosphokinase (TPK) deficiency which is in turn caused by mutations in various genes including *TPK1* (thiamine pyrophosphokinase defieicny), *SLC19A3* (thiamine transporter; biotin-thiamine-responsive basal ganglia disease), or *SLC25A19* (mitochondrial thiamine phosphate carrier) [12–15]. This collection of pathologies lead to conditions that may present with a severe Leigh-like neurodegenerative disease that is fatal if untreated but may be amenable to high doses of thiamine with or without the ketogenic diet, depending on the etiology [16].

Ataxia with vitamin E deficiency typically manifests between the ages of 5 and 15, presenting with chronic progressive cerebellar ataxia, loss of proprioception, areflexia, and dystonia [17]. The diagnosis is established in individuals with a suggestive clinical presentation and findings of biallelic pathogenic variants in *TTPA* [18]. This disorder is treatable with lifelong high doses of vitamin E. When treatment is initiated in the presymptomatic stage, clinical manifestations of the disease may not develop [17,19]. Early clinical manifestations, such as mild ataxia and cognitive difficulties, can be reversed with treatment [20], but in older patients with significant disability, treatment will halt progression, although deficits may remain [17,21,22].

Niemann-Pick disease type C (NPC) is a neurodegenerative lysosomal disorder with a broad spectrum of clinical severity. Disease onset in early infancy is often primarily hepatic, presenting with jaundice and ascites [23]. When the onset occurs in late infancy or early childhood, symptoms include hypotonia, developmental delay, ataxia, supranuclear gaze palsy, and bulbar symptoms. Onset in adolescence or adulthood often presents with progressive cognitive deficits and psychiatric issues, with other neurological signs developing later. Gelastic cataplexy is a unique feature found in NPC and may be a strong clue to the diagnosis if observed [24]. A high index of clinical suspicion, aided by published clinical scoring tools [25], is crucial, as their neurological manifestations can be stabilized with miglustat treatment [26]. Two additional agents have recently received FDA approval for the management of NPC: arimoclomol and levacetylleucine. Arimoclomol is approved as an add-on therapy for patients using miglustat, based on a 2.2-point improvement at 12 months compared to placebo add-on therapy on the 4-domain NPC Clinical Severity Scale [27]. Levacetylleucine is approved as monotherapy for managing patients with NPC, demonstrating a 1.28-point improvement compared to placebo at 12 weeks on the Scale for Assessment and Rating of Ataxia; a rescored functional version of this scale showed a 0.4-point benefit over placebo [28].

Several other IMDs may present with ataxia with or without additional movement disorder phenomenologies. Maple syrup urine disease is caused by decreased activity of the branched-chain alpha-ketoacid dehydrogenase complex which catalyzes a key step in the degradation of the branched-chain amino acids, leading to accumulation of leucine, isoleucine, and valine [29]. During periods of acute illness, there can be buildup of these amino acids leading to toxic encephalopathy and symptomatic ataxia, dystonia, or parkinsonism [29]. Succinic semialdehyde dehydrogenase deficiency affects the degradation of gamma-aminobutyric acid, leading to buildup of gamma-aminobutyric acid in body fluids [30]. This leads to multiple movement disorders including ataxia, dystonia, chorea, and hypokinesia in addition to behavioral problems, impaired speech, and epilepsy [31]. Peroxisome biogenesis

disorders (PBD) are a group of conditions caused by a partial or generalized defect in peroxisome biogenesis. They encompass two phenotypic groups: 1. The Zellweger spectrum disorders (ZSD) including severe, intermediate and milder forms and 2. Rhizomelic Chondrodysplasia Punctata type 1 (RCDP1), as well as the variant phenotypes now being described for both groups [32]. Phenomenology of movement disorders in Zellweger spectrum disorders include cerebellar ataxia with adolescent- or adult-onset forms, in addition to ocular abnormalities, sensorineural hearing loss, craniofacial dysmorphic features, developmental delay, peripheral neuropathy, and pyramidal tract signs [33]. Congenital disorders of glycosylation are another heterogenous group of disorders that often present with ataxia, developmental delay, dysmorphic features, and additional systemic findings [34].

Glucose transporter type 1 deficiency syndrome (GLUT1-DS) is a disorder of insufficient glucose transport from serum to CSF caused by pathogenic variants in *SLC2A1* [35]. This presents with variable degrees of treatment resistant epilepsy with multiple seizure types including absence seizures before 4 years of age, acquired microcephaly, intellectual disability, and paroxysmal exertional dyskinesia [35,36]. The dyskinesia can manifest with various movement phenomenologies, including dystonia, chorea, and ataxia; it is typically brought on by fasting, prolonged exercise, or increased metabolic demand such as infection. Diagnosis is supported by identification of a pathogenic variant in *SLC2A1*, fasting hypoglycorrhachia with normal serum glucose, or by low uptake of 3-*O*-methyl-D-glucose in erythrocytes. The ketogenic diet, supplemented with L-carnitine, if serum carnitine levels become insufficient, is first line therapy to control seizures and abnormal movements and is often highly effective [37].

3.2. Dystonia

Dystonia is a hyperkinetic movement disorder characterized by sustained or intermittent muscle contractions, resulting in abnormal, often repetitive movements, postures, or both. These movements are typically patterned, twisting, and sometimes tremulous. Dystonia is often initiated or exacerbated by voluntary actions and is associated with overflow muscle activation [38]. Dystonia is classified along two axes: Axis I describes the clinical characteristics of dystonia, including age at onset, body distribution, temporal pattern, and associated features. In association with IMDs, dystonia often has an acute or subacute onset with a generalized, progressive course [39]. Axis II addresses etiology, encompassing inherited, acquired, and unknown causes [38]. Dystonia caused by IMDs can be broadly sorted into two groups: Neurotransmitter deficiencies such as dopa-responsive dystonia, and pathologies that injure the basal ganglia leading to symptomatic dystonia such as glutaric aciduria type I and pantothenate kinase-associated neurodegeneration.

Dopa-responsive dystonia represents a genetically and phenotypically heterogeneous group of neurotransmitter disorders characterized by a deficiency in dopamine synthesis without substantia nigral cell loss [40]. The most well-known example is autosomal-dominant GTP cyclohydrolase 1 (*GCH1* gene) deficiency, also known as Segawa syndrome. The typical presentation involves lower extremity dystonia that spreads over time to other limbs, often following a diurnal pattern. Adult-onset forms may also include parkinsonism [40]. Other rare recessive forms of dopa-responsive dystonia include sepiapterin reductase deficiency, tyrosine hydroxylase deficiency, and other monoamine neurotransmitter disorders. Classic dopa-responsive dystonia is readily treatable with low doses of levodopa/carbidopa, though some refractory cases with difficult motor control may benefit from deep brain stimulation [41].

Glutaric aciduria type I is a rare organic acid disorder that most commonly presents with infantile-onset encephalopathic crises and dystonia triggered by catabolic stressors [42]. Neuroimaging classically reveals widened sylvian fissures with a “bat wing” appearance and subdural collections; the latter, like in Menke’s disease, may mimic non-accidental injury and may therefore delay diagnosis [41,43]. This condition characteristically leads to bilateral striatal injury and subsequent dystonia [44,45]. Less common later-onset forms of the disease (i.e., those presenting after age 6) may manifest with headache, macrocephaly, seizures, tremor, and cognitive decline [46]. Newborn screening can measure glutarylcarnitine (C5DC) in dried blood spots, which has a diagnostic sensitivity of 95 % [29]. Episodes of encephalopathic crises can be prevented with a low-lysine diet, carnitine supplementation, and emergency treatment during crises to minimize the brain’s exposure to toxic metabolic compounds [42].

Pantothenate kinase-associated neurodegeneration (PKAN) is the most common type of neurodegeneration with brain iron accumulation (NBIA) and is caused by biallelic pathogenic variants in *PANK2*. Classic PKAN typically presents in early childhood with progressive generalized dystonia, prominent oromandibular dystonia, rigidity, and choreoathetosis [47]. Brain MRI classically reveals the “eye of the tiger” sign, which appears in the bilateral globus pallidus as a central region of hyperintensity surrounded by a rim of hypointensity [48]. Management of this degenerative condition is largely supportive, although there may be a role for bilateral internal globus pallidus (GPi) deep brain stimulation in the management of dystonia for select cases of PKAN [49].

Wilson disease is a treatable inherited disorder of copper metabolism that causes multiple abnormal movements and other neurological features, liver disease, and psychiatric symptoms. Dystonia is often the most severe and functionally disabling symptom [50] though tremor, parkinsonism, chorea, and ataxia can also be seen [51,52]. Dystonia in Wilson disease may present in the face with risus sardonicus or vacuous smile. With disease progression, dystonia may also spread and become generalized; status dystonicus can also occur [53]. Diagnosis is established with biallelic pathogenic variants in *ATP7B* or with a combination of clinical, biochemical, and molecular findings [54]. All individuals with Wilson disease are managed with reduction of dietary copper intake. Copper chelating agents such as D-penicillamine or trientine are indicated for treatment of symptomatic and asymptomatic patients with Wilson disease [55]. 10–20 % of patients receiving D-penicillamine or trientine experience transient neurological symptom worsening during initial phase of treatment which is thought to be due to transient increase in non-ceruloplasmin-bound copper [56]. Zinc salts may be used in some asymptomatic individuals to reduce copper absorption in the gastrointestinal tract, but not in combination with copper chelators. Orthotopic liver transplantation is indicated for some individuals who are not responsive or intolerant to medical treatment [55].

Additional IMDs causing dystonia secondary to basal ganglia injury include disorders of organic acid metabolism, such as methylmalonic acidemia and propionic acidemia [57]. Both of these are autosomal recessive disorders impacting the conversion of certain amino acids and odd-chain fatty acids to succinyl-CoA. In times of catabolic stress or excess protein intake, there can be buildup of toxic compounds which notably cause injury to the striatum in the case of propionic acidemia and globi pallidi in the case of methylmalonic acidemia. Patients experience acute and chronic dystonia, chorea, spasticity in addition to intellectual disability, epilepsy, and renal injury [58]. These disorders are treated by limiting natural protein intake, supplementation with levocarnitine, maintain a high calorie diet, and reduction of propionic acid production by gut bacteria such as with metronidazole [58]. Some forms of methylmalonic acidemia are also responsive to vitamin B12 supplementation [59].

Mitochondrial disorders are a broad category of pathology stemming from genetic variants in mitochondrial DNA or nuclear DNA leading to impairment in energy production. These disorders can manifest at any age and have very heterogeneous presentations. Due to impaired energy production, mitochondrial disorders preferentially impact tissues highly dependent on oxidative metabolism, including neural, muscular, and cardiac, hence the subcategory termed “mitochondrial encephalomyopathies” [60]. Neurological features include movement disorders such as dystonia and ataxia, epilepsy, stroke-like episodes, psychomotor

impact, and migraine [61]. Leigh syndrome is one example of a mitochondrial disorder presenting with a broad spectrum of movement disorders. This typically manifests between 3 and 12 months as metabolic decompensation from a catabolic stressor [62]. This leads to significant developmental delay or regression, hypotonia, spasticity, seizures, movement disorder, ataxia, peripheral neuropathy, and brainstem dysfunction [63].

Lesch-Nyhan disease is caused by deficient activity of hypoxanthine-guanine phosphoribosyltransferase 1 which leads to accumulation of hypoxanthine and guanine which is then converted to uric acid [64]. Patients present with severe dystonia, chorea, and spasticity; most are cognitively impaired and exhibit the hallmark finding of self-injurious behaviour; and the overproduction of uric acid leads to nephrolithiasis and gout [64,65]. Diagnosis is made by identification of a pathogenic variant in *HPRT1* or low hypoxanthine-guanine phosphoribosyltransferase 1 activity [64]. Symptoms are managed with allopurinol or febuxostat, in case of drug hypersensitivity to allopurinol, to reduce uric acid production, and treatment is otherwise supportive [66]. Some patients may benefit from DBS, however more research is needed [67].

3.3. Chorea/Athetosis

Chorea, derived from the Greek word *choreia*, meaning "dancing," refers to involuntary, brief and random movements that are neither stereotyped nor predictable. When chorea predominates in the proximal muscle groups leading to large amplitude movements, it is termed "ballismus," whereas when it predominates in the distal muscle groups and is slow and writhing, it is termed "athetosis."

The evaluation of chorea in a patient should be conducted carefully, as rapid, brief movements can also be observed in dystonias and tics. Additionally, slow choreiform movements are developmentally appropriate in infants up to around 12 months of age and can be triggered by excitement, anger, or frustration [68]. Although chorea is not typically the dominant movement disorder phenomenology associated with IMDs, it can be an important phenotype.

Nonketotic hyperglycinemia is a disorder of glycine metabolism that results in the accumulation of large quantities of glycine in all body tissues, including the brain. Eighty-five percent of patients present in the neonatal period with progressive lethargy evolving to coma and epilepsy; less severe forms may present in childhood with developmental delays and chorea [69]. Many affected infants make little to no meaningful developmental gains. Benzoate can be administered to reduce plasma glycine levels, and some infants may subsequently achieve spontaneous bottle feeding, visual attentiveness, and a social smile. Chorea, if present, is sometimes episodic and associated with febrile illness [70].

Chorea can develop after an encephalopathic crisis in glutaric aciduria type I [71], and these events can be prevented with dietary modifications, as previously described.

3.4. Myoclonus

Myoclonus is a brief (<100 ms) involuntary movement that can be classified as epileptic if originating from the cortex or as a movement disorder if originating lower in the neuraxis. While myoclonus is not typically the prominent movement disorder in IMDs, it is often present and may suggest underlying neurodegeneration.

Neuronal ceroid lipofuscinosis (NCL) is a genetically heterogeneous group of disorders characterized by a progressive clinical course that includes vision loss, dementia, epilepsy, and movement disorders. These lysosomal storage diseases are marked by progressive neurodegeneration with intracellular accumulation of autofluorescent lipopigments [72]. Management for most forms of NCL is largely supportive, although patients with CLN2 disease may benefit from disease-modifying therapy through intraventricular administration of cerliponase alfa, a proenzyme form of human TPP1, the deficient enzyme responsible for the pathophysiology of CLN2-related disease [72,73].

Various mitochondrial disorders can cause myoclonus, including POLG-related disorders, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), and myoclonic epilepsy with ragged red fibers (MERRF) [74–76]. Myoclonus is often challenging to manage in mitochondrial disease, and treatments should be tailored based on the origin of the myoclonus [77]. Valproic acid is contraindicated for treating myoclonus in most mitochondrial disorders, as it can exacerbate symptoms, particularly in POLG-related disorders, where it can trigger fulminant hepatic failure [78].

Progressive myoclonic epilepsy, Lafora type (LD), and progressive myoclonic epilepsy type 1 (EPM1), also known as Unverricht-Lundborg disease, are phenotypically related genetic disorders presenting with progressive stimulus-induced myoclonic seizures starting in childhood or adolescence, often accompanied by ataxia and tremor [79,80]. LD, unlike EPM1, exhibits characteristic cognitive decline soon after seizure onset and has a life expectancy of approximately ten years from diagnosis [80]. Management for both disorders is supportive.

3.5. Tremor

Tremor is an involuntary, rhythmic, oscillatory movement. It should be classified as occurring at rest or with action, with the latter further subdivided into postural, isometric, and kinetic tremors. Care should be taken when assessing fine hyperkinetic movements to avoid mistaking a primary tremor for tremulous movements better categorized as chorea or mobile dystonia. Tremor can occur alongside other movement disorder phenomenologies in IMDs but is seldom the hallmark sign that leads to diagnosis.

3.6. Hypokinetic-rigid syndrome

"Hypokinetic-rigid syndrome" (HRS) is a term used to describe hypokinetic movement presentations in children, sometimes synonymously with parkinsonism. Parkinsonism refers to a syndrome characterized by bradykinesia along with at least one of the following features: resting tremor, rigidity, and postural instability. Examination maneuvers designed to elicit bradykinesia in children, such as repeated finger or foot taps, may not be feasible depending on the child's stage of cognitive development. Additionally, resting tremor is not typically present in children with parkinsonism. Hypokinesia can often be more readily assessed by observing the child regardless of their cooperation, and rigidity can be evaluated through passive movement of their limbs. Therefore, the term "hypokinetic-rigid syndrome" is most accurate in pediatric hypokinetic movement disorders.

Hypokinetic-rigid syndrome is an important clinical feature in neurotransmitter disorders, of which the dopa-responsive dystonias are often responsive to low doses of levodopa. Hypokinetic-rigid syndrome is also noted in various lysosomal storage disorders, most commonly in Niemann-Pick type C (NPC), followed by different types of neuronal ceroid lipofuscinoses (NCLs) and mucopolysaccharidoses (MPS). Some subtypes of GM1 and GM2 gangliosidoses, including MPS type IVB, can also involve the HRS, but not as the key clinical feature [81,82]. Hypermanganesemia with Dystonia 1 is a very rare entity associated with variants in *SLC30A10* which has been reported to present in childhood with dystonia, tremor, bradykinesia, or spastic paraplegia; and is reported to present in adults with parkinsonism [83]. Chelation therapy, iron supplementation, and a low-manganese diet may help prevent manifestations in affected individuals [84].

3.7. Spasticity

Spasticity is an increase in muscle tone with a velocity-dependent resistance to passive movement that reflects pyramidal tract dysfunction and is often accompanied by other pyramidal signs including

hyperreflexia, clonus or a Babinski sign. Upper motor neurons are particularly vulnerable to metabolic disruption due to their high energy demands [85], making spasticity a common feature in many neurometabolic disorders. Spasticity rarely occurs as an isolated entity among IMDs; rather, the constellation of other neurological and non-neurological findings provides clues to the underlying diagnosis.

Cases of urea cycle disorders have been reported to resemble a slowly progressive complex form of hereditary spastic paraplegia, including two associated with *ARG1*-associated arginase 1 deficiency and one with *SLC25A15*-associated hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome. Arginase 1 deficiency typically presents in early childhood with the insidious onset of distal spastic diplegia and relatively rare occurrences of hyperammonemic crises [86]. Patients also present with developmental delay, seizures, and extrapyramidal movements, including dystonia and ataxia [51]. HHH syndrome presents with acute hyperammonemic crises, progressive spasticity, learning disabilities, cerebellar dysfunction, and epilepsy [87]. Both conditions are managed by restricting protein intake and supplementing with essential amino acids. Early diagnosis and treatment of arginase 1 deficiency generally produce an asymptomatic trajectory, whereas protein restriction, along with additional citrulline and arginine supplementation in HHH syndrome, can temper the frequency of hyperammonemic crises and developmental delay [88].

Molybdenum cofactor deficiency is caused by biallelic pathogenic variants in *GPHN*, *MOCS1*, *MOCS2*, or *MOCS3*. It presents with a broad spectrum of chronic progressive spasticity and intellectual disability, punctuated by periods of encephalopathy and seizures during catabolic stress [89]. Neuroimaging may mimic neonatal hypoxic ischemic encephalopathy with bilateral changes in the globi pallidi, thalamic and subthalamic nuclei, and this could lead to delayed diagnosis [90]. *MOCS1*-related disease has a novel targeted treatment with cyclic pyranopterin monophosphate (cPMP), known as fosdenopterin. Evidence supporting the use of cPMP in *MOCS1*-related disease remains limited; however, early studies indicate that daily infusion of synthetic cPMP is associated with decreased mortality compared to historical controls [91], which led to its FDA approval. Regardless of genotype, all individuals with molybdenum cofactor deficiencies should be placed on a cysteine-restricted diet to reduce oxidative cysteine catabolism and downstream sulfite production [92].

X-linked adrenoleukodystrophy is caused by a pathogenic variant in *ABCD1* leading to adrenomyeloneuropathy (AMN), cerebral adrenoleukodystrophy (CALD), and/or primary adrenocortical insufficiency [93]. AMN presents with leg weakness, spasticity, clumsiness, pain, and bladder or bowel dysfunction, often in early adulthood. Presently, only supportive treatment is available for AMN [94]. A recent trial compared leriglitazone, a selective peroxisome proliferator-activated receptor gamma agonist, to placebo in a double-blind multi-centre format [95]. This enrolled 116 adult men with adrenomyeloneuropathy and followed them for 96 weeks. The primary efficacy endpoint was change in baseline in the Six-Minute Walk Test was no different between treatment and control groups, though no participants receiving leriglitazone progressed to CALD whereas 6 of the 39 (15 %) receiving placebo did.

Multiple disorders of sphingolipid degradation can present with spasticity and are worth mentioning despite not having approved disease-modifying treatment at this time [96]. Tay-Sachs disease, the classic phenotype of the *HEXA* disease continuum, often presents in infancy with progressive regression in motor skills between 3 and 6 months. Subacute juvenile forms present later, with normal development until 2–5 years of life, then plateauing of skills, then regression including progressive spasticity, bulbar dysfunction, and epilepsy with brain atrophy [97]. Proof of concept for gene therapy in Tay-Sachs disease has been demonstrated in a trial of two infants treated with a combination of two recombinant adeno-associated viruses, AAVrh8-HEXA and AAVrh8-HEXB [98]. Both participants tolerated the treatment without significant adverse events, and they had increased HexA activity compared to baseline. One participant showed 3 months of clinical stabilization before showing ongoing disease activity at 6 months. *GLB1*-related disorders include GM1 gangliosidosis and mucopolysaccharidosis type IVB. Type 1 (or infantile-onset) GM1 gangliosidosis may present with infantile hypotonia then lead to rapid neurological degeneration in the first year with spasticity and motor regression, leading further to vision loss, hearing loss, rigidity, seizures, feeding difficulties and oral secretions. Macular cherry red spot, hepatosplenomegaly, cardiomyopathy, and coarse facial features are present on systemic examination [99]. Subacute juvenile and late-onset Sandhoff disease can manifest with spasticity, dysphagia, and gait difficulty. The juvenile form also involves motor and cognitive decline and optic atrophy, and most patients are in a vegetative state with decerebrate posturing by age 10–15 years old.

Metachromatic leukodystrophy (MLD) is an autosomal recessive lysosomal storage disease caused by deficiency of arylsulfatase A and has three clinical subtypes which are functions of the age of onset: late-infantile, juvenile, and adult. The late-infantile onset form is most common and is characterized by a plateau of gross motor skills which evolves to include spasticity, seizures, vision and hearing impairment, cognitive decline, and peripheral neuropathy [100,101]. Late stages involve tonic spasms, and decerebrate posturing. Juvenile and adult-onset forms tend to involve a more neuropsychiatric phenotype early in disease course and a slower decline in motor function, though the late stages are similar [102]. Neuroimaging classically reveals a periventricular leukodystrophy with tigroid appearance and sparing of U-fibers [103]. Finding of gallbladder polyps is also highly suggestive of the diagnosis [104]. Ex vivo gene therapy is approved for management of pre-symptomatic late-infantile, presymptomatic early-onset juvenile, and early-symptomatic early-onset forms of MLD [105]. This involves ex vivo transduction of autologous CD34+ stem cells using a lentiviral vector containing human ARSA, atidarsagene autotemcel. In an open-label phase 1/2 trial including 26 patients followed for a median of 3.16 years, this therapy was associated with increased arylsulfatase A activity, improved progression in gross motor skills, cognitive development, and prevention of central and peripheral demyelination [106,107].

Krabbe disease is a neurodegenerative autosomal recessive disease caused by galactocerebrosidase deficiency and has a clinical spectrum consisting of infantile-onset progressive irritability, spasticity, and developmental regression to a later-onset more modest phenotype [108]. Onset of neurodegeneration typically follows normal early development. Hematopoietic stem cell transplantation (HSCT) can arrest progression of Krabbe disease [109], and optimal results are achieved with pre-symptomatic treatment [109–111]. Consensus guidelines recommend that asymptomatic newborns with a family history of Krabbe disease or an abnormal newborn screening result undergo further testing to identify those with infantile-onset Krabbe disease [112]. HSCT should be offered before 30 days of life in infantile-onset Krabbe disease [112]. Symptomatic individuals with later-onset Krabbe disease may also benefit from HSCT [113]. The role of HSCT in asymptomatic infants identified to be at risk of later-onset Krabbe disease remains unclear [114]. Animal models of Krabbe disease have demonstrated promising outcomes with AAV serotype rh10 treatment carrying human GALC (AAVrh.10-GALC), including extended lifespan and improved neuropathology [115]. Human trials with AAVrh.10-GALC are underway [91].

4. Diagnosis

The diagnostic approach is fundamentally phenomenology-based. A comprehensive clinical history and examination are conducted to identify the leading movement disorder phenomenology and evolution of the movement disorders, exacerbating factors such as catabolic stressors, and the family history. Following this, a careful examination is performed to identify other neurological and non-neurological abnormalities that may suggest a particular syndrome. Clinical features that

Table 3
High level overview of treatable inborn metabolic disorders presenting with movement disorders.

Disease	Gene	Age of Onset	Movement Disorder	Other Manifestations	Diagnostic Tests	Treatment
Aromatic l-amino acid decarboxylase deficiency	*DDC*	Early infancy	**Dystonia, oculogyric crises,** hypokinesia	Impaired autonomic function, global developmental delay	● CSF neurotransmitter analysis ● Plasma AADC activity ● *DDC* sequencing	Eladocagene exuparvovec intraputamenal delivery Evidence level 4 FDA and EMA approval for patients with AADC-deficiency age $\geq$ 18 months Targeted therapy also indicated, which may include dopamine agonists, MAO inhibitors, pyridoxine, folinic acid, and/or levodopa
Ataxia with vitamin E deficiency	*TTPA*	Late childhood	**Ataxia**, dystonia	Dysarthria, areflexia, loss of proprioception and sensory disturbance, upper motor neuron signs	● Plasma vitamin E level ● Brain MRI ● *TTPA* sequencing	Oral vitamin E Evidence level: 4 Special considerations: Monitor vitamin E levels in regular intervals (i.e., every 6 months).
Glucose transporter 1 deficiency syndrome (GLUT1-DS)	*SLC2A1*	Early childhood/ adulthood	**Ataxia**, **dystonia**, spasticity, chorea, myoclonus Paroxysmal exertion-induced dyskinesia	Infantile-onset epileptic encephalopathy or other seizure disorder, acquired microcephaly, DD/ID	● CSF/plasma glucose ratio ● *SLC2A1* sequencing	Ketogenic (or related) diet Evidence level: 4 Special considerations: monitoring per ketogenic diet protocol
Glutaric aciduria type 1	*GCDH*	Abrupt onset in early childhood	**Dystonia, parkinsonism, chorea**	Acute encephalopathic crises during episodes of catabolism, macrocephaly, hypotonia, DD/ID, seizures	● Included in newborn screening in many countries ● Plasma and urine organic acids ● Plasma acylcarnitines ● Brain MRI ● *GCDH* sequencing ● GCDH enzyme analysis	Lysine and tryptophan restricted diet, carnitine supplementation, intensified emergency treatment during periods of catabolism Evidence level: 2c Special considerations: Treatment guidelines have been established and are published periodically
Metachromatic leukodystrophy	*ARSA*	Late infantile / juvenile / adult	**Spasticity**	Developmental regression, seizures, vision and hearing impairment, peripheral neuropathy	● Arylsulfatase A enzyme activity ● Brain MRI ● Urinary sulfatides ● *ARSA* sequencing	Autologous hematopoietic stem cell gene therapy, atidarsagene autotemcel Evidence level: 4 Special considerations: Indicated for pre-symptomatic late-infantile, presymptomatic early-onset juvenile, and early-symptomatic early-onset forms of MLD.
Neuronal ceroid lipofuscinosis type 2	*CLN2*	Childhood	**Myoclonus**, dystonia, spasticity, chorea, tremor	Vision loss, dementia, epilepsy	● low levels of TPP1 enzyme activity ● *CLN2* sequencing	Recombinant human TPP1 (cerliponase alfa) Evidence level: 4 Clinical practice guidelines are published.
Niemann-pick disease type C	*NPC1* *NPC2*	Early childhood/ adulthood	**Ataxia, dystonia**	DD/ID, dysarthria, supranuclear vertical gaze palsy, hepatosplenomegaly, dysphagia, dysarthria, seizures, gelastic cataplexy, acute psychosis, depression, obsessive-compulsive disorder and other neuropsychiatric symptoms	● Biomarkers (oxysterols, lysosphingomyelin derivatives,bile acids) ● *NPC1/NPC2* sequencing	Arimoclomol with miglustat Evidence level: 1b Special considerations: Arimoclomol, in combination with miglustat, are approved by the FRA to treat NPC. Levacetylleucine Evidence level: 1b Special considerations:

(*continued on next page*)

Table 3 (*continued*)

Disease	Gene	Age of Onset	Movement Disorder	Other Manifestations	Diagnostic Tests	Treatment
Segawa's disease (autosomal dominant GTPCH deficiency)	*GCH1*	Childhood	**Dystonia**, postural tremor, hypokinetic-rigid syndrome		● CSF neurotransmitter levels ● Phenylalanine load test ● L-dopa trial ● *GCH1* sequencing	Approved by FDA as monotherapy for NPC L-dopa/carbidopa Evidence level: 4 Special considerations: Initiate at low dose and gradually titrate to standard treatment dose of L -dopa. Effective in almost all patients and response is sustained. There might be a decrease in dosage requirement over time
Wilson disease	*ATP7B*	Childhood/ young adulthood	**Dystonia, Tremor,** parkinsonism, chorea, ataxia	Liver disease, Kayser-Fleischer rings, seizures, psychiatric symptoms, hemolytic anemia	● Low serum ceruloplasmin ● Increased liver copper ● Increased urinary copper ● *ATP7B* sequencing	Copper chelation therapy (D-penicillamine or trientine) Evidence level: 1a Special considerations: No controlled trials have compared these two agents. Monitor closely for side effects and measure 24-h copper excretion to evaluate adequacy of treatment. Clinical practice guidelines are published.

Levels of evidence (source: www.cebm.net): Level 1a = systematic review of randomized controlled trials (RCT), 1b = individual RCT, 1c = "All or None" (=[prolongation of] survival with therapy); Level2a = systematic review of cohort studies, 2b = individual cohort study, 2c = "outcomes research" (focused on end results of therapy for chronic conditions, including functioning and quality of life; http://www.ahrq.gov/clinic.outfact.htm); Level 3 = systematic review of case-control studies; Level 4 = individual case-control study or case series/report; Level 4 to 5 = single case report; Level 5 = expert opinion without critical appraisal.
Abbreviations: FDA, U.S. Food and Drug Administration; CBC, complete blood count.

should raise concern for an IMD include associations with paroxysmal spells of altered consciousness, headache, vomiting, seizures, or organ-specific functional derangement.

We recommend brain MRI to further phenotype patients presenting with movement disorders who are suspected to have an IMD. Neuroimaging is often unremarkable in metabolic movement disorders, though there are notable exceptions, and an organized approach can help narrow the differential diagnosis. These disorders can be broadly organized into predominant white versus grey matter diseases or a combination of the two [116]. White matter disease can be further split into hypomyelination (eg. Pelizaeus-Merzbacher disease or hypomyelination with atrophy of the basal ganglia) or other white matter diseases [117]. The latter is often sorted by topography of white matter involvement [117,118]. Frontal predominant white matter diseases include Alexander disease and frontal variant of X-linked adrenoleukodystrophy. Parieto-occipital white matter predominance is suggestive of X-linked adrenoleukodystrophy, neuronal ceroid lipofuscinosis, and sometimes Krabbe disease. Periventricular white matter involvement is suggestive of Krabbe disease, metachromatic leukodystrophy, neuronal ceroid lipofuscinosis, and mucopolysaccharidosis. A more global pattern of white matter involvement is seen with vanishing white matter disease, Aicardi-Goutières syndrome particularly when calcification is present, and the end-stage of all progressive white matter disorders. Disorders of predominant grey matter involvement can be sorted by those with predominant striatal involvement (glutaric aciduria type 1 with subdural collections and widened sylvian fissures, propionic acidemia, Leigh disease, and MELAS) versus those with globus pallidal involvement (methylmalonic acidemia, MSUD) [119]. Others still present with a mixture of grey and white matter disease. In these, a combination of white matter and thalamic involvement is suggestive of Krabbe disease; white matter and striatal involvement is suggestive of glutaric aciduria type 1, propionic acidemia, Leigh disease, and MELAS; and a combination of white matter and globus pallidal involvement can be seen with Canavan disease, methylmalonic acidemia, MSUD, and urea cycle disorders [116].

Biochemical and genetic testing is performed, guided by the detailed phenotype, with a particular focus on identifying treatable causes [120]. Due to the often overlapping and non-specific presentation of IMDs, we recommend broad genetic testing with whole exome or whole genome sequencing when available [121,122].

5. Treatment

Therapeutic strategies for IMDs are evolving as new therapeutic entities are able to address the underlying mechanisms of disease and as the biotechnology and pharmaceutical industries continue to gain interest in treating rare disorders (Table 3).

Strategies for the targeted treatment of IMDs are diverse and aimed at the underlying pathophysiology. In various small molecule disorders, reducing toxic compounds is paramount to minimize intoxication and the resultant neurological symptoms, as seen in glutaric aciduria type 1. Depending on the underlying metabolic issue, toxic products can be reduced through dietary changes to avoid the offending agent or by the addition of chelation agents like penicillamine in Wilson disease [55]. Dietary manipulation is another viable strategy for treating some IMDs. Dietary protein restriction is a common intervention in several IMDs to avoid an offending amino acid. The ketogenic diet has been widely used to treat epilepsy for decades, and its generation of ketone bodies can be beneficial in managing IMDs. In glucose transporter type 1 deficiency syndrome (GLUT1-DS) and pyruvate dehydrogenase complex (PDHc) deficiency, the ketogenic diet serves as the primary treatment to address the underlying biochemical abnormality [123]. New licensed and investigational enzyme replacement therapies are emerging for several disorders, including infantile and late-infantile neuronal ceroid lipofuscinosis [124]. Gene therapies represent the newest class of treatments, commonly utilizing viral vectors such as adeno-associated

viruses (AAVs) or lentiviruses to the affected cells. Intraputamenal administration of recombinant AAV9 packaged with human AADC gene (rAAV9-hAADC) has been approved for treatment in select individuals with AADC deficiency [125], and subsequent trials are evaluating delivery of the therapy to the ventral tegmental area [126]. This includes ex vivo gene therapy in cerebral adrenoleukodystrophy where the patient's own hematopoietic stem cells are transduced with a gene therapy vector followed by an autologous stem cell transplantation [127]. AAV-based gene therapy trials are also underway for male infants with ornithine transcarbamylase deficiency [91]. Gene editing with site-specific endonucleases, such as zinc-finger nucleases and CRISPR/Cas9 systems, has yielded promising results in murine models of metabolic disease and represents an emerging class of novel gene therapies [128–133]. Finally, knockdown-and-replace models are being explored, utilizing a combination of gene-specific interfering RNA (RNAi) in a tail-to-tail configuration and complementary DNA to replace the aberrant gene [134].

In addition to, or in the absence of, disease-modifying therapy clinical support of patients with metabolic movement disorders involves a combination of symptom management, developmental support, and holistic support that involve the patient and their care team. Symptom management of metabolic movement disorders is phenomenology-based and is not typically different than in other movement disorders. One notable exception is to provide a trial of levodopa in suspected dopa-responsive dystonia [135]. Treatment of metabolic movement disorders should target function of the patient and ease of caregiving.

6. Conclusion

IMDs presenting with movement disorders are individually rare diagnoses but collectively are clinically substantial when aggregated, and each IMD requires a high degree of resources to support. A careful clinical history in a patient presenting with movement disorder may identify features suggestive of an IMD, such as association with encephalopathy, seizures, and altered level of consciousness in times of catabolic stressors. A detailed physical exam should be performed to characterize the dominant movement phenomenology, other neurological signs, and non-neurological abnormalities as well. Neuroimaging, biochemical testing, and next-generation sequencing genetic testing should then be arranged, prioritizing diagnosis of treatable causes for movement disorders. Even when non-treatable causes are identified, a diagnosis is prudent for genetic counseling, family planning, to identify rational targeted screening, and to offer enrolment in research.

The complete list is accessible at www.iembase.org/gamuts and will be regularly maintained and updated.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2025.109084.

CRediT authorship contribution statement

Dakota J.S.J. Peacock: Writing – review & editing, Writing – original draft, Validation, Conceptualization. **Carlos R. Ferreira:** Writing – review & editing, Supervision, Formal analysis, Data curation, Conceptualization. **Gabriella Horvath:** Writing – review & editing, Validation, Formal analysis. **Georg F. Hoffmann:** Writing – review & editing, Validation, Formal analysis, Conceptualization. **Nenad Blau:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Darius Ebrahimi-Fakhari:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization.

Declaration of competing interest

None.

Acknowledgements

This work was supported by the Nenad Blau IEMBase Endowment Fund of the MCF, Marin County, CA, USA and in part by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (HD009024-1 to C.R.F.).

Data availability

Data will be made available on request.

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