

Treatable Inherited Rare Movement Disorders

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ABSTRACT: There are many rare movement disorders, and new ones are described every year. Because they are not well recognized, they often go undiagnosed for long periods of time. However, early diagnosis is becoming increasingly important. Rapid advances in our understanding of the biological mechanisms responsible for many rare disorders have enabled the development of specific treatments for some of them. Well-known historical examples include Wilson disease and dopa-responsive dystonia, for which specific and highly effective treatments have life-altering effects. In recent years, similarly specific and effective treatments have been developed for more than 30 rare

inherited movement disorders. These treatments include specific medications, dietary changes, avoidance or management of certain triggers, enzyme replacement therapy, and others. This list of treatable rare movement disorders is likely to grow during the next few years because a number of additional promising treatments are actively being developed or evaluated in clinical trials. © 2017 International Parkinson and Movement Disorder Society

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The World Health Organization does not endorse a single definition for rare diseases.¹ Although all rare diseases are characterized by low prevalence, the threshold that defines rare differs across the world. The European Union defines “rare” as a prevalence ≤ 50 people per 100,000 population,^{1,2} whereas the United States sets a numerical maximum of $\leq 200,000$ citizens affected.^{1,3} Although they are rare, more than 7000 different disorders are recognized. All combined, they affect 6% to 8% of the population, for an estimated total of 300 million people worldwide.⁴ These statistics lead to the paradox that rare disorders as a group are not uncommon and are responsible for a significant burden in terms of health care needs.

Of rare disorders, 80% are genetically determined, whereas the remainder result from infections, environmental factors, autoimmune diseases, and degenerative or proliferative mechanisms. They may be inherited as autosomal recessive or dominant disorders, but de novo mutations are common in sporadic neurological disorders, so there may be no family history.⁵ Most have a neurologic phenotype and approximately half affect children. There is great interest in the mechanisms of pathogenesis of rare disorders in part because understanding these mechanisms contributes to a better understanding of more common diseases.⁶ Inherited rare disorders were instrumental in mapping the human genome and in cloning genes. They offer opportunities for faster progress in therapeutics, especially given scientific and technological advances that identify their genetic basis to find molecular targets for the development of new treatments. This interest in rare disorders has translated into greater involvement of the pharmaceutical and biotechnology industry in developing new treatments.^{2,4}

The majority of movement disorders can be classified as rare disorders. The Rare Movement Disorders (RMD) Study Group within the International Parkinson Disease and Movement Disorders Society was

established to focus on those that are particularly rare. It provides an important opportunity for education in RMD and may facilitate certain activities such as patient registries and centers of expertise. Such infrastructure would facilitate the collection and evaluation of patients with RMD, greatly advancing our understanding of these disorders and their management.⁷ The main goal of the current review is to promote awareness of inherited RMD, especially those where specific treatments are available.

Basic Principles in the Treatment of Rare Disorders

Clinical trials that establish safety and efficacy for rare disorders differ from trials for more common disorders in many ways.^{8,9} Because these disorders are infrequent, recruiting large numbers of participants into clinical trials often is not feasible, and the small target populations discourage industry from investing in large and expensive development efforts. Some RMD are life threatening, raising ethical concerns for placebo-controlled designs, especially where there is strong preclinical evidence that a treatment may be effective. In view of these considerations, much of the evidence for treatments in RMDs does not come from large, double-blinded, placebo-controlled trials. Clinical trials for RMD are often smaller than those for more common disorders, and they often use alternative trial designs. A recent study of 24,088 clinical trials registered at clinicaltrials.gov found that 11.5% were for rare disorders, and trials for rare disorders typically enrolled fewer participants (median = 29) than those for common disorders (median = 62).¹⁰ Rare disorder trials also were more likely to be single arm, nonblinded, and nonrandomized. The European Medicines Authority and the U.S. Food and Drug Administration apply different criteria for approval of new treatments for rare disorders. For example, they

will sometimes grant approval after only a single study in a rare disorder, compared to at least 2 studies required for common disorders.

In some cases, treatments have become standard of care without approval from any regulatory agencies in any part of the world. In these situations, the clinician must balance the weight of the evidence of efficacy against the severity of the disease and potential consequences of withholding treatment. A good example is the use of levodopa in dopa-responsive dystonia. This treatment has become standard of care, without the approval of the European Medicines Authority or the U.S. Food and Drug Administration. There have never been any double-blind placebo-controlled trials, and it is unlikely that such trials will ever be conducted. Yet no clinician would withhold levodopa treatment for dopa-responsive dystonia. In this situation, the idealistic goals of “evidence-based medicine” become a more practical dilemma of “evidence-limited medicine.” In view of these unique features of rare disorders, treatment recommendations are sometimes based on consensus opinion guidelines or principles of good clinical practice.¹¹

Because of the large numbers of RMDs, it is challenging to provide a comprehensive summary that addresses all of them. Most prior reviews have focused on smaller subsets of disorders, such as those with a shared genetic basis or similar movement disorder. Here we focus on RMDs with mechanism-based treatments. Because many RMDs have mixed or pleiomorphic phenotypes, the individual disorders are grouped according to therapeutic mechanism. A summary of these disorders is provided in Tables 1 to 5, with the predominant movement disorder listed in boldface type. These tables include only those RMD where there is strong clinical evidence for efficacy that comes from well-designed clinical trials or guidelines based on published reports of consensus opinion. The tables do not include many examples where the evidence comes only from anecdotal case reports, from ongoing clinical trials that are not yet completed, or from pre-clinical studies such as animal or cell models.

This review focuses on inherited RMD. It does not address the many RMDs caused by infectious or immunological mechanisms, toxins or medications, or dietary deficiencies. It also does not cover disorders where there is strong evidence for efficacy for treating clinical problems other than the movement disorder. Examples include the need for regular surveillance for early treatment of certain disorders with high risk for malignancy (eg, ataxia-telangiectasia), or the treatment of kidney stones to prevent renal failure in Lesch-Nyhan disease. Recognition of the movement disorder may facilitate early diagnosis and therefore treatment of these other disorders, but here we focus predominantly on treatment of the movement disorder.

TABLE 1. Reduction of toxic products

Disorder	Cause (gene)	Movement disorder	Other clinical features ²	Treatment	Outcome
Cerebrotendinous xanthomatosis	Sterol-27 hydroxylase (CYP27A)	Ataxia, spastic paresis, dystonia, parkinsonism, myoclonus	Tendon xanthomas, cataracts, neuropathy, seizures, cognitive impairment	Chenodeoxycholic acid	Early treatment prevents symptoms ¹⁹
Dystonia/parkinsonism with manganese accumulation	Manganese transport (SLC39A14, SLC30A10)	Dystonia, parkinsonism	Liver disease, polycythemia	EDTA chelation therapy	Complete or partial reversal of symptoms ¹⁸
Gaucher disease (neurologic subtype 3)	Glucocerebrosidase (GBA)	Parkinsonism, ataxia, spasticity	Developmental delay, epilepsy, organomegaly, cytopenia	Enzyme replacement therapy, N-butyl-deoxynojirimycin (Miglustat)	Early treatment mitigates symptoms ¹⁶
Niemann Pick type C ¹	Cholesterol trafficking (NPC1 or NPC2)	Ataxia, dystonia, myoclonus, spasticity	Dementia, seizures, supranuclear gaze palsy	N-butyl-deoxynojirimycin (Miglustat)	Early treatment mitigates symptoms ²⁰
Wilson disease	Copper transporter (ATP7B)	Dystonia, parkinsonism, tremor, chorea, myoclonus	Liver disease, Kayser-Fleischer rings, cognitive or psychiatric impairment	Penicillamine, trientine, zinc	Complete prevention of symptoms ¹⁷

Many of these disorders have variable or mixed phenotypes. The most common or most dominant movement disorder is shown in boldface type.

Many of the disorders described in this review first present in children and are therefore evaluated and managed by pediatric neurologists. However, some frequently present in adulthood such as abetalipoproteinemia, cerebrotendinous xanthomatosis, Refsum's disease, or Wilson's disease. Even for disorders that classically present in children, atypical adult-onset cases have been described for many.¹²⁻¹⁴

In addition, many patients with pediatric-onset disorders live into adulthood and must transition care to adult neurologists. For disorders that require special diets, noncompliance is common in adults and can cause decompensation with emergence of a movement disorder. An increasing number of patients with inherited RMD desire children, and pregnancy can present especially difficult management problems.^{15,16} The physiological changes that occur during pregnancy can cause metabolic decompensation with emergence of a movement disorder. Also, many of the medications used by patients with inherited RMD have not been safety tested in pregnancy, yet they must not be stopped. Knowledge of diagnostic and treatment strategies is therefore important for both pediatric and adult neurologists.

Mechanism-Based Treatments

Reduction of Toxic Target Molecules

A common principle for the treatment of several RMD involves reducing the amount of a substance that is toxic to the nervous system (Table 1). For all of these disorders, early treatment is believed to be important to prevent onset or progression of symptoms. Treatment is still effective when started later, although symptom resolution may not be complete.

One of the best-known examples is Wilson's disease.¹⁷ It is caused by mutations in the *ATP7B* gene, which encodes a copper transporter. It is associated with pathological accumulation of copper in the liver and brain. Symptoms first emerge in children or young adults with dystonia, parkinsonism, and/or tremor. However, other phenotypes with predominant ataxia or spasticity may occur. Treatments that reduce copper stores are essential for prevention of neurological damage, and they may reverse existing symptoms if started early.¹⁷ They include chelation of heavy metals with penicillamine or trientine, and/or reduction of intestinal copper uptake with zinc. Dystonia/parkinsonism due to a manganese transporter defect is a more recently described disorder that is treated using a similar strategy that involves chelation of heavy metals with ethylene diamine tetra-acetic acid (EDTA).¹⁸

Cerebrotendinous xanthomatosis is caused by deficiency of mitochondrial sterol 27-hydroxylase, an enzyme involved in cholesterol metabolism. Symptoms can develop in childhood or adulthood. Affected individuals develop solid deposits known as xanthomas

near large tendons, although these may be asymptomatic and are easy to miss. The movement disorder typically involves progressive ataxia with spasticity, but other phenotypes dominated by dystonia or parkinsonism may occur. Other symptoms may include neuropathy, cognitive decline, seizures, and cataracts. Supplementation with the bile acid chenodeoxycholic acid can prevent or reverse neurological symptoms.¹⁹ Chenodeoxycholic acid works by binding to and reducing the accumulation of cholestanol and related metabolites that are damaging to the nervous system.

Niemann-Pick type C is a lysosomal storage disorder caused by defects in intracellular cholesterol trafficking. The clinical manifestations typically begin in childhood or early adulthood and include slowly progressive dementia, often with seizures. Most patients also have progressive ataxia with a supranuclear vertical gaze palsy, although other phenotypes with dystonia, spasticity, myoclonus, or parkinsonism may also occur. N-butyl-deoxynojirimycin (Miglustat; Actelion, Basel Switzerland) is a synthetic glucose analog that reduces lysosomal storage products by inhibiting glycosylceramide synthase, the enzyme responsible for the first step in the synthesis of glycosphingolipids that accumulate in lysosomes. Several studies have shown that the treatment of patients with Niemann-Pick type C with this drug can mitigate biomarkers of disease and slow progression of neurological symptoms, especially among patients with late-onset disease.²⁰ N-butyl-deoxynojirimycin also is used for adults with Type 1 Gaucher disease in whom enzyme replacement therapy is not suitable (see later).

Dietary Interventions

For several RMD, dietary interventions can provide an effective therapy by reducing the source of a substance that is toxic to the nervous system (Table 2). Here again, early intervention is essential to avoid often irreversible nervous system damage.

The most well-known example is phenylketonuria. In this disorder, deficiency of the enzyme phenylalanine hydroxylase leads to accumulation of toxic phenylalanine metabolites. Untreated patients suffer from developmental delay with cognitive and behavioral difficulties. Many also develop a mixed movement disorder that combines spasticity, parkinsonism, and other features. If introduced early, a phenylalanine-restricted diet prevents most of the neurobehavioral problems.²¹ Fortunately, most cases are detected early, because neonatal screening is methodically conducted for this disorder in most countries. Symptomatic cases are occasionally seen in children or adults when screening was missed or with dietary noncompliance.

Homocystinuria is another disorder of amino acid metabolism caused by deficiency of cystathione beta-synthase, with toxic accumulation of homocystine and

TABLE 2. Dietary interventions

Disorder	Cause (gene)	Movement disorder	Other clinical features ²	Treatment	Outcome
Abetalipoproteinemia (Bassen-Kornzweig)	Microsomal triglyceride transfer protein (<i>mtgp</i>)	Ataxia, chorea, dystonia, parkinsonism	Retinitis pigmentosa, dementia, seizures, acanthocytosis, fat malabsorption	Dietary fat restriction, vitamins E & A	Early treatment prevents symptoms ^{2,6}
Cerebral creatine deficiency	Creatine synthesis (<i>GAMT</i> , <i>AGAT</i>)	Chorea, dystonia, ataxia	Developmental delay, epilepsy, behavioral deficits, myopathy	Creatine ± ornithine and dietary restriction of arginine	Partial improvement of symptoms ^{3,5}
GLUT1 deficiency	Glucose transporter (<i>GLUT1</i>)	Paroxysmal or chronic dystonia, ataxia, chorea, myoclonus	Developmental delay, seizures, alternating hemiplegia	Ketogenic diet, triheptanoin	Treatment reduces symptoms ^{50,84}
Glutaric aciduria type 1	Glutaryl Co-A dehydrogenase (<i>GCDH</i>)	Dystonia, parkinsonism	Developmental delay, encephalopathic crises (often triggered by metabolic decompensation)	Avoid or treat triggers, dietary lysine restriction, L-carnitine	Treatment mitigates long-term deficits ^{42,43}
Homocystinuria	Cystathione beta synthase (<i>CBS</i>)	Dystonia, parkinsonism	Developmental delay, myopia, ectopic lens, psychiatric features	Vitamin B6, dietary restriction of methionine, betaine	Early treatment prevents most symptoms ²²
Maple syrup urine disease	Branched chain alpha-ketoacid dehydrogenase complex (<i>BCKDHA</i> , <i>BCKDHB</i> , <i>DBT</i>)	Dystonia, tremor, ataxia (may be paroxysmal)	Developmental delay, episodic encephalopathy (often triggered by metabolic decompensation)	Avoid or treat triggers; dietary leucine restriction	Treatment mitigates episodes ⁸⁵
Methylmalonic aciduria	Methylmalonyl Co-A mutase (<i>MUT</i>)	Dystonia, chorea	Developmental delay, auditory impairment, encephalopathic crises (often triggered by metabolic decompensation)	Avoid or treat triggers; dietary protein restriction, L-carnitine	Treatment may attenuate crises ⁴⁴
Phenylketonuria	Phenylalanine hydroxylase (<i>PAH</i>)	Parkinsonism, spasticity	Intellectual disability	Dietary restriction of phenylalanine	Early treatment prevents most symptoms ^{2,1}
Propionic acidemia	Propionyl Co-A carboxylase (<i>PCCA</i> , <i>PCCB</i>)	Dystonia, chorea	Developmental delay, encephalopathic crisis, seizures optic atrophy (often triggered by metabolic decompensation)	Avoid or treat triggers, dietary protein restriction, L-carnitine	Treatment prevents or mitigates symptoms ⁴⁴
Pyruvate dehydrogenase complex deficiency	Pyruvate dehydrogenase complex (multiple genes)	Chronic or paroxysmal dystonia, ataxia	Developmental delay, encephalopathy, seizures	Thiamine, ketogenic diet, triheptanoin	Treatment mitigates symptoms ^{29,30}
Refsum disease	Phytanyl Co-A hydroxylase (<i>PHYH</i>)	Ataxia	Retinitis pigmentosa, neuropathy, auditory impairment, skin changes	Dietary restriction of phytanic acids, plasmapheresis	Complete or partial prevention or reduction of symptoms ^{24,25}

Many of these disorders have variable or mixed phenotypes. The most common or most dominant movement disorders are shown in boldface type. The term *metabolic decompensation* refers to a state in which the body's consumption of a metabolite (eg, energy) exceeds supply.

homocysteine. If untreated, homocystinuria causes variable expression of developmental delay, myopia with ectopic lens, thromboembolism, tall stature, hypopigmentation, psychiatric features, and sometimes parkinsonism or dystonia. Therapy is aimed at reducing toxic levels of homocysteine using a combination of a methionine-restricted low-protein diet²² and/or betaine to provide an alternative route for metabolic elimination of methionine.

Maple syrup urine disease is another amino acid disorder that is caused by deficiency of the branched chain ketoacid dehydrogenase complex. The enzyme deficiency causes accumulation of plasma branched chain amino acids leucine, isoleucine, and valine. The classic presentation is neonatal encephalopathy, ophtis-totonus, and stereotyped movements of the limbs. However, the disorder may present later in childhood with encephalopathy, ataxia, and other features.²³ Therapy requires a lifelong low protein and leucine-restricted diet that reduces plasma branched chain amino acids. Noncompliance with the diet can cause recurrence of encephalopathy with a paroxysmal movement disorder in older children and adults. Even with a strict diet, metabolic decompensation may occur during periods of fasting or fever, which result in catabolism of muscle proteins with elevation of plasma amino acids. Therefore, avoidance or management of these triggers is an important aspect of management in both children and adults.

Patients with Refsum disease present in late childhood or early adulthood with progressive ataxia, neuropathy, retinitis pigmentosa, and skin changes. It is caused by deficiency of the enzyme phytanyl CoA hydroxylase, which is required for metabolism of branched chain fatty acids such as phytanic acid. A diet reduced in phytanic acids can prevent or reverse symptoms in Refsum disease.^{24,25}

Abetalipoproteinemia (Bassen-Kornzweig disease) presents with symptoms of fat malabsorption and acanthocytes in the blood, along with adult-onset dementia, seizures, and progressive ataxia. It is a result of defects in the microsomal triglyceride transfer protein, which is critical for the transfer and metabolism of fats in the body. Early intervention with a low-fat diet combined with supplements of the fat-soluble vitamins A and E can prevent onset of symptoms.²⁶

Two disorders may be treated with the ketogenic diet. Mutations in the *SLC2A1* gene cause dysfunction of the brain glucose transporter (GLUT1), with reduced glucose into the central nervous system. Severely affected patients present with neonatal encephalopathy and seizures, although some do not develop symptoms until later in childhood or as young adults, when they present with paroxysmal exercise-induced dystonia or paroxysmal ataxia.²⁷ An established treatment is the

ketogenic diet, which results in at least partial control of the neurological disability and is associated with improved long-term prognosis.²⁸ Presumably, the glucose transporter defect that deprives the nervous system of adequate glucose can be bypassed through the diet's induction of metabolic changes that produce ketones, which do not require the glucose transporter and can be used by neurons as an alternative energy source.

Pyruvate dehydrogenase complex deficiency is another disorder where the ketogenic diet or triheptanoin can be effective by providing an alternative energy source to bypass a metabolic defect in glucose metabolism.^{29,30} Some patients may also respond to thiamine supplements.³¹

Supplements With Vitamins and Other Natural Substances

Several RMD can be treated with vitamins or other naturally occurring molecules. Examples include biotin (biotinidase deficiency),³² biotin plus thiamine (biotin-thiamine-responsive basal ganglia disease),³³ coenzyme Q10 (certain CoQ10 defects),³⁴ creatine (cerebral creatine deficiency),³⁵ cyclic pyranopterin monophosphate (molybdenum cofactor complex deficiency caused by mutations in *MOCS1*),³⁶ folinic acid (cerebral folate deficiency),¹⁹ and vitamin B12 (certain cobalamin-related defects).³⁷ In these cases, the therapeutic mechanism involves bypassing a specific defect in metabolism, and therapy can be dramatically effective when instituted early (Table 3).

Ataxia with vitamin E deficiency is a slowly progressive ataxic disorder, although dystonia may sometimes predominate. It is caused by defects in the alpha tocopherol transfer protein leading to vitamin E deficiency, so high-dose vitamin E supplements are useful.³⁸ In abetalipoproteinemia (discussed previously), the fat malabsorption syndrome leads to deficiency of fat soluble vitamins (vitamins E and D), so supplementations with both are beneficial.²⁶

Vitamin supplements are sometimes useful for subgroups of patients with other RMD. For example vitamin B6 can be effective in a subgroup of patients with homocystinuria²² or mild forms of aromatic amino acid decarboxylase deficiencies^{39,40} because both enzymes use the activated form (pyridoxal phosphate) as a cofactor. Similarly, vitamin B1 is useful for subgroups of patients with pyruvate dehydrogenase complex deficiency because this enzyme uses the activated form (thiamine pyrophosphate) as a cofactor.³¹ In these cases, the additional cofactor presumably stabilizes or improves the function of the associated mutant enzyme.

Betaine (trimethylglycine) is a naturally occurring amino acid that can serve as a methyl donor. It is U.S. Food and Drug Administration–approved for the

TABLE 3. Vitamin supplements

Disorder	Cause (gene)	Movement disorder	Other clinical features ²	Treatment	Outcome
Abetalipoproteinemia (Bassen-Kornzweig)	Microsomal triglyceride transfer protein (<i>MTTP</i>)	Ataxia, chorea, dystonia, parkinsonism	Retinitis pigmentosa, dementia, seizures, acanthocytes, fat malabsorption	Dietary fat restriction, vitamin E & A	Early treatment prevents symptoms ²⁶
Aromatic amino acid decarboxylase deficiency	Aromatic amino acid decarboxylase (<i>AADC</i>)	Dystonia	Developmental delay, hypotonia, oculogyric crises	Dopamine agonists, monoamine oxidase inhibitors, vitamin B6	Partial reversal of symptoms in some cases ^{39,40}
Ataxia with vitamin E deficiency	Alpha tocopherol transfer protein (<i>TTPA</i>)	Ataxia, dystonia	Neuropathy, visual impairment	Vitamin E	Early treatment prevents symptoms ³⁸
Biotin-thiamine responsive basal ganglia disease	Thiamine transporter (<i>SLC19A3</i>)	Episodic or progressive dystonia, parkinsonism, ataxia	Encephalopathy, seizures (often triggered by metabolic decompensation)	Biotin plus thiamine, avoid or treat triggers	Early treatment prevents or reverses symptoms ³³
Biotinidase deficiency	Biotinidase (<i>BTD</i>)	Ataxia, spastic paresis, dystonia	Developmental delay, seizures, visual and auditory impairment, skin changes	Biotin	Early treatment prevents symptoms ³²
Cerebral folate deficiency	Folate transport (<i>FLR1</i> , <i>SLC46A1</i>)	Ataxia, dystonia, spasticity	Developmental delay, seizures, psychiatric impairment	Folinic acid	Early treatment prevents symptoms ³⁷
Cobalamin deficiency	Cobalamin deficiency (multiple genes)	Ataxia, dystonia, spasticity	Developmental delay, encephalopathy, seizures (often triggered by metabolic decompensation)	Cobalamin derivatives	Early treatment mitigates symptoms ³⁷
CoEnzyme Q10 deficiency	Coenzyme Q10 deficiency (multiple genes)	Ataxia, dystonia, tremor, spasticity	Multiple distinct phenotypes	Coenzyme Q10	Treatment prevents or reverses symptoms ³⁴
Homocystinuria	Cystathione beta synthase (<i>CBS</i>)	Dystonia, parkinsonism	Developmental delay, myopia, ectopic lens, psychiatric features	Vitamin B6, dietary restriction of methionine, betaine	Early treatment prevents most symptoms ²²
Pyruvate dehydrogenase complex deficiency	Pyruvate dehydrogenase complex (multiple genes)	Chronic or paroxysmal dystonia, ataxia	Developmental delay, encephalopathy, seizures	Thiamine, ketogenic diet, triheptanoin	Treatment mitigates symptoms ³⁰

Many of these disorders have variable or mixed phenotypes. The most common or most dominant movement disorder is shown in boldface type. The term *metabolic decompensation* refers to a state in which the body's consumption of a metabolite (e.g. energy,) exceeds supply.

treatment of homocysteinuria (discussed previously) for reducing homocysteine levels and associated thromboembolic events. Betaine is also at least partly effective in mitigating progressive spastic paraplegia in methylenetetrahydrofolate reductase deficiency.⁴¹

Management of Triggers

Several RMD are treated by management of known triggers (Table 4). In several cases, the mechanisms by which a trigger causes symptoms are well known. As noted previously, the intermittent encephalopathy and movement disorder associated with maple syrup urine disease is triggered by transient elevations of serum branched chain amino acids and can be managed by avoiding catabolic states that increase plasma amino acids.

In other cases, the triggers are well known, but the mechanisms are only partly characterized. A classic example is glutaric aciduria type 1, which is caused by deficiency of glutary-CoA dehydrogenase, an enzyme that is involved in the catabolism of lysine and tryptophan. Most patients are normal until symptoms are triggered by routine immunization, uncomplicated infection or surgery, or some other metabolic stress. Patients develop an acute encephalopathic crisis with striatal necrosis leading to permanent cognitive sequelae, dystonia, and parkinsonism. For reasons that are not entirely understood, this syndrome develops during a vulnerable developmental window (less than 2 years of age), and does not typically develop in older individuals. Dietary restriction of lysine combined with aggressive prevention or management of known triggers during the vulnerable period is important to avoid encephalopathic crises and permanent brain damage.^{42,43}

Two additional disorders, methylmalonic aciduria and propionic aciduria, are also associated with permanent striatal injury triggered by metabolic decompensation, with severe and permanent parkinsonism and dystonia, often combined with cognitive impairment. Management of known triggers is combined with a protein-restricted diet, which reduces the load of organic acid precursors in the relevant metabolic pathways.⁴⁴ Hydroxycobalamin can also be used in cases of B12-responsive methylmalonic aciduria.

Rapid-onset dystonia-parkinsonism is another disorder in which control of environmental triggers may play an important role in management.⁴⁵ Classically, this disorder presents in older children or adults, again with an encephalopathic crisis followed by a permanent movement disorder that is dominant by dystonia and parkinsonism. However, acute striatal necrosis does not occur. In addition to the triggers that lead to catabolic states described above for glutaric aciduria, other triggers may include overuse of alcohol or even psychological stress. Unlike glutaric aciduria where

the triggers cause decompensation only in young children, these triggers may cause decompensation even in older adults with rapid-onset dystonia-parkinsonism. The reasons for rapid decompensation remain unclear. The responsible gene (*ATP1A3*) encodes a sodium-potassium adenosine triphosphatase (ATPase), which plays a major role in maintaining the gradient of ions that provides the basis for neuronal signalling. Maintaining these ion gradients comprises a very large proportion of the energy used by the brain, so it seems feasible that specific triggers cause metabolic decompensation when the demand for energy exceeds the capacity to supply it. The same gene also causes a spectrum of other phenotypes, where the value of treating triggers is less certain.⁴⁵

There are several other movement disorders where symptoms are triggered by specific factors including paroxysmal dyskinesias, paroxysmal ataxia, alternating hemiplegia of childhood, and others (Table 4). Although the exact mechanisms by which these factors trigger the movement disorder remain unknown, avoiding the triggers can play a useful role in management.

Specific Small Molecule Therapies

Several RMD can be treated with drugs that interact specifically with the disease mechanism (Table 5). One of the best examples is dopa-responsive dystonia, a group of disorders characterized by dystonia, sometimes with parkinsonism, in children and young adults.⁴⁶ The disorder can be caused by various defects in the synthesis of dopamine. It is most commonly caused by defects in the *GCH1* gene, which encodes an enzyme required in the synthesis tetrahydrobiopterin. Reductions in tetrahydrobiopterin reduce the synthesis of dopamine by tyrosine hydroxylase because it is a required cofactor. Bypassing the defect in dopamine synthesis with the precursor levodopa dramatically alleviates symptoms of dystonia and parkinsonism. Less commonly, dopa-responsive dystonia can be caused by defects in tyrosine hydroxylase itself.⁴⁷ Here again, dystonia and parkinsonism can be at least partially alleviated with levodopa in some cases.

Several other disorders affect the synthesis of tetrahydrobiopterin and may cause an early-onset movement disorder, often with a more general encephalopathy. Included are sepiapterin reductase deficiency,⁴⁸ 6-pyruvoyl tetrahydropterin synthase deficiency,⁴⁹ and dihydropteridine reductase deficiency. These disorders are treated with tetrahydrobiopterin in combination with levodopa and 5-hydroxytryptophan, the precursor for serotonin.

As noted previously, the paroxysmal dyskinesias associated with GLUT1 deficiency can be treated with triheptanoin.⁵⁰ The attacks of ataxia associated with mutations in the *CACNA1A* gene and episodic ataxia

TABLE 4. Trigger avoidance

Disorder	Cause (gene)	Movement disorder	Other clinical features	Common triggers to avoid or treat	Other treatment	Outcome
Alternating hemiplegia of childhood	Sodium-potassium pump (<i>ATP1A3</i>)	Paroxysmal weakness, dystonia, chorea	Developmental delay, seizures, abnormal eye movements	Stress, fatigue	Flunarizine, sleep	Symptoms can be prevented or attenuated ⁴⁵
Biotin-thiamine responsive basal ganglia disease	Thiamine transporter (<i>SLC19A3</i>)	Episodic or progressive dystonia, parkinsonism, ataxia	Encephalopathy, seizures	Metabolic decompensation caused by fasting, infection or fever	Biotin plus thiamine	Early treatment prevents or reverses symptoms ³³
Episodic ataxia type 2	Cacna1a	Ataxia (episodic and progressive), dystonia	Migraines, epilepsy	Stress, fasting, fatigue	4-aminopyridine, acetazolamide	Prevention or reduction of attacks ⁵¹
Glutaric aciduria type 1	Glutaryl coa dehydrogenase (<i>GCDH</i>)	Dystonia, parkinsonism	Developmental delay, encephalopathic crises	Metabolic decompensation caused by fasting, infection or fever	Dietary lysine restriction, L-carnitine	Treatment of triggers mitigates long-term deficits ^{42,43}
Maple syrup urine disease	Branched chain alpha-ketoacid dehydrogenase complex (<i>BCKDHA</i> , <i>BCKDHB</i> , <i>DBT</i>)	Dystonia, tremor, ataxia (may be paroxysmal)	Developmental delay, episodic encephalopathy	Dietary non-compliance, or metabolic decompensation caused by fasting, infection or fever	Dietary leucine restriction	Treatment of triggers mitigates episodes ⁸⁵
Methylmalonic aciduria	Methylmalonyl coa mutase (<i>MUT</i>)	Dystonia, chorea	Developmental delay, auditory impairment, encephalopathic crises	Dietary non-compliance, or metabolic decompensation caused by fasting infection, or fever	Dietary protein restriction, L-carnitine	Treatment of triggers may attenuate crises ⁴⁴
Paroxysmal kinesigenic dyskinesia	Multiple causes (eg, <i>Prrt2</i>)	Dystonia, chorea, tremor				Prevents symptoms in many cases ⁵²
Paroxysmal nonkinesigenic dyskinesia	Multiple causes	Dystonia, chorea, tremor		Sudden movement, stress, fatigue	Carbamazepine, other anticonvulsants	Prevents symptoms in many cases ⁵²
Propionic acidemia	Propionyl coa carboxylase (<i>PCCA</i> , <i>PCCB</i>)	Dystonia, chorea	Developmental delay, encephalopathic crisis, seizures optic atrophy	Dietary non-compliance, or metabolic decompensation caused by fasting, infection or fever	Dietary protein restriction, L-carnitine	Early treatment prevents or mitigates symptoms ⁴⁴
Rapid onset dystonia-Parkinsonism ¹	Sodium-potassium pump (<i>ATP1A3</i>)	Dystonia, parkinsonism, tremor, ataxia	Cognitive or psychiatric impairment, seizures	Emotional or physical stress, fatigue, alcohol		Complete or partial prevention of symptoms ⁴⁵

Many of these disorders have variable or mixed phenotypes. The most common or most dominant movement disorder shown in boldface type. The term *metabolic decompensation* refers to a state in which the body's consumption of a metabolite (e.g. energy.) exceeds supply.

TABLE 5. Specific drugs

Disorder	Cause (gene)	Movement disorder	Other clinical features ²	Treatment	Outcome
Aromatic amino acid decarboxylase deficiency	Aromatic amino acid decarboxylase (<i>AADC</i>)	Dystonia	Developmental delay, hypotonia, oculogyric crises	Dopamine agonists, monoamine oxidase inhibitors, pyridoxine	Partial reversal of symptoms in some cases ^{39,40}
Dopa-responsive dystonia, classic	GTP cyclohydrolase (<i>GCH1</i>)	Dystonia, parkinsonism, spasticity	Motor delay	Levodopa	Complete reversal of most symptoms ^{46,86}
Dopa-responsive dystonia, complex	Tyrosine hydroxylase (<i>TH</i>)	Dystonia, parkinsonism, spasticity, myoclonus	Developmental delay, encephalopathy, oculogyric crises, autonomic dysfunction	Levodopa	Complete or partial improvement of symptoms ⁴⁷
Dopa-responsive dystonia, complex	6-pyruvoyl tetrahydropterin synthase (<i>PPTS</i>)	Dystonia, parkinsonism, spasticity	Developmental delay, encephalopathy, oculogyric crises, autonomic dysfunction	Levodopa, 5-hydroxytryptophan	Complete or partial improvement of symptoms ⁴⁹
Dopa-responsive dystonia, complex	Sepiapterin reductase (<i>SPR</i>)	Dystonia, parkinsonism, spasticity	Developmental delay, encephalopathy, oculogyric crises, autonomic dysfunction	Levodopa, 5-hydroxytryptophan	Complete or partial improvement of symptoms ⁴⁸
Episodic ataxia type 2	Calcium channel <i>CaV2.1</i> (<i>CACNA1A</i>)	Ataxia (episodic and progressive), dystonia	Migraines, epilepsy	4-aminopyridine, acetazolamide	Prevention or reduction of attacks ⁵¹
GLUT1 deficiency	Glucose transporter (<i>GLUT1</i>)	Paroxysmal or chronic dystonia, ataxia, chorea, myoclonus	Developmental delay, seizures, alternating hemiplegia	Ketogenic diet, triheptanoin	Treatment reduces symptoms ^{50,84}
Molybdenum cofactor deficiency	Multiple molybdenum-dependent enzymes (eg, <i>MOCST</i>)	Dystonia, parkinsonism	Developmental delay, encephalopathy, seizures	Cyclic pyranopterin monophosphate (for <i>MOCST</i>)	Early treatment prevents symptoms ⁸⁶
Paroxysmal kinesigenic dyskinesia	Multiple causes (eg, <i>Prr12</i>)	Dystonia, chorea, tremor	Triggered by sudden movement, stress, other factors	Carbamazepine, other anticonvulsants	Prevents symptoms in many cases ⁸²

Many of these disorders have variable or mixed phenotypes. The most common or most dominant movement disorder shown in boldface type.

type 2 can be treated with acetazolamide or 4-aminopyridine. A randomized controlled trial comparing these 2 agents for this disorder is under way.⁵¹ The exact mechanism of action is not known, but these drugs are likely to affect the function of the calcium channel that is affected in this disorder. The attacks of dystonia in paroxysmal kinesigenic dyskinesia can be suppressed with small doses of carbamazepine and sometimes other anticonvulsants.⁵² Here, the exact mechanism of action also is not known, but the drugs are often quite effective.

Diagnostic Strategies

For many of the RMD described previously, early treatment is often needed to prevent permanent neurological symptoms that result from irreversible injury to the nervous system. Because of the large numbers of RMD with overlapping phenotypes, fast and accurate diagnosis is often challenging. Although it is beyond the scope of the current review to provide detailed diagnostic algorithms for all RMD, some general principles are very useful for early recognition. One helpful strategy focuses on the recognition of red flags, which are specific clinical or laboratory findings that point to a single disorder or group of disorders.⁵³⁻⁵⁵ Examples include Kayser-Fleischer rings of Wilson's disease or the tortuous scleral blood vessels of ataxia telangiectasia. When present, these red flags can be very useful. However, this strategy is not sufficient in many circumstances, because the number of red flags is constantly growing, and it is challenging to be aware of all of them. In addition, many red flags are subtle or sometimes missing where they are expected. Finally, many rare disorders lack specific red flags.

Another helpful strategy involves delineating phenotypic syndromic patterns.⁵⁶⁻⁶⁰ Here, a thorough examination is conducted to identify the full spectrum of clinical abnormalities. The exam may be supplemented by laboratory studies or neuroimaging, and various algorithms have been proposed to guide workup of certain RMD.^{59,61-63} Collectively, the findings constitute a pattern of clinical and laboratory features that point to a diagnosis. For example, the combination of any movement disorder with impaired range of eye movements and hearing loss is suspicious for a mitochondrial disorder, especially when combined with evidence for elevated plasma lactic acid.⁶⁴ When apparent, syndromic patterns can provide very useful diagnostic aids. However, this strategy has some of the same limitations as the red flag strategy. There are many overlapping syndromes, and it is hard to keep informed about all of them. Furthermore, partial or atypical syndromes may not present a readily recognizable pattern. For example, some patients with ataxia telangiectasia present with dystonia or chorea rather than ataxia, and they may lack ocular telangiectasias.⁶⁵⁻⁶⁸ Therefore, the syndromic approach to diagnosis is not always successful.

Neuroimaging studies can also provide an important guide to diagnosis by providing information for broad differentiation between disorders of gray matter versus white matter (leukoencephalopathies).⁵⁷ Neuroimaging studies that can also provide red flags or aid in recognition of a syndromic pattern. A classic red flag is the "eye of the tiger" sign on brain MRI in pantothenate kinase associated neurodegeneration.^{69,70} Other patients present with highly characteristic imaging abnormalities that are anatomically limited to the caudate, putamen, pallidum, thalamus, and/or cerebellum.^{69,70} For certain genetic disorders, abnormal T2 or fluid attenuated inversion recovery (FLAIR) signal abnormalities limited to the putamen are characteristic of Leigh disease, whereas those that more prominently affect the pallidum point to methylmalonic aciduria or neurodegeneration with brain iron accumulation. Anatomically specific lesions precisely demarcating various portions of the basal ganglia or other regions can also be seen with infectious disorders such as acute striatal necrosis due to mycoplasma infection⁷¹ or immune-mediated disorders that target basal ganglia antigens such as dopamine receptors.⁷² The absence of MRI abnormalities (other than atrophy) may itself narrow the differential diagnosis because few disorders remain entirely normal, including some genetic causes of parkinsonism, Niemann-pick type C, the neuronal ceroid lipofuscinoses, and *ADCY5*-associated disorders.

For genetic disorders, modern genetic methods have begun to provide another approach for diagnosis. It is now possible to sequence the entire exome or genome as a clinical diagnostic test or to sequence large panels of genes associated with a movement disorder.⁷³⁻⁷⁶ For example, currently available ataxia panels may evaluate more than 300 genes at once. The main challenge in using the modern genetic methods is that the results can be difficult to interpret, with abnormal findings in multiple genes, often of uncertain significance. The use of these methods often requires that the results are discussed with clinicians who can provide the expertise whether the molecular findings fit the clinical phenotype of the patient and can lead the clinician to reevaluate the patient in a search for additional clinical evidence relating to any unexpected genetic findings.^{75,76} The rapid advances in genetics and increased numbers of genetically defined diseases with varying clinical manifestations call for close multidisciplinary cooperation between neurologists and geneticists. Joint case conferences and international internet-based resources may facilitate exchange of expertise with respect to both diagnosis and management of rare disorders.

Educational Resources

Counseling and education play an important role in raising awareness of RMD and in establishing effective

treatment plans. Because it is challenging to provide a comprehensive review of all RMD, guides for additional resources are very valuable. These resources have become plentiful in the past 5 years. Previously, patients and family members sought information on the web focusing on individual disorders. As each individual illness is rare, scaling up resources and advocacy become imperative. Thus, organizations exist to connect patients to information such as www.rarediseases.org (USA), www.raredisorders.ca (Canada), www.eurordis.org (Europe), and www.orpha.net (multilingual portal for information on diagnosis and treatment of rare diseases). These resources provide excellent information on definitions, government policy surrounding development of treatments, and access to resources in the community as well as medical information. Most sites link to the National Institutes of Health website GARD (Genetic and Rare Diseases Information Center). This site contains some information, but many rare disorders are not included.

Physician resources for rare disorders need to aid diagnosis and must be integrated into phenotypically based guides to the differential diagnosis of movement disorders. Comprehensive resources for rare disorders include Orphanet (www.orpha.net), Simulconsult (www.simulconsult.com), and Online Mendelian Inheritance in Man (www.omim.org). For genetically determined movement disorders, an online tool named MDSGene (www.mdsgene.org), supported by the International Parkinson and Movement Disorders Society, has recently been launched. It aims to facilitate searches to match symptoms and signs to genetic diagnoses.⁷⁷ To our knowledge, an analogous tool tailored to nongenetic movement disorders has not been developed. These resources must also educate on the natural history, treatment, and required monitoring of these disorders. For many genetically determined rare disorders, GeneReviews is a frequently updated resource. Orphanet also includes an online library of review articles and practice guidelines for health care professionals; however, the coverage of rare movement disorders is not complete. As for patient resources, identifying gaps in existing resources is a natural role for the RMD Study Group.

Future Developments

Rapid advances in inherited diseases have led to the discovery of multiple tractable therapeutic targets in recent years. As a result, numerous clinical trials are underway. For example, excessive brain iron deposition has been identified for several disorders including neurodegeneration with brain iron accumulation, Friedreich's ataxia, and others. Trials with iron chelators are underway and will likely require longitudinal study designs sensitive to disease progression to

establish efficacy. A number of other disorders have been linked with limitations in brain energy production via glucose, such as GLUT1 deficiency. These observations have led to preliminary trials of triheptanoin, a triglyceride that can also provide an alternative brain energy substrate, for patients with GLUT1-related paroxysmal dyskinesia.⁵⁰ A larger trial that includes other GLUT1 phenotypes is now underway.

For many inherited diseases, the replacement of the defective gene or protein provides an obvious approach to therapy. Although preclinical studies have shown the promise of this strategy for many diseases, only one has reached clinical application. Gaucher disease is an autosomal recessive lysosomal storage disorder caused by glucocerebrosidase deficiency, with accumulation of glucosylceramide and its deacylated form, glucosylsphingosine. Three classical phenotypes are recognized: nonneuropathic, acute neuropathic with infantile onset, and chronic neuropathic. The neurological manifestations are thought to result from glucosylsphingosine accumulation in the brain. Intravenous enzyme replacement therapy is available via recombinant glucocerebrosidase.⁷⁸ This therapy is remarkably effective in reducing glucocerebroside storage in peripheral tissues and preventing systemic complications. Unfortunately, establishing any potential effect of this therapy on the neurological features is more challenging. Any potential symptomatic effects depend on whether the enzyme can reach the brain and whether pathology and associated symptoms are reversible or at least stabilized by therapy.⁷⁹ It remains to be determined if enzyme replacement therapy might benefit the brain and associated movement disorder. Gaucher disease has classically been viewed as an autosomal recessive disorder with three distinct phenotypes. Recently, the heterozygous carrier state has been shown to increase the risk of adult-onset Parkinson disease.⁸⁰ The mechanisms by which the gene defect might contribute to development of disease remains uncertain, and no information is available on the use of enzyme replacement therapies in this population.

Although enzyme replacement therapy is a theoretically attractive strategy for many inherited disorders, it is not always certain that the nervous system will benefit. In some cases, the effects of peripherally administered enzyme may be effective in some regions of the body, but they may not reach the brain where they may be needed to prevent or reverse symptoms. In other cases, nervous system injury may not be reversible, and neurological symptoms may not improve. Here, the treatment strategy may slow or stop progression of disease, or may require early institution of therapy as a preventive approach. Establishing efficacy is challenging because of the requirement for long-term studies.

Despite remarkable therapeutic advances in recent years, many disorders lack specific therapies, and many questions regarding existing therapies remain to be answered. For example, the spectrum of side effects and long-term outcomes are poorly characterized for many treatments. In principle, these knowledge gaps can be addressed by disease-specific patient registries. Such registries have been developed for many rare disorders already.

Another challenge arises when multiple treatment options are available because it can be challenging to know which is the best choice. One good example is Wilson's disease, where copper chelation with penicillamine was the first available treatment, and the additional options of trientine or zinc were developed later. Another option, tetrathiomolybdenate, has been in clinical trials for several years. Although some experts continue to view penicillamine as the gold standard, others prefer the alternatives because they have a lower risk of causing deterioration after therapy is started.⁸¹ Rigorous trials comparing these treatment options are difficult, although patient-registries may provide sufficient observational data to make recommendations.

Summary

Although the main focus of this review is on mechanism-based treatments for inherited RMD, in principle, all disorders are "treatable," at least symptomatically. For many RMD, apart from the specific treatments outlined above, a mainstay of treatment involves physiotherapy and balance training, and ambulatory aids to maintain autonomy and prevent falls. Counseling of patients and caregivers and providing information about support groups are important for comprehensive management of all RMDs.⁵¹

The current review summarizes more than 30 RMD that now have more specific treatments based on underlying disease mechanisms. Overall, there are some important general principles. First, approximately one third are managed by dietary restrictions, which must be maintained throughout life to reduce symptoms or avoid their recurrence. The emergence of symptoms in an adult may indicate poor adherence to the diet. Second, several RMD are triggered or worsened by specific factors, and avoidance or rapid management of the triggers plays a critical role in management. Thus early diagnosis is important to develop a plan to address the triggers before they cause problems. Third, many available treatments completely prevent or eliminate symptoms when initiated at a young age, although partial benefits may sometimes occur even after symptoms are well-established. These observations reinforce the need for early diagnosis. Fourth, many RMD first present in infants or young children, but in virtually all cases, may

not present until adolescence or adulthood. These observations mean that RMD are relevant for both pediatric and adult neurologists. Fifth, many RMD present with classical syndromes, but partial or atypical phenotypes are frequent. These observations mean that clinicians must maintain a high index of suspicion.

Fortunately, a variety of strategies can be used to facilitate the early recognition and diagnosis of inherited RMD, using red flags, pattern recognition, and neuroimaging. Large gene sequencing panels or whole-exome or genome sequencing are playing an increasingly important role. These new genetic methods do not eliminate the need for careful evaluation of the clinical phenotype, but instead place the clinician in a new role of validating genetic findings through further clinical assessments or functional assays.⁷⁵ The rapidly growing molecular definition of RMDs is paving the way for a shift from symptomatic to disease-specific treatments. Fortunately, special rules are available for rare disorders in most countries, and they are being increasingly used to obtain approvals for new treatments on a "fast track."^{82,83} These advances may ultimately be relevant to more common neurological disorders. ■

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