



Treatable Inherited Movement Disorders in Children: Spotlight on Clinical and Biochemical Features

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ABSTRACT: Background: About 80% of monogenic metabolic diseases causing movement disorders (MDs) emerges during the first 2 decades of life, and a number of these conditions offers the opportunity of a disease-modifying treatment. The implementation of enlarged neonatal screening programs and the impressive rapid increase of the identification of new conditions are enhancing our potential to recognize and treat several diseases causing MDs, changing their outcome and phenotypic spectrum.

Methods and Findings: A literature review of monogenic disorders causing MDs amenable to treatment was conducted focusing on early clinical signs and diagnostic biomarkers. A classification in 3 broad categories based on the therapeutic approach has been proposed. Some disorders result in irreversible neurotoxic lesions that can only be prevented if treated in a presymptomatic stage, and others present with a progressive neurological impairment that a timely diagnosis and treatment may reverse or improve. Some MDs are the result of the failure of intracellular energy supply or altered glucose transport. The treatment in these conditions includes vitamins or a metabolic shift from a carbohydrate to a fatty acid catabolism, respectively. Finally, a group of highly treatable MDs are the result of defects of neurotransmitter metabolism. In these disorders, the supplementation of precursors or mimetics of neurotransmitters can deeply change the disease natural history.

Conclusions: To prevent serious and irreversible neurological impairment, the diagnostic work-up of MDs in children should consider a number of clinical red flags and biomarkers denoting specifically treatable diseases. View Supplementary Video

Movement disorders (MDs) are among the most severe causes of neurological disability emerging during childhood and adolescence. Epidemiologic data are available for specific conditions, such as cerebral palsy,¹ whereas the cumulative prevalence of childhood-onset MDs is unknown. Many reasons underlie this difficulty, such as (1) the relevant etiological heterogeneity and phenotypic pleiotropy of diseases causing early-onset MDs; (2) age-related variability of phenomenology during the first years of life; (3) the lack of a consensus classification of MDs in infancy and early childhood besides that for cerebral palsy; (4) the presence of comorbid conditions, such as epilepsy, developmental delay (DD), or intellectual disability (ID), which may polarize the clinical classification; and (5) an impressive rapid

increase of the identification of new conditions because of the implementation in clinical practice of Next Generation Sequencing (NGS) techniques.

About 80% of monogenic metabolic diseases causing MDs emerges during the first two decades of life.² DD, neurological deterioration, epilepsy, and MDs are the most recurrent symptoms associated with these conditions. For a growing number of them, a specific treatment is now available aimed at correcting the metabolic alteration as such and/or its pathological consequences. This approach, which may be considered disease modifying, in contrast with a pure symptomatic treatment, results in a variable positive outcome depending on the timely incisiveness of the treatment with respect to the physiopathology of the

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disease. Focusing on the treatment strategy, we can classify these diseases according to the main target of the interventional approach:

1. Preventing or minimizing neurotoxic damage resulting from the metabolic alteration. In a few conditions, neurotoxic damage may be early, rapid, and irreversible, and the only way to prevent it is a presymptomatic diagnosis made possible by a newborn screening (NBS) program implementation. In other disorders, the neurotoxic effect is more progressive and partially reversible and/or they are not included in presymptomatic diagnostic programs so that the therapy follows a conventional clinically oriented diagnostic work-up.
2. Correcting energetic failure. In a few treatable conditions, the neurometabolic alteration affects primarily the intracellular mechanisms of energy supply from which the basal ganglia (BG) are strictly dependent. The treatment in these conditions is aimed at improving the activity of the defective enzyme or at producing a compensatory metabolic shift.
3. Supplementing defective metabolites (or medicaments mimicking their effects) that the brain is not able to synthesize.

Virtually each metabolic alteration involving the central nervous system (CNS) may present with or develop later MDs. Several recent articles offered a systematic review of this topic.³ The aim of this article is to focus on early-onset diseases with MD as a main or presenting symptom. Table S1 summarizes the relevant disorders according to the different treatment approaches.

Treatment Aimed at Preventing or Minimizing Neurotoxic Damage

Diagnosis Through NBS and Consequent Presymptomatic Treatment

Glutaric Aciduria Type 1

Glutaric aciduria type 1 is the result of the recessive inherited defect of the enzyme glutaryl-CoA dehydrogenase, a flavin adenine dinucleotide-dependent mitochondrial matrix protein involved in the catabolism of L-lysine, L-hydroxylysine and L-tryptophan. The glutaryl-Coenzyme A (CoA) dehydrogenase defect results in the accumulation of glutaric acid, 3-OH-glutaric acid, and glutaconic acid in biological fluids and particularly in nervous tissue.⁴ Multiple cellular mechanisms are involved in the pathogenesis of brain toxicity.⁵ According to the residual enzyme activity, the biochemical phenotype is characterized by high (<2% of residual activity) or low (3%–30% of residual activity) excretion of glutaric acid in urine.⁶ The 3-hydroxy (OH)-glutaric acid in urine is usually elevated whatever the subtype. Approximately 90% of affected children present with clinical symptoms before age 36 months.^{7–9} Classical presentation is

characterized by severe neurological regression emerging as encephalopathic crisis precipitated by catabolic status (eg, intercurrent illnesses, routine vaccinations, etc.) or minor head trauma. Severe impairment of postural reactions is associated with generalized dystonia and dyskinesia (Video S1).^{7–9} Associated neuroradiological findings include frontotemporal atrophy, bilateral striatal lesions, delayed myelination, subependymal pseudocysts, chronic subdural effusions, hematomas, and white matter alterations (Fig. 1).^{9–11} Acute encephalopathic crises are improbable after age 5 years, suggesting a specific vulnerability of the immature brain to the metabolic alterations as a result of the disease.

Alternative clinical presentations include insidious and late (after the age of 6) onset forms. The former is characterized by the progressive emergence of generalized dystonia without obvious precipitating events. Brain lesions are circumscribed to the dorsolateral putamen without atrophy on follow-up.¹¹ The latter embraces a wide range of ages at onset (including individuals aged older than 60 years) and patterns of clinical penetrance including absence of symptoms, minor occasional neurological symptoms (headache, vertigo), ID, epilepsy, progressive dementia, tremor (persistent or paroxysmal), orofacial dyskinesia, peripheral polyneuropathy, and chronic kidney disease.¹² Brain magnetic resonance imaging (MRI) alterations include frontotemporal hypoplasia, white matter changes, and subependymal mass lesions.¹²

Metabolic treatment, consisting of a low-lysine and a carbohydrate-enriched diet, carnitine supplementation, and a low-protein to no-protein diet during catabolic status,¹³ is aimed at reducing the cerebral accumulation of neurotoxic dicarboxylic metabolites.¹⁴ Although this approach improves the outcome of symptomatic patients by preventing the consequences of further metabolic decompensations, it cannot restore the damaged nervous tissue. To make presymptomatic treatment possible, NBS for Glutaric aciduria type 1 (GA1) has been implemented in several countries disclosing a different clinical spectrum of this complex disease: (1) 93% of patients identified by NBS and receiving timely and strict metabolic treatment according to the guideline recommendations remains asymptomatic; (2) delayed or inadequate treatment and/or delayed treatment during catabolic status results in acute onset dystonia in children younger than 3 years and insidious dystonia later; (3) glomerular filtration rate declines over time, or intermittently in some cases, and does not seem to be prevented by the treatment.¹⁵ Whether this precludes to overt kidney failure remains to be established.

Homocystinuria

Homocystinuria is a disorder of methionine metabolism caused by cystathionine β -synthase (CBS) deficiency, leading to an abnormal accumulation of homocysteine (Hcy) and its metabolites in blood and urine.¹⁶ Hcy is detoxified in the cells via trans-sulfuration (liver and kidney) and remethylation pathways (vascular tissues and skin). In the case of excessive cellular methionine levels, the trans-sulfuration pathway plays an important role in Hcy metabolism and converts Hcy into cystathionine with the help of the enzyme CBS. Cystathionine is then converted into

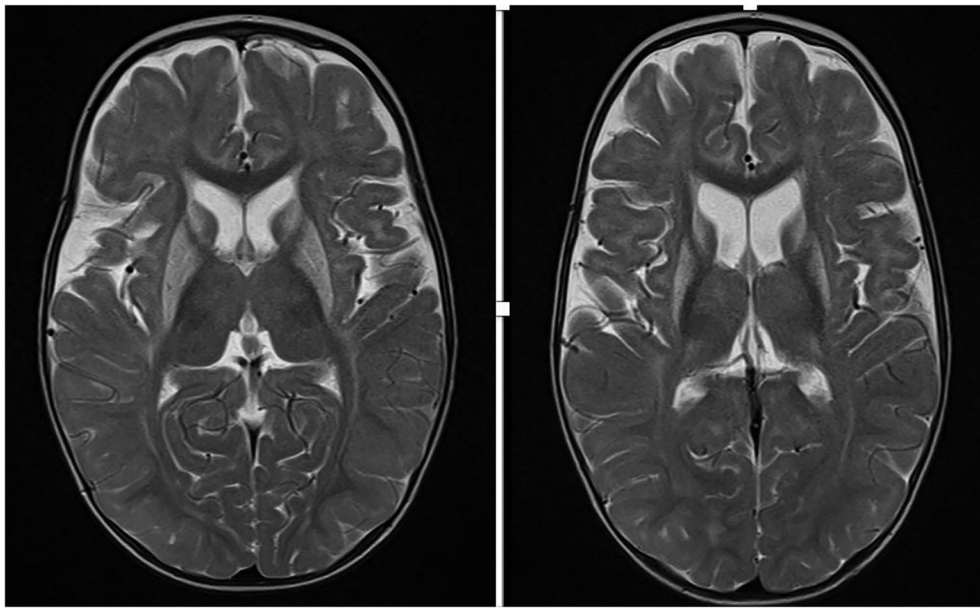


FIG. 1. Brain magnetic resonance imaging T2 sequences of a personal case with glutaric aciduria type 1 (patient shown in Video S1) disclosing bilateral basal ganglia lesions and atrophy with mild enlargement of sylvian fissures.

cysteine by cystathionine γ -lyase. However, under a low cellular methionine level, Hcy is remethylated back to methionine via the remethylation pathway.¹⁷ According to their genotype, about 47% of patients are responsive to the administration of pyridoxine (B6), which improves the biochemical alterations and the disease outcome.¹⁷

In untreated individuals, CBS deficiency results in a chronic and progressive multisystemic disease presenting during the first years of life (Table S1).¹⁷ MDs have been reported in several patients with CBS deficiency and may present as isolated during the first and second decades of life^{18,19} or associated with ID and/or optic lens dislocation.^{20,21} Both responsive and non-responsive B6 patients are equally affected. The pattern of MD is characterized by spasmodic cervical dystonia and oromandibular dystonia, progressing over time to severely disabling generalized dystonia and myoclonus dystonia unresponsive to antidystonic medications. MDs are not associated with specific brain MRI alterations or neuropathological findings²⁰ and should be differentiated from the later onset thromboembolic complications of the disease.²² MDs have been reported in untreated individuals as well as in late-treated patients with poor adherence to therapy.

In contrast, a significant reduction of vascular events has been observed in early and continuously treated patients.¹⁶ No MD has been so far reported in these patients.

Among the inherited disorders of the catabolism of branched chain amino acid (BCAAs) 4 conditions potentially detectable by NBS program—maple syrup urine disease, propionic acidemia, methylmalonic acidemia, and cobalamin C defects—may cause acute or subacute onset of MDs as result of the neurotoxic lesion of BG (Fig. 2).²³ Although it is rather exceptional that these

multisystem diseases present with MD²⁴ and, if so, in patients with late-onset presentation,²⁴ more than 20% of late-treated patients can experience dystonia and/or spasticity as a cumulative result of acute or subacute metabolic decompensations triggered by the increasing breakdown of BCAAs and circulating toxic metabolites.^{24–26} Severe forms of propionic acidemia, methylmalonic acidemia, and maple syrup urine disease are candidates for early liver transplantation to prevent severe and irreversible neurological impairment. In cobalamin C patients, presymptomatic treatment prevents or limits metabolic decompensations, Globus pallidus (GP) lesions, and related MDs.²⁷

Another possible (but currently not included in NBS programs) candidate for a disease-modifying preventive approach is the disorder of creatine synthesis as a result of guanidinoacetate methyl transferase deficiency. The disease presents with early onset neurological deterioration/developmental arrest, epilepsy, MDs (in about 50% of patients), and bilateral pallidal alterations on brain MRI (in about 30% of patients).²⁸ Although a late treatment is effective just in improving epilepsy control, a presymptomatic specific therapy proved to result in a normal neurological development.^{29,30}

Treatments Following a Classic Diagnostic Work-Up

Biotin-thiamine-responsive BG disease (BTBGD) is a potentially lethal autosomal recessive disorder caused by mutations in the *SOLUTE CARRIER FAMILY 19 (THIAMINE*

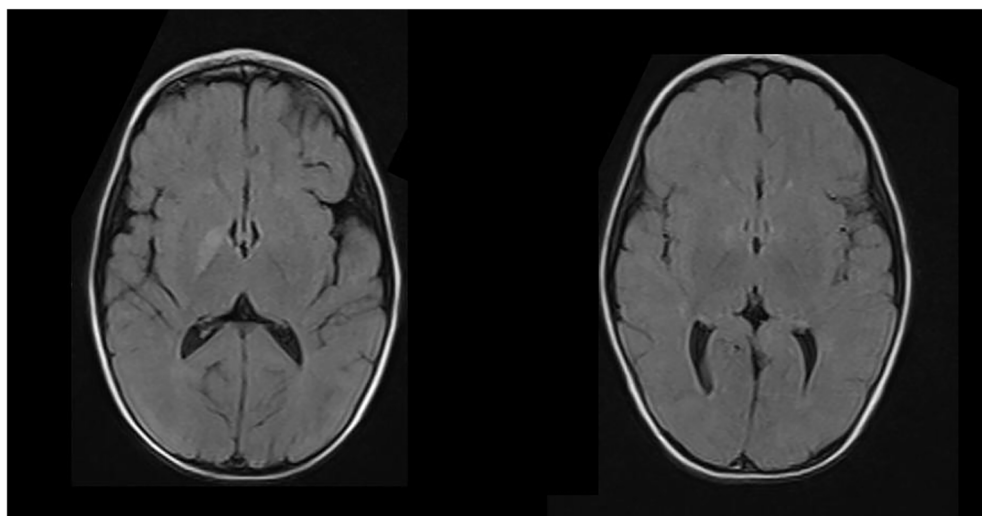


FIG. 2. Brain magnetic resonance imaging T1 sequence in a 3-year-old girl affected by cobalamin C (*MMACHC* genotype: homozygous c. 331C>T [Arg111Ter]) showing alteration of the right pallidum and head of caudatus during a metabolic decompensation episode (triggered by fever) manifesting as lower limbs dystonia (right>left) improving during the following months.

TRANSPORTER) (*SLC19A3*) gene encoding human thiamine transporter 2.³¹ This is so far the only treatable disease among those included under the term *infantile bilateral striatal necrosis*,³² primarily reported in the Saudi Arabia population. More than 100 patients have been reported so far.³³ Associated phenotypes are an early infantile (Leigh-like syndrome or atypical infantile spasms) and an adult Wernicke's-like encephalopathy.³⁴ Because human thiamine transporter 2 is not implied in biotin metabolism and transport, the therapeutic effect of biotin remains to be elucidated.³⁴ (A metabolic shift from pyruvate dehydrogenase to pyruvate carboxylase to compensate Krebs cycle impairment? Promoting effect of biotin on mRNA expression of the *SLC19A3* gene?)

BTBGD presents between 3 and 7 years of age (range 5 months to 15 years) with acute or subacute encephalopathy with confusion, dysarthria, dysphagia, occasional supranuclear facial nerve palsy or external ophthalmoplegia that progresses to severe cogwheel rigidity, dystonia, partial or generalized seizures, ataxia, quadriparesis, and coma or even death if treatment is not promptly introduced.³³ Unusual presentations were reported in a few cases, such as exercise-induced paroxysmal cephalic tremor and nystagmus,³⁵ paroxysmal focal dystonic attacks,³⁵ limbs intermittent dystonia, psychomotor regression, sudden hemiplegia, and DD.³⁶ Triggering factors such as febrile illness, mild trauma, or surgery were reported.³⁶

Brain MRI shows bilateral and symmetric lesions in the caudate head with complete or partial involvement of the putamen. The GP is usually spared. In many cases, abnormal signal changes were observed in the mesencephalon, cortical–subcortical regions, and the medial dorsal nuclei of the thalami. In advanced stages of the disease, patchy alterations were found in deep white matter.

Cerebellar cortex and vermis were involved in a few patients. The affected brain regions showed variable swelling and vasogenic edema during the acute/subacute phase. Interestingly, neither cytotoxic edema nor altered pattern of diffusion restriction on diffusion-weighted images or contrast enhancement were detected.³⁷ Brain Proton magnetic resonance spectroscopy (¹H-MRS) showed elevation of lactate within the affected regions and decrease in NAA peak and N-Acetylaspartic acid and Cr for Creatine (NAA/Cr) ratio.³⁷

The treatment of BTBGD consists of lifetime biotin and thiamine supplementation (Table S1). The timeliness of the treatment influences the neurological outcome. Late diagnosis as well as an earlier age at onset are associated with poor outcome. As a result, about one third of reported patients were normal, one third showed mild to moderate neurological deficit, and one third suffered from severe neurological impairment or died.³⁶ Under therapy, brain MRI shows vanishing of mesencephalon and cerebral/cerebellar cortical and subcortical alterations with persistence of BG alterations and the disappearance of the lactate peak at the ¹H-MRS.³⁷

One third of the patients on biotin therapy alone experiences recurrent, and in some cases lethal, encephalopathic crises that may be prevented by thiamine supplementation.³⁶ However, there is not conclusive evidence that thiamine alone may be as effective as biotin plus thiamine in BTBGD on long-term follow-up.

Defects of Valine Metabolism

Two defects of valine metabolism, deficiency of short-chain enoyl-CoA hydratase (ECHS1) and deficiency of 3-OH-

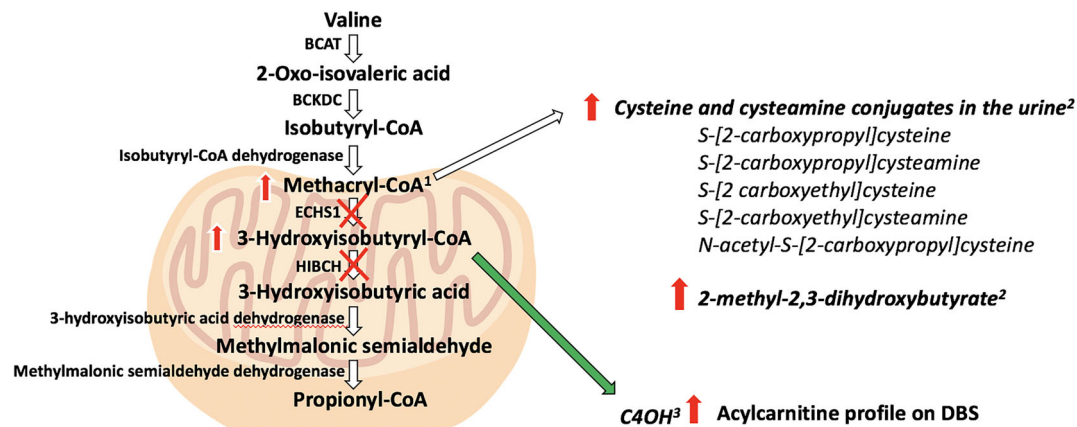


FIG. 3. Valine catabolic pathway. In italics, diagnostic biomarkers for the diagnosis. ¹Intramitochondrial methacrylyl-Coenzyme A (CoA) reacts with thiol compounds to form cysteine and cysteamine conjugates. ²Metabolites detectable in urine by Tandem Mass Spectrometry (MS/MS) and Gas Chromatography Mass Spectrometry (GCMS). ³Increased C4OH distinguish HIBCH from ECHS1 deficiency. BCAT, branched chain amino acid aminotransferase; BCKDC, branched-chain α -keto acid dehydrogenase complex; C4OH, 3-hydroxyisobutyryl-carnitine; ECHS1, short-chain enoyl-CoA hydratase; HIBCH, 3-OH-isobutyryl-CoA hydrolase.

isobutyryl-CoA hydrolase (HIBCH) are potentially treatable disorders associated with Leigh syndrome or Leigh-like syndrome.^{38–41}

ECHS1 and HIBCH enzymes catalyze the fourth and fifth steps of valine degradation (Fig. 3), respectively, and unlike their considerable clinical and biochemical overlap, can be distinguished according to specific patterns of urinary and plasmatic metabolites.³⁸

ECHS1 is a multifunctional mitochondrial matrix enzyme that hydrates the double bond between the second and third carbons of enoyl-CoA in many metabolic pathways, including mitochondrial fatty acid β -oxidation and BCAA catabolic pathways. Different authors presented evidence that despite this broad substrate specificity, ECHS1 is crucial in valine catabolism but is only of limited importance for mitochondrial fatty acid oxidation and isoleucine metabolism.^{38,42}

The accumulation of methacrylyl-CoA and acryloyl-CoA, 2 toxic intermediates that spontaneously react with sulphhydryl groups of cysteine and cysteamine, is suspected to cause brain pathology and the biochemical pattern found in HIBCH and ECHS1 deficiencies.³⁸ The cause of reduced activity of pyruvate dehydrogenase and decreased activity of the mitochondrial respiratory chain complexes in these disorders^{40,42} is not clear³⁸ but is suspected to be secondary to the accumulation of toxic metabolites. Biochemical features and diagnostic biomarkers are summarized in Figure 3 and Table S1.

A total of 40 patients with ECHS1 deficiency have been described so far, with phenotypes ranging from neonatal lactic acidosis to infantile-onset DD or regression, MDs, and seizures, with elevated plasma lactate and brain MRI abnormalities consistent with Leigh syndrome or Leigh-like syndrome.^{38,42–44} About half of the patients show a severe MD characterized by fixed and paroxysmal dystonia or choreoathetosis, with exacerbations during infectious

diseases. In the mildest affected individuals, MD can be isolated or episodic, and metabolic alterations subtle and intermittent. Isolated paroxysmal exercise-induced dystonia (PED) involving the lower limbs with bilateral pallidal MRI abnormalities has been reported in 2 patients,^{43,44} 1 of them improved after 3 months of treatment with a mitochondrial cocktail.⁴⁴

To date, about 20 patients with HIBCH deficiency have been reported, most of them presenting in early infancy with DD, neurological regression, or encephalopathic crises triggered by catabolic status. Associated neurologic features include dystonia, ataxia, spasticity, epilepsy, and optic atrophy (Video S2). The clinical course is characterized by a continuous or infections triggered neurological decline, with death in early infancy or childhood in about one third of reported cases.^{39,40,45} Bilateral hyperintense lesions in the GP and a progressive dystonic disorder are quite typical (Fig. 4). Reversible dystonic gait or paroxysmal dystonia have been reported in patient with milder phenotypes.⁴⁵

The elevation of toxic 2-enoyl-CoA compounds in HIBCH and ECHS1 deficiencies can be influenced by dietary intake. Treatment should focus on L-valine restriction, as the main pathogenesis could possibly be the accumulation of toxic methacrylyl-CoA in the mitochondria during the valine catabolic pathway.³⁹ Restricting leucine, isoleucine, and valine, instead of valine restriction alone, does decrease brain valine levels, so this approach may show better benefits. In addition, the maintenance of high glucose levels, as recommended in fatty acid oxidation defects, might be protective, preventing excess Adenosine Triphosphate (ATP) production from the catabolism of BCAAs. The administration of carnitine to activate the excretion of 3-hydroxyisobutyryl-CoA as 3-hydroxyisobutyryl-carnitine in urine could reduce the production of methacrylyl-CoA in

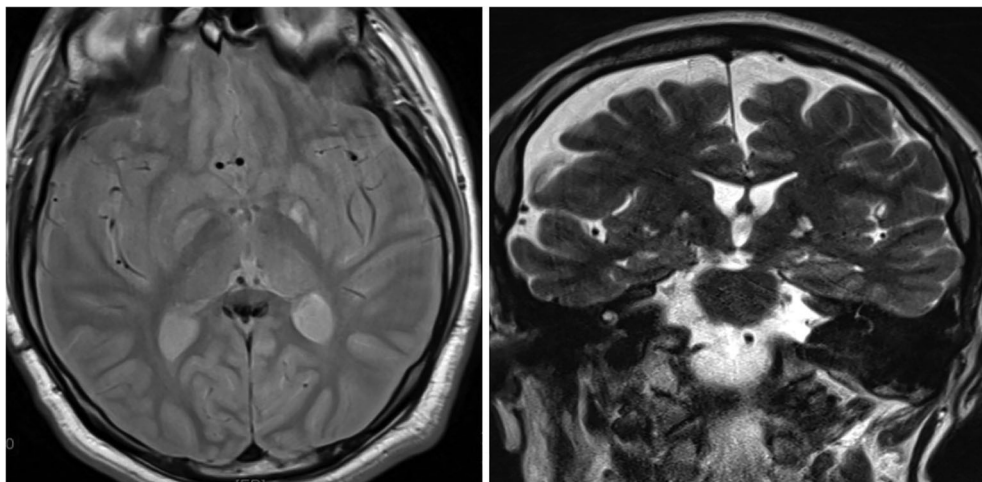


FIG. 4. Brain T2 axial and coronal sequences of a patient with 3-OH-isobutyryl-CoA hydrolase deficiency at the age of 27 years showing bilateral, discrete lesions in the globus pallidus bilaterally. The patient, now 34 years old, is shown in Video S2.

neuronal cells and is also recommended.⁴⁶ Although the efficacy and safety of these therapeutic strategies remain to be investigated, successful treatments leading to the relief of neurological symptoms have been reported (personal case and refs. 38,39, and 41).

Moreover, because the pathogenesis of both HIBCH and ECHS1 deficiencies are considered to be via the binding of thiol compounds and essential cysteine residues of mitochondrial enzymes to accumulated methacrylyl-CoA, detoxifying drugs, such as cysteamine and N-acetylcysteine, have been considered to increase intramitochondrial glutathione and suppress its consumption caused by increased methacrylyl-CoA.

Wilson Disease (WD)

WD, probably the first and most popular inherited metabolic disease associated with MD, is a disorder of copper metabolism as a result of the defect of a metal-transporting P-type ATPase, encoded by the *ATP7B* gene, leading to the decreased biliary excretion of copper. In WD, copper accumulates in the liver, CNS, and cornea, causing a degeneration of the lenticular nucleus in the brain and hepatocytes. There are 2 distinct clinical presentations: neurologic and hepatic. In children, a primary hepatic presentation, with hepatitis, cirrhosis, and hepatic decompensation in the teenage years is frequent; in adolescents and young adults, neurologic presentation is more common.⁴⁷ Psychiatric and acute hemolytic presentation have been reported. About 300 mutations in the *ATP7B* gene have been described. Severe mutations are associated with an earlier onset of the disease, but a correlation with the type of presentation (neurological vs. hepatic) has not been found.⁴⁸

The following 3 main different neurological forms of the disease have been described: the dystonic juvenile form with subacute

onset and severe progression; the pseudosclerotic or Westphal form, with juvenile–adulthood onset of tremor and dysarthria as main symptoms; and the parkinsonian form.⁴⁹ Dysarthria, gait abnormalities, dystonia, *risus sardonicus*, parkinsonian features, and dysphagia are the most frequent presenting features, typically between the first and the fourth decades of life. The majority of cases presented with complex MD. The Kayser–Fleisher ring is found virtually in all cases with neurological signs.⁵⁰

Besides the characteristic “giant panda sign” in the midbrain, brain MRI is relevant for both hepatic and neurologic presentations, with BG hyperintensities on T1-weighted images reflecting the hepatic involvement and hyperintensities on T2-weighted images nicely correlating with clinical findings in neurological forms.⁵¹

The diagnosis of WD requires a combination of tests: serum ceruloplasmin, 24-hour urinary copper, serum “free” copper, hepatic copper, and Kayser–Fleisher rings by slit lamp examinations. A diagnostic algorithm is based on the Leipzig score.⁵²

The treatment of WD consists in reducing the amount of circulating free copper via chelation of copper or reducing the intestinal absorption of dietary copper (Table S1). Treatment can be divided into initial therapy, maintenance therapy, and treatment of the presymptomatic patient.^{53,54} Penicillamine avidly chelates copper so that it is rapidly mobilized from tissues and eliminated in the urine. Neurological deterioration on initiation of treatment is a major concern of this drug as initial treatment in WD (Video S3, Fig. S1). Indeed, about 50% of those experiencing neurological deterioration on initiation of treatment never recovered to their baseline functioning. The other chelating agent, trientine, acts with a mechanism of action similar to penicillamine but with a less precipitous decoppering effect. Zinc acetate reduces intestinal absorption of dietary copper via induction of metallothionein formation in intestinal enterocytes.

Metallothionein binds both zinc and copper, trapping them within the intestinal mucosal cells, which are eventually sloughed and excreted in the feces, producing a negative copper balance. It is primarily used as maintenance therapy following initial “decoppering” treatment. Some investigators also advocate using zinc monotherapy as initial treatment. Tetrathiomolybdate has a dual mechanism of action: (1) it limits the gastrointestinal absorption of copper by forming a nonabsorbable tripartite complex with copper and albumin within the gut lumen, and (2) it forms the same complex within the bloodstream, preventing the cellular uptake of free copper.

Manganese Transport Disorders

The manganese efflux transporter Solute Carrier Family 30 (Zinc Transporter), Member 10 (SLC30A10) and the uptake transporter Solute Carrier Family 39 (Zinc Transporter), Member 14 (SLC39A14) have been recently associated with hypermanganesemia and early-onset dystonia-parkinsonism secondary to manganese (Mn) accumulation in the BG.^{56–58}

Chronic liver disease, polycythaemia, and abnormal iron indices are distinguishing features of SLC30A10 deficiency,^{56,57} with polycythemia usually preceding the MD onset. A total of 40 patients have been described with the following 2 main phenotypes: a childhood-onset predominant dystonia⁵⁹ and an adult-onset predominant parkinsonism.^{56,57,59} The majority of individuals present with a peculiar gait disturbance within the first 10 years of life (“cock-walk” gait). Writing difficulties can be a sneaky presenting sign. Motor impairment is progressive, and many patients become wheelchair bound. Early psychomotor development is usually normal, and cognition remains relatively preserved.

Biallelic mutations in *SLC39A14* have been associated with childhood-onset progressive dystonia with hypermanganesemia without polycythaemia and liver disease. The disorder, described in 14 cases, is characterized by a loss of developmental milestones and infantile-onset or early childhood-onset generalized dystonia with prominent bulbar involvement and parkinsonism. Even here clumsiness of writing can be a presenting sign.⁵⁸

The pattern of cerebral Mn deposition looks similar in patients with *SLC30A10* and *SLC39A14* mutations and is pathognomonic, with brain MRI characterized by T1-weighted hyperintensities in the GP and, to a lesser extent, the striatum, and generalized white matter T1-hyperintensity involving the cerebellum, spinal cord, and dorsal pons.

In both disorders, chelation therapy with disodium calcium edetate significantly reduces Mn levels, improves motor symptoms, and prevents disease progression.^{56–58} As in WD, chelation therapy can potentially lead to a worsening of neurological symptoms as a result of the rapid mobilization of Mn. Better outcomes have been reported in early treated patients, but clinical response is variable, possibly a result of the genotype and disease severity at treatment onset.⁵⁸

Lysosomal Disorders

CNS involvement in lysosomal disorders is scarcely influenced by current enzymatic replacement therapy. Relevant exceptions are late-infantile ceroid lipofuscinosis as a result of *TPP1* mutations Neuronal ceroid-lipofuscinosis type 2 (NCL2), and Niemann-Pick type C disease (NPC).

CLN2 is caused by biallelic mutations in *TPP1*, which encodes the lysosomal enzyme tripeptidyl peptidase 1, and is typically characterized by early-onset (2–4 years) seizures, myoclonic jerks, progressive cognitive impairment, and early (4–6 years) and dramatic visual impairment, rapidly leading to blindness. Life expectancy is usually poor. A milder phenotype with a delayed onset and a more protracted course, characterized by dystonia-parkinsonism and mental deterioration (without epilepsy or visual impairment), has been associated with the occurrence of the R447H variant in *TPP1* (in compound heterozygosity with other loss-of-function variants).⁵⁹ The recently demonstrated efficacy of intraventricular cerliponase alfa in delaying or plateauing the progression of the disease makes a timely diagnosis of the disease now important, whatever the phenotypic presentation.⁶⁰

NPC is an autosomal recessive (AR) neurovisceral disorder as a result of either *NPC1* or *NPC2* gene mutations. The pathogenesis relies on abnormal endosomal-lysosomal trafficking of cholesterol, resulting in the accumulation of multiple lipids in the lysosomes.⁶¹ Clinical features and diagnostic biomarkers are summarized in Table S1. The classic presentation is in middle to late childhood with subtle ataxic features, vertical supranuclear gaze palsy, and an insidiously progressive cognitive decline. A combination of cerebellar ataxia and action dystonia, with dystonia in 1 limb and gradually generalizing is typical. Reduced pursuit movements, impaired horizontal saccades,⁶² mixed dysarthria and dysphonia, and dysphagia progressing in parallel with speech difficulties further characterize the disease course.^{61,63}

Miglustat, a glucosylceramide synthase that prevents ganglioside accumulation in the brain through a substrate reduction mechanism, has proven a long-term impact on neurological progression in patients with late infantile, juvenile, and adult forms, regarding to ocular motility disturbances, dysphagia, ambulation, fine/gross motricity, and cognitive decline.⁶⁴ Treatment benefits seem less predictable in patients with early infantile onset, with severe manifestations at treatment start, and in those who start treatment late in the disease course.

In parallel, the diagnostic approach to this condition has radically changed in recent years as a result of the emergence of a number of peripheral biomarkers that have made the diagnosis much easier, replacing the Filipin staining in fibroblast, the historical gold standard assay for diagnosis.

Furthermore, a number of plausible biomarkers and imaging measures for treatment monitoring have been proposed or are still under investigation, such as chitotriosidase and chemokine (C-C motif) ligand 18 (CCL18) values, CSF calbindin immunoassay, Choline/Creatine (Cho/Cr) ratio in ¹H-MRS studies, cerebral metabolism evaluated by positron emission tomography

imaging, and fractional anisotropy of specific white matter regions in diffusion tensor imaging studies.⁶⁴

Treatments Aimed at Correcting Energetic Failure

Glucose Transporter 1 (GLUT1) Deficiency

GLUT1 deficiency syndrome (Glut1-DS) is caused by impaired glucose transport across the blood–brain barrier and into astrocytes as a result of heterozygous, mostly de novo, mutations in the *SLC2A1* gene encoding GLUT1.

The reduced cerebral glucose availability observed in Glut1-DS leads to impairment of acetyl-CoA production, reduced glucose-dependent neurotransmitter production (eg, glutamate and GABA), and synaptic dysfunction. Milder phenotypes with intermittent symptoms may be associated with 25% to 35% reduction in GLUT1 transporter function, whereas more severe phenotypes result from reductions between 40% to 75%.⁶⁵

The accumulated data on Glut1-DS has led to a revision of the classification in distinct phenotypes⁵⁴ in favor of a spectrum including the pleiotropic manifestations of this condition.^{65,66}

MDs, both paroxysmal (episodic ataxia, PED, choreoathetosis, paroxysmal nonkinesigenic dyskinesia [PNKD], alternating hemiplegia) and nonparoxysmal (ataxia, spastic-ataxia, dystonia, myoclonus, tremor, chorea), can present isolated or as part of a broader syndromic combination. Complex MDs can be observed at any age and can be fixed, paroxysmal, or fixed with fluctuations triggered by fasting and infectious events.^{66,67} PED is the most typical MD associated with this condition. Episodic eye-head movements can be the presenting sign of infantile forms.⁶⁸

Paroxysmal events such as weakness, unresponsiveness, confusion, lethargy, headache, vomiting, dysautonomia, and dysphoria are quite typical.⁶⁹ The phenotype varies according to the age at onset, with epilepsy more frequent in childhood and MD in adulthood. Varying degrees of cognitive and language impairment are observed.

Diagnosis is established in a proband with suggestive clinical findings, CSF glucose concentration <60 mg/dL, and/or a pathogenic variant in *SLC2A1*. The CSF/blood glucose ratio, previously considered the main criteria for diagnosis, has been demonstrated to be less reliable than the absolute CSF glucose value.⁷⁰ A ketogenic diet (KD) is still considered the standard of care and is highly effective in controlling seizures and paroxysmal episodes; other neurological symptoms such as ataxia, dysarthria, and cognition tend to be less responsive.⁷¹ Individuals treated effectively at a younger age have a better outcome.⁶⁷

Recently, an increased rate of detection of Glut1-DS patients with less severe phenotypes has raised interest in the adaptation of KD, such as the modified Atkins diet, and nutritional variants. In this regard, triheptanoin, a synthetic odd-chain triglyceride

with anaplerotic properties, has shown efficacy in patients with nonepileptic paroxysmal manifestations.⁷²

Pyruvate Dehydrogenase Deficiency

Pyruvate dehydrogenase complex (PDHC) deficiency is a rare metabolic disorder affecting tissues with high energy demand such as the CNS and resulting in a wide spectrum of clinical presentations and outcomes.^{73,74}

PDHC is an enzymatic assembly located in the mitochondrial matrix that serves as a link between glycolysis and the Krebs cycle, catalyzing the oxidative decarboxylation of pyruvate to acetyl-CoA. Defects in PDHC results in decreased acetyl-CoA synthesis and the accumulation of pyruvate and lactate.

PDHC includes 3 main subcomplexes (E1–E3) and several coenzyme factors. E1, a heterotetramer of alpha and beta subunits encoded by the *PDHA1* and *PDHB* genes, respectively, is the main regulatory site of the complex binding thiamine pyrophosphate (TPP) and catalyzing a TPP-dependent decarboxylation of pyruvate. E2 and E3 catalytic enzymes are encoded respectively by the *DLAT* and *DLD* genes. E3 is bound to E2 by the E3 binding protein encoded by *PDHX*.

Between 70% and 90% of PDHC deficiencies arise from mutations in the X-linked *PDHA1* gene.⁷⁴ Most of them involve or are near to the TPP binding site of *PDHA1* and are responsive to thiamine treatment.⁷⁵ Rarer mutations have been identified in the *PDHX*, *DLAT*, *DLD*, and *PDHB* genes.

The reports of paroxysmal dystonia in a minority of patients with *PDHA1*, *DLAT*, and *PDHX* mutations expanded the clinical spectrum of PDHC deficiency.^{73,76–79}

In some cases, a paroxysmal MD occurs in children already suffering from neurological impairment (inconsolable crying, feeding difficulties, nystagmus, jerky head movements, floppiness, DD, ataxia, and oculomotor apraxia).^{76,77,80} In a few patients,^{76,80} paroxysmal MD was the presenting sign, with age at onset 5 months to 15 years, variable distribution (focal/segmental or generalized), and triggering circumstances suggestive of PNKD, PKD, or PED.^{73,78,80} Almost all patients showed MRI pallidal alterations.^{73,77,78,80}

Patients with PDHC deficiency do not oxidize carbohydrates efficiently, hence the pyruvate derived from glycolysis is reduced to lactate. This has led to the widespread use of KD, which reduces the intake of exogenous carbohydrates and bypasses the entire PDHC, providing an alternate source of acetyl-CoA.

KD in PDHC deficiency helps to control epilepsy, paroxysmal dystonia, and ataxia and improve motor control and cognitive functioning;⁷⁷ this benefit in the most severely affected patients remains controversial.⁷³

A remarkable response to thiamine has been reported in 2 patients with MD, one with isolated PED⁷⁸ and the other with acute ataxia during a febrile illness,⁷⁵ carrying *PDHA1* variants affecting a specific residue located in the TPP binding site (p. Leu-216).^{75,78}

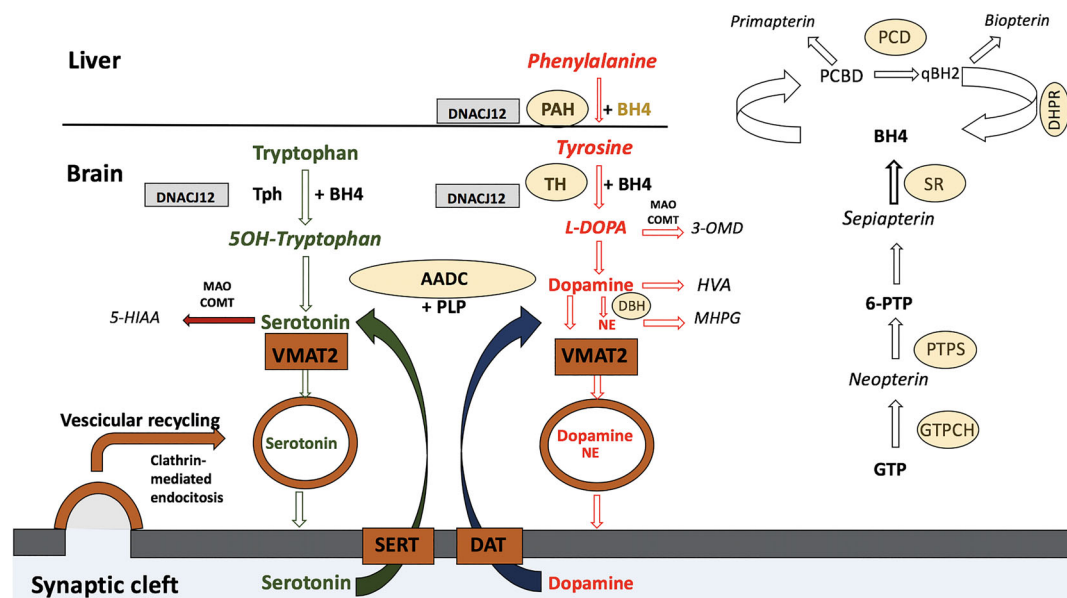


FIG. 5. Metabolic pathways of biogenic monoamine neurotransmitters. In italics, diagnostic biomarkers on cerebrospinal fluid for the diagnosis of these conditions. AADC, aromatic-L-amino acid decarboxylase; BH2, quinonoid dihydrobiopterin; BH4, tetrahydrobiopterin; COMT, catechol-O-methyltransferase; DAT, dopamine transporter; DBH, dopamine beta-hydroxylase; DNACJ12, XXXXXXX; GTP, guanosine triphosphate; GTPCHI, GTP-cyclohydrolase I; 5-HIAA, 5-hydroxyindoleacetic acid; 5-HTP, 5-hydroxytryptophan; HVA, homovanillic acid; MAO, monoamine oxidase; MHPG, 3-methoxy-4-hydroxyphenylglycol; NE, norepinephrine; OMD, XXXXXXX; PAH, XXXXXXX; PCBD, XXXXXXX; PCD, XXXXXXX; PLP, pyridoxal-5-phosphate; PTP, XXXXXXX; PTPS, 6-pyruvoyl-tetrahydropterin synthase; qBH2, XXXXXXX; SERT, serotonin transporter; SR, XXXXXXX; Tph, tryptophan hydroxylase; TH, tyrosine hydroxylase; VMA, vanillylmandelic acid; VMAT2, vesicular monoamine transporter 2.

Although thiamine-sensitive forms are potentially restricted to *PDHA1* mutations involving the thiamine fixation site,⁷⁵ clinical benefits have been reported in patients with mutations out of the thiamine binding site or in other subunits of the complex.^{73,79} Hence, a combination of thiamine and KD seems to be the most effective therapy in PDHC deficiency, regardless of the genetic cause.

Treatments Aimed at Supplementing Defective Metabolites

Defects of Biogenic Amine Metabolism

Neurotransmitter defects are probably the most frequent inherited causes of MDs in children. This continuously expanding constellation of neurometabolic diseases encompasses disorders of synthesis, intracellular and extracellular trafficking of the neurotransmitters (Fig. 5).⁸¹ They present generally during the first months/years of life with DD/neurological deterioration and dyskinesias. Adolescence or adulthood onset are usually associated with isolated MD.

Dopamine and serotonin synthesis are both altered in some defects, whereas isolated dopamine depletion is the result of tyrosine hydroxylase (TH) defect. The internalization of dopamine and serotonin in presynaptic vesicles and the recycle of synaptic dopamine are affected in vesicular monoamine transporter 2 and dopamine transporter defects, respectively (Fig. 5). Because of the involvement of the enzyme phenylalanine hydroxylase, several defects are associated with hyperphenylalaninemia (AR guanosine-triphosphate-cyclohydrolase [GTP-CH], 6-pyruvoyl-tetrahydropterin synthase, dihydropteridine reductase, a co-chaperone of PAH (phenylalanine hydroxylase) (DNACJ12) defects; Fig. 5) and detectable in a presymptomatic stage by NBS.

The defect of the enzyme GTP-CH may present as a severe and early-onset recessive disorder or as an autosomal-dominant (AD) dopa-responsive dystonia (Segawa disease). All of the others are recessive disorders.

AD-GTP-CH deficiency is probably the most frequent MD due to a defect of monoaminergic neurotransmitters (Table S1). The disease has variable sex-influenced penetrance. Of patients, 20% to 30% are symptomatic by the second or third years of life, but typically the disease onset is at about the age of 6 in a previously healthy child. Core symptoms at presentation are PED with slow spreading (1–10 years), diurnal fluctuations with evening worsening or emerging dystonia, and remarkable responsiveness to levodopa.

The spectrum of alternative presentations includes spastic diplegia mimicking a cerebral palsy, or, in later onset forms, spastic paraplegia; early-onset rigid-hypokinetic syndrome; focal dystonia; poor coordination; bradykinesia; myoclonus dystonia; and paroxysmal painful dystonia associated with restless legs syndrome.⁸²

In children, AD-GTP-CH deficiency is dramatically and persistently responsive to levodopa, which is well tolerated without the motor complications observed in advanced Parkinson's disease (Video S4 and S5).

Although with some minor differences, 5 defects of biogenic amine synthesis (AR GTP-CH, 6-pyruvoyl-tetrahydropterin synthase, sepiapterin reductase (SR), TH, aromatic L-amino acid decarboxylase [AADC] deficiencies) onset during the first months of life with common core symptoms that include generalized hypotonic-hypokinetic or rigid-hypokinetic syndromes, impairment of postural development with the absence of head control and antigravity reactions (apostural status) in the setting of a progressive global developmental delay (Video S6 and S7), multifocal erratic myoclonic jerks (in rigid-hypokinetic presentation), patterns of spontaneous motor activity reminiscent of fetal movements, hypomimia, oculogyric crisis, and diurnal or weekly fluctuations of motor symptoms associated with irritability or sedation. An atypical postural/rest tremor may be observed during the first 2 to 4 months of life in patients with TH and sepiapterin reductase deficiencies (Video S6). A severe hypotonic-hypokinetic presentation mimicking a neuromuscular disease may occur in AADC and TH defects.^{83,84} Less frequent neurological symptoms are epileptic seizures, sleep disturbance, irritability, dysarthria, increased startle, poor eye fixation, ptosis, miosis, and temperature instability. Common nonneurologic symptoms are short stature, nasal congestion, excessive drooling, stridor, diarrhea, constipation, feeding difficulties, gastroesophageal reflux, and hypoglycemia.

Milder and late-onset presentations have been described for autosomal recessive GTP-CH, TH, and sepiapterin reductase defects, with dopa-responsive dystonia and parkinsonism-dystonia syndrome.^{82,85} Mild forms of 6-pyruvoyl-tetrahydropterin synthase deficiency may remain asymptomatic or develop chorea or parkinsonism later in the disease course.⁸⁶

Biogenic amine synthesis defects are potentially treatable disorders even though the outcome is less favorable than in AD-GTP-CH deficiency. The delay in diagnosis and treatment significantly influences motor and cognitive outcomes, with ID as the most frequent consequence in late-treated patients (Table S1). Levodopa-carbidopa treatment and 5-hydroxytryptophan (according to the defective enzyme) are the first-line medications because they replenish the precursors of dopamine and serotonin. Dopamine mimetics are generally nonapproved for children and should be a second-line option.

In dihydropteridine reductase deficiency, both biogenic amines and brain folate depletion contribute to the pathogenesis. MDs are less frequent than in other conditions of this group, mainly affecting untreated or late-treated patients. Dystonia can result from a stroke (Video S8, Fig. S2), whose emergence is unpredictable and not related to the metabolic control.⁸²

Conclusive Remarks

In this review, we offered an overview of the main clinical, biochemical, and genetic features of a selected group of conditions amenable to treatment manifesting in childhood with prominent MD. We focused on those that cannot be missed, as accumulating literature has demonstrated a partial or dramatic efficacy of an early etiological treatment.

We are aware that the list of treatable conditions is longer, and a systematic review is out of the scope of this work. An example is immune therapy in acquired immune-mediated disorders, able to modify the disease course avoiding motor, cognitive, and psychiatric sequelae. Further examples are some symptomatic treatments that have produced a dramatic and unexpected therapeutic response in specific disorders, suggesting an interference with the disease mechanisms, namely carbamazepine in *PRRT2* gene mutations,⁸⁷ acetazolamide in *CACNA1A*,⁸⁸ tetrabenazine in *GNAO1* (Video S9),⁸⁹ and neuromodulation in *DYT1* and *KMT2B*.^{90,91} The personal observation of a dramatic and sustained response to levodopa in a patient with isolated cervical dystonia and reduced CSF dopamine levels, subsequently diagnosed as *KMT2B* dystonia (Video S10 and patient 10 in ref. 91,⁹¹ could be considered a further example.

Genetic therapies, now available for severe and untreatable disorders, such as AADC deficiency⁹² and neuronal ceroid lipofuscinosis types 2 and 6,⁹³ will be implemented in the future to cover further conditions for which a disease-modifying approach is not available. Most likely a number of conditions reported here will continue to be treated with a traditional medical approach, as they already have a treatment able to change their natural history if started in the early or asymptomatic phases.

The continuously growing number of early diagnoses and treatments, resulting from the virtuous interaction between clinical knowledge, metabolic studies, and advanced genetic techniques, will answer the key questions about which disorders should be treated with a genetic approach and which are susceptible to conventional medical treatments.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

S.G.: 1A, 1B, 1C, 2A

F.N.: 1B, 1C, 2A

V.L.: 1A, 1B, 1C, 2B

Disclosures

Ethical Compliance Statement: We declare that the patients and/or their parents consented for video publication and provided a signed release form authorizing the offline and/or online

distribution of this video material. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Fig. S1. Brain magnetic resonance imaging T1 of a 17-year-old girl with Wilson disease experiencing neurological deterioration with the start of chelation therapy (penicillamine). Bilateral lesion of globus pallidus, while hyperintense material is present in putamina and peri-aqueductal area of brainstem.

Fig. S2. Brain magnetic resonance imaging T2 and fluid attenuation inversion recovery sequences of a patient with dihydropteridine reductase deficiency at the age of 12 showing multiple white matter lesions involving the left occipital cortex, posterior areas and the centrum semiovale (right>left), and a focal lesion in right pulvinar. The patient is shown in Video S9.

Table S1. Clinical features including very early manifestations of the disease, typical presenting symptoms, and clinical manifestations in untreated or late-treated subjects, diagnostic biomarkers, and therapeutic approach in childhood-onset treatable inherited movement disorders.

Video S1. Severe generalized dystonia with prominent axial involvement and tongue dystonia in a 15-month-old girl with untreated glutaric aciduria type 1 presenting at the age of 9 months with rapid neurological deterioration triggered by an intercurrent febrile disease.

Video S2. Hypokinesia, head titubation, action tremor, and dystonic posturing and movements of the upper limbs in a 34-year-old male with 3-OH-isobutyryl-CoA hydrolase deficiency (c.777T>A [p.Phe259Leu]).

Video S3. Segment 1: dramatic neurological deterioration with severe jaw-opening dystonia, hypomimia, and dystonic posturing of the upper limbs in a 13-year-old girl with Wilson disease soon after starting penicillamine treatment. Lesions of basal ganglia and periaqueductal area detected by brain magnetic resonance imaging are shown in Figure S1. Segment 2: during the following years, she was treated with zinc acetate (150 mg/day), and at the age of 24 years she was an intelligent woman with a residual mild choreic syndrome.

Video S4. Segment 1 (before treatment): generalized dystonia with prominent lower limb involvement worsening with exercise and with diurnal fluctuations in a 7-year-old girl with autosomal-dominant guanosine triphosphate cyclohydrolase deficiency (c.631–632del[p.Met211fs]). Segment 2 (under treatment): marked improvement of movement disorders after a few months of treatment with levodopa–carbidopa 5/1,25 mg/kg/day.

Video S5. Segment 1 (before treatment): lower limb dystonia and loss of postural reactions with diurnal fluctuations in a 7-year-old girl with *CGH1 exon 1* deletion. Segment 2 (under treatment): resolution of MD after a few weeks of treatment (levodopa–carbid 5/1.25, 25 mg/kg/day).

Video S6. Segment 1: generalized tremor and orofacial dyskinesia as presenting symptoms of tyrosine hydroxylase deficiency (c.707T>C[Leu236Pro]; c.1254G>C[Gly422Arg]) between 4 and 8 months of age. Segment 2: hypokinesia, lack of postural reactions, and immature pattern of spontaneous motor activity with massive jerky flexion of lower limbs at the age of 12 months when cerebrospinal fluid examination showed reduced homovanillic acid (47.24 nmol/L, r.v. 302–845) and 5-MHPG (6.3 nmol/L, reference value. 51–112). Treatment (levodopa/carbidopa 3/0.75 mg/kg/day) was started at the age of 12. Segment 3: the video shows the relevant improvement of the girl at the ages of 19 and 24 months.

Video S7. Segment 1: severe rigid-hypokinetic syndrome with generalized dystonia, multifocal myoclonic jerks, spontaneous startle reflex, and severe developmental delay with impairment of postural control and reactions in a 5-month-old girl with 6-pyruvoyl-tetrahydropterin synthase deficiency (c.200C>T[Thr67Met]; c.385A>G[Lys129Glu]). Treatment with tetrahydrobiopterin, levodopa/carbidopa, 5-hydroxytryptophan, and pyridoxin was started at the age of 6 months. Segment 2: the girl at the age of 24 months under treatment with only mild dystonia mainly affecting the lower limbs and strabismus. Social interaction is adequate for age, whereas language development is mildly delayed.

Video S8. Severe right spastic and dystonic hemiparesis as sequelae of 2 cerebrovascular events in a 11-year-old girl with dihydropteridine reductase deficiency (c.41T>V[p.Leu14Pro]). The 2 strokes occurred despite a strict adherence to treatment with 5-hydroxytryptophan, levodopa/carbidopa, tetrahydrofolate, and low phenylalanine diet. Cerebrospinal fluid examination, performed during the 2 events, disclosed a very low level of tetrahydrofolic acid in cerebrospinal fluid with normal biogenic amine concentrations.

Video S9. Segment 1 (before treatment): severe developmental delay and choreic movements in a 8-month-old girl with de novo c.736G>A(p.Glu246Lys) GUANINE NUCLEOTIDE-BINDING PROTEIN, ALPHA-‘OTHER’; GNAO (*GNAO1*) variant. Segment 2 (under treatment): remarkable reduction of dyskinesias with improvement of postural control under treatment with tetrabenazine (0.7 mg/kg/day).

Video S10. Segment 1: cervical dystonia and mandibular dystonia in a 15-year-old girl with cerebrospinal fluid finding of low homovanillic acid (109 nmol/L, r.v. 148–434). Segment 2: sustained response to levodopa/carbidopa in a follow-up period of 6 months. Genetic analysis disclosed a new LYSINE-SPECIFIC METHYLTRANSFERASE 2B (*KMT2B*) pathogenic variant (c.3431A>T [p.Asp1144Val]). This patient has been recently published as part of a single-center cohort by Carecchio and colleagues.⁹¹