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Perspective

Treatment of neurometabolic epilepsies: Overview and recent advances

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ABSTRACT

The rarity and heterogeneity of neurometabolic diseases make it challenging to reach evidence-based principles for their specific treatments. Indeed, current treatments for many of these diseases remain symptomatic and supportive. However, an ongoing scientific and medical revolution has led to dramatic breakthroughs in molecular sciences and genetics, revealing precise pathophysiologic mechanisms. Accordingly, this has led to significant progress in the development of novel therapeutic approaches aimed at treating epilepsy resulting from these conditions, as well as their other manifestations. We overview recent notable treatment advancements, from vitamins, trace minerals, and diets to unique medications targeting the elemental pathophysiology at a molecular or cellular level, including enzyme replacement therapy, enzyme enhancing therapy, antisense oligonucleotide therapy, stem cell transplantation, and gene therapy.

1. Introduction

Epilepsy is a salient symptom of the numerous existing neurometabolic diseases, a group of phenotype and genotype heterogeneous conditions for which there is a considerable challenge to meeting evidence-based treatment principles [1]. Furthermore, treatment specificity and timing may be prerequisites for improved outcomes. Current treatments for seizures deriving from the majority of these unique diseases are supportive and symptomatic. Recently, however, there has been dramatic progress in therapy for many neurometabolic conditions. Treatments vary and range in their accessibility and affordability from vitamins, trace minerals, and diets to unique medications targeting the elemental pathophysiology at a molecular or cellular level, including enzyme replacement therapy, antisense oligonucleotide therapy, stem cell transplantation, and gene therapy. Fig. 1 illustrates the unique therapeutic approaches that exist for neurometabolic diseases.

We provide an overview of exciting recent advances in the creation and application of "tailored" precise treatments for epilepsies stemming from an etiology of neurometabolic diseases. Table 1 summarizes the current approved and investigated therapies for potentially treatable neurometabolic epilepsies. A broad framework that classifies neurometabolic diseases according to their pathophysiology and clinical presentations includes *small molecule diseases* resulting from the accumulation of substrates due to defects of intermediary metabolism, such as that of amino acids, organic acids, fatty acids, ketones, and ammonia; *large molecule diseases* reflecting problems in the synthesis or catabolism of complex molecules as lysosomes, peroxisomes, lipids, and processes as glycosylation; *defects of cerebral energy metabolism* hindering the bioenergetics of the mitochondria, and the transport of glucose

Abbreviations: AADC, Aromatic L-amino acid decarboxylase; AAV, Adenovirus-associated vector; AMO, Antisense morpholino oligonucleotides; ARG1, Recombinant arginase 1; ASL, Arginosuccinate lyase; ASS1, Arginosuccinate synthetase-1; BBB, Blood-brain-barrier; BCAA, Branched-chain-amino-acids; CGDs, Congenital disorders of glycosylation; CLN2, Ceroid lipofuscinosis or; CNS, Central nervous system; CPT1, Carnitine palmitoyltransferase I; CPT2, Carnitine palmitoyltransferase type 2; DEND, Developmental delay-epilepsy-neonatal diabetes; EET, Enzyme enhancement therapy; ERT, Enzyme replacement therapy; FAO, Fatty acid oxidation; FDA, Food and Drug Administration; GABA, γ-aminobutyric acid; GDH, Glutamate dehydrogenase; Glut-1, Glucose transporter type I; GSDs, Glycogen storage diseases; HIHA, Hyperinsulinism hyperammonemia; IVA, Isovaleric acidemia; IVIG, intravenous immune globulin; LCHAD, Long-chain 3-hydroxy acyl-CoA dehydrogenase; LND, Lesch–Nyhan disease; LNP, Lipid nanoparticles; LSDs, Lysosomal storage diseases; MCAD, Multiple acyl-CoA dehydrogenase; MCT, Medium-chain triglyceride; MDs, Mitochondrial Diseases; mtDNA, Mitochondrial deoxyribonucleic acid; MMA, Methylmalonic acidemia; MPS, Mucopolysaccharidoses; MSUD, Maple syrup urine disease; OTC, Ornithine Transcarbamylase; PA, Propionic acidemia; PKU, Phenylketonuria; PLP, Pyridoxal-5-phosphate; PNPO, Pyridoxamine-5′-phosphate oxidase; PPAR, proliferator-activated receptor; SSADH, Succinic semialdehyde dehydrogenase; TPP1, Tripeptidyl peptidase 1; UCDs, Urea cycle disorders; VLCAD, Very-long-chain acyl-CoA dehydrogenase; XLALD, X-linked adrenoleukodystrophy.

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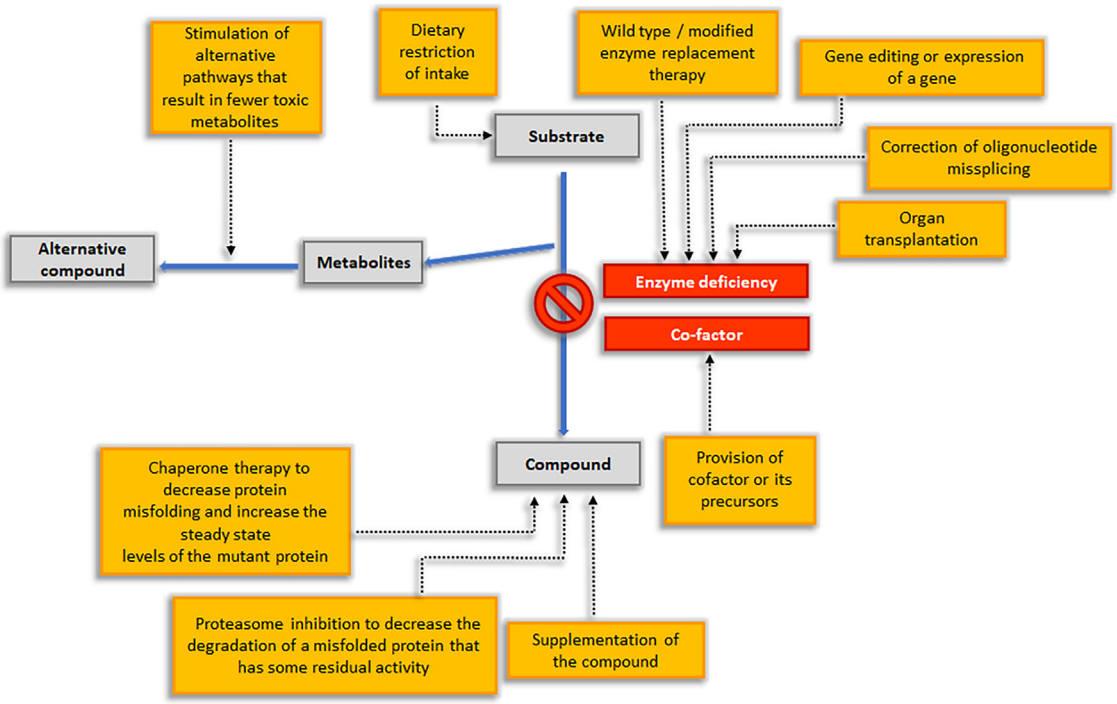

Fig. 1. A depiction of ten different therapeutic approaches that are used for neurometabolic diseases. Some are simple, affordable, and accessible, some have been serendipitously discovered, and some are complex and expensive. In several diseases, a combination of one or more of these approaches is used.

into the CNS; and *other neurometabolic diseases* that are not readily classifiable and consist of conditions ensuing from defects in the metabolism of carbohydrates, purines, pyrimidines, neurotransmitters, and vitamins.

2. Small molecule neurometabolic diseases

2.1. Aminoacidemias: A general treatment approach is to reduce toxic metabolites, or stabilize or increase the catalytic activity of incompletely defective enzymes.

Branched-chain ketoaciduria [maple syrup urine disease (MSUD)] results from a deficiency of mitochondrial branched-chain α-ketoacid dehydrogenase complex. This leads to accumulated branched-chain amino acids (BCAA) and branched-chain α-ketoacids, leading to five phenotypes of the disease that are categorized on the grounds of their clinical phenotype, level of enzyme activity, and response to thiamine (classic, intermediate, intermittent, thiamine-responsive, and dihydrolipoyl dehydrogenase [E3] deficiency) [2]. Chronic treatment involves dietary therapy of a BCAA-free formula combined with a limited amount of protein, and isoleucine, valine, and thiamine supplementation [3]. Newer formulas that have also been found beneficial, diminish the concentrations of cerebral BCAA by optimizing the transport of other amino acids (Tyr, Trp, His, Met, Thr, Gln, Phe) that compete with the entry of BCAA into the brain [4]. Implementation of dietary therapy is difficult, however, as it permits the intake of only ~10% of natural nutrition and fails to prevent encephalopathic crises [5]. Liver transplantation is another option for long-term classic MSUD, enabling BCAA concentrations to return to acceptable limits, but associated with the risks of surgery and life-long immunosupression[6]. There are two emerging therapies for MSUD. The first is sodium phenylbutyrate which lowers BCAA levels by increasing the activity of branched-chain ketoacid dehydrogenase [7]. The second is supplementation with the antioxidant L-carnitine to reduce oxidative stress, part of the pathophysiology of MSUD [8]. Early treatment of seizures may improve the outcome of individuals with the classic form of MSUD [9].

Phenylketonuria (PKU) is a condition classically caused by deficient phenylalanine hydroxylase activity, and in a minority of cases by deficiency of tetrahydrobiopterin (BH4), an essential cofactor in the conversion of phenylalanine to tyrosine. As a result, phenylalanine accumulates, resulting in neurotoxicity [10]. Individuals with PKU who remain untreated develop a severe intellectual disability and different types of seizures. However, treated individuals may have normal development and be seizure-free. A modified low-phenylalanine and low-protein diet, supplemented by tyrosine and a small number of proteins that provide the necessary quantity of phenylalanine, comprise the basic treatment. Individuals with BH4-responsive PKU may be treated with BH4 or its synthetic formulation, sapropterin dihydrochloride [11]. There are several newer treatment options for PKU. First, dietary treatments with large, neutral amino acids decrease phenylalanine levels by reducing its intestinal absorption and reuptake by the kidneys [12]. Second, supplementation with omega-3, long-chain, polyunsaturated fatty acids, and carnitine may reduce the neurotoxic effects of phenylalanine [13]. Third, sepiapterin may have an advantage over sapropterin for the treatment of individuals with BH4-responsive PKU, as it is biologically more active [14]. Fourth, the reduction of phenylalanine levels by converting it to a harmless compound named transcinnamic acid is now achievable via the nonmammalian enzyme phenylalanine ammonia-lyase (PAL) or its pegylated form, pegvaliase, which prevents the breakdown of the enzyme and diminishes its immunogenicity [15]. Finally, clinical trials of gene therapy for PKU are in progress (www.clinicaltrials.gov; NCT04480567; NCT03952156) and the development of an mRNA replacement therapy to treat PKU is emerging [16].

Homocystinuria primarily results from defects of three different enzymes: cystathionine β-synthase (a vitamin B_6 dependent enzyme), methylene tetrahydrofolate reductase, and methionine synthase but also by several mutations that cause methylmalonic acidemia and by deficiencies of vitamins B6, B_{12}, and folate. The

Table 1
Approved and Investigated Treatments for Neurometabolic Epilepsies.

Neurometabolic Epilepsy	Therapeutic Approach	Treatment	Further information from ClinicalTrials.gov
6-pyruvoyl-tetrahydropterin synthase deficiency	Dietary; Vitamins, cofactors, and minerals; Pharmacotherapy	Phenylalanine-reduced diet; Folinic acid; L-dopa + carbidopa, 5-Hydroxy-tryptophan, sapropterin dihydro-chloride	
ARG1 deficiency	Enzyme-replacement therapy (clinical trials)	Pegzilarginase	NCT03378531
Aromatic L-amino acid decarboxy-lase (AADC) deficiency	Pharmacotherapy; Vitamins, cofactors, and minerals; Gene therapy	Dopamine agonist, monoamine oxidase (MAO) inhibitors, L- dopa + carbidopa (mutation dependent); Pyridoxine, folinic acid; Intraputaminal, AAV-mediated gene transfer (eladocagene exuparvovec)	NCT01395641
Biotinidase deficiency	Vitamins, cofactors, and minerals	Biotin	
Carbamoyl phosphate synthetase, aspartate transcarbamylase, dihydroorotase (CAD) deficiency	Pyrimidine supplementation	Uridine	
Cerebral folate deficiency	Vitamins, cofactors, and minerals	Folinic acid	
Cerebrotendinous xanthomatosis	Pharmacotherapy	Chenodeoxycholic-acid	
Congenital Disorder of Glycosylation GNE Myopathy	Supplementation (hexosamine monosaccharide)	N-acetyl-D-mannosamine (ManNAc)	NCT04231266
Congenital Disorder of Glycosylation PMM2	Pharmacotherapy	Acetazolamide	
Creatine synthesis and transport deficiencies	Dietary	Creatine	
Cystathionine beta-synthase deficiency (classic homocystinuria)	Dietary; Vitamins, cofactors, and minerals; Enzyme-replacement therapy	Protein-defined diet, methionine restriction; Pyridoxine, betaine; Pegtibatinase	NCT03406611
Glut-1 transporter Defects	Dietary	Ketogenic diet	
Glutaric aciduria type I	Dietary	Protein defined diet, lysine restriction, carnitine	
Glycine encephalopathy (nonketotic hyperglycinemia)	Pharmacotherapy	Sodium benzoate, NMDA receptor antagonists	
Methymalonic acidemia	Gene therapy (clinical trials)	hLB-001 mRNA-3705	NCT04581785, NCT04899310, NCT05506254
Molybdenum cofactor deficiency type A	Pharmacotherapy	Cyclic pyranopterin monophosphate	
Multiple acyl-CoA dehydrogenase deficiency type 2A/2B/2C (glutaric aciduria type 2A/2B/2C	Dietary	Beta-hydroxybutyrate	
Ornithine transcarbamylase (OTC) deficiency	mRNA-based enzyme replacement therapy (preclinical trials); Gene replacement therapy (clinical trials)	MRT5201; DTX301	NCT03767270; NCT02991144
Phenylketonuria	mRNA-based gene therapy (preclinical trials); Gene-replacement (clinical trials)	BMN 307; HMI-102	NCT04480567; NCT03952156
Pyridoxine dependent epilepsy	Dietary; Vitamins, cofactors, and minerals	Lysine restriction, arginine; Pyridoxine	
Serine synthesis defects	Dietary	L-serine	
Tripeptidyl-peptidase 1 deficiency (CLN2 disease)	Enzyme replacement therapy	Cerliponase alfa	NCT02485899, NCT04476862
Urea cycle disorders	Dietary; Pharmacotherapy; Organ transplantation	Protein-defined diet, arginine or citrulline; Sodium phenylbutyrate, glycerol phenylbutyrate, sodium benzoate; Hemodialysis, peritoneal dialysis; Liver transplantation	
X-linked adrenoleukodystrophy	Gene therapy	Elivaldogene autotemcel (Lenti-D^{TM}, SKYSONA^{TM}).	NCT01896102

mainstay dietary treatment aims to reduce hyperhomocysteinemia and depends on biochemical abnormality [17]. In the case of cystathionine β-synthase deficiency, the most common type, individuals who are responsive to vitamin B_6 can be treated with pyridoxine in combination with folic acid and vitamin B_{12}. For vitamin B_6 non-responders, treatment includes a methionine-restricted diet supplemented with cysteine. The methylator betaine, or trimethylglycine, may lower homocysteine levels [18]. These treatments have some efficacy, however, generalized tonic clinic and focal seizures may persist [19]. Chemical modification of human cystathionine β-synthase (a complex intracellular multimeric enzyme that depends on three cofactors- pyridoxal phosphate, heme, and S-adenosylmethionine) yielded a novel therapeutic approach of enzyme replacement therapy (ERT). Preclinical testing of this therapy has been demonstrated to be efficacious in reducing the concentrations of homocysteine and diminishing symptoms such as facial alopecia, low bone, mass, and zonulopathy-associated lens subluxation in mice with homocysteinemia [20]. Ongoing clinical trials are investigating the use of ERT in homocystinuria (www.clinicaltrials.gov; NCT03406611). Additionally, gene therapy utilizing adenovirus-associated vector (AAV) DNA given to cystathionine β-synthase deficient mice has resulted in their increased enzymatic activity, decreased homocysteine levels, and improvement of clinical signs such as alopecia and bone loss [21].

2.2. Organic acidemias

The acute and chronic treatment of the systemic organic acidemias [propionic acidemia (PA), methylmalonic acidemia (MMA), and isovaleric acidemia (IVA)] is conceptually similar and is based on reversal or prevention of catabolism, restriction of precursors, scavenging of intermediate toxic metabolites, and provision of deficient products and cofactors [22]. If conventional management fails, including the persistence of seizures, liver transplantation may also be an optional treatment [23]. In recent years, the treatment of organic acidemias has been advanced by several novel treatment approaches. Two specific treatments for IVA are glycine and carnitine, which conjugate with isovaleryl-CoA, resulting in nontoxic products which are excreted [24,25]. Gene therapies for MMA that include canonical gene addition by an AAV with and without immune modulation, codon-optimized lentiviral vector, gene induction, and splicing-restoring systemic mRNA therapy using antisense morpholino oligonucleotides (AMO), have shown promising outcomes in preclinical studies [26]. Additionally, there are ongoing investigations of therapeutic approaches including systemic mRNA therapy using lipid nanoparticles (LNP), and AAV-mediated, nuclease-free directed albumin editing [27]. Similar to MMA, there have been emerging therapeutic approaches for PA that have shown success in preclinical trials. Gene delivery via an AAV was shown to effectively rescue mice with PA from neonatal lethality and significantly decrease the negative biomarkers of the disease [28] and a functional propionyl-CoA carboxylase was shown to be effectively produced in mice with PA, by an enzyme replacement approach via an LNP encapsulated mRNA [29].

2.3. Fatty acid oxidation (FAO) disorders

Whether resulting from disruption of mitochondrial β-oxidation or carnitine transport pathways, FAO disorders share a common clinical presentation and accordingly, are treated similarly. Severe attacks of hypoketotic hypoglycemia leading to seizures may ensue from the infantile type of carnitine palmitoyltransferase II deficiency. Seizures may also occur in carnitine acylcarnitine translocase deficiency in the neonatal period. Correction of the hypoglycemia and hepatic impairment in these conditions and other FAO disorders may reduce the seizures as well as other manifestations [30]. The mainstay of their treatment includes avoidance of precipitating factors such as prolonged fasting, prolonged aerobic efforts, and cold temperatures, together with the consumption of a high-carbohydrate and low-fat diet [30]. Medium-chain triglyceride (MCT) oil and riboflavin have also been shown to have a partial benefit in long and medium FAO disorders, respectively [30]. Carnitine therapy has a clear value in cases of a carnitine transporter (OCTN2) defect, but in FAO disorders stemming from intra-mitochondrial β-oxidation defects, it is recommended only in cases in which free carnitine levels are decreased [31]. There have also been sporadic reports about individuals with long-chain 3-hydroxy acyl-CoA dehydrogenase (LCHAD) deficiency that experienced a reversal of their limb-girdle myopathy symptoms after oral prednisone treatment [32] and improvement of their visual function after docosahexaenoic acid supplementation [33]. Newer treatment approaches of FAO disorders include: triheptanoin, which functions as an anaplerotic substrate that leads to the production of ketone bodies, suppresses lipolysis, and decreases the accumulation of toxic metabolites in long-chain FAO disorders [34]; bezafibrate, a proliferator-activated receptor (PPAR) agonist which activates gene transcription, has led to varying degrees of symptom improvement in individuals with very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency and carnitine palmitoyltransferase type 2 (CPT2) deficiency [35]; ataluren, which has the propensity to increase protein expression in fibroblasts of individuals with carnitine palmitoyltransferase I (CPT1) deficiency by promoting readthrough of nonsense mutations [36]; glycerol phenylbutyrate, which has elicited good responses in individuals with multiple acyl-CoA dehydrogenase (MCAD) deficiency [37]; S-nitroso-N-acetylcysteine, which was demonstrated in a proof-of-concept study to induce cysteine nitrosylation and by that increase the activity of VLCAD by 7–10-fold in fibroblasts of an individual with VLCAD deficiency caused by a missense mutation[38]; and a gene replacement strategy using AAV, that has shown to have positive biochemical outcomes in VLCAD-deficient mice [39].

2.4. Urea cycle disorders (UCDs)

Historically, UCDs were treated by protein restriction and hemodialysis during hyperammonemic crises. Nitrogen-scavenging agents (sodium benzoate, sodium phenylacetate, sodium phenylbutyrate, and the more recently approved glycerol phenylbutyrate) have since then been introduced, serving as first-line therapies during acute hyperammonemic states in which seizures typically occur. L-arginine and L-citrulline are also essential parts of therapy; the synthesis of L-arginine is impaired in all the UCDs [except arginase 1 (ARG1) deficiency] and therefore supplementing individuals with UCDs with L-arginine or its precursor, L-citrulline, is essential. Moreover, in arginosuccinate synthetase-1 (ASS1) deficiency, citrulline serves as a vehicle for nitrogen removal by its urinary excretion and thus decreases the proneness for hyperammonemic crises [40]. The mainstay chronic treatment of UCDs combines a low-protein diet, supplementation of urea cycle intermediates, and alternative-pathway therapy [40]. Severe cases have been increasingly dealt with by liver transplantation [41]. In recent years, newer and more diverse therapeutic approaches for UCDs have been studied in preclinical and clinical settings. Hepatocyte transplantation via human heterologous liver cell transplant has been suggested as a lower-risk substitute for liver transplantation but it did not lead to significant levels of urea synthesis [42]. Similarly, while transplantation of hepatocyte-differentiating mesenchymal stem cells did prove to induce partial ureagenesis [43], it showed only a modest effect on the survival of argininemic mice [44]. Nitrous oxide donor drugs have been shown to improve the symptoms of nitrous oxide depletion (and not hyperammonaemia) in ASL-deficient and ASS1-deficient mice [45], and ongoing clinical trials are assessing their therapeutic role in humans [46]. The bile-acid-dependent Farnesoid X Receptor which is part of the treatment of primary biliary cholangitis has been shown to induce several urea-cycle enzymes leading to ureagenesis and ammonia detoxification in mice; however, its clinical utility is yet to be determined [47]. Ongoing phase II clinical trials are investigating the therapeutic potential of a recombinant ARG1 enzyme for the treatment of individuals with ARG1 deficiency (www.clinicaltrials.gov; NCT03378531) after it was shown preclinically that a pegylated human recombinant ARG1 was effective at reducing arginine levels in argininemic mice [48]. Dissimilar to the recombinant enzyme replacement methods, mRNA-based enzyme replacement has been shown to normalize ammonia levels and increase the survival of mice with ornithine transcarbamylase (OTC) deficiency [49], and a clinical trial assessing this approach (www.clinicaltrials.gov; NCT03767270) is also taking place. Finally, gene replacement therapy using AAV has been demonstrated to normalize the urea cycle metabolism in OTC, ASS1, ASL, and ARG1 deficient murine models [50]. Despite the challenge to implement this clinically, there is an ongoing phase 1/2 open-label clinical trial investigating this method in adults with late-onset OTC deficiency (www.clinicaltrials.gov; NCT02991144).

3. Large molecule neurometabolic diseases

3.1. Lysosomal storage diseases (LSDs)

While supportive and palliative care remains the principal treatment for most LSDs, novel therapeutic approaches have emerged. Bone marrow or hematopoietic stem cell transplantation was used for particular cases but carried high procedural risks which impeded their utilization [51]. Hematopoietic or mesenchymal stem cells and conditioning regimens that are less rigorous (i.e., nonmyeloablative) are currently being studied as a measure to minimize procedural risks [52]. Enzyme replacement therapy using recombinant human enzymes exists for a few LSDs as Pompe, Gaucher, Fabry, and several of the mucopolysaccharidoses (MPS)-Hurler (MPS I H/S), Hunter (MPS II), Morquio A (MPS IVA) and Maroteaux–Lamy (MPS VI) [53]. Furthermore, cerliponase alfa, which is an intraventricularly delivered recombinant human tripeptidyl peptidase 1 (TPP1) was approved for the treatment of late infantile neuronal ceroid lipofuscinosis or CLN2, after proving to improve the outcomes (including the seizures) resulting from this disorder [54]. Fig. 2 depicts the cellular influences of ERT in Pompe disease. In addition to ERT, enzyme enhancement therapy (EET) is also utilized in LSDs. This treatment method increases the residual capacity of mutated proteins with the help of chaperones, which can cross the BBB and stabilize misfolded and mutant enzymes [55]. However, since chaperones are mutation-specific, not all the genotypes are responsive to them. Examples of the use of EET in LSDs are migalastat for Fabry disease [56], and duvoglustat which is being clinically investigated as a treatment option for Pompe disease in combination with ERT [57]. Substrate reduction is another treatment approach for LSDs, which operates by slowing down the production of stored macromolecules rather than degrading them [58]. Substrate-reducing drugs such as miglustat and eliglustat are currently approved for moderately symptomatic Gaucher patients who are not eligible for ERT [59]. Miglustat has also been repurposed for the treatment of Niemann-Pick type C [60]. Gene therapy, which can be delivered *in vivo* (using AAV) or *ex vivo* (using autotransplantation of hematopoietic stem cells that were modified by a lentiviral vector) is conceptually a good treatment option for LSDs as many of them are single-gene disorders with a relatively simple regulatory mechanism of enzyme expression. Preclinical studies showed encouraging results for gene replacement therapy in various LSDs [61], and on these grounds, there are currently around 40 clinical trials investigating gene therapies for individuals with LSDs [Fabry disease, Gaucher disease type 1, Pompe disease, MPS VI, cystinosis, metachromatic leukodystrophy, mucopolysaccharidoses (MPSIIIA, MPSIIIB, MPS II, and MPSI), GM1 gangliosidosis and ceroid lipofuscinosis (CLN2, CLN3, and CLN6)] [62].

3.2. Peroxisomal disorders

Peroxisomal Disorders- are subdivided into disorders resulting from defective peroxisome biogenesis (as the Zellweger spectrum disorders and rhizomelic chondrodysplasia punctata) and disorders resulting from single-enzyme defects [as X-linked adrenoleukodystrophy (XLALD)]. To date, the treatment of the systemic and neurological manifestations of peroxisome biogenesis disorders is mainly supportive and rehabilitative. Accordingly, the focal, myoclonic, generalized tonic-clonic, and epileptic spasms sustained by 80% of these patients remain difficult to treat [63]. Oral ether lipid therapy and dietary restriction of VLCFA and phytanic acid can be implemented to normalize the biochemical abnormalities. Ursodeoxycholic acid can diminish liver dysfunction by reducing the bile acid intermediates levels. Docosahexaenoic acid is given to replenish its low plasma levels but does not have a major clinical utility. Likewise, treatment with clofibrate, a peroxisome proliferator, has failed to induce the formation of catalase-containing peroxisomes and clinical improvement. Genetic approaches are not available for these disorders, which are caused by mutations in any of the 14 *PEX* genes that code for the proteins responsible for peroxisomal assembly, peroxins. How-

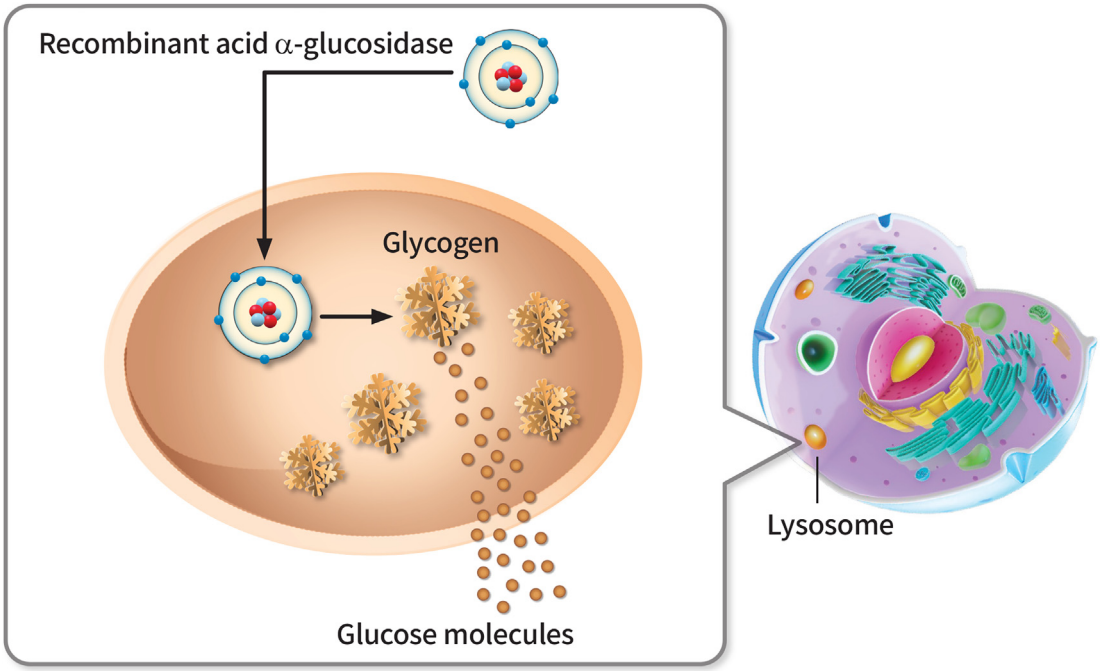

Fig. 2. An illustration of enzyme replacement therapy for Pompe disease. A deficiency in acid α-glucosidase caused by a *GAA* mutation leads to the pathologic accumulation of glycogen in lysosomes. By the provision of an analogous enzyme, lysosomal glycogen is broken down into glucose molecules, enabling skeletal and cardiac muscles to regain healthy function.

ever, genetically engineered murine models of *PEX* genes and invertebrate models of Zellweger spectrum disorders do exist and maybe the cornerstones for future genetic treatment avenues [63]. Contrastingly, the treatment of XLALD, a peroxisomal disorder caused by a single-enzyme defect, has considerably progressed in recent years. Despite the lack of clinical benefit seen from various treatment methods of XLALD in the past [dietary restrictions of VLCFA, glyceryl trioleate combined with glyceryl trierucate (Lorenzo's oil), intravenous immune globulin (IVIG), cyclophosphamide, and high-dose steroids] [64], boys with the cerebral disease at its early stages have shown to respond well to bone marrow transplantation [65–67] and gene therapy using a lentivirus vector. This led the FDA to grant a breakthrough therapy designation to the genetic therapeutic for XLALD elivaldogene autotemcel (Lenti-D™, SKYSONA™) in 2018, and to the European Union approving it in 2021 [68,69].

3.3. Congenital disorders of glycosylation (CDGs)

Congenital disorders of glycosylation (CDGs)- are a group of exceedingly rare neurometabolic diseases that result from mutations in genes that are involved in the course of protein and lipid glycosylation. Their pathomechanisms mainly stem from defects in N-linked glycosylation but also derive from defects in the O-linked glycosylation pathway, glycosaminoglycan biosynthesis, glycophosphatidylinositol (GPI) anchors, and others. Different types of seizures have been reported for CDGs, including myoclonic, atonic, focal, migrating focal, generalized, and spasms, for which the treatment options are restricted [70]. Treatment concepts that do exist have been applied to various degrees, some being more clinically recognized and others only on a preclinical or single-case basis. Substrate/cofactor supplementation is one main treatment approach used in CDGs, enabling the bypass of different enzymatic blocks. Some examples include galactose supplementation which has proved to be safe and clinically efficacious in the treatment of *PGM1*-CDG [71] and is under clinical trials for the treatment of *SLC35A2*-CDG [72]. Moreover, galactose and manganese supplementation were shown to have a positive clinical effect in *SLC39A8*-CDG [73] and *TMEM165*-CDG [74]. Fructose supplementation has mostly improved the immunological manifestations of individuals with *SLC35C1*-CDG [75] and uridine supplementation led to dramatic improvements in seizure control and development in children with *CAD* deficiency [76]. Supplementation therapy for the most prevalent subtype of CDG, *PMM2*-CDG, has not shown favorable outcomes. However, mannose-containing liposomes which are currently under production, are a promising treatment for this disease [77]. Likewise, treatment for *GNE*-CDG is non-existent at this point, but its treatment via *N*-acetyl-D-mannosamine (ManNAc) supplementation is currently being investigated in a clinical trial (www.clinicaltrials.gov; NCT04231266). Organ transplantation has been shown to achieve a cure in particular CDGs and symptomatically improve others; liver transplantation has been reported to treat liver failure in *MPI*-CDG and *CCDC115*-CDG [78]; heart transplantation effectively treated the cardiomyopathy in *DOLK*-CDG, and HMCT improved the immunological deficiency in *PGM3*-CDG [79].

Treatment of the secondary manifestations of CDGs is dealt with by many different known treatments, based on the clinical symptom. Examples include cholinesterase inhibitors for CGD manifesting with a congenital myasthenic syndrome (*GFPT1*-CDG, *ALG2*-CDG, and *ALG14*-CDG) and acetazolamide which has been shown to improve the cerebellar symptoms in *PMM2*-CDG [80].

Treatment of one GPI anchoring defect, *PIGM*-CDG, is especially noteworthy as it is not similar to that of any other CDG. This treatment enhances histone acetylation using butyrate, resulting in increased expression of *PIGM*, leading to its biochemical normalization and clinical effect- eliminating the intractable seizures [81]. Additionally, secondary neurologic manifestations of several of the GPI anchoring defect CDGs have been responsive to various treatments; pyridoxine has been shown to effectively treat seizures caused by *PIGO*-CDG and *PIGS*-CDG [82], and a ketogenic diet has proved to help treat the early epileptic encephalopathy caused by *PIGA*-CDG [83].

4. Neurometabolic diseases resulting from defects in cerebral energy metabolism

4.1. Mitochondrial Diseases (MDs)

To date, treatment of seizures resulting from the majority of MDs is only supportive and symptomatic. Attempts to treat these conditions with anti-seizure medications and invasive stimulation techniques have not proved efficacy. Treatments that have a certain benefit include thiamine, riboflavin, biotin, or niacin supplementation for MDs with a cofactor deficiency; coenzyme Q_{10} for primary and secondary forms of coenzyme Q_{10} deficiency; idebenone, an antioxidant, for Leber hereditary optic neuropathy (LHON); hematopoietic stem cell transplantation (HSCT) for neurogastrointestinal encephalomyopathy; and L-arginine and taurine for the stroke-like episodes in mitochondrial encephalomyopathy, lactic acidosis, and stroke (MELAS) [84].

In resonance with the tremendous advancements that have been made in the last decade in our understanding of the pathomechanisms of MDs, new treatment concepts are being investigated: compounds such as acipimox, bezafibrate, and omaveloxolone are that function by increasing the cellular concentration of nicotinamide adenine dinucleotide$^+$ (NAD^+) aim to increase the production of mitochondrial DNA (mtDNA) in a subgroup of MDs termed mitochondrial depletion syndromes [85]; antioxidants (for example cysteamine) and other medications (as nab-sirolimus and dichloroacetate) seek to protect and improve the functionality of the mitochondrial oxidative phosphorylation [86,87]; and deoxythymidine and deoxycytidine, which have shown to delay the disease onset and restore the mtDNA copy number as well as the respiratory chain enzyme activities in mice with the myopathic mtDNA depletion syndrome (TK2 deficiency) [88]. Other exciting treatment approaches for MDs on the horizon are cell replacement therapy, mitochondrial augmentation therapy (MAT), hypoxic therapy, gene therapy, mtDNA base editing, and mitochondrial replacement therapy (MRT) [89].

4.2. Defects of cerebral glucose homeostasis

Developmental delay-epilepsy-neonatal diabetes (DEND) syndrome is caused by mutations in genes (the majority of which are gain of function mutations in the *KCNJ11* gene) coding for the sulfonylurea receptor or the I_{KATP} potassium channel [90,91]. Treatment of this syndrome with sulfonylureas may lead to an improvement of diabetes and alleviation of some of the sensorimotor manifestations but does not necessarily amend the associated neurocognitive deficits or seizures [92]. Future treatment options for DEND syndrome are based on repurposing or developing I_{KATP} potassium channel-blocking drugs [93].

Hyperinsulinism hyperammonemia (HIHA) syndrome is associated with activating mutations of glutamate dehydrogenase (GDH) that influence the insulin secretion pathway and the elimination of ammonia [94]. This syndrome is treated by a combination of a protein-restricted diet, glucagon, antiseizure medications, and diazoxide, which inhibits the release of insulin by its agonistic action on a potassium-ATP channel [95]. Prospective therapeutic direc-

tions of HIHA syndrome are based on developing GDH modulators and inhibitors that will restore the normal function of GDH [96].

Glucose transporter type I (Glut-1) deficiency caused by mutations of the *SLC2A1* gene, results in decreased amounts of glucose in the CNS, as this transporter enables the passage of glucose across the BBB. The ketogenic diet, which provides the CNS with ketone bodies in replacement of the devoid glucose, constitutes its main therapy for seizures ensuing from this disorder and should be maintained long-term [97]. The carbonic anhydrase inhibitor acetazolamide has been reported in several studies to improve the movement disorder associated with Glut1 deficiency [98]. Gene replacement therapy is currently not available for Glut1 deficiency but preclinical proof-of-concept investigations that treated Glut1 deficient murine models with an AAV-related gene transfer have shown that there is a premise for its success [99].

5. Other neurometabolic diseases

5.1. Primary defects in carbohydrate metabolism

Glycogen storage diseases (GSDs) are all derived from genetic mutations leading to enzyme deficiencies along the metabolic pathway of glycogen, with the outcome of glycogen being pathologically accumulated in various tissues. With the exception of GSD II (Pompe disease), of which the treatment was discussed in section 3.1 (as it is also considered to be a lysosomal storage disease), the management of the rest of the GSDs is based on dietary modifications that aim to maintain a normal glucose level, organ transplantation in severe cases in which conservative treatment failed, and other symptomatic treatments [100]. Hence, there is a substantial need to develop new therapies for GSDs. Gene therapy using AAV, designed to restore the deficient enzymes, is currently in the early phases of clinical trials for GSD Ia and in preclinical phases for GSD III, I V, and V [101].

5.2. Diseases of purine and pyrimidine metabolism

Notable treatments of diseases from this category include the uridine-responsive epileptic encephalopathy caused by *CAD* mutation that was mentioned in section 3.3 (as it is also considered a CDG) and Lesch–Nyhan disease (LND). Lesch–Nyhan disease results from the genetically driven loss of hypoxanthine–guanine phosphoribosyl transferase (HPRT), a purine salvage enzyme. Many treatment approaches have been tried for this syndrome (adenine, serotonin, L-dopa, or dopamine receptor modifiers), however, with almost no gain [102,103]. The partially successful existing treatments such as uric acid, improve gout and liver failure manifestations of the disease, but not the dystonia, self-mutilating behavior, or other neurological symptoms including seizures [104]. Deep-brain-stimulation (DBS) of the globus pallidus has been attempted in the treatment of LND, showing variable outcomes [105]. Similarly, treatment with S-adenylmethionine has been shown to improve the self-mutilating behaviors in some individuals with LND but to their worsening in others [106,107]. A therapeutic concept that holds some promise for LND, involves the use of induced pluripotent stem cells (iPSCs) to develop patient-specific cellular models of LND [108]. If achieved, this may enable rapid gene editing with tools such as CRISPR/Cas9, to create isogenic controls of the disease, which could be the basis for the development of more effective therapeutic options for LND [109,110].

5.3. Neurotransmitter-related disorders

Aromatic L-amino acid decarboxylase (AADC) deficiency is caused by a mutated dopa decarboxylase (DDC) gene that codes for AADC. This disorder typically presents with dystonia, hypotonia, ptosis, oculogyric crises, and autonomic and behavioral disturbances. Seizures are not very common but may appear [111]. Until recently, treatments for AADC deficiency have not addressed directly the underlining cause of the disease and have been variably successful. Monoamine oxidase inhibitors, anticholinergics, dopamine receptor agonists, and pyridoxine have been shown to have a clinical benefit in a minority of patients [111]; L-DOPA has yielded some improvement in particular cases of AADC deficiency in which the genetic mutation is located at the dopa-binding site [112]; and transdermal rotigotine, a dopamine agonist, has been efficacious to some extent in early disease [113]. In recent years, the introduction of an intra-putaminal injected recombinant AAV2 vector containing the human AADC gene (rAAV2-hAADC, eladocagene exuparvovec) (Fig. 3), has been shown to improve the cognitive and functional motor abilities of children with AADC deficiency [114–116].

Succinic semialdehyde dehydrogenase deficiency (SSADHD) results from mutations of the *ALDH5A1* gene, leading to the functional impairment of SSADH, a pivotal enzyme in the metabolism of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). This results in the pathologic accumulation of GABA and its metabolite γ-hydroxybutyrate (GHB) in the CNS [117] (Fig. 4). Nowadays, the treatment of SSADHD is only supportive. The seizures of affected individuals have shown some response to lamotrigine and carbamazepine. Vigabatrin will reduce GHB levels but exacerbate elevated GABA, and has not had clear benefit [118]. Recently, proof-of-concept studies that offer a premise for the

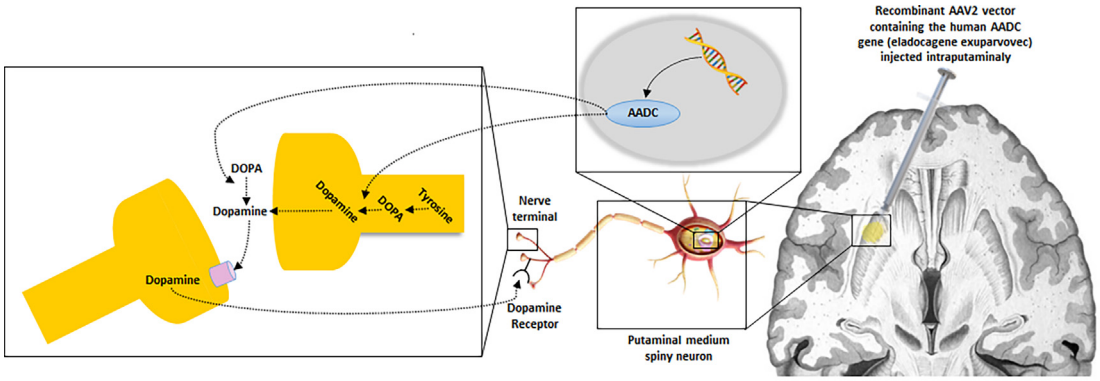

Fig. 3. The intraputaminal delivery of the recombinant adenovirus-associated vector 2 (AAV2) that contains the aromatic L-amino acid decarboxylase (AADC) gene (rAAV2-hAADC, eladocagene exuparvovec), facilitates the formation of the enzyme AADC. As a result, dopamine is produced, leading to improvements in motor and cognitive function, physical growth, reduction of symptoms such as mood lability, sweating, and oculogyric crises, and increased quality of life of children with AADC deficiency.

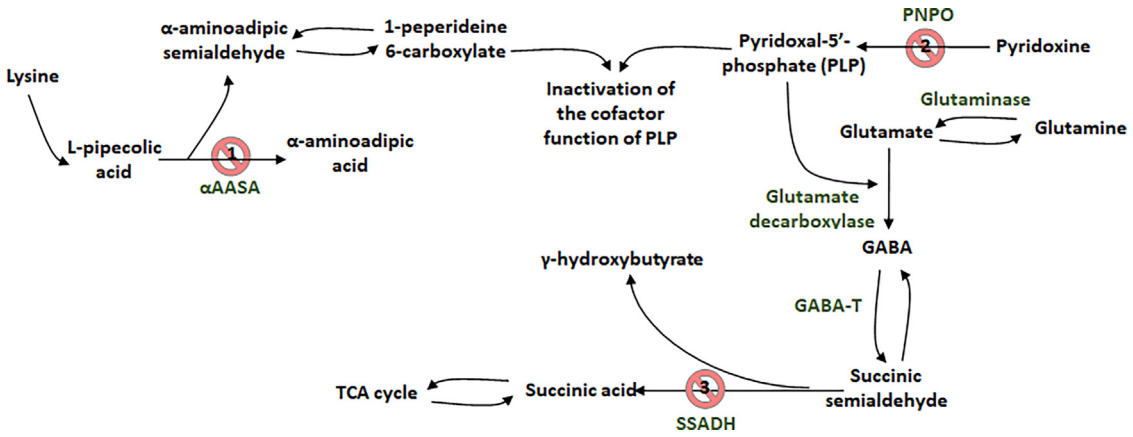

Fig. 4. A simplified graphical representation of the intricate metabolic pathways of lysine, pyridoxine, and gamma-aminobutyric acid (GABA). Inactivation of pyridoxal 5′-phosphate (PLP) is driven by the so-called Knoevenagel condensation: accumulation of Δ1-pyrroline-5-carboxylate (P5C) (in hyperprolinemia type II) caused by a block in the pathway degrading pyridoxine to PLP (1) and piperidine 6′carboxylate, resulting from the deficiency of α-amino adipic semialdehyde (αAASA) enzyme (antiquitin) (2). As noted by the figure, this has many consequential effects, one of them which is disruption of GABA metabolism. Another GABA-related metabolic pathway block (3) can be caused by a deficiency of the enzyme succinic semialdehyde dehydrogenase (SSADH). This leads to the accumulation of γ-hydroxybutyrate and the disease SSADH deficiency. GABA-T- gamma-aminobutyric acid transaminase; PNPO- Pyridoxamine 5′-phosphate oxidase; TCA- tricarboxylic acid.

development of targeted therapy for SSADHD deficiency demonstrated that ERT [119] or liver-directed AAV gene therapy [120] increases the survival of an SSADHD mouse model. Yet, the model that was used in these studies mimics only the severe form of the disease, and as such, it restricts the ability to attain information on the efficacy and dose–response relationships of different therapeutics [121]. Addressing these limitations, a recently introduced SSADH-deficient mouse model that is a better mimicker of human SSADHD and has a unique 'on-demand' function that allows the reactivation of the deactivated *ALDH5A1* gene, may offer the possibility of understanding the clinical effect of SSADH restoration. This eventually may bring forth novel therapeutics for SSADHD [122].

5.4. Mineral and vitamin metabolism defects

The number of neurometabolic disorders which are responsive to vitamins has increased in recent years. The hallmark and perhaps most studied example is pyridoxine-dependent epilepsy (PDE). The principal etiology of PDE is a mutated *ALDH7A1* gene leading to deficiency of the lysine pathway enzyme, alpha-aminoadipic semialdehyde dehydrogenase (AASAD). Other etiologies of PDE include pyridoxamine-5′-phosphate oxidase (PNPO) deficiency, PROSC/PLPBP deficiency, hyperprolinemia type II, and severe neonatal hypophosphatasia [123–126]. Some of the severe forms of KCNQ2-related epilepsy have also been shown to be responsive to pyridoxine [127]. Lifelong pyridoxine administration is the mainstay treatment of seizures resulting from PDE and recent consensus guidelines also advise arginine supplementation and a lysine-restricted diet as part of the management [128]. Pyridoxal-5-phosphate (PLP) dependency involves mutations in the gene of PNPO, that are responsible for the conversion of pyridoxine to PLP. Individuals with PLP dependency are only partially responsive to pyridoxine and are treated with PLP [129]. Fig. 4 illustrates some of the metabolic pathways that relate to pyridoxine and PLP. Folinic acid-responsive neonatal epileptic encephalopathy is clinically similar to PDE. Treating the seizures in this condition with a combination of pyridoxine and folinic acid or only folinic acid shows a good response, although the biochemical explanation for this is not entirely clear [130].

The biotin-responsive conditions should also be noted, as several new diseases belonging to this group have emerged in recent years. Besides biotinidase deficiency [131], other diseases that are now treated with biotin are holocarboxylase synthetase deficiency, biotin-thiamine responsive basal ganglia disease, thiamine phosphokinase deficiency, and sodium-dependent multivitamin transporter (SVMT) deficiency [131–134].

6. Conclusions

Remarkable progress has been accomplished in recent years in the research of genetic and molecular biology systems, which has expanded our understanding of the pathophysiological mechanisms of epilepsies resulting from neurometabolic diseases. In resonance, many potential therapeutic approaches for these diseases have been established or are currently being developed. However, there is still a pressing unmet need for the treatment of this rare and heterogeneous group of diseases. Their unique characteristics make the process of their novel-drug development challenging at almost every level: creating high-quality preclinical studies with animal models which are geno- and phenotypically similar to humans; translating successful preclinical investigations to bedside by creating well-controlled and long-termed clinical trials; choosing objective outcome measures that have relevance to the quality of life of these patients; assessing the efficiency of therapies that are already in use; and creating evidence-based treatment guidelines. Overcoming the challenges posed by this exceptional group of diseases should be continuously gained by conducting multicenter collaborations that gather information from numerous subgroups of homogenous neurometabolic diseases-bearing individuals. The emerging therapies covered in this review provide an inspiring promise for the furtherance of clinically applicable treatments for neurometabolic diseases.

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