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Review article

Exploring the intersecting paths between metabolic disorders and neurological manifestations

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ABSTRACT

The metabolic derangements associated with inborn errors of metabolism, metabolic syndrome, and defective autophagy have been linked to neurological manifestations and an increased risk of developing certain neurological diseases or worsening their prognosis. Said metabolic derangements are primarily a consequence of genetic mutations that result in deficiencies of essential cellular components or the accumulation of toxic metabolites that negatively impact neuronal morphology and functionality. Additionally, blood-brain barrier dysfunction, increased quantity and damage of nonneuronal cells, diminished synaptic plasticity, and impediment of protein and neurotransmitter synthesis, among many others, are all neurological implications associated with various metabolic disarrangements. The past few decades have shown substantial efforts in linking various neurological pathologies to genetic variants of metabolic disorders. This review explores the implications of several inborn errors of metabolism, such as phenylketonuria, Wilson's disease, maple syrup urine disease, *POLG*-related diseases, and lysosomal storage diseases, and the implications of the components of metabolic syndrome in neuronal dysfunction and their link to neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and epilepsy. The correlation between defective autophagy, neurodegenerative diseases, and neurodevelopmental diseases is also explored at a molecular level. Congenital disorders of autophagy and their link to neurological pathologies are also discussed. Hence, these correlations provide insight into the underlying biological mechanism of metabolic diseases from a neurological standpoint. This review emphasizes the cruciality of understanding metabolic diseases as important variables in neurological health as well as isolated systemic problems.

1. Introduction

Living organisms demand networks that can efficiently generate and supply energy; this plays a fundamental role in promoting and

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List of abbreviations

AD	Alzheimer's Disease
ADHD	Attention-Deficit Hyperactivity Disorder
AHS	Alpers-Huttenlocher Syndrome
ALS	Amyotrophic Lateral Sclerosis
ANS	Ataxia Neuropathy Spectrum
ASD	Autism Spectrum Disorder
ASM	Acid Sphingomyelinase
ASMD	Acid Sphingomyelinase Deficiency
Atg	Autophagy-Related
ATP7B	Atpase Copper Transporting Beta
AV	Autophagic Vacuoles
Aβ	B-Amyloid
BBB	Blood-Brain Barrier
BCAA	Branched-Chain Amino Acid
BCKDC	Branched-Chain A-Ketoacid Dehydrogenase Complex
CDG	Congenital Disorders of Glycosylation
CNS	Central Nervous System
GCE	Glucocerebrosidase Enzyme
GFAP	Glial Fibrillary Acidic Protein
HDL:	High-Density Lipoprotein
LAT1	Large Neutral Amino Acid Type 1
LB	Lewy Body
LC3	Light Chain 3
LDL:	Low-Density Lipoprotein
LNAA: Large Neutral Amino Acid	
LSD	Lysosomal Storage Disorder
MCHS	Childhood Myocerebrohepatopathy Spectrum
MEMSA	Myoclonus Epilepsy, Mitochondrial Myopathy and Sensory Ataxia (MEMSA)
MetS	Metabolic Syndrome
MIRAS	Mitochondrial Autosomal Recessive Ataxia Syndrome
MSUD	Maple Syrup Urine Disease
mtDNA	Mitochondrial DNA
NPD A	Niemann-Pick Disease Type A
NPD B	Niemann-Pick Disease Type B
NPD	Niemann-Pick Disease
OCD	Obsessive-Compulsive Disorder
PAH	Phenylalanine Hydroxylase
PD	Parkinson's Disease
PEO	Progressive External Ophthalmoplegia
PI3KC3	Class III Phosphatidylinositol-3 Kinase
PI3KC3-C1	Class III Phosphatidylinositol-3 Kinase Complex 1
PI3KC3-C2	Class III Phosphatidylinositol-3 Kinase Complex 2
PKU	Phenylketonuria
ROS	Reactive Oxygen Species
SANDO	Sensory Ataxia Neuropathy Dysarthria and Ophthalmoplegia
T2D	Type 2 Diabetes
ULK1	Autophagy-Activating Kinase 1
WD	Wilson Disease
γ	Gamma

conserving proper molecular and cellular function. Enzyme-catalyzed metabolic reactions fulfill this need by providing sustainable and well-coordinated routes of energy production and release through a series of interconnected anabolic and catabolic reactions occurring simultaneously. Metabolic disorders arise from disruptions in metabolic processes which precipitate adverse systemic effects on homeostatic mechanisms, circadian rhythms, and physiological processes, resulting in a disordered body state. The impairment or deficiency of an enzymatic or functional component of a metabolic pathway results in the diminishment or accumulation of certain metabolites that may be vital for sustenance or toxic to the body, respectively [1]. Metabolism may also be disturbed by viral or

bacterial infections, medication overuse, toxicity, hormonal imbalance, dietary and lifestyle changes, environmental impact, and most commonly genetic mutations [2]. Furthermore, several research studies have linked the deficiency or accumulation of metabolites in various metabolic disorders to neurological manifestations and disorders such as Parkinson's disease (PD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), attention-deficit hyperactive disorder (ADHD), autism spectrum disorder (ASD), epilepsy, schizophrenia, and many others. This paper will explore the prominent relationship between metabolic disorders and their associated neurological manifestations and disorders (Fig. 1).

2. Overview of specific inborn errors of metabolism associated with neurological pathologies

Inherited metabolic disorders, commonly known as inborn errors of metabolism, are disorders of heterogeneous etiologies that involve a defect in the catabolism, anabolism, or storage of macromolecules or their monomers as a result of an inherited or acquired genetic mutation [3]. Such genetic abnormalities disrupt normal metabolic processes, leading to an accumulation of toxic substances or deficiencies in crucial metabolic components. Inherited metabolic disorders therefore encompass an array of phenotypes involving an intoxication type, which includes defects in the catabolism, anabolism, or storage of typical or atypical metabolites, an error in energy production or utilization type, and an error in the catabolism or anabolism of 'complex molecules' type involved in organelle processes [4], as summarized in Fig. 2. Intoxication such as in the case of phenylketonuria (PKU), Wilson disease (WD), and maple syrup urine disease (MSUD), may involve metabolite accumulation in the brain which begins to emulate neurotransmitters, induce autophagy, or diminish synaptic plasticity and neuronal excitability. Disorders belonging to this group may also involve metabolite deficiencies due to reduced synthesis as a result of a metabolic block or impaired transportation and more often than not exhibit impaired neurodevelopment during infancy. An error in energy production or utilization involves a defect in ATP-producing pathways in the cytoplasm or mitochondrial defects such as in the case of *POLG*-related disorders. Mitochondrial defects are often accompanied by neurological manifestations, most of which are severe and progressive. Finally, an error in the anabolism or catabolism of 'complex molecules' may lead to metabolite deficiencies or accumulation, such as in the case of lysosomal storage disorders (LSDs) [5], or disruption in the remodelling, recycling, and trafficking of complex molecules, such as in congenital disorders of glycosylation (CDG). LSDs commonly present with neurological manifestations, such as neurodegeneration, due to the neurons' significant lifelong reliance on lysosomal function [5,6]. Similarly, various CDG subtypes commonly manifest with neurological abnormalities such as developmental delay, hypotonia, and other cognitive or motor impairments [7].

2.1. Phenylketonuria

PKU is a rare, autosomal recessive inherited disorder that hinders the body's capacity to effectively metabolize the amino acid phenylalanine. The accumulation of phenylalanine and its metabolites is attributed to the deficiency or complete absence of the enzyme phenylalanine hydroxylase (PAH) or its cofactor tetrahydrobiopterin, or due to low levels of the amino acid tyrosine (Table 1). The severity of the disorder correlates with the degree of PAH deficiency. PAH is a monooxygenase enzyme encoded by a gene of the same name on chromosome 12 that, through hydroxylation, converts phenylalanine to tyrosine, a large neutral amino acid (LNAA) crucial for the production of various neurotransmitters, including catecholamines and monoamine neurotransmitters, and thus for behavioral and cognitive function [8,9]. If left untreated, an excess of phenylalanine can accumulate in the bloodstream, causing

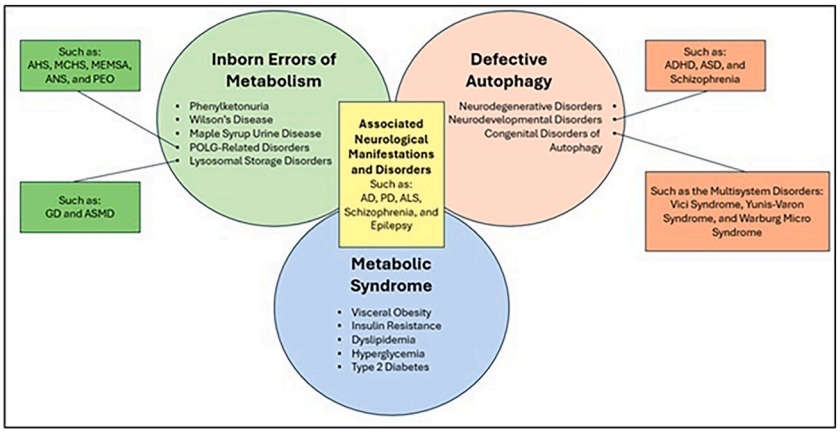

Fig. 1. Metabolic disorders associated with neurological pathologies. Metabolic syndrome, defective autophagy, and several inborn errors of metabolism arise due to various metabolic derangements that have been established to negatively impact neurons giving rise to neurological manifestations and an increased risk of developing certain neurological diseases. AD, Alzheimer's Disease; ADHD, Attention-Deficit Hyperactivity Disorder; AHS, Alpers-Huttenlocher Syndrome; ALS, Amyotrophic Lateral Sclerosis; ASD, Autism Spectrum Disorder; ANS, Ataxia Neuropathy Spectrum; ASMD, Acid Sphingomyelinase Deficiency; GD, Gaucher's Disease; MCHS, Childhood Myocerebrohepatopathy Spectrum; MEMSA, Mitochondrial Myopathy and Sensory Ataxia; PD, Parkison's Disease; PEO, Progressive External Ophthalmoplegia; POLG, DNA Polymerase Subunit Gamma.

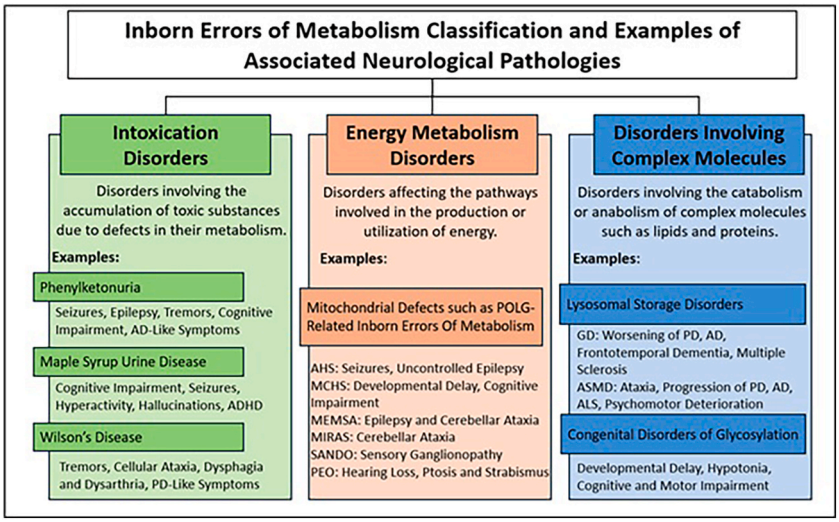

Fig. 2. Classification of inborn errors of metabolism and their associated neurological pathologies. Inborn errors of metabolism are classified into intoxication disorders, defective energy metabolism disorders and disorders involving complex molecules. AD, Alzheimer's Disease; ADHD, Attention-Deficit Hyperactivity Disorder; AHS, Alpers-Huttenlocher Syndrome; ALS, Amyotrophic Lateral Sclerosis; ASMD, Acid Sphingomyelinase Deficiency; GD, Gaucher's Disease; MCHS, Childhood Myocerebrohepatopathy Spectrum; MEMSA, Mitochondrial Myopathy and Sensory Ataxia; MIRAS, Mitochondrial Autosomal Recessive Ataxia Syndrome; PD, Parkison's Disease; PEO, Progressive External Ophthalmoplegia; POLG, DNA Polymerase Subunit Gamma; SANDO, Sensory Ataxia Neuropathy Dysarthria and Ophthalmoplegia.

cognitive impairments, developmental delays, and behavioral changes. For phenylalanine to access the brain, it must traverse the blood-brain barrier (BBB) with the aid of a specialized LNAA transporter, the large neutral amino acid type 1 (LAT1)-transporter. Among the LNAA, phenylalanine has the highest affinity to the LAT1 transporter. Consequently, elevated levels of phenylalanine in the blood result in its increased uptake into the brain and a reduction in the uptake of other LNAA, including tryptophan, threonine, histidine, leucine, isoleucine, valine, and methionine, due to competitive inhibition. This heavily hinders protein and neurotransmitter synthesis [10].

Elevated levels of phenylalanine in the brain have been associated with a decrease in the antioxidant capacity causing DNA, protein, and lipid damage. Lipid damage generates hypomyelination causing white matter disruption in the brain and is associated with decreased levels of docosahexaenoic acid and arachidonic acid (omega-3 and omega-6 fatty acids, respectively) [9,11]. The brain is highly vulnerable to oxidative stress due to multiple factors, therefore, minor alterations in the antioxidant capacity or prooxidant levels may disrupt oxidation-reduction reactions and induce oxidative damage.

Neurotransmitter metabolism is also impaired due to the inhibition of enzymes such as tryptophan hydroxylase, tyrosine hydroxylase, and 5-hydroxytryptophan decarboxylase as a result of phenylalanine metabolite accumulation. Other enzymes affected are those of the glycolytic pathway, such as pyruvate kinase, hexokinase, and pyruvate dehydrogenase complex, and oxidative phosphorylation enzymes suggesting glucose metabolism impairment in some parts of the brain [9,11]. Due to its multifaceted nature, several mechanisms behind the neurological manifestations associated with PKU have been proposed and yet remain unclear [9]. The neurotoxic effects of phenylalanine and its metabolites as a result of increased oxidative stress is the primary hypothesis.

Due to its neurological implications, PKU has been associated with various neurodegenerative disorders such as AD (Table 1). In fact, phenylalanine can self-assemble to form amyloid-like fibrillar aggregates in the brain, causing progressive deterioration of mental health which presents with AD-like symptoms [12]. A study conducted by Pilotto et al., in 2021 aimed to assess the correlation between the levels of phenylalanine in the bloodstream and both cognitive function and neuropsychiatric manifestations in adult individuals with PKU [10]. It was revealed that patients with PKU exhibited higher β-amyloid (Aβ), total tau, and phosphorylated tau levels compared to the control group, suggesting a higher risk of AD. Additionally, there was a strong correlation between the number of unsatisfactory neuropsychological tests and plasma phenylalanine levels [10]. A study proposed serum glial fibrillary acidic protein (GFAP) as a potential biomarker to detect alterations in the central nervous system (CNS) in PKU patients, thus enabling early detection of the disease's progression. GFAP is an intermediate filament expressed by non-neuronal cells, such as astrocytes, exclusively in the CNS. Therefore, the presence of GFAP in the serum suggests increased numbers of damaged astrocytes and other non-neuronal cells as a result of innate immunity activation and neurodegeneration. Moreover, the levels of serum GFAP and phenylalanine have been observed to be correlated, which indicates that monitoring serum GFAP levels can be beneficial when evaluating neurological symptoms in PKU patients [13].

2.2. *Maple syrup urine disease*

This disease is an autosomal recessive inherited disorder characterized by a deficiency of the enzyme branched-chain α-ketoacid

Table 1
A summary of the types of metabolic disorders, their molecular etiologies, their associated biological disturbances, and the resulting neurological pathologies including manifestations and diseases/disorders.

Disorder/Disease	Type of Disorder	Deficient/Defective Enzyme	Biological Disturbance	Associated Neurological Manifestations and Diseases	References
Inborn Errors of Metabolism					
Phenylketonuria (PKU)	Amino acid metabolism	Phenylalanine hydroxylase (PAH) (EC 1.14.16.1) due to a mutation in the *PAH* gene	Accumulation of phenylalanine and reduced synthesis of tyrosine due to a metabolic block	Seizures, epilepsy, tremors, mental retardation and cognitive impairment, behavioral changes, Alzheimer's disease (AD)-like symptoms	[8–13]
Maple Syrup Urine Disease (MSUD)	Amino acid metabolism	Branched-chain α-ketoacid dehydrogenase (BCKAD) complex due to mutations in the *BCKDHA*, *BCKDHB, DBT,* or *DLD* genes	Accumulation of branched-chain amino acids (BCAAs), including valine, leucine, and isoleucine, accompanied by reduced glutamate synthesis	Developmental delay, cognitive impairment, seizures and 'bicycling' movements, hyperactivity, hallucinations, glutamate deficiency are associated with anxiety, depression, attention-deficit hyperactivity disorder (ADHD), and obsessive-compulsive disorder (OCD) behaviors	[14–40]
Wilson's Disease (WD)	Metal storage disorders	Copper transporting P-type ATPase (ATP7B) (EC 7.2.2.9) due to a mutation in the *ATP7B* gene	Accumulation of copper in various organs, particularly in the liver, inducing organ damage	Tremors, cellular ataxia, dysphagia and dysarthria, behavioral changes, Parkinson's disease (PD)-like symptoms	[41–46]
Alpers-Huttenlocher syndrome (AHS)	Mitochondrial DNA (mtDNA) depletion	mtDNA polymerase gamma due to a mutation in the *POLG* gene	Reduction in mtDNA	Seizures (first sign of AHS), uncontrolled epilepsy including status epilepsy, refractory convulsive status epilepticus, hypotonia, ataxia, anxiety, hallucinations, migraines, and spastic paraparesis	[47,48,] [49–55]
Childhood Myocerebrohepatopathy Spectrum (MCHS)	mtDNA depletion	mtDNA polymerase gamma due to a mutation in the *POLG* gene	Reduction in mtDNA	Developmental delay, failure to thrive, cognitive impairment, behavioral changes, dementia	[47,56]
Myoclonic Epilepsy Myopathy Sensory Ataxia (MEMSA)	mtDNA deletion	mtDNA polymerase gamma due to a mutation in the *POLG* gene	mtDNA deletion	Epilepsy including focal epilepsy and generalized refractory epilepsy, cerebellar ataxia, sensory neuropathy	[48,56]
Ataxia Neuropathy Spectrum (ANS)	mtDNA deletion	mtDNA polymerase gamma due to a mutation in the *POLG* gene Adenine nucleotide translocator-1 (ANT1) due to a mutation in the *ANT1* gene Mitochondrial dynamin-like GTPase due to a mutation in the *OPA1* gene	mtDNA deletion	**Mitochondrial recessive ataxia syndrome (MIRAS):** cerebellar ataxia, sensory and motor neuropathy **sensory ataxic neuropathy, dysarthria, and ophthalmoparesis (SANDO):** sensory ganglionopathy, progressive external ophthalmoplegia, and speech impairment	[56–58]
Progressive External Ophthalmoplegia (PEO)	mtDNA deletion	mtDNA polymerase gamma due to a mutation in the *POLG* or *POLG2* genes Mitochondrial DNA helicase due to mutation in the *TWNK* gene Other genes involved include *TOP3A*, *DNA2*, *MGME1*, *SLC25A4*, *TK2*, *RRM2B*, and *SPG7*	mtDNA deletion	Hearing loss, ptosis and strabismus, ataxia, depression, tremor, bradykinesia, postural instability, ataxia, and axonal neuropathy neuropathy, PD-like symptoms	[48,59,60]
Gaucher's Disease (GD)	Lipid metabolism (lysosomal storage disorder (LSD))	Glucocerebrosidase (lysosomal enzyme) (EC 3.2.1.45) due to a mutation in the *GBA1* gene Rarely saposin C (glucocerebrosidase activator) due to mutation in the *PSAP* gene	Accumulation of glucocerebrosides coupled with increased glucosylsphingosine, sphingosine, and sphingosine-1-phosphate levels	Worsening of PD, AD, frontotemporal dementia, multiple sclerosis GD1: absence of neurological symptoms (by conventional definition), however, increased risk of PD and peripheral neuropathies have been observed GD2: developmental delay, apnea, laryngeal	[61–82]

(*continued on next page*)

Table 1 (*continued*)

Disorder/Disease	Type of Disorder	Deficient/Defective Enzyme	Biological Disturbance	Associated Neurological Manifestations and Diseases	References
				spasms, seizures GD3: similar neurological symptoms as GD1, cerebellar ataxia, dementia, myoclonus epilepsy	
Acid Sphingomyelinase Deficiency (ASMD)	Lipid metabolism (LSD)	Acid sphingomyelinase (ASM) (lysosomal enzyme) (EC 3.1.4.12) due to mutation in the *SMPD1* gene	Accumulation of sphingomyelin and formation of foam cells	Ataxia, progression of PD, AD, and amyotrophic lateral sclerosis (ALS), psychomotor deterioration, learning difficulties	[83–96]
Congenital Disorders of Glycosylation	Protein and lipid glycosylation	Most commonly phosphomannomutase 2 (CDG-Ia) due to mutations in the *PMM2* gene Mannose-6-phosphate isomerase due to mutations in the *MPI* gene	Defects in glycosylation of proteins and lipids resulting in their impaired folding, stability and trafficking	Developmental delay, hypotonia, seizures, ataxia and strabismus in most types Cerebellar hypoplasia, retinitis pigmentosa and intellectual disabilities in some types	[7,97,98]
Metabolic Syndrome					
Metabolic Syndrome (MetS)	Components include obesity, dyslipidemia, hypertension, and insulin resistance	Not typically associated with a single gene mutation but rather involves a combination of genetic, epigenetic, and environmental factors Genes involved in MetS components vary widely	Disturbances in various metabolic processes giving rise to obesity, dyslipidemia, hypertension, and insulin resistance and overall increased inflammation and tissue dysfunction	Cognitive impairment, neuropathies, cerebral small vessel disease, cerebral perfusion inadequacy, and potential links to neurogenerative diseases such as AD	[99–110]
Defective Autophagy					
Neurodegenerative Diseases	Include AD, PD, ALS, and Huntington's disease	May potentially arise due to mutations in genes involved in autophagy resulting in defective autophagy in the brain	Defective autophagy causes neuron damage due to accumulation of misfolded proteins, a hallmark of neurodegenerative disorders	AD, PD, ALS, and Huntington's disease	[111–117]
Neurodevelopmental Diseases	Include ADHD, autism spectrum disorder (ASD) schizophrenia, intellectual and cognitive disabilities, communication and learning disorders, mood disorders, and motor disorders such as tic disorders	May potentially arise due to mutations in genes involved in autophagy resulting in defective autophagy in the brain	Defective autophagy interferes with neuronal and glial development as well as maintaining neuronal viability at a young age	ADHD, ASD, schizophrenia, intellectual and cognitive disabilities, communication and learning disorders, mood disorders, and motor disorders such as tic disorders	[118–122]
Congenital Disorders of Autophagy (A Type of Inborn Errors of Metabolism Involving Complex Molecules)	Include lysosomal storage disorders, beta propeller-associated neurodegeneration, cerebral ataxia, spastic paraplegias, and multisystem disorders such as Vici syndrome, Younis-Varon syndrome, and Warburg Micro syndrome	May potentially arise due to mutations in genes involved in autophagy resulting in defective autophagy in the brain	Defective autophagy due to internal stresses and metabolic derangements or other causes cause developmental impairment and affect multiple organs	Developmental delay, cognitive impairment, intellectual disability, seizures, PD-like symptoms, neuropathy, dysphagia (all depending on the type of disorder)	[123]
	Multisystem Disorders Vici syndrome	Ectopic P-granules protein 5 homolog (EPG5) due to a mutation in the *EPG5* gene	Defective autophagy due to impaired fusion of autophagosomes with lysosomes and late endosomes	Developmental delay, failure to thrive, seizures (>50% of patients), corpus callosum agenesis, microcephaly, and demyelination	[112,124, 125]
	Younis-Varon syndrome	Polyphosphoinositide phosphatase due to a mutation in Fig. 4 gene	Defective autophagy due to impaired endosomal trafficking	Developmental delay, difficulty feeding and swallowing, neuropathy	[123, 126–129]

(*continued on next page*)

Table 1 (*continued*)

Disorder/Disease	Type of Disorder		Deficient/Defective Enzyme	Biological Disturbance	Associated Neurological Manifestations and Diseases	References
		Warburg Micro syndrome	Mutations in the *RAB18*, *RAB3GAP1*, *RAB3GAP2*, or *TBC1D20* genes	Defective autophagy due to impaired trafficking, autophagosome formation, or autophagosome maturation	Similar to Vici syndrome; seizures, motor disorders, spastic paraplegia, developmental delay	[123, 126–129]

dehydrogenase complex (BCKDC) due to mutations in the *BCKDHA*, *BCKDHB,* or dihydrolipoamide branched-chain transacylase E2 (*DBT*) genes, resulting in an inability to catabolize the branched-chained amino acids (BCAAs) leucine, isoleucine, and valine [14,15] (Table 1). Disruption in the catabolism of these amino acids, which is physiologically necessary for protein synthesis and cell signaling, elicits various pathologic changes that ensue as MSUD [16]. Naturally, as the body fails to metabolize BCAAs into their end products, they accumulate in high quantities in various parts of the body. In MSUD patients, such elevations may instigate neurological manifestations such as seizures, apnea, ataxia, intellectual impairment, and motor delay due to imbalances of amino acids and neurotransmitters [17,18] (Table 1). According to two studies, the levels of glutamate, N-acetyl-aspartate, phenylalanine, tyrosine, tryptophan, and methionine are decreased in the CNS of MSUD patients [17,19]. Glutamate plays a vital role in the mechanisms of learning and memory [20]; therefore, any alterations in the glutamate pathway may cause learning and memory deficits and this has been extensively demonstrated by various studies [21,22]. Glutamate alterations have also been implicated in anxiety [23,24] and depression disorders [25]. In addition, studies investigating disorders like ADHD and obsessive-compulsive disorder (OCD) revealed a potential link to glutamic activity [26,27] (Table 1). Current studies determined that MSUD patients are still at higher risk of ADHD and OCD despite the availability of treatment options that aid in restoring peripheral BCAA homeostasis [19,28,29].

MSUD patients presenting with low brain N-acetyl aspartate levels exhibited higher graveness of depression, anxiety, and ADHD symptoms [19,30] (Table 1). In the oligodendrocytes, the catabolism of N-acetyl aspartate supplies the acetyl group necessary for myelin lipid synthesis. Consequently, MSUD patients with N-acetyl aspartate deficiency suffer defective myelination, which is implicated in depression [31] and ADHD [32] pathogenesis. A pathogenic role of severe N-acetyl aspartate deficiency has also been implicated in infantile epilepsy in patients carrying homozygous mutations in the aspartate-glutamate carrier 1 gene [33]. Aspartate is a nonessential amino acid that modulates neuronal activity in the brain. The shortage of aspartate in the CNS of MSUD patients elicits a decrease in malate-aspartate shuttle flux, contributing to neurological symptoms. In addition to that, mutations in *BCKDK*, where BCAA levels were low in plasma, were linked to ASD and epilepsy [34]. This was demonstrated by multiple studies showing that lower BCAA levels were detected in the urine, plasma, and cerebrospinal fluid of autistic patients whose disease had no molecular etiology [35–37]. To further support that notion, the intracerebroventricular administration of BCAAs had significantly improved autistic-like neurobehavioral abnormalities in mouse models [38]. Moreover, the role of oxidative damage in MSUD neuropathology has been suggested in animal studies [39,40].

2.3. Wilson's disease

WD is an autosomal recessive inherited disorder involving impaired hepatic copper metabolism due to mutations in the *ATP7B* gene and is commonly associated with a range of clinical manifestations, primarily neurological and hepatic manifestations (Table 1). As such, WD has two main forms, namely hepatic-type and neurological-type WD. Around 60% of WD patients exhibit neurological and psychological manifestations, most of which are unpredictable, however may display improvement after treatment [41,42]. Due to its variable clinical symptoms, proper diagnosis is frequently delayed, contributing to more neurological symptoms [15].

WD arises due to a defect in the copper-transporting beta ATPase (ATP7B) located in the trans-Golgi network of hepatocytes, brain cells, placenta, cardiomyocytes, and other types of cells. It plays a role in transporting copper across membranes in an ATP-dependent manner resulting in firstly, the incorporation of copper into ceruloplasmin and its release into the bloodstream and secondly, the excretion of copper in bile. ATP7B also transports copper to copper-dependent enzymes such as copper-zinc superoxide dismutase 1, dopamine β-hydroxylase, tyrosinase, ceruloplasmin, and the respiratory chain enzyme cytochrome *c* oxidase, among others. Therefore, a loss of function of ATP7B leads to the accumulation of copper in various organs, notably in the liver, brain, and ocular tissues, low levels of copper in the plasma, impaired production of active ceruloplasmin, and impaired function of copper-containing enzymes [43,44]. The primary cause of the clinical manifestations in WD is attributed to the oxidative stress induced by copper toxicity.

Copper plays an essential role in oxidation-reduction reactions. Paradoxically, an excess of copper induces oxidative stress, cellular damage, apoptosis, and necrosis. However, cells are adept at detoxifying excess copper. For instance, the toxicity of free copper is impeded by metallothioneins and glutathione [43]. However, hepatocyte damage and exceeding the hepatic copper capacity result in free copper overflowing into the bloodstream and eventually crossing the BBB and accumulating in astrocytes. Upon exceeding a particular threshold, the excess copper induces oligodendrocyte and astrocyte damage and astrocytosis. Astrocytes form and maintain the BBB and, along with oligodendrocytes, promote myelination and neuron survival. Thus, their impairment ultimately results in demyelination and BBB dysfunction. Furthermore, mitochondrial damage, white matter damage, and spinal tract damage also arise due to copper deposition [42]. The overall increase in copper across all regions of the brain leads to neuronal dysfunction, particularly due to the neurons being exposed to and more vulnerable to toxic substrates, including free radicals, as a result of the dysfunctional BBB and astrocyte damage. Additionally, the reduced detoxification capacity of the liver further exacerbates neurological symptoms of WD due to the presence of higher levels of toxic substances systemically [43]. Some of the neurological changes that may be noted constitute atrophy, neuron reduction, Opalski cells, increased quantity of non-neuronal cells, and cavitation in various parts of the brain including the basal ganglia, thalamus, and brain stem, all resulting from oxidative stress [45,46]. Such changes affect motor activity, reward processes, cognitive abilities, memory, and learning capabilities. When paired with neurotransmitter imbalances, changes in the basal ganglia cause psychiatric manifestations such as behavioral, cognitive, and personality changes. The most common neurological symptom of WD is the tremor, caused by midbrain lesions as a result of copper toxicity [43] (Table 1). Copper toxicity manifestations have significant variations and are dependent on the rate of copper increase and the duration of its accumulation in tissues.

2.4. Inborn errors of energy metabolism due to POLG-related mtDNA deletions

The DNA polymerase enzyme plays an essential role in the process of genomic replication and one prime example is mitochondrial DNA (mtDNA) polymerase encoded by the *POLG* gene, also known as *POLG1* (Table 1). The *POLG1* gene encodes the catalytic subunit of the mtDNA polymerase enzyme, the polymerase gamma (γ), which is crucial for mtDNA replication and repair and overall healthy upkeep of mitochondrial function and number. This ensures an ample supply of ATP to vital organs such as the brain which particularly demands high energy levels for its proper development and operation. In the brain, neurons receive most of their ATP through oxidative phosphorylation in the mitochondria. Mutations in the *POLG1* gene lead to diminished or defective functionality of polymerase γ, which in turn compromises vital mitochondrial functions, such as ATP production. Accordingly, the accumulation of such mutations may instigate early childhood mtDNA depletion or later-onset mtDNA deletion syndromes which are often associated with neurological manifestations. These *POLG1*-related syndromes may manifest initially during infancy, childhood, adolescence, or late adulthood. Common neurological presentations associated with mtDNA syndromes include encephalopathy, developmental delay, myopathy, ataxia, and most commonly, epilepsy. More than 80% of pediatric patients possessing *POLG1* pathogenic variants experience epilepsy [47]. Although phenotypically overlapping, there have been various syndromes identified and characterized as possessing recessive *POLG1* mutations. The diseases under this heterogeneous spectrum of neurological and musculoskeletal diseases are characterized by cerebellar, spinocerebellar, or sensory ataxia [130]. The primary *POLG1* mutation-driven disorders comprise the extremely severe Alpers-Huttenlocher syndrome (AHS), childhood myocerebrohepatopathy spectrum (MCHS), myoclonus epilepsy, mitochondrial myopathy and sensory ataxia (MEMSA), ataxia neuropathy spectrum (ANS) and both autosomal recessive and autosomal dominant progressive external ophthalmoplegia (PEO) [48] (Fig. 3).

2.4.1. Alpers-Huttenlocher Syndrome

AHS is a severe and rare mitochondrial disorder characterized by autosomal recessive mutations in the *POLG1* gene. Consequently, there is notable mitochondrial dysfunction and ATP reduction. The brain and liver are prominent organs that demand high levels of energy; reduced mitochondrial function leading to unmet energy demands in these organs prompts various neurological and hepatic symptoms such as seizures and liver failure, respectively. Therefore, the manifestation of neurological and hepatic symptoms in children is often indicative of AHS [49]. This disease progresses rapidly and severely, often presenting early in life and invariably resulting in fatalities [50]. However, the disease onset, neurological deterioration rate, and mortality age often vary between patients according to the disease severity. Mild atrophy, astrocytosis, reactive gliosis, spongiosis, and neuronal loss are commonly observed in cerebral cortex neural tissue. Moreover, recent findings in AHS patients' post-mortem brain tissue indicated complex I impairments altering Purkinje cells and interneurons and substantial involvement of GABAergic neurons [51]. These histopathological findings align with the symptoms of cognitive decline clinically displayed [52]. AHS symptoms commonly include neurodevelopmental decline, intractable seizures [53], psychomotor regression, and hepatopathy (Table 1). Patients with AHS present with severe encephalopathy and uncontrollable epilepsy which is often diagnosed during infancy [48]. Infants with AHS develop focal motor seizures that advance to status epilepticus; most patients manifest refractory convulsive status epilepticus [47]. Blindness may also be experienced temporarily initially but often permanently [54]. Some AHS patients experience hypotonia and mild developmental delay [55]. Other manifestations may comprise ataxia, anxiety, hallucinations, migraines, and spastic paraparesis [54] (Table 1). This disease is characterized by the worst prognosis of all *POLG* gene mutation-driven diseases.

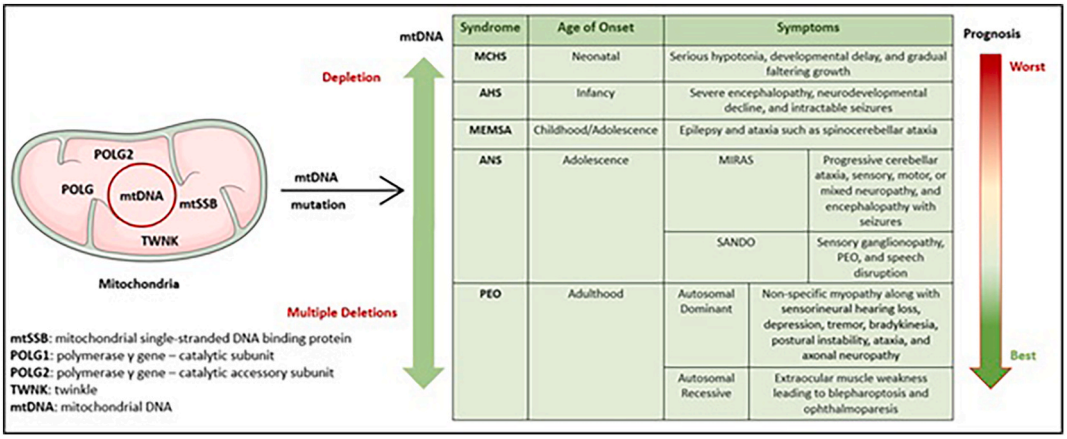

Fig. 3. Molecular and clinical aspects of POLG-related disorders. Depletion and deletion mutations in mitochondrial genes, such as the *POLG1* gene, induce various neurological manifestations of different severities, disease onsets, and prognoses. MCHS, Childhood Myocerebrohepatopathy Spectrum; AHS, Alpers-Huttenlocher Syndrome; MEMSA, Myoclonus Epilepsy, Mitochondrial Myopathy and Sensory Ataxia; ANS, Ataxia Neuropathy Spectrum; MIRAS, Mitochondrial Autosomal Recessive Ataxia Syndrome; SANDO, Sensory Ataxia Neuropathy Dysarthria and Ophthalmoplegia; PEO, Progressive External Ophthalmoplegia.

2.4.2. Childhood myocerebrohepatopathy spectrum

Biallelic *POLG* mutations instigate early presentations of myocerebrohepatopathy [56]. MCHS disorders are often characterized by an infancy onset of serious hypotonia, developmental delay, lactic acidosis, and gradual faltering growth (Table 1). Other symptoms include hepatic impairment, renal tubular acidosis, cyclic vomiting, hearing loss, and roving eye movements induced by cataracts. Seizures do not commonly manifest in this disorder; it is hypothesized that infants do not live long enough to develop and experience seizures as liver failure, sepsis, and status epilepticus are the typical reasons for death within the first year of life [47]. Similar to AHS, this disease is characterized by the worst prognosis of all *POLG* gene mutation-driven diseases.

2.4.3. Myoclonus epilepsy, mitochondrial myopathy, and sensory ataxia

Formerly known as spinocerebellar ataxia with epilepsy or SCAE, MEMSA comprises a variety of disorders with epilepsy and ataxia with no ophthalmoplegia [48] that typically manifest at an older age than the previous diseases, particularly during young adulthood. The first symptom is usually sensory polyneuropathy which leads to cerebellar ataxia. Other manifestations that appear years later include recurrent myoclonic seizures that initially localize to the right arm but may generalize, accompanied by progressive interictal encephalopathy, distal or proximal myopathy, and unrestricted muscular jerks or myoclonus (Table 1). MEMSA patients often exhibit exercise intolerance due to the myopathy present [56]. Generally, MEMSA has a better prognosis than early-onset AHS and MCHS.

2.4.4. Ataxia neuropathy spectrum

ANS is another POLG-related disorder characterized by a mid-teen onset that often causes premature mortality. This spectrum comprises mitochondrial autosomal recessive ataxia syndrome (MIRAS) and sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO) [57]. MIRAS patients present with progressive cerebellar ataxia and sensory, motor, or mixed neuropathy; some patients manifest encephalopathy with seizures. Patients treated with valproate, which is commonly used to alleviate neuropathic pain, may display gradual progressive encephalopathy and hepatic failure. Although clinical myopathy is uncommon in ANS, cramps are experienced by approximately 25% of patients [56]. On the other hand, SANDO patients manifest sensory ganglionopathy, PEO, and speech impairment (Table 1). Upon examination of brain tissue, cortical cerebellar atrophy, Purkinje cell loss, dorsal column atrophy, and deep cerebellar nuclei alterations are observed [58]. Other symptoms of AHS may include hepatic dysfunction, myoclonus, and blindness [56]. It is common for migraines to precede other manifestations by years. Similar to MEMSA, ANS has a better prognosis than early-onset AHS and MCHS.

2.4.5. Progressive external ophthalmoplegia

PEO is a relatively common *POLG*-related disorder that manifests during adulthood. It was formerly characterized by defective eye mobility, progressive ptosis, bilaterality, multi-innervated muscles, spared pupils, gradual progression over time, and no remissions or aggravations [59]. However, advances in molecular genetic studies allowed the identification of various etiologically distinct PEO types. Mutations in the *POLG* gene may be of autosomal dominant or autosomal recessive inheritance. Patients with autosomal recessive PEO experience extraocular muscle weakness which may lead to blepharoptosis and ophthalmoparesis. On the other hand, autosomal dominant PEO patients experience non-specific myopathy, often inducing fatigue and exercise intolerance, along with a spectrum of other neurological symptoms with variable degrees of severity like sensorineural hearing loss, depression, tremor, bradykinesia, postural instability, ataxia, and axonal neuropathy [48] (Table 1). However, the hallmarks of autosomal dominant PEO are ptosis and strabismus caused by progressive extraocular eye muscle weakness [60]. Amongst all the other *POLG*-related disorders, all forms of PEO show the best prognosis.

2.5. Inborn errors of metabolism involving complex molecules

2.5.1. Lysosomal storage disorders

LSDs are a set of metabolic disorders that primarily concern any defects and deficiencies altering lysosomal function [131] and according to the literature, many LSDs are characterized by neurological dysfunction and impairment. LSDs are inherited, mostly autosomal recessive, metabolic disorders characterized by the accumulation of substrates due to their impaired catabolism within the endosomal-lysosomal system. This impairment primarily revolves around lysosomal dysfunction due to mutations in genes encoding for enzymes and proteins that are instrumental in normal lysosomal activity [132]. In addition to their role in substrate degradation, lysosomes are indispensable in the autophagic pathway, which is essential for maintaining cellular homeostasis by degrading damaged organelles and proteins. In LSDs, impaired lysosomal function exacerbates cellular dysfunction by disrupting both lysosomal degradation and autophagic processes, resulting in the accumulation of waste materials and dysregulated cellular components. This triggers cellular stress responses and neuroinflammation leading to progressive neuronal damage [133]. Regardless of the genotypic and phenotypic heterogeneity of LSDs, they frequently present with progressive neurological symptoms [134]. Interestingly, neurological manifestations in LSDs have overlapping pathophysiology with neurodegenerative diseases such as AD and PD. Mutations in genes such as *GBA*, *SCARB2*, *SMPD1*, *ASAH1*, and *PSAP* have also been associated with both neurodegenerative diseases and LSDs. Over 50 monogenic diseases encompass the LSD group, with approximately 1300 genes involved, most of which arise from mutations in genes that encode for lysosomal hydrolases. Other defects are associated with endosomal trafficking, lysosomal endocytosis, exocytosis, autophagy, and phagocytosis, proteins such as transporters and channels, lipofuscin production, and post-translational processes, to name a few [132,135]. LSDs are typically classified based on the type of accumulated substrate or by the underlying functional defect [134].

Occasionally, cells exhibit the capacity to manage slight accumulations of substrates they originally synthesized or metabolized.

However, predominantly, substrates accumulate within lysosomes initiating a cascade of events that ultimately lead to cell damage and death. In the case of CNS involvement, dying or damaged neurons release damage-associated molecular patterns that trigger microglia activation and thus inflammatory cytokines and chemokines production including interleukins and tumor necrosis factor-α. In other words, they activate innate immunity in the brain. Thus, LSD progression is generally characterized by chronic neuronal inflammation, cellular damage and death, and sometimes autoimmune responses [24].

The distinct mechanisms underlying the various LSDs are wide-ranging. In recent years, it has been proposed that LSDs may not stem solely from anomalies within the endosomal-lysosomal system that led to the accumulation of substrates, but perhaps from defective signal transduction pathways due to said substrate accumulation or mis-localization. For instance, in mucopolysaccharidoses, the accumulated glycosaminoglycans, which normally bind to proteoglycans, may interfere with signaling pathways such as Wnt/β-catenin and Sonic hedgehog pathways. In sphingolipidoses, accumulation of glycol- and phospho-sphingolipids impairs lysosomal trafficking of membrane constituents, activates cellular apoptosis, and interferes with signaling pathways [26,27]. The disrupted signaling pathways, accumulated substrates, and toxic metabolites each contribute to increased production of reactive oxygen species (ROS) and/or reduced antioxidant capacity resulting in subsequent neuron degradation. Consequently, the neurological hallmark of LSDs is neuroinflammation and neurodegeneration with increased quantity and activation of microglia and astrocytes [132].

2.5.1.1. Gaucher's disease. GD, a common sphingolipidosis, is an inherited LSD in which sphingolipid catabolism is defective. Mutations in the *GBA1* gene, which encodes the lysosomal hydrolase glucocerebrosidase enzyme (GCE), lead to impaired hydrolysis of glucosylceramide into ceramide and glucose [61]. Consequently, glucosylceramide accumulates and forms twisted fibrillar aggregates in macrophages, turning them into Gaucher cells which infiltrate various organs [62] (Table 1). Additionally, the accumulation of glucosylceramide, which is particularly significant when GCE activity levels are markedly reduced, favors a pathway in which it serves as the substrate for a ceramidase which converts it directly into glucosylsphingosine [63,64]. According to research conducted on the fetal brain of a GD mouse model, the accumulation of glucosylsphingosine triggers neuronal impairment and death, and this manifests as neurological symptoms [65]. Glucosylsphingosine is usually not present in the human brain but is traceable in the brains of GD patients with neurological lesions; this makes glucosylsphingosine a specific and sensitive biomarker [63,66]. The precise mechanisms behind GD-associated neurological pathologies remain poorly understood. There have been three clinical phenotypes of GD identified as type 1, type 2, and type 3 where types 2 and 3 were specifically linked to neurological impairment [67] and are known as neuronopathic-GD [68].

Furthermore, some *GBA1* mutations place patients with GD at an imminent risk for PD [69]. Additionally, GD patients with null or recombinant alleles experience an earlier onset of PD [70] and those with neuropathic *GBA* mutations may experience a worse PD progression [71].

Patients with absent or decreased GCE may be at a higher risk of AD as a result of the compromised lysosomal degradation of α-synuclein, which prompts its oligomers and fibrils to accumulate in the substantia nigra of the brain and instigate neurotoxicity (Table 1). Glucosylceramide stabilizes these soluble oligomers which aggregate into Lewy bodies (LBs) in nerve cells [72,73]. This process is further instigated because these dysfunctional lysosomes perform impaired autophagy and autophagosome fusion [74]. The build-up of lipids, particularly cholesterol, in endo-lysosomes is a common feature in neurodegenerative diseases, indicating that defective lipid catabolism is a common mechanism in the development of dementia [75].

Moreover, according to various papers, GD type 1 patients are at a 4 to 20 times higher risk of developing PD with an earlier onset [72,76,77] (Table 1). Also, GD type 1 patients often sustain peripheral neuropathies and small fiber neuropathies at a rate 14% higher than healthy individuals [78]. Additionally, patients with GD type 2 experience an early onset of severe neurological dysfunction, often starting at 3 to 6 months old. Symptoms commonly manifest as opisthotonos, oculomotor paralysis, trismus, and hypertonia with pyramidal and extrapyramidal rigidity [79,80]. Another subtype of GD is subacute neurological GD or GD type 3. It commonly manifests as peripheral neuropathy and small fiber neuropathy often accompanied by an early onset of oculomotor neurological impairment (Table 1). The symptoms manifesting in patients with this heterogeneous type may range from moderate such as having only horizontal ophthalmoplegia to severe such as developing progressive myoclonus epilepsy, cerebellar ataxia, and sometimes dementia [81,82].

2.5.1.2. Acid sphingomyelinase deficiency. Another rare autosomal recessive LSD is acid sphingomyelinase deficiency (ASMD), also commonly known as Niemann-Pick disease (NPD). ASMD is historically classified into two types, type A (NPD A) and type B (NPD B), depending on the disease severity and involvement of neurologic symptoms. The NPD A phenotype is predominantly characterized by neurological findings, which makes it the most severe form of the disease [83,84].

This disorder is induced by mutations in the *SMPD1* gene that encodes acid sphingomyelinase enzyme (ASM) [85]. When the ASM enzyme is deficient or insufficient, its substrate sphingomyelin accumulates in various cells including cells of the monocyte-macrophage system and hepatocytes [84] (Table 1). The pathophysiology of this disease is primarily characterized by the formation of foam cells, which are huge lipid-laden cells, and their deposition in the liver, lungs, spleen, adrenal cortex, lymph nodes, and bone marrow. To mimic the pathological accumulation of sphingomyelin accumulation observed in NPD A, a research team extracted fibroblasts from an NPD A patient and loaded them with exogenic sphingomyelin. It was demonstrated that the autophagy-flux, mitochondrial function, electron transport chain, and cholesterol biosynthesis pathway were compromised and impaired [86]. Dysregulation of these processes can contribute to the development and progression of various neurodegenerative diseases such as PD [87], AD [88], and ALS [89] (Table 1). In infants, the disease manifests as severe psychomotor deterioration which

occurs due to extensive brain changes, cerebral and cerebellar neuronal loss, gliosis, demyelination, and foam cell infiltration [90].

As previously mentioned, the NPD A represents the most severe form of the disease [83,84]. According to the findings of a study conducted by McGovern et al., these neurologic manifestations were initially detected at the age of 7 months and had prevailed by the age of 10 months, where all infants suffered progressive neurodegeneration as well as behavioral, language, and motor skills deterioration. Moreover, all the patients exhibited hypotonia with deep tendon reflex loss. Upon performance of magnetic resonance imaging, it was revealed that a couple of patients had hydrocephalus, three patients had delayed myelination, and one patient had an arachnoid cyst. Some common manifestations recorded were irritability, sleep disturbances, and prolonged periods of crying, which were related to neurologic dysfunction [83].

Typically, infants with NPD A manifest distinctive lesions in the cerebellum more commonly than in the cerebrum alongside bulging, vacuolated ganglion cells, severe demyelination, and lipid-laden glial cells and foam cell deposition in the brain and perivascular connective tissue [90]. Another study by Hollak et al. revealed that all infants diagnosed with NPD A within the first year of life exhibited a progressive decline in psychomotor function [84]. On the other hand, some ASMD patients do not manifest typical NPD A symptoms but have a later onset of a spectrum of neurologic indications that fluctuate from mild to severe and do not rapidly progress. Those NPD B patients may experience mild hypotonia and hyporeflexia or severe motor function loss, mental deterioration, and language delay [84,91–95]. One astounding relationship recently suggested is that at least some *SMPD1* mutations correlate to a higher risk of PD [96].

2.5.2. Congenital disorders of glycosylation

CDGs represent a group of clinically heterogeneous inherited disorders, encompassing over a hundred diseases, characterized by the defective synthesis of glycoproteins and glycolipids. This occurs due to defects in various steps along glycan biosynthesis and glycosylation pathways. Errors in the assembly of N-glycans in the endoplasmic reticulum or their processing in the Golgi apparatus, as well as defects in the assembly of O-glycans, underline the defective glycosylation of proteins and lipids. The function of glycoproteins and glycolipids is therefore impaired, and this notably disrupts cellular processes such as protein trafficking and signaling. Although other forms of inheritance, such as autosomal dominant and X-linked, have been described, the majority of these disorders are inherited in an autosomal recessive manner. Currently, CDGs are classified into four different categories based on the associated afflicted pathway and these include N-linked glycosylation, O-linked glycosylation, combined N- and O-glycosylation linked/multiple glycosylation, and lipid and glycosylphosphatidylinositol anchor biosynthesis.

While CDGs are known to present with a broad spectrum of multisystemic manifestations, such as hypotonia, developmental delay, failure to thrive, coagulopathy, and hepatopathy, neurological abnormalities are among the most prominent presentations often seen in patients [97]. The age of onset and severity of these neurological symptoms can vary widely, ranging from mortality in neonates to cognitive deficits in adults [98]. Neurological abnormalities are common across a variety of CDG subtypes, with the most frequently observed symptoms constituting developmental delay, hypotonia, and other cognitive or motor impairments. Hallmark neurological manifestations include ataxia, seizures, strabismus, atypical eye movements, and cerebellar hypoplasia [7]. The most common form of CDG, an N-glycosylation type known as CDG-Ia (Table 1), is characterized by neurological manifestations presenting from infancy and include psychomotor retardation, strabismus, ataxia, hypotonia, and hyporeflexia. Children with CDG-Ia often experience development, speech, and motor delays alongside other symptoms like peripheral neuropathy, retinitis pigmentosa, seizures, and stroke-like episodes. On the contrary, CDG-Ib (Table 1) presents with minimal or no neurological involvement, primarily affecting the gastrointestinal and hepatic systems. Other N-glycosylation disorders also present with developmental delay, strabismus, ataxia, and seizures, though these manifestations tend to be milder compared to those observed in CDG-Ia. Furthermore, disorders affecting lipid glycosylation elicit a variety of clinical manifestations. Defects in ganglioside biosynthesis can cause severe neurodegenerative diseases, with afflicted individuals manifesting spastic paraplegia, severe intellectual delay, and epilepsy. Patients with disorders of glycosylphosphatidylinositol anchor biosynthesis often present with intellectual disabilities, infantile spasms, hypotonia, and epilepsy [97].

3. Metabolic syndrome and neurological manifestations

Metabolic syndrome (MetS) is a comprehensive term that defines the coexistence of various metabolic disarrangements that increase the risk of developing conditions such as cardiovascular disease, insulin resistance, hypertension, and dyslipidemia, among others. Such metabolic disarrangements include obesity, increased levels of triglycerides, low-density lipoprotein (LDL) and fasting glucose, low levels of high-density lipoprotein (HDL) cholesterol, and hypertension. The core concept behind MetS involves tissue dysfunction and increased inflammation as a result of excess fat deposition (Table 1). Consequently, this predominantly contributes to insulin resistance, endothelial dysfunction, vascular damage, and cardiovascular diseases [99,100]. However, recent evidence reinforces the contribution of MetS to neurological conditions such as cryptogenic sensory peripheral neuropathy which also intensifies the risk of developing diabetic peripheral neuropathy, a condition characterized by peripheral nerve damage prevalent in both type 1 and type 2 diabetes (T2D) patients. Inflammation of the neurons results from increased production of inflammatory cytokines and chemokines and increased ROS production. Dyslipidemia in MetS leads to dysfunctional mitochondria by affecting their motility and morphology, hence contributing to neuronal injury and damage to the Schwann cells. [100]. Both MetS and T2D peripheral neuropathies are characterized by preferential small nerve fibers injury [101].

3.1. Obesity, diabetes, and neuropathy

Obesity and hypertriglyceridemia pose injuries to small unmyelinated axons while hyperglycemia poses injuries to large, myelinated fibers. Although hyperglycemia negatively impacts large, myelinated fibers, the results of a cross-sectional study held on obese patients revealed the association of obesity with neuropathy even in normoglycemic cases [51]. Similarly, another study concluded that more MetS components were present in normoglycemic patients as they exhibited remarkably higher levels of HDL, LDL, triglycerides, and total cholesterol [102]. According to Callaghan B. et al. in a cross-sectional and a longitudinal study, patients with all components of MetS were 4.4% more likely to experience distal symmetric polyneuropathy when compared to patients with no MetS entities [103]. Furthermore, the association of MetS and obesity with CNS impairment was explored in the book "*Cerebral Small Vessel Disease*" in which it is stated that obesity, insulin resistance, and diabetes induce adverse alterations to the BBB integrity, cerebrovascular structure, and physiology through promoting pathological neovascularization. Such alterations result in cerebral perfusion inadequacy, microbleeds, and chronic inflammation which prompt cognitive deterioration and neurodegeneration [104] (Table 1).

3.2. Insulin resistance in Alzheimer's disease

Insulin resistance, associated with T2D, is established as the diminished sensitivity of body tissues to the actions of the hormone insulin. When brain cells fail to respond appropriately to insulin, it is referred to as brain insulin resistance [105]. Such resistance, in both the periphery and the brain, may elicit a diminished capacity of metabolism regulation or impaired mood and cognition [105, 106]. Primarily discovered in 1975, the tau protein was identified as the principal constituent of AD neurofibrillary tangles and has been associated with insulin signaling dysregulation in the brain [107]. Tau protein is modulated via phosphorylation and its expression and modulation are regulated by insulin stimulation. In AD patients' brains, tau proteins appear to be three times more hyperphosphorylated compared to normal healthy brains [108] (Table 1). Impairment in insulin signaling may amplify tau phosphorylation by increased activation of GSK3-β, a major phosphorylating molecule of tau and is a potential key player in AD development and PI3-K/AKT pathway inhibition [108,109]. Activation of GSK3- β is also triggered by oxidative stress which represents an implication of insulin resistance. Moreover, insulin resistance leads to decreased glucose metabolism which downregulates tau *O*-GlcNAcylation, and this in turn promotes tau hyperphosphorylation [110].

4. Defective autophagy and neurological disorders

Autophagy is a 'self-eating' metabolic stress adaptation mechanism in which obsolete cellular components, which may include lipids, proteins, polysaccharides, and nucleic acids as well as organelles, such as the mitochondria, are degraded and recycled in lysosomes to ensure cell survival [136,137]. In mammals, there are currently 31 autophagy-related (*Atg*) genes that are involved in this process [123]. The initiation of autophagy begins with the formation of the UNC-like autophagy-activating kinase 1 (ULK1) complex. Upon its activation, the ULK1 complex activates another complex, the class III phosphatidylinositol-3 kinase (PI3KC3) complex I (PI3KC3-CI) to produce phosphatidylinositol-3-phosphates which, together with microtubule-associated protein light chain 3 (LC3)-I (LC3-I), come together to form the phagophore with the aid of the Atg12 complex, WD repeat domain phosphoinositide interacting 2, and double FYVE-containing protein 1, or WIPI2 and DFCP1 respectively, and among other factors. Atg9 plays an essential role in phagophore elongation and trafficking. Microtubule-associated protein light chain 3 (LC3) is converted to LC3-I which is in turn transformed to phosphatidylethanolamine-conjugated LC3-II to recruit the ubiquitin-binding scaffold protein, p62, to the cargo and forms the p62-cargo complex facilitating membrane closure. PI3KC3-CII and the HOPS complex, among other factors, promote the fusion of the autophagosome with the lysosome [138]. Non-transcriptional regulation of all subtypes of autophagy is through the mammalian target of rapamycin (mTOR), which inhibits autophagy induction. The interconnection of autophagy with the various roles of lysosomes constitutes the lysosomal network, which collectively functions to eliminate obsolete cellular components, recycle their subunits, and reflect the overall health status of the cell and its surroundings [111]. Microautophagy, chaperone-mediated autophagy, and primarily, macroautophagy are the three main subtypes of autophagy that all result in lysosomal digestion but differ in their mode of delivering the cargo to the lysosome [136]. Neurons heavily rely on autophagy due to their exceptionally large cytoplasm in dendrites and axons, associated with more dysfunctional organelles and cellular waste accumulation. Neurons are easily impacted by low cellular waste clearance, as evidenced by the implication of defective autophagy not only in neurodegenerative and neurodevelopmental diseases but also in a type of inborn errors of metabolism involving complex molecules, referred to as congenital disorders of autophagy [111,112] (Table 1).

4.1. Defective autophagy in neurodegenerative disorders

Autophagy is essential in the elimination of defective or misfolded proteins and in maintaining proteostasis, a dynamic process of regulating proteins to maintain proteome homeostasis. A defect in the autophagic pathway results in the accumulation of misfolded protein aggregations, the pathological hallmark of numerous neurodegenerative diseases such as AD, PD, ALS, and Huntington's disease [113] (Table 1). In macroautophagy, de-novo synthesis of double-membrane vesicles, termed autophagosomes, engulf and deliver the cargo to the lysosome. Autophagosomes fuse with the lysosome to form an autolysosome where the cargo is digested by lysosomal enzymes [136]. Elevated numbers of such autophagic vacuoles (AV) are evident in neurodegenerative diseases, casting doubts on whether it is due to increased autophagy induction or reduced autolysosome formation, therefore promoting the

accumulation of autophagosomes. The precise defect in the autophagic pathway and its variant contributions to neurological diseases remain unclear [114].

The two major hallmarks of AD are the tau-containing neurofibrillary tangle in neurons and Aβ aggregates that form the neuritic plaque, with degeneration of the dendrites and axons of the neurons. In an attempt to recover from neuron damage, the lysosomal network is highly activated, eventually leading to the exacerbation of neuron damage as waste and AV accumulate [114]. A study conducted on presenilin-1-null mouse blastocytes resulted in impaired cellular waste clearance due to impaired autophagy, contributing, if slightly, to AD pathogenesis [115]. In AD, the accumulation of autophagosomes and other AVs in Aβ-containing neurons and dendrites exhibiting AD pathology was present in post-mortem human AD brain tissues. This suggests the extensive involvement of macroautophagy in the pathophysiology of AD and could be attributed to either a defect in the maturation of autophagosomes or their failure to fuse with lysosomes [116].

The hallmark of PD is characterized by the development and accumulation of aggregates of the protein α-synuclein in neurons, forming filamentous inclusions called LBs. Neurodegeneration in PD is limited to the substantia nigra of the brain in which cells stop producing enough dopamine. It has been proposed that the autophagic pathway may participate in the development of LBs. In fact, structures resembling autophagosomes were reported in neurons of PD patients [114]. One study revealed that macroautophagy was impaired in cases of α-synuclein accumulation, as they inhibit autophagosome formation. This resulted in the accumulation of cellular waste and a decrease in LC3-II lipidation [117].

4.2. *Defective autophagy in neurodevelopmental disorders*

Defective autophagy has not only been correlated with neurodegenerative disorders but also with neurodevelopmental disorders. Neurodevelopmental disorders describe a multifaceted group of clinically diverse neurological or psychiatric disabilities that result from an obstruction in proper brain development mostly occurring during childhood. Neurodevelopmental disorders include, but are not limited to, ADHD, ASD, schizophrenia, intellectual and cognitive disabilities, communication and learning disorders, mood disorders, and motor disorders such as tic disorders [118] (Table 1). Autophagy plays a crucial role in neurodevelopment by eliminating ubiquitinated proteins, toxic substrates, and damaged organelles, regulating neuronal growth and plasticity, and maintaining neuronal stem cells [119]. Various studies have demonstrated the relationship between autophagy and neurons and the development of glia from neuronal stem cells. A recent study highlighted the association of human *Atg7* variants, one of the core genes involved in the autophagic pathway, with neurodevelopmental disorders accompanied by abnormalities in the corpus callosum and cerebellum [120]. The results of this study suggest that the loss of function of Atg at an early stage might interfere with normal neuron development just as it interferes with maintaining neuron viability in the late stage. The ASD-related genes *TSC1*, *TSC2*, *mTOR*, and *PTEN* are all involved in autophagy regulation in the development of neuronal stem cells. In ASD patients, autophagy has also been associated with the synaptic function of neurons [121]. Epigenetic changes to autophagy-related genes have been observed in patients with

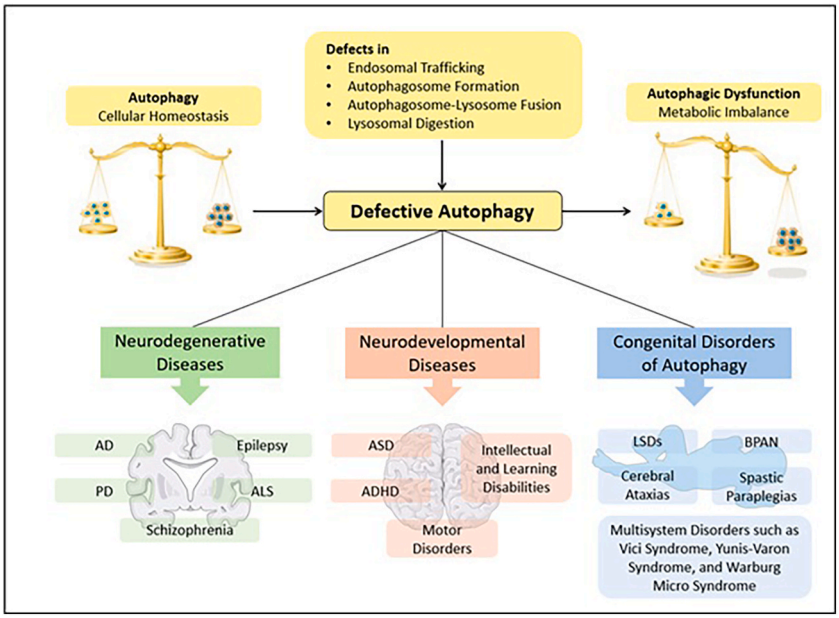

Fig. 4. The metabolic effects of defective autophagy. Defects in endosomal trafficking, autophagosome formation, autophagosome-lysosome fusion, or lysosomal digestion all result in dysfunctional autophagy and thus, metabolic imbalances. Various neurological pathologies have been associated with defective autophagy such as neurological manifestations, neurodegenerative diseases, neurodevelopmental diseases, and congenital disorders of autophagy. AD, Alzheimer's Disease; ADHD, Attention-Deficit Hyperactivity Disorder; ALS, Amyotrophic Lateral Sclerosis; ASD, Autism Spectrum Disorder; BPAN, Beta-Propeller Protein-Associated Neurodegeneration; LSD, Lysosomal Storage Disorders; PD, Parkinson's Disease.

neurodevelopmental phenotypes. For instance, variants of the *MECP2* gene have been associated with Rett syndrome. In context to autophagy, MECP2 promotes the methylation of the promoter region of *FOXO3,* which encodes for a transcription factor involved in the regulation of autophagy induction [122].

4.3. Congenital disorders of autophagy

Recently, evidence suggested the involvement of defective autophagy in inborn errors of metabolism associated with notable neurological manifestations. Primary autophagic dysfunction due to genetic mutations has emerged as an essential cause of inborn errors of metabolism. This diagnostic category comprises congenital multisystem disorders that occur mainly due to altered primary players of the autophagic pathway [112]. These disorders are therefore characterized by metabolic disruptions in the degradation and recycling of various components such as organelles, lipids, and proteins and could be classified as inborn errors of metabolism involving complex molecules [139]. Similarly, sarcopenic obesity, insulin resistance, and T2D represent some conditions marked by metabolic imbalance and internal stresses that also lead to the buildup of impaired cellular components [138]. Many proteins involved in these disorders are also associated with common neurodegenerative disorders such as dementia, PD, and ALS [87,140,141] (Fig. 4). The associated neurodevelopmental and neurodegenerative disorders appear throughout life with an early onset and an adult-onset, respectively. Congenital autophagy disorders, or those that appear at an early age, are characterized by prominent neurological features such as structural CNS defects, spasticity, peripheral nerve pathology, and cerebellar involvement as well as associated myopathy in several cases. Beta propeller-associated neurodegeneration, cerebral ataxias, spastic paraplegias, and the multisystem disorders Vici syndrome, Yunis-Varon syndrome, and Warburg Micro syndrome are all examples of early-onset neurodevelopmental disorders with defective autophagy, referred to as congenital disorders of autophagy [123] (Table 1).

Congenital disorders of autophagy are characterized by neurological and neuromuscular manifestations, developmental impairment, and the involvement of multiple organs. The most extensively studied multisystem disorder due to defective autophagy is Vici syndrome [123]. In 2013, it was discovered that Vici syndrome can arise due to mutations in the *EPG5* gene which encodes for a protein of the same name that plays a role in autophagy. This causes a defect in the later stages of autophagy. Almost all patients exhibit failure of the corpus callosum to develop, among other malformations [112,124]. In EPG5-deficient mouse models, corpus callosum agenesis, developmental delay, and psychomotor delay were evident [125]. Other multisystem disorders related to defective autophagy include Warburg Micro syndrome due to mutations in the RAB3 GTPase activating protein catalytic subunit 1 (*RAB3GAP1*) gene and Yunis Varon syndrome due to mutations in Fig. 4 gene. Beta-propeller protein-associated neurodegeneration (BPAN) occurs due to mutations in the *WDR45* gene, and cerebellar ataxia occurs due to mutations in the *SNX14* and the *Atg15* genes [123].

Autophagy plays a crucial role in preserving cellular balance when faced with internal stress. Mutations in the autophagy gene, *WDFY3*, have been shown to hinder neurodevelopment by the failure of autophagic removal of aggregated proteins [123]. In autistic patients, where early brain overgrowth is a common feature, the loss of *WDFY3* has been implicated as a risk factor [126]. Knocking out the autophagy regulator gene, *Ambra1*, developed neural tube defects in mice, suggesting the potential role of autophagy in neurodevelopmental stages [127]. Apart from its critical role in neuronal development, autophagy appears to be fundamental for the maintenance of the nervous system, as demonstrated in mice, knocking out *Atg5* and *Atg7*, which represent principal autophagy genes, from their brains, promoted axonal swellings and cerebellar Purkinje cells and hippocampal pyramidal neurons degeneration [128, 129].

5. Conclusion

The underlying biological mechanisms of certain metabolic derangements and diverse neurological manifestations, including, but not limited to, tremors, seizures, ataxia, altered mental state, and neurological diseases, such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and epilepsy, hint at their potential overlapping pathologies. Increasing evidence suggests a significant correlation between genetic metabolic disorders such as inborn errors of metabolism, metabolic syndrome, and defective autophagy with neuronal dysfunction and hence, neurological implications. This sheds light on more details about their pathophysiology and potentially new therapeutic targets. However, this leaves questions concerning metabolic regulation and diagnostics of these correlations. The diverse phenotypes associated with several of the metabolic disorders discussed align with the need to further investigate their underlying mechanisms. This manuscript explores the relationship between many metabolic disorders and their impact on neurological health from a molecular point of view. Understanding the underlying mechanism paves the way to identifying new biomarkers and therapeutic targets.

CRediT authorship contribution statement

Nermin Eissa: Writing – original draft, Supervision, Investigation, Conceptualization. **Dana Chkier:** Writing – original draft. **Aala Ahmed:** Writing – original draft. **Reem Attia:** Writing – original draft. **Mohammed Zia:** Writing – review & editing. **Rami Beiram:** Writing – review & editing. **Bassem Sadek:** Investigation, Conceptualization.

Data availability statement

No new data were created or analyzed in this study. Data sharing does not apply to this article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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