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Review

Insights into neurometabolic diseases

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Abstract: *Background:* Neurometabolic diseases are the results of genetic changes that lead to an imbalance in energy utilization and metabolism.
Aim: Our aim was to explore the update in treatment and diagnosis of neurometabolic disease. Methods: PubMed, Scopus, Google scholar, and the web of science were searched for studies reported in the last 20 years (1997–30/10/2020). The data was searched and archived by keywords like "Neurometabolic", "neurogenesis", and "role of neuro-degeneration in neurometabolic disease" without narrowing or limiting search items. Only abstracts of searched publications were reviewed. A total of 389 publications were found in the initial research, in which 62 publications were considered for the study and the remaining were excluded because of their specificity to the subject.
Study update: The neurometabolic disease affects one in 500 newborns, causing a major burden of illness and infant mortality. However, the cause of the disease is unclear in up to 50% of neurological-like cases. Thus, we ask why are they referred to as neurometabolic disorders (NMD), despite extensive genetic and biochemistry investigations? Treatment is possible for some metabolic diseases. For instance, the devastating neurological effects of phenylketonuria have been recognized for many years. Except for some notable exceptions, treatment remains largely unsatisfactory. Therefore, research efforts concentrate on corrective genetic approaches applicable after early detection by newborn screening or before fertilization. We considered recent studies on treating neurometabolic diseases. We focused on the most common neurometabolic diseases and the associated clinical advancements in their therapy.

Keywords: neurometabolic disease; clinical treatment; gene; metabolism; obesity

1. Introduction

Neurometabolic disorders are caused by gene mutations that cause undesirable declines in the enzymatic performance of any of the enzymes required for normal cell 'operation and maintenance' functions [1]. Most such situations are characterized by the deposition of deleterious quantities of non-degraded substances within lysosomes and are generally referred to as lysosomal accumulation disorders. Lysosomes are sub-cellular organelles that contain a multitude of enzymes required to biodegrade sub-cellular materials. Similar enzymes are ideally activated under acidic conditions which are distinctive of the lysosomal intraluminal system [1,2]. Compounds undergoing lysosomal biodegradation include glycogen, mucopolysaccharides, and the main lipid category known as sphingolipids [3]. Since strategies for enzyme replacement therapy (ERT) and gene therapy in sphingolipid accumulation disorders are especially innovative, we have restricted this study mainly to considerations of these conditions, although the common steps of gene and ERT are broadly applicable to many metabolic diseases in the brain. We would further briefly outline what has been achieved to date, and then explain methods that we assume would be needed to effectively care for patients where only neurological intervention is a notable cause of illness and death [1–5].

A number of diseases are the outcome of gene enzymatic defects, the biochemical effects of those who influence central nervous growth or activity [6]. The spectrum of metabolic diseases is broad, as is the number of clinical syndromes that occur. While most occur in infancy, others can happen in early adulthood, and growing percentages of infancy impact adult life. Others can or are being created for particular therapies [7]. Over the last two decades, our knowledge of the hereditary and biochemical basis of several neurological disorders has grown considerably. Ataxias, motor disturbances, infant seizures, or sensory neuropathy provide specific clinical manifestations of neurometabolic disturbances [8]. Comprehensive analysis of the full spectrum of hereditary nervous system metabolic disorders is accessible in supplementary texts [9].

2. Materials and methods

The study was designed and the content were collected from different online resources like PubMed, Scopus, Google scholar, and the web of science were searched for studies reported in the last 20 years (1997–30/10/2020). The data was searched and archived by keywords like “Neurometabolic”, “neurogenesis” and “role of neurodegeneration in neurometabolic disease” without narrowing or limiting search items. Only abstracts of searched publications were reviewed. A total of 389 publications were found in the initial research, in which 62 publications were considered for the study and the remaining were excluded because of their specificity to the subject.

3. Signs and symptoms

The signs of neurometabolic disorders that arise are triggered by gradual loss of memory, sensory, and cognitive functions. From neonates until maturity, their signs may happen at any time. In certain neurometabolic conditions, the brain anatomy has formed abnormally since conception (as seen in Zellweger syndrome), but signs become evident in certain diseases after conception and also at the beginning of eating. The signs involve epilepsy, lack of control, hypotonic, inadequate eating, and, among others, respiratory failure [10]. Many neurometabolic conditions of neurodevelopment latency

are found in young children. These babies struggle to adapt to regular growth and experience repeated bouts of diarrhea, tiredness, and lack of cognition induced, etc., by environmental factors such as diseases of the respiratory system, vaccines, or operations [11]. Unnatural odors of the body and urine, microcephaly or macrocephaly, vision disturbances, and hearing impairment, and convulsions in such patients could result in more research related to neurometabolic disorders. Children may show multiple regressions during one or two years, i.e., acquired motor and mental abilities [6,12]. Aged babies can often experience hepatosplenomegaly, coarse facies, structural defects, and spontaneous seizures [13]. Families often notice hair and skin abnormalities, particularly skin lesions in sun-exposed areas. Kids may also have abnormal behaviours such as ataxia, mental decline, abnormalities, and sleep disturbances. Behavioral evaluations might well show irregular tones, spasticity, or hypotonicity, and rapid deep tendon reflexes [14]. However, kids can display vision impairment, low concentration, speech disruption, and symptoms of cerebellar disorders [15]. Throughout maturity, neurological disorders are mostly characterized by clinical symptoms of aggressiveness, personality disturbances, and conduct problems, which are a significant indicator of neurometabolic disturbances [16] (Figures 1 and 2).

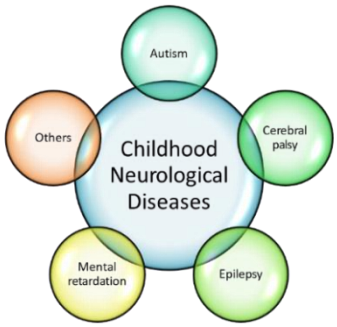

Figure 1. Neurometabolic disease in childhood.

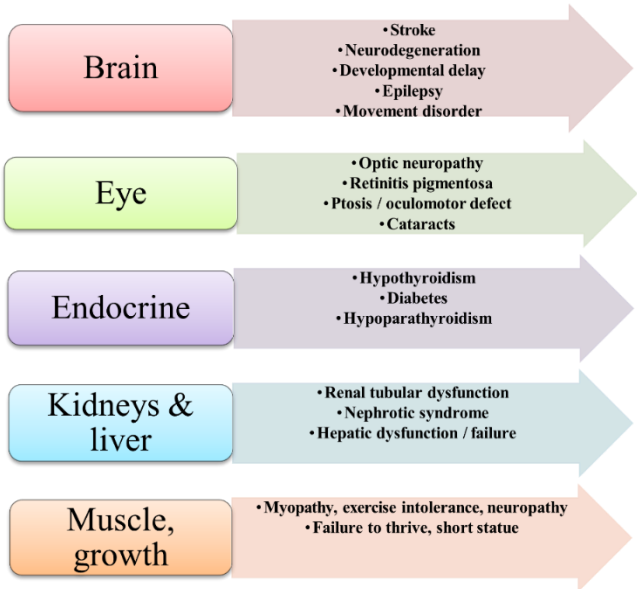

Figure 2. Neurometabolic disease complications in humans.

4. Classification of neurometabolic disease

Group 4.1: Disorders of Intoxication
Group 4.2: Disorders of Energy Metabolism
Group 4.3: Disorders of Complex Molecules
Group 4.4: Disorders of Unique Pathophysiology

Group 4.1: Disorders of intoxication

This includes disorders of intermediary metabolism that lead to acute and/or progressive intoxication from the accumulation of toxic compounds proximal to the metabolic block [17].

- Amino acid catabolism [Phenylketonuria (PKU), Maple syrup urine disease (MSUD), etc.]
- Most organic acidurias (methylmalonic, propionic, isovaleric)
- Urea cycle disorders [Ornithine transcarbamylase (OTC)]
- CHO metabolism (galactosemia & hereditary fructose intolerance)
- Copper metabolism (Wilsons & Menkes)
- Cholesterol metabolism (Niemann-Pick C & Smith-Lem l-Opitz)
- Neurotransmitter metabolism (Tetrahydrobiopterin deficiency)

Features of Group 4.1

- Rarely dysmorphic [some urine organic acids (UOAs), Menkes, Smith-Lemli-Opitz syndrome]
- Symptom free interval
- Intoxication (acute, intermittent or chronic) triggered by fever, intercurrent illness, catabolic states
- Diagnosis often with laboratory tests (UOAs, acylcarnitine profile, Cu, ceruloplasmin, NTS, etc.)
- Treatment with diet restriction, toxin removal, and trigger avoidance [17].

Maple Syrup Urine Disease (MSUD)

Disorder of branched-chain amino acid metabolism (leucine, isoleucine, and valine) Classic (neonatal), Intermediate, Intermittent, and Thiamine- Responsive forms. The three genes associated with MSUD are branched chain keto acid dehydrogenase E1 subunit alpha (BCKDHA) (E1ai subunit gene), branched chain keto acid dehydrogenase E1 subunit beta (BCKDHB) (E1b subunit gene), and Dihydrolipoamide Branched Chain Transacylase E2 (DBT) (E2 subunit gene).

Management

This includes dietary leucine restriction, high-calorie Branched-chain amino acids (BCAA)-free formulas, judicial supplementation with isoleucine and valine, and frequent clinical and biochemical monitoring.

Metabolic decompensation is corrected by treating the precipitating stress while delivering sufficient calories, insulin, free amino acids, isoleucine, and valine to achieve sustained net protein synthesis in tissues [18].

Wilson's disease: It is a disorder of copper metabolism that can present with hepatic, neurological, and/or psychiatric disturbances: Liver: recurrent jaundice, acute self-limited hepatitis, autoimmune-type hepatitis, fulminate hepatic failure, or chronic liver disease. Neurologic: Movement disorders

(tremors, poor coordination, chorea, rigid dystonia, Parkinsonism), Psychiatric: Depression, psychosis, and, occasionally, intellectual deterioration.

Ophthalmologic: Kayser-Fleisher rings & sunflower cataracts

Systemic: osteoporosis, renal stones, haemolytic anaemia, gall- stones, and rarely cardiomyopathy.

Wilson's disease characteristics

- The age of onset ranges from 3–50 years; symptoms vary among and within families.
- Diagnosis with low serum copper and ceruloplasmin concentrations, increased 24 hr urinary copper excretion, the presence of Kayser-Fleisher rings in the cornea, and/or increased hepatic copper concentration.
- ATPase Copper Transporting Beta (ATP7B) is the only gene known.
- Molecular genetic testing is clinically available.
- Treatment includes interfering with copper absorption (zinc), copper chelating therapy (penicillamine or Trientine), and dietary restriction of copper.
- Liver transplantation is reserved for those who fail medical management [19].

Group 4.2: Disorders of energy metabolism

This includes disorders of intermediary metabolism, which lead to deficient energy for the liver, heart, skeletal muscles, the brain, and other high energy tissues. This group of disorders can be divided into cytoplasm and mitochondrial energy defects [20].

Cytoplasmic Defects: Generally, less severe & treatable glycogen storage diseases (Pompe's & McArdle's) Mitochondrial Defects-generally severe and untreatable congenital lactic acidemias (defects of pyruvate transporter, pyruvate carboxylase, pyruvate dehydrogenase, and the Krebs cycle) Mitochondrial and respiratory chain defects [Leigh's, Myoclonic epilepsy with ragged-red fibers (MERRF), Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes (MELAS)], fatty acid oxidation defects (carnitine transporter deficiency and MCAD)-partially treatable [20].

Features of Group 4.2

Dysmorphic features are possible, but rare. Common symptom profile: Multi systemic due to energy failure in high-energy requiring tissues like the brain, heart, and muscles. Hypoglycaemia, hyperlactatemia, hepatomegaly, cardiomyopathy, myopathy, hypotonia, failure to thrive, SIDS (circulatory collapse), and degenerative brain involvement diagnosis is very difficult. In some screening labs and special tests, and biopsies and molecular genetic testing are needed [21].

- MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes)
- Mitochondrial non-mendelian inheritance
- Multisystem disorder with an onset typically in childhood between 2–10 years.
- The most common initial symptoms are generalized tonic-clonic seizures, recurrent headaches, anorexia and recurrent vomiting.
- Stroke-like episodes of transient hemiparesis or cortical blindness. These stroke-like episodes may be associated with altered consciousness and may be recurrent.
- The cumulative residual effects of the stroke-like episodes gradually lead to permanent impairment.
- Exercise intolerance or proximal limb weakness can be the initial manifestation.

- Sensory neural hearing loss is common.
- Growth failure is common.
- The diagnosis of MELAS is based on a combination of clinical findings and molecular genetic testing.
- Mutations in the mitochondrial DNA (mtDNA) gene MT-TL1 encoding tRNA Leu are causative [16,21].
- The most common mutation, present in about 80% of individuals with typical clinical findings, is an A-to-G transition at nucleotide 3243 (m.3243A>G)

Management

No specific treatment for MELAS exists.

- Mitochondrial vitamin cocktail
- L-arginine
- Symptomatic therapies

Group 4.3: Disorders of complex molecules

This includes disorders of cellular organelle and the synthesis or catabolism of complex molecules [22].

- Lysosomal storage disorders
- (Gangliosidosis I & II, Gaucher, Krabbe, Fabry, etc.)
- Mucopolysaccharide doses and Oligosaccharide doses (Hurler, Hunter, Sanfilippo, etc.)
- Peroxisomal disorders [Zellweger spectrum, X-linked adrenoleukodystrophy (X-ALD), etc.]
- Congenital disorders of glycosylation

Features of Group 4.3

- Dysmorphic features (embryo-fetalis) common
- Symptoms are progressive and permanent; unrelated to triggers
- Multisystemic: Hepatosplenomegaly, skeletal deformities, CNS, and PNS white matter and CNS malformations

Generally untreatable, but enzyme replacement and bone marrow transplant emerging for specific disorders [22].

Hexosaminidase: A deficiency Infantile-Onset (3–6 months) w/ progressive weakness, loss of motor skills, decreased attentiveness, and increased startle response. Progressive neurodegeneration includes ng: Seizures, blindness, spasticity, eventual total incapacitation, and death, usually before age four years.

Cheery Red Spot. The juvenile and late-onset variants of hexosaminidase A deficiency have later onsets, slower progression, and more variable neurologic findings, including Progressive dystonia, spinocerebellar degeneration, motor neuron disease, and, in some individuals with adult-onset disease, a bipolar form of psychosis.

- Differential of Cherry Red Spot
- Monosialotetrahexosylganglioside-1 (GM1)
- Monosialotetrahexosylganglioside-2 (GM 2)- Tay-Sachs, Sandhoff
- Niemann Pick A & C
- Sialidosis
- Galactosialidosis

- Tay-Sachs disease

The diagnosis relies on the demonstration of absent to near-absent Hexadecimal (HEX), An enzymatic activity in the presence of normal or elevated activity of HEX B. Molecular genetic testing of HEXA is clinically available and is used to identify the specific disease-causing mutations in an affected individual to allow for genetic counselling of at-risk family members [23].

Management

Treatment is supportive.

Group 4.4: Disorders of Unique Pathophysiology

This includes disorders that I could not fit into the first 3 categories.

- Purine and Pyrimidine disorders (Lesch-Nyhan syndrome)
- Creatine deficiency syndromes
- Vitamin-responsive disorders (multiple-carboxylase deficiency, pyridoxine deficiency, and folinic acid deficiency)
- Other Neurodegenerative diseases (leukodystrophy's, neuronal ceroid lipofuscinoses (NCLs), DNA-repair etc.)
- Lesch-Nyhan Syndrome

Onset <1 year with hypotonia and psychomotor developmental delay, are evident by age three to six months. With n the first few years, extrapyramidal involvement (e.g., dystonia, choreoathetosis, and opisthotonos) and pyramidal involvement (e.g., spasticity, hyperreflexia, and extensor plantar reflexes) become evident. Cognitive impairment and behavioural disturbances emerge between ages 2–3 years. Persistent self-injurious behaviour is a hallmark of the disease. Over production of uric acid may lead to deposition of uric acid crystals or calculi in the kidneys, ureters, or bladder. Gouty arthritis may occur later in the disease [24].

Investigations

Screening done with a urinary urate-to creatinine ratio greater than 2.0, indicating uric acid over production (hyperuricemia). Hyperuricemia/hyperuricemia is not sensitive or specific enough for diagnosis. Hypoxanthine-guanine phospho ribosyl transferase (HPRT) enzyme activity less than 1.5% of normal in cells from any tissue (e.g., blood, cultured fibroblasts, and lymphoblasts) is diagnostic. Sequence analysis of HPRT1, the only gene known to be associated with Lesch-Nyhan syndrome, is available on a clinical basis.

Management

Control in production of uric acid with allopurinol reduces the risk of nephrolithiasis and gouty arthritis, but has no effect on behavioral and neurological symptoms.

- Only supportive treatment for behavioural & neurological symptoms.
- Investigations:
- Routine/General Investigations of CBC, electrolytes, glucose, blood gas, AST/ALT, and BUN/Cr
- Urinalysis: Odor and ketones
- Intermediary Metabolism of Ammonia, lactate, pyruvate, plasma amino acids, and urine organic acids

- Acyl-carnitine profile
- Urine Guanidinoacetate and Creatine
- Cerebrospinal fluid (CSF) glucose and neurotransmitters
- Complex molecule metabolism
- Lysosomal/Storage disorders: Urine mucopolysaccharides, Urine oligosaccharides, and Specific enzyme studies
- Peroxisomal disorders: Very Long Chain fatty acids and Phytanic acid
- Carbohydrate glycoprotein deficiency disorders: Transferrin Isoelectric focusing

Cholesterol disorders

- Cholesterol
- Electrophysiologic
- Electromyography (EMG)/ Nerve Conduction Study (NCS)
- Myopathy-mitochondrial /fatty acid oxidation defects
- Neuropathy-metachromatic leukodystrophy, Krabbe
- Electroencephalogram (EEG)
- PME- Sialidosis, MELAS, MERRF, GM1, and GM2
- Imaging
- Magnetic resonance imaging (MRI)
- White matter changes

Leukodystrophy/peroxisomal disorders

- Basal ganglia changes
- PKAN, organic acidemias, and Wilson
- Specific enzymatic and molecular analysis
- Cerebrospinal Fluid (CSF)
- Lactate
- Mitochondrial disorders
- Glucose
- Glucose transporter-1 (GLUT1)
- Biopsy
- Muscle
- Mitochondrial and fatty acid oxidation disorders
- Nerve
- Neuroaxonal dystrophies and leukodystrophies
- Skin
- PME-neuronal ceroid lipofuscinosis

Treatment options

- Dietary restrictions & Dietary supplementation [Phenylketonuria (PKU), Maple syrup urine disease (MSUD), and Urea Cycle]
- Avoidance of catabolic states (PAAs & UOAs)
- Alternative energy sources (ketogenic diet in GLUT-1)
- Promotion of alternative pathways

- Sodium benzoate/Phenylbutyrate in urea cycle disorders
- Metabolic inhibitors
- Allopurinol in Lesch-Nyhan
- Removal of toxic compounds
- dialysis in hyperammonaemia
- chelating in Wilson's
- Replacement of vitamins
- Pyridoxine
- Folinic Acid
- Co-factor activation
- Cobalamin in methylmalonic acidaemia
- Thiamine in MSUD
- Thiamine, biotin, riboflavin in mitochondrial disorders
- Protein replacement
- Enzyme replacement:Fabry's & Gaucher
- Bone marrow transplant: Hurler's, MLD, X-ALD [22–25]

5. Treatment

Treatment is possible for some metabolic diseases. For instance, the devastating neurological effects of phenylketonuria have been recognized for many years. Neonatal screening for this disorder and dietary modification in the developed world has removed phenylketonuria from the list of important causes of serious neurological disability in children [26]. This success has led to new challenges in the management of the adult with phenylketonuria and the unexpected and devastating effect of the disorder on the unborn child of an untreated Phenylketonuria mother. More recently Biotinidase deficiency has been recognized as an important and easily treatable cause of serious neurological disease usually presenting with early-onset drug-resistant seizures. This and some other neurometabolic diseases can be identified on neonatal blood screening although a full range of screening is not yet routine in the United Kingdom. More disorders are likely to be picked up at an earlier asymptomatic stage as the sophistication of screening tests increases [27].

Although individual metabolic disorders are rare, collectively such disorders are relatively common. In reality, most clinicians will see an individual condition only rarely in a career. Furthermore, patients with certain rare conditions are often concentrated in specialist referral centres, further reducing the exposure of general and paediatric neurologists to these disorders [28]. A recent study into progressive intellectual and neurological deterioration, PIND, gives some information about the relative frequency and distribution of some childhood neurodegenerative diseases in the United Kingdom. Although primarily designed to identify any childhood cases of variant Creutzfeldt-Jakob disease, the study also provided much information about the distribution of neurometabolic disease in children in the United Kingdom [29]. The most common five causes of progressive intellectual and neurological deterioration over 5 years were Sanfilippo syndrome, 41 cases, adrenoleukodystrophy, 32 cases, late infantile neuronal ceroid lipofuscinosis, 32 cases, mitochondrial cytopathy, 30 cases, and Rett syndrome, 29 cases. Notably, geographical foci of these disorders were also found and correlate with a high rate of consanguinity in some local populations [30].

5.1. Treatment approach

5.1.1 Development of ERT

An exogenous enzyme is given to a patient in whom a mutation-induced disease and later referred to as 'enzyme replacement therapy.' Such initial studies were conducted using protein derived from human tissue until recombinant DNA techniques allowed the gene to be cloned and the resulting protein to be expressed without the need for biological content [2].

5.1.2 Substrate depletion

An inhibition of glucocerebroside formation (substrate depletion) was introduced as a therapeutic approach for the therapy of metabolic storage disorders [7] a couple of years ago. The impact of stopping the synthesis of glucocerebroside with N-butyl-deoxynojirimycin (NB-DNJ) was already investigated in patients with Type 1 Gaucher's disease, and some positive effects were reported [8].

5.1.3. Gene therapy in neurometabolic disorders

Over the last decade, the field of gene therapy has undergone a revival thanks to key interpretations and advances in vector design, stem cell manipulation, modulation protocols, and cell/vector delivery. Such initiatives were effectively incorporated with exceptional clinical outcomes of research using the recently developed technology, and new educational-industrial collaborations were formed.

Growing and bolstered interest in gene-based methodologies to inherited neurometabolic disorders with serious neurological intervention is improving. Hereditary metabolic disorders are monogenic diseases characterized by enzymatic or systemic abnormalities causing lysosomal or peroxisomal metabolic function. A metabolic defect may mainly affect the brain, resulting in neuronal damage, microglial activation, inflammatory demyelination, and axonal degeneration.

In this article, we provide an overview of the gene-editing strategies currently undergoing research for neurometabolic Lysosomal and Peroxisomal Storage Diseases like Adreno and Metachromatic Leukodystrophies, as well as comparatively new implications such as Mucopolysaccharidosis, Gangliosidosis, and Neuronal Ceroid Lipofuscinosis, with a detailed description of the key features and pathways [9].

5.2. Advances in treatment

The 3 logic-specific stages of neurometabolic disorders may be fixed. First, gene therapy will substitute for a safe copy of the mutated DNA code and thereby have a chance for the cells affected to make normal protein again. Second, the body will be supplied with the required protein by enzyme replacement therapy. Thirdly, metabolite-level treatments seek to reduce the pathway flux (in defects that result in toxicity or build-up) or re-plant substrates to make up for deficiencies. The difficult usability of the CNS and security issues due to its vulnerability is typical challenges encountered in therapy development [6,31].

5.3. Current clinical options for patients

Neurometabolic disorders all seem to be genetic disorders that disrupt how the body converts or generate stored energy. If that occurs, there could be several of those chemicals (nutritional energy) or too few others required to remain well. Neurometabolic disorders can contribute to unexpected epilepsy, irregular gestures, or the lack of phases in growth. Neurometabolic diseases are caused by genetic abnormalities which are genetic code-change shifts. Such abnormalities can be acquired by the affected family or can arise from a recent alteration in the genome of a newborn [1].

5.4. Neurometabolic diseases from a paediatric neurological point of view

Neurometabolic disorders are a significant category of diseases often found in babies and infants. In this category of disorders, clinical presentations are common signs and symptoms. Epilepsy is a popular symptom in untreated neurometabolic cases, and is frequently resistant to antiepileptic medications. The initiation of signs with neurometabolic disorders happens following a period of healthy or near healthy growth. However, disabled children can do better before there is a metabolism condition. People with neurometabolic diseases experience extreme clinical symptoms during a metabolic disturbance, which involves inadequate eating, fatigue, tiredness, epilepsy, and lack of cognition. This condition is always terminal but may result in significant neurological insult and deterioration of neurocognitive achievements as a prominent indicator of cases examined. No matter the source, severe signs should be handled promptly. A variety of neurometabolic disorders patients react favourably and, in certain situations, react significantly to the medication. In certain cases, avoidance of catabolism and typical or close typical neurodevelopment changes is important for early diagnosis and early action. This article addresses neurometabolic conditions, solutions to this category of illnesses (from a paediatric neurologist's point of view), psychiatric and neurological causes, developments of neuroimaging and electroencephalography, early diagnosis, and early care [6–8].

Childhood epilepsy is a diverse set of diseases with varying diagnostic criteria, treatment, and outcomes. Late-infantile neuronal ceroid lipofuscinosis type 2 (CLN2) is a neurodegenerative disorder caused by biallelic TPP1 mutations. This illness begins with modest and largely non-specific symptoms that resemble those seen in more frequent pediatric epilepsies, followed by fast psychomotor decline and drug-resistant epilepsy. A prompt diagnosis is essential to adopt appropriate treatment and disease management strategies. The efficacy of target re-sequencing in the identification of the genetic causes of childhood epilepsy suggests that this technique might prove successful in the early detection of CLN2 as well as other neurodevelopmental conditions [32].

Developmental and epileptic encephalopathy 35 (DEE 35) is a severe neurological disorder caused by biallelic variations in ITPA, which encodes inosine triphosphate pyrophosphatase, an enzyme required for purine metabolism. A published study depicts the genotypic and phenotypic spectrum of DEE 35, examining potential drivers of poor clinical outcomes. A brain MRI review indicated a recurring pattern of delayed myelination and restricted diffusion of early myelinating regions. Congenital microcephaly and heart involvement were statistically significant new clinical predictors of poor outcomes. We enhanced the molecular, clinical, and neuroradiological characterization of ITPase deficiency and identified new clinical predictors, which may have a potentially significant impact on diagnosis, counselling, and follow-up of afflicted individuals [33].

Human 4-hydroxyphenylpyruvate dioxygenase-like (HPDL) is a putative iron-containing non-heme oxygenase of unknown specificity and biological significance. A study reported 25 families

containing 34 individuals with neurological disease associated with biallelic HPDL variants. Study reported biallelic HPDL variants cause a syndrome varying from juvenile-onset pure hereditary spastic paraplegia to infantile-onset spastic tetraplegia associated with global developmental delays [34].

Gamma-aminobutyric acid (GABA) and glutamate are the most common amino acid neurotransmitters in the brain. GABA, an inhibitory neurotransmitter, is produced by glutamic acid decarboxylase. The GAD1 gene encodes the main isoform GAD67, which accounts for approximately 90% of the CNS's base-level GABA. Disruption of GAD1 leads in an imbalance of inhibitory and excitatory neurotransmitters, and because Gad1-/- mice die neonatally of severe cleft palate, it has been impossible to determine any potential neurological impairment. Furthermore, very little is known about the effects of GAD1 disruption in people. A study was published in which six affected individuals from six unrelated families with bi-allelic GAD1 variants presented with developmental and epileptic encephalopathy, characterized by early-infantile onset epilepsy and hypotonia, as well as variable non-CNS manifestations such as skeletal abnormalities, dysmorphic features, and a cleft palate. This work demonstrated a significant role for GAD1 in seizure induction, neuronal and extraneuronal development and introduces GAD1 as a new gene related with developmental and epileptic encephalopathy [35].

6. Neurometabolic disorders

6.1. Disorders of Amino acids and neurometabolic disease

It is an inherited disorder where a patient is unable to metabolize certain proteins like lysine, hydroxylysine, and tryptophan derived proteins. The disorder results in the build-up of organic acids in blood (organic acidemias) so as in urine (organic aciduria) which is toxic to tissue and causes serious health problems (Figures 3 and 4). Patients of glutaric acid type-I have inadequate availability of enzymes to break such protein and results in the accumulation of amino acids and their unprocessed products, which cause brain damage especially basal ganglia to affect cognitive movements and disability to neurons [3]. In small infants, it causes macrocephaly (large head) may experience spasms, jerking, rigidity, or decreased muscle tone. In some cases, it also leads to bleeding in the brain or from the eyes that may result from a neurological disorder, but strict dietary control and meditation therapy could limit the progression of this disorder (Figure 5).

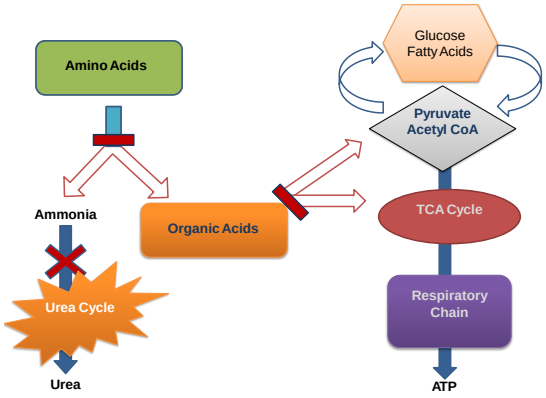

Figure 3. Neurometabolic disease in childhood.

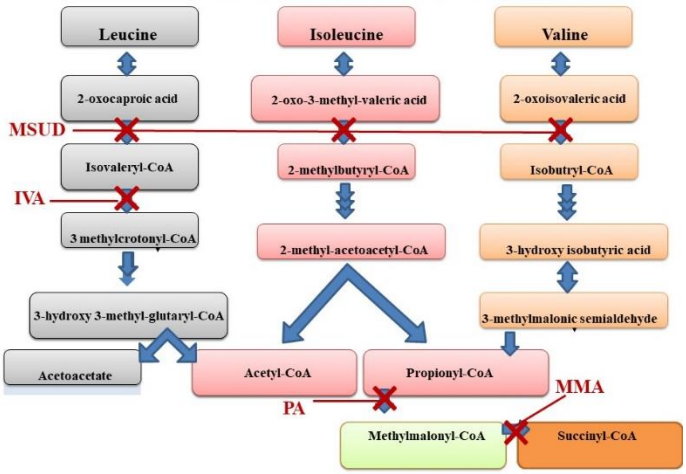

Figure 4. Catabolism of branched amino acids.

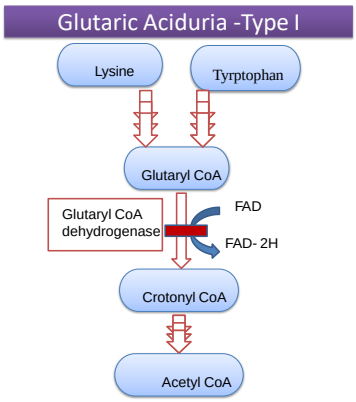

Figure 5. Glutaric Aciduria Type-I in Disease.

Macrocephaly affects up to 5% of the pediatric population and is defined as an abnormally big head with an occipitofrontal circumference (OFC) greater than two standard deviations (SD) above the mean for a given age and gender. Given that approximately 2–3% of the healthy population has an OFC between 2 and 3 SD, macrocephaly is classified as "clinically relevant" when the OFC exceeds 3 SD. Macrocephaly should be distinguished from megalencephaly (MEG), which is defined as brain expansion that exceeds twice the SD (3SD—"clinically relevant" megalencephaly). While macrocephaly might be isolated and harmless, it can also be the first sign of an underlying congenital, genetic, or acquired illness. Megalencephaly is almost always caused by a genetic factor. Aside from the head size assessment, a full family and personal history, neuroimaging, and a thorough clinical evaluation are required to provide an accurate diagnosis [36].

6.2. Succinic semi aldehyde dehydrogenase (SSADH) deficiency

Succinic semi aldehyde dehydrogenase (SSADH) deficiency is a rare neurometabolic disease caused by a change in X-linked genetic pattern which affects the metabolism of inhibitory

neurotransmitters like gamma-amino butyric acid (GABA). Patients with such disease observed suppressed electrical activity in nerve cells due to GABA and accumulation of succinic semi aldehyde compound which is not further transformed to GABA. SSADH impairment leads to cognitive and neuromuscular signs like psychomotor retardation, hypotonia, ataxia, brain seizures, nystagmus, hyperkinesia, and behavioral abruptions Figure 6.

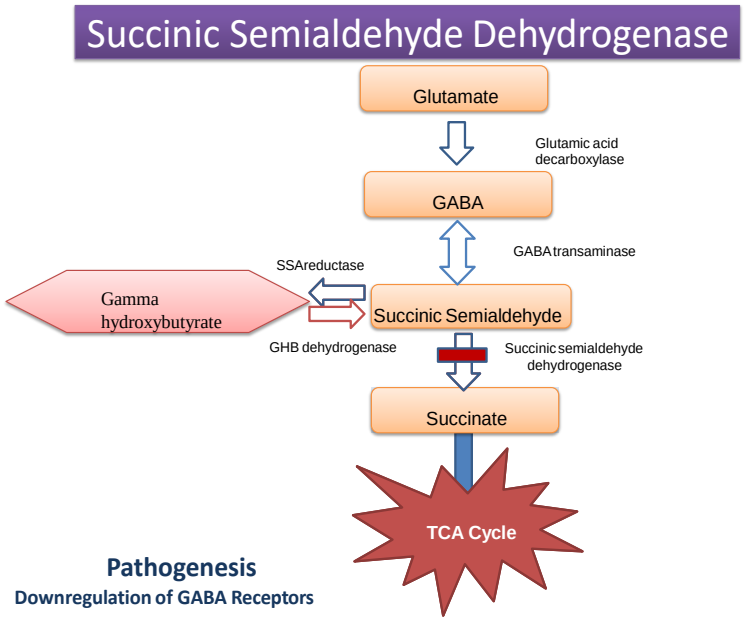

Figure 6. Succinic semialdehyde dehydrogenase Disease.

6.3. Urea cycle disease

The enzyme disorders of Urea Cycles include carbamyl-phosphate synthesis genetic defects, argininosuccinic aciduria, ornithine transcarbamylase imbalance, lignite, angina imbalance, and N-acetyl glutamate synthesis abnormalities [7]. Urea cycle disease enzyme defects contribute to hyperammonemia and show a showing of unconsciousness and brain wounds. Specific signs that represent very serious diseases, illness, diarrhea, fatigue, eating problems, septicemia, failure of growth, convulsions, and medical variability with the same diseases are normal. Correct evaluation is scientifically complex (see Figures 7 and 8).

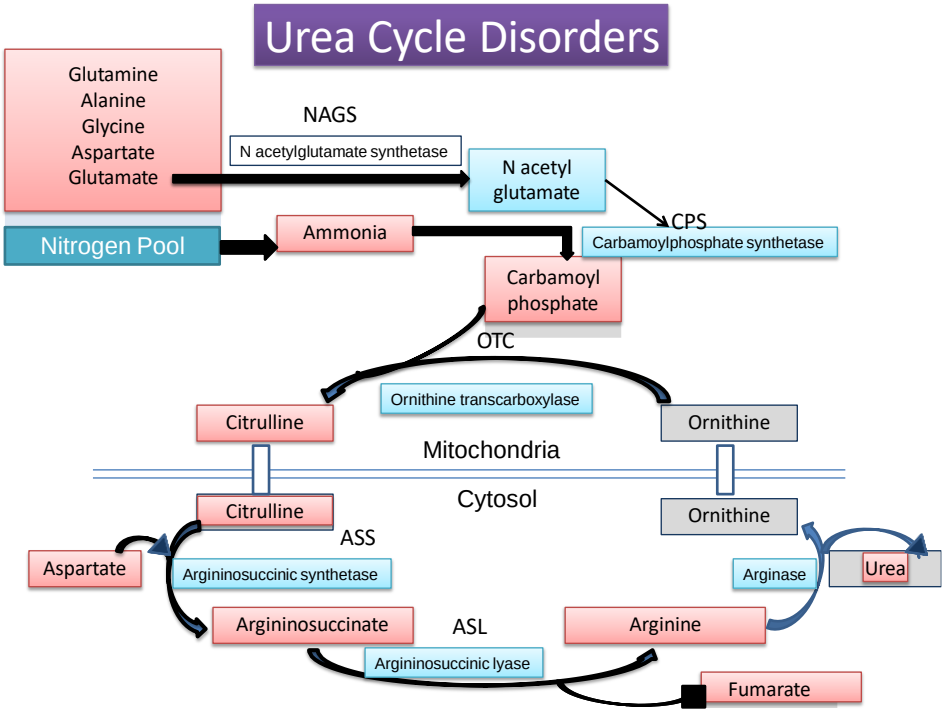

Figure 7. Urea cycle disorders Pathophysiology.

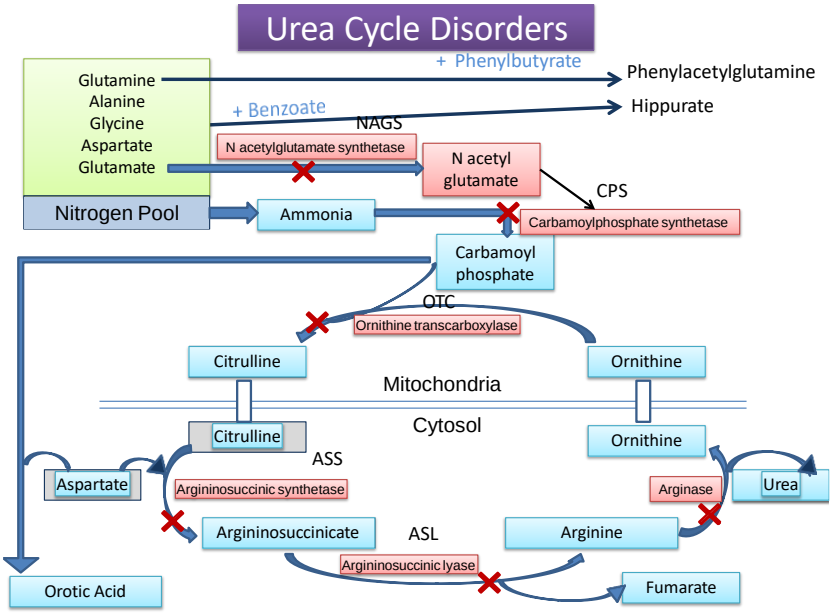

Figure 8. Urea cycle disorders treatment.

6.4. Non-ketotic hyperglycinemia (NKH)

This is a rare, genetic, metabolic disorder caused by a defect in the enzyme system that breaks down the amino acid glycine, resulting in an accumulation of glycine in the body's tissues and fluids.

There is a classical form of NKH and a variant form of NKH [4]. The classical form is then further divided into severe disorder or an attenuated form (mild form) (Figures 9–11).

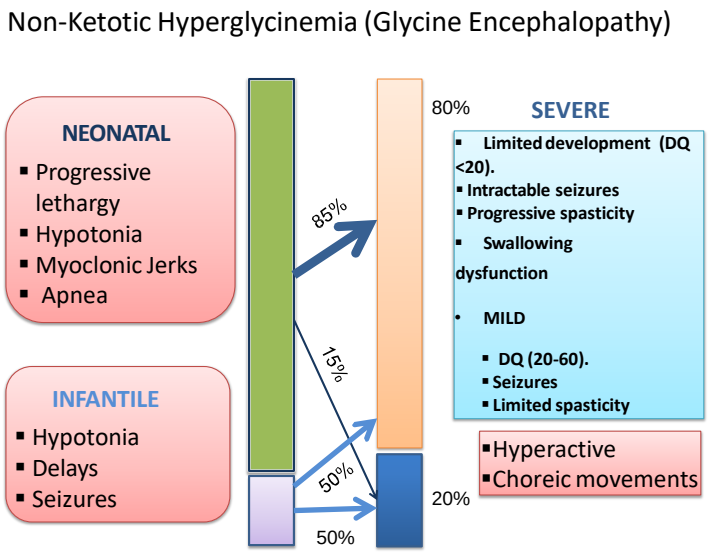

Figure 9. Non-Ketotic Hyperglycinemia (Glycine Encephalopathy).

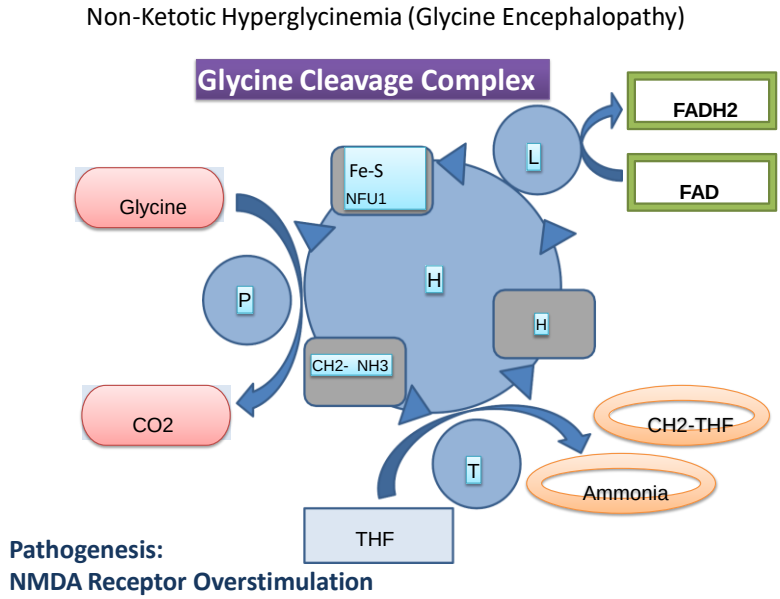

Figure 10. Non-Ketotic Hyperglycinemia (Glycine Encephalopathy).

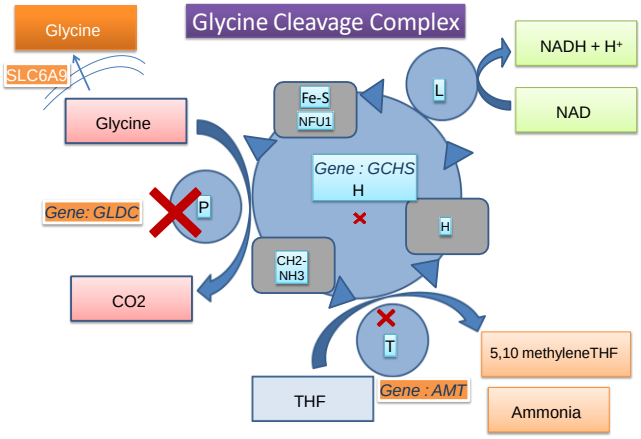

Figure 11. Non-Ketotic Hyperglycinemia (Glycine Encephalopathy).

6.5. Molybdenum cofactor deficiency

Molybdenum cofactor deficiency is a rare disease marked by brain dysfunction (encephalopathy) that worsens over time is molybdenum cofactor deficiency (Figure 12). Babies with this condition appear fine at birth but have trouble feeding within a week and experience convulsions that do not improve with treatment (intractable convulsions). Brain abnormalities, including degeneration (atrophy) of brain tissue, contribute to extreme developmental retardation; affected individuals typically do not learn to sit unattended or speak. A small percentage of the persons in question have an exaggerated stupid response to unwanted stimuli such as noisy noises (hyperekplexia). Tests indicate that people affected have high levels in the urine of chemicals called sulphite, S sulfocysteine, xanthine, and hypoxanthine, and low levels in the blood of a chemical called uric acid. Due to severe health complications caused by molybdenum cofactor deficiency, affected individuals typically do not survive in early childhood [5].

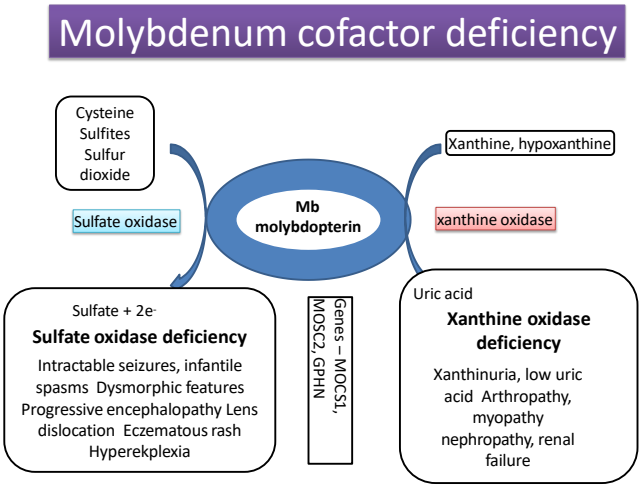

Figure 12. Molybdenum cofactor deficiency.

6.6. Adrenoleukodystrophy

X-linked adrenoleukodystrophy (X-linked ALD) is a hereditary, recessive, degenerative condition affecting the white matter of the brain and adrenal gland. The diseases are caused by defects in the ABCD1gene and progress to a malfunction in the peroxisomal trans membrane protein (ABCD1), which affects peroxisomal β oxidation, and afterward results in the deposition of very-long-chain fatty acids. This is a chronic condition marked by disability, depression, and worsening in Addison's neurology [3]. Many different disease phenotypes are varying by adrenomyeloneuropathy (AMN) to cortical manifestations.

Asymptomatic or discrete insufficiency of the adrenal without CNS intervention, i.e., Addison's disease alone. Infant cerebral ALD and adult adrenomyeloneuropathy are common clinical phenotypes. Cerebral X-ALD may be viewed in childhood, juvenile, and adult manifestations. Commonly appear before 10 years of age (typically between 4–8 years of age) influenced kids to a teenage type defined as a severe disease. Ataxia, spasticity, hearing loss, visual impairment, temperament swings, and seizures. Over less familiar teenage form showed consistent course upon age 10. Cerebral X-ALD is often synonymous with Addison's disease, although, after developmental disorders, primary adrenal insufficiency may co-occur. Common MR results of people with cerebral ALD are well established and comprise of longitudinal white-matter anomalies. These usually develop primarily in the rear cerebral areas and advance consecutively through parietal, temporal, and eventually frontal lobes. All these a pattern is discovered in about 80 percent of cases; thus, the X-ALD assessment is suggested by MRIs [9].

X-ALD becomes one of the most common PDs associated with mutations with the ABCD1 gene, coding the ATP binding cassette subfamily D member 1, also known as the protein adrenoleukodystrophy (ALDP). Such a protein is situated in the peroxisomal cell wall and facilitates the entry of VLCFAs into the damaged peroxisome. ALDP absence results in the accumulation of VLCFA in the CNS and all body tissues, leading to a wide variety of chronic and cognitive neurological signs [3].

6.7. Zellweger syndrome

Zellweger or cerebrohepatorenal syndrome is a rare neurometabolic condition distinguished by usable peroxisomes in cells being decreased or missing. Zellweger continuum diseases involve three characteristics of peroxisome biogenesis as observes: Zellweger syndrome, neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease. While both have a common molecular origin, Zellweger syndrome is the most serious of the three disorders. Cultured skin fibroblasts of patients display high fatty acids, phytanic acid, and plasminogen in the very long chain. Neurological symptoms identified as neuronal immigration defects, craniofacial anomalies, eye disabilities, punctata chondrodysplasia, and hepatomegaly. Anomalies in the craniofacial structure involve a large forehead, epicanthal fold, broad fontanel, and hypoplasia in the midface [17].

6.8. Intracerebral injection of mannose-terminal

6.8.1. Glucocerebrosidase

In patients with Type 2 Gaucher's disease, glucocerebrosidase activity is very low, typically within the range of 1–2 percent of normal. The patients could benefit if, throughout this neonatal phase,

glucocerebrosidase can be delivered to the brain to catabolise glucocerebroside in neurons throughout this crucial development age. Researchers in the National Institute for Neurological Disorders and Stroke (NINDS) Division of Surgical Neurology have developed a technique called convection-enhanced target to deliver proteins to the brain [1].

6.8.2. Metachromatic leukodystrophy (MLD)

MLD is a genetic disorder LSD (frequency of 1-1 million newborns) caused by mutations in the ARSA gene encoding the Arylsulfatase A (ARSA) lysosomal enzyme. Lysosomal deposition of sulfatides occurs especially in oligodendrocytes in MLD patients and findings in progressive and unrelenting demyelination, which causes serious degradation of the locomotive and neurologic operations in affected individuals [5].

6.8.3. Mucopolysaccharidoses (MPSs)

Mucopolysaccharidoses (MPSs) are a subcategory of autosomal recessive LSDs (except for X-linked MPS II) describing approximately one-third of an LSDs identified, with a shared incidence of 1:22,500–1:52, 00036. They were also induced by the defect of a unique lysosomal enzyme responsible for the degradation of sulfated glycosaminoglycans (GAGs), which leads to the deposition of their undegraded metabolites in the entire cells of the body and particularly in neurons [1].

6.8.4. Gangliosidoses

GM1 gangliosidosis (MIM# 230500) is an LSD caused by β-galactosidase (β-gal') enzyme deficiency hydrolyzing GM1 ganglioside, glycoprotein, and glycosaminoglycans to residues in the terminal β-galactosyl. GM1 gangliosidosis is due to mutations in GLB1 and its overall incidence in Brazil (1:17,000), in the Gypsy population (1:10,000), and in the island of Malta and Cyprus (1:3700) is estimated to be 1 in 100,000-200,0000 live births. GM1 is characterized in different tissues and especially in the CNS as broad storage of GM1 ganglioside and related glycoconjugates. Typical symptoms of the disease are neuronal cell death and demyelination combined with extreme astrogliosis. Neuro-inflammatory responses are known to contribute significantly to pathogenesis and the development of diseases [9].

6.8.5. Neuronal Ceroid Lipofuscinoses (NCLs)

The GT family also includes a series of diseases, the Neuronal Ceroid Lipofuscinoses (NCL) and the fatal LSD group, mainly focused on lysosomal enzyme deficiency (CLN1, CLN2, and CLN5) and transmembrane proteins, the CLN3, CLN6, CLN7, CLN8, and CLN12. Other high attractiveness indications are those linked to GT: Among neuropathic gene-based therapeutic strategies, very promising approaches are focused on site-specific editing of the human genome, either to correct the pathogenic gene or to add a copy to a particular genomic position of the therapeutic gene. CRISPR / Cas9 are a relatively easy and flexible method for the modification of eukaryotic cells. The genome-editing system focused on the Clustered Frequently Inter-Spacious Short Palindromic Repeats-associated protein-9 nucleases.

7. Discussion

Neurometabolic conditions may be controlled at 3 stages unique to the nature of the condition. First, gene therapy will substitute healthier clones of the mutant DNA code and thereby give affected cells the chance to generate normal protein again. Second, enzyme replacement will provide the body with the protein it needs. Third, metabolite-level treatments seek to minimize the flux through the pathway (in the case of defects leading to accumulation or toxicity) or regenerate substrates to substitute for deficiencies. The difficult usability of the CNS and safety concerns due to its insecurity is typical challenges encountered in therapy development. Also, because of the restricted regenerative ability of the brain, the early timing of therapeutic therapies is of great importance. The new progress in gene therapy may match the best of all innovation in the field of neurometabolic disorder therapies in this article. While heavily hyped as the solution to several genetic disorders in the early 1990s, gene therapy has only fulfilled its promises over the last few years.

Metachromatic leukodystrophy (MLD) is a severe white matter disease that commonly affects the central and peripheral system but is not primarily found in the pediatric population [30]. Based on its standard MRI pattern, MLD can be identified, and diagnosis is simple by showing the defective activity of the enzyme arylsulfatase A (ARSA) in leukocytes and examination of ARSA gene mutation. There is currently no disease-specific available treatment for MLD. French investigators evaluated the safety and efficacy of ARSA gene delivery in the brain of children with MLD in an open-label, single-arm phase I/II clinical trial. Patients before early stage of the disease undergoes 12 simultaneous injections of the investigational medicine into the white matter of both cerebral hemispheres via image-guided pathways (for details, see www.clinicaltrials.gov [identifier: NCT01801709].

The initial findings of this analysis are cautiously stated as positive (personal communication, 15 Years Centre for Childhood White Matter Disorders symposium, Amsterdam, the Netherlands, October 2015). Unlike MLDs, where large brain areas are impaired and researchers logically strive for global gene delivery, other neurometabolic disorders may benefit from injections aimed at specific brain areas (local gene delivery). The latter was demonstrated as an autosomal recessively inherited neurotransmitter biosynthesis defect in aromatic amino acid decarboxylase (AADC) deficiency [30,31]. The AADC catalyzes the final phase of dopamine (as seen in Figure 1) and serotonin biosynthesis. Evaluation in terms of irregular neurotransmitter metabolites in CSF, revealing plasma AADC enzyme deficiency and AADC gene mutation analysis, this condition can be diagnosed.

Some individuals have a childhood-onset, severe neurological condition that is dominated by a complex movement disorder. AADC deficiency is hard to treat and as a result, life expectancy is significantly reduced [36]. The first studies with AADC gene delivery to the human brain derive from adult neurology, where individuals with Parkinson's disease have experimentally had an AAV vector intrastriatal infusion containing the AADC gene. To effectively treat patients with lower (orally administered) doses of levodopa, the investigators aimed to improve the capacity of putaminal neurons to synthesize dopamine and thus avoid the common side effects associated with higher doses [37]. In AADC deficiency, delivery of the AADC gene to the substantia nigra will potentially be the ultimate curative therapy.

Gene therapy has been further developed and introduced by Taiwanese researchers in pediatric patients with AADC deficiency following technical developments in the context of Parkinson's disease and with a relatively high occurrence of AADC deficiency in Taiwan [38,39]. Although the first, short-term findings indicate beneficial motor responses, a second gene therapy trial for AADC deficiency is

being planned in the context of AADC deficiency [39].

8. Challenges in future care transitions

Most of the above advances have led to an increase in sensitivity to neurometabolic disorders both in clinical research and in the scientific community, resulting in a substantial increase in understanding of these disorders in kids and adults [40]. Also, increased survival of kids with classical phenotypes and identification of late-onset disorders in adults have resulted in a significant increase in the number of adult patients with neurometabolic disorders. Treatment for these patients is a very new and expanding sub-specialty, particularly in emergency medicine and neurology [41]. The Society for the Study of Inborn Metabolism Errors (SSIEM) Adult Metabolic Physicians Group has recently emphasized the increasing need for multidisciplinary services specialized in the treatment of adults with inborn metabolic errors [42].

Phenylketonuria (20.8 percent of all patients), mitochondrial disorders (14 percent), and lysosomal storage disorders such as Fabry disease (8.9 percent) and Gaucher disease were the most prevalent diseases followed by these specialist clinics (4.2 percent) [43]. While many of them are not primary neurological conditions, many of them endanger normal brain function in the long run as part of their natural history if left untreated or during acute decompensation periods. Because all these diseases are very rare, many neurologists are not connected with cell metabolism in general and metabolic medication in specific, and training programs and congresses for residents and seniors in neurobiology usually do not address this subject in much detail, several problems can be anticipated [44]. For these vulnerable adolescents and adult patients, health care providers, neurologists, and pediatricians who are now or in the future may be responsible for the transfer of neurological care should not hesitate but expect these challenges. They should look forward to exploring an interesting environment while doing so, which helps us understand not only many different complex neurological disorders but also the metabolic basis for the proper functioning of the brain [45,46].

9. Conclusions

We conclude that there is lack of information and research needs to be done on neurometabolic diseases. The literature and reports stated that neurometabolic disease affects mostly in pediatric patients and due to less mature metabolic system in infants so more research will explore the alternative therapy in such disease.

Use of AI tools declaration

The authors declare that they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors confirm that this chapter contents have no conflicts of interest.

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