INHERITED METABOLIC DISEASES CAUSED BY ENZYME DEFICIENCIES

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Thesis mentor: Assoc. Prof. Lara Batičić, PhD

The graduation thesis was graded on _____ in _____, before the Committee composed of the following members:

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The graduation thesis contains 111 pages, 12 figures, 15 tables, and 81 references.

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Abbreviations

AAT – Alpha-1 antitrypsin

ASM – Acid sphingomyelinase

BCAAs - Branched-chain amino acids

BCKAD – Branched-chain alpha-ketoacid dehydrogenase

BH4- Tetrahydrobiopterin

BIA – Bacterial inhibition assay

BMP – Bis(monoacylglycero)phosphate

CACT- Carnitine-acylcarnitine translocase

CBS – Cystathionine beta-synthase

CNS – Central Nervous System

COPD – Chronic Obstructive Pulmonary Disease

CPS - Carbamoyl Phosphate Synthetase I

CPT - Carnitine Palmitoyltransferase

CTLN2 – Citrullinemia Type II

DBS – Dried Blood Spot

DLD - Dihydrolipoamide Dehydrogenase

EIKD – Early Infantile Krabbe Disease

ER – Endoplasmatic Reticulum

ERT - Enzyme Replacement Therapy

EXPORT - Energy-Requiring Amino Acid Exporter

FAOD – Fatty Acid Oxidation Disorders

FBPase – Fructose-1.6-Bisphosphatase

FMA – Fluorimetric Microassay

FTTDCD – Failure To Thrive And Dyslipidemia Caused By Citrin Deficiency

G6Pase – Glucose-6 Phosphatase

GA-1 – Glutaric Acidemia Type 1

GALC – Galactosylceramide Beta Hydrolase

GALE – UDP-galactose 4-epimerase

GALK – Galactokinase

GALM – Galactose Mutarotase

GALT – Galactose-1-phosphate Uridylyltransferase

Gb3 - Globotriaosylceramide

GCase – Glucocerebrosidase

GCS – Glycogen Storage Disease

GGT – Gamma-glutamyl Transpeptidase

GlcCer – Glucosylceramide

HCC – Hepatocellular Carcinoma

HCLS – Holocarboxylase Synthetase

HDL – High-Density Lipoprotein

HFI – Hereditary Fructose Intolerance

HHH – Hyperornithinemia-Hyperammonemia-Homocitrullinuria

HPA – Hyperphenylalaninemia

HPRT - Hypoxanthine-guanine Phosphoribosyltransferase

HRCT – High-resolution Computed Tomography

HSCT – Hematopoietic Stem Cell Transplant

IEM – Inborn Errors Of Metabolism

IOPD – Infantile-onset Pompe Disease

IUGR – Intrauterine Growth Restriction

IVA – Isovaleric acidemia

KIC – Alpha-ketoisocaproic acid

KIV – Alpha-ketoisovaleric acid

KMV – Alpha-keto-beta-methylvaleric acid

LC-FAOD - Long-Chain Fatty Acid Oxygenation Disorders

LCHAD - Long-chain L-3 Hydroxy Acyl-CoA Dehydrogenase Deficiency

LDL – Low-Density Lipoprotein

LNAAs – Large Neutral Amino Acids

LOKD – Late Infantile Krabbe Disease

LOPD – Late-onset Pompe Disease

LSD – Lysosomal Storage Disease

MADD – Multiple acyl-CoA Dehydrogenase Deficiency

MCAD – Medium-chain acyl-CoA Dehydrogenase

MCT – Medium-chain Triglyceride

MMA – Methylmalonic Acidemia

MPS – Mucopolysaccharidosis

MRI – Magnetic Resonance Imaging

MSUD - Maple Syrup Urine Disease

MS/MS - Tandem Mass Spectrometry Amino Acid Profiling

MTHFR – Homocystinuria/ Methylene Tetrahydrofolate Reductase

NAGS – N-Acetylglutamate Synthase

NBS – Newborn Screening

NE – Neutrophil Elastase

NICCD – Neonatal Intrahepatic Cholestasis Caused By Citrin Deficiency

NPD - Niemann-Pick Disease

ORNT – Ornithine Translocase Deficiency

OTC – Ornithine Transcarbamylase

PA- Propionic Acidemia

PAH – Phenylalanine Hydroxylase

PDH – Pyruvate Dehydrogenase

PEG-ADA – Polyethylene Glycol-conjugated Adenosine Deaminase

Pi – Protease Inhibitor

PKU – Phenylketonuria

PNS – Peripheral Nervous System

pPAL – Pegylated Phe Ammonia Lyase

rhASM – Recombinant Human Acid Sphingomyelinase

SCAD - Short-chain acyl-CoA Dehydrogenase Deficiency

SCID – Severe Combined Immunodeficiency

SMPD1 – Sphingomylein Phosphodiesterase 1

SRT – Substrate Reduction Therapy

TFP – Tri-Functional Protein

TFP – Trifunctional Protein Deficiency

TIA – Transient Ischemic Attack

TMS – Tandem Mass Spectrometry

UCCS – Uncooked Cornstarch

USA – United States of America

VLCAD - Very-long-chain Acyl-CoA Dehydrogenase

VLCAD – Very long-chain Acyl-CoA Dehydrogenase Deficiency

1. Introduction

Rare metabolic diseases caused by enzyme deficiencies are genetic disorders, most of which are inherited autosomal recessively. The deficiencies lead to a blockage along any of the metabolic pathways, which are responsible for the degradation of nutrients (1). Inborn errors of metabolism (IEM) originate from mutations in certain genes leading to an absent or decreased catalytic function of the affected enzyme. Currently, over 500 IEMs have been described, most of which are not treatable. Luckily, 91 disorders can be treated if diagnosed early (2).

The worldwide prevalence of all IEMs combined is 1:1,500 births. The presence of an IEM can be tested either during screening programs or because of the appearance of clinical features that correlate with an IEM. Screening programs include pre-conceptional carrier testing of future parents and/or newborn screening (NBS). NBS has been established in the nineteen-sixties by Dr. Robert Guthrie. He firstly developed a test to screen for the disease phenylketonuria from a single drop of blood. Since the establishment of tandem mass spectrometry numerous metabolic diseases can be tested from one blood spot. Every country has its own defined Screening Panel. In the USA a 'Recommended Uniform Screening Panel' has been created, which includes 34 core diseases (25 IEMs) and 26 secondary diseases that a newborn should be tested for (1). Currently, the NBS program in Germany includes the screening of 13 metabolic diseases, two endocrinopathies, SCID, cystic fibrosis, 5q-associated spinal muscular atrophy, and crescent-cell anemia (3). For a condition to be added to the list, specific criteria must be met like the capacity to perform the screening, proof of screening benefit as well as the possibility of successful treatment (1). Numerous IEMs can also be tested according to the appearance of clinical features. Prenatally, certain IEM can present with irregularities identified during an ultrasound examination of a pregnant woman. Examples of anomalies seen during second-trimester ultrasonography that are caused by IEMs include intrauterine growth restriction, brain abnormalities, fetal hydrops, hyperechogenic large intestine, polyhydramnios, hepatic steatosis, and/or left ventricular noncompaction. As these findings are only suggestive, an ultimate diagnosis can be achieved either with amniocentesis or chorionic villi sampling. However, most commonly, clinical features of IEM appear during the first months of life. In utero, accumulated metabolites have been broken down and excreted via the placental circulation. The accumulation of metabolites eventually leads to the appearance of symptoms. Unfortunately, symptoms are unspecific and include difficulties feeding, lethargy, atypical breathing, vomiting, seizures, and/or hypotonia. The most common

cause of these symptoms is infections; however, IEM should be thought about as differential diagnosis. Metabolic acidosis, inexplicable hypoglycemia, constitutional hepatic defect, and encephalopathy are further findings indicative of IEMs. The further evaluation of newborns unresponsive to antibiotics should include several blood tests (electrolytes, creatine kinase, creatinine, coagulation status and liver enzymes, glucose, ammonia, blood gas analysis, acylcarnitines, amino acids, and lactates) and urine tests (ketones and organic acids). Several IEMs first become apparent during adolescence or adulthood. These late-onset diseases are usually characterized by reduced enzyme activity leading to a slower accumulation of metabolites (1).

During acute deterioration, all newborns with questionable underlying IEM should receive the same treatment. This therapy includes the cessation of feeding (to avoid the accumulation of metabolites) and giving a high-rate glucose infusion (to avoid catabolism). Long-term therapy must be introduced after establishing the definitive diagnosis and is depending on the biochemical origin of the disorder (1).

2. Most frequent inherited metabolic diseases

2.1. **Krabbe Disease**

Krabbe Disease belongs to the category of lysosomal storage diseases (LSD) and is an autosomal recessive and neurodegenerative disease. The incidence of Krabbe's disease in Europe is 1:100.000 with a higher incidence in Scandinavia. Due to consanguineous marriages, the Israeli Druze community has an incidence of 1:1.000. The cause of the disorder is a loss of function mutation in a gene coding galactosylceramide beta hydrolase (GALC). The gene can be found on chromosome 14q31. Large deletions (>30 kilobases), gene deletions, frameshift mutations, truncations, and nonsense mutations correspond to a more severe clinical picture (4). The mother and father of an affected child are obligate heterozygotes, who are asymptomatic. The risk for a sibling to be affected by the disease is 25%, 50% to be a carrier (asymptomatic), and 25% to be unaffected by the disease (5).

The disease can be split into four subsections in relation to the age of onset of symptoms. However, the age ranges differ according to literature: Early infantile type (0 - 13 months), late infantile type (13 - 26 months), juvenile type (3 - 16 years), and adult type (over 16 years) (4). 85%-90% of patients with Krabbe disease have an infantile-onset disease (5).

GALC is responsible for the metabolism of galactosylceramide and psychosine (galactosyl sphingosine). Oligodendroglia cells and Schwann cells have a high concentration of galactosylceramides. The deficiency in GALC causes their built up in lysosomes in the CNS and PNS. Psychosine is usually rapidly degraded, however, in Krabbe Disease, psychosine accumulates and has a cytotoxic effect causing apoptosis and therefore demyelination. The process of apoptosis further leads to the transformation of microglial cells to multinucleated giant cells, which are pathognomonic for the disorder and can be seen during brain autopsy. Due to the fact, that the enzyme can be found inside lysosomes of microglial cells in central and peripheral nervous system, the phenotype is purely neurological (4).

The disease severity corresponds to the age of onset. Patients with infantile-onset of the disease have a rapidly progressive course and the disease is mostly fatal by 24 months. However, some children can die earlier from infections or pulmonary deficiency, while others may survive for nine years. The late-onset disease has a longer expectancy of life. Due to the fact, that myelination occurs more rapidly between birth and 24 months, symptoms also occur more rapidly before the age of 24 months (5).

In early-infantile disease, the progression of symptoms can be explained according to four stages. In the first stage, the child develops regularly in the first couple of months of life, then shows its first symptoms at 4-6 months. The symptoms involve irritability, restlessness, failure

to thrive, emesis, hypersensitivity to noise, touch and bright light, feeding difficulty, and the development of spasms (4). Many infants have their hands fisted (5). During the second stage of early-onset infantile Krabbe disease, the patient experiences visual impairment, optic degeneration, and opisthotonic posturing. Seizures, which are unresponsive to anti-seizure drugs, may occur. In the third stage, the child suffers from blindness, deafness, and decerebrate posturing as well as poor temperature and heart rate control (4,5). The fourth and last stage is defined by hypotonia and the absence of voluntary movements (5). During the late onset of the infantile disease (13-26 months), the child develops irascibility, visual impairment, and abnormal walking. The signs aggravate as the disease progresses with the occurrence of convolutions, apneic intervals, and temperature fluctuations. The overall life expectancy in this subgroup is six years. Children with juvenile-onset disease show visual impairments, trembling, walking abnormalities, and attention deficit hyperactivity disorder and usually die within 10 years after the diagnosis. In the adult-onset group, symptoms include burning paresthesia, mood, and behavior changes, ataxia, spasticity, visual difficulties leading up to blindness, seizures, hearing loss leading up to deafness as well as psychomotor retardation. Survival can vary widely; however, the mean survival time is eight years after the first appearance of symptoms (4).

Screening of Krabbe disease differs depending on every country's recommendation and the clinical situation. In the US, New York has been the first state in 2006 to introduce Krabbe disease in regular newborn screening. 10 further states have included Krabbe in the newborn screening. The blood that is collected during the newborn screening can be tested by measuring the activity of galactocerebrosidase. The cutoff value is 5% of the normal range. Newborns with values below 5 % are diagnosed with Krabbe disease. Due to the fact, that the specificity of the screening is very low, a second testing must be performed to rule out false positive results. Secondary testing includes the measurement of blood psychosine levels or sequencing GALC gene. Not every laboratory has the capacity to measure GALC gene mutations and there is a large variability of GALC mutations. This leads to the fact that psychosine levels are more meaningful in secondary testing (4).

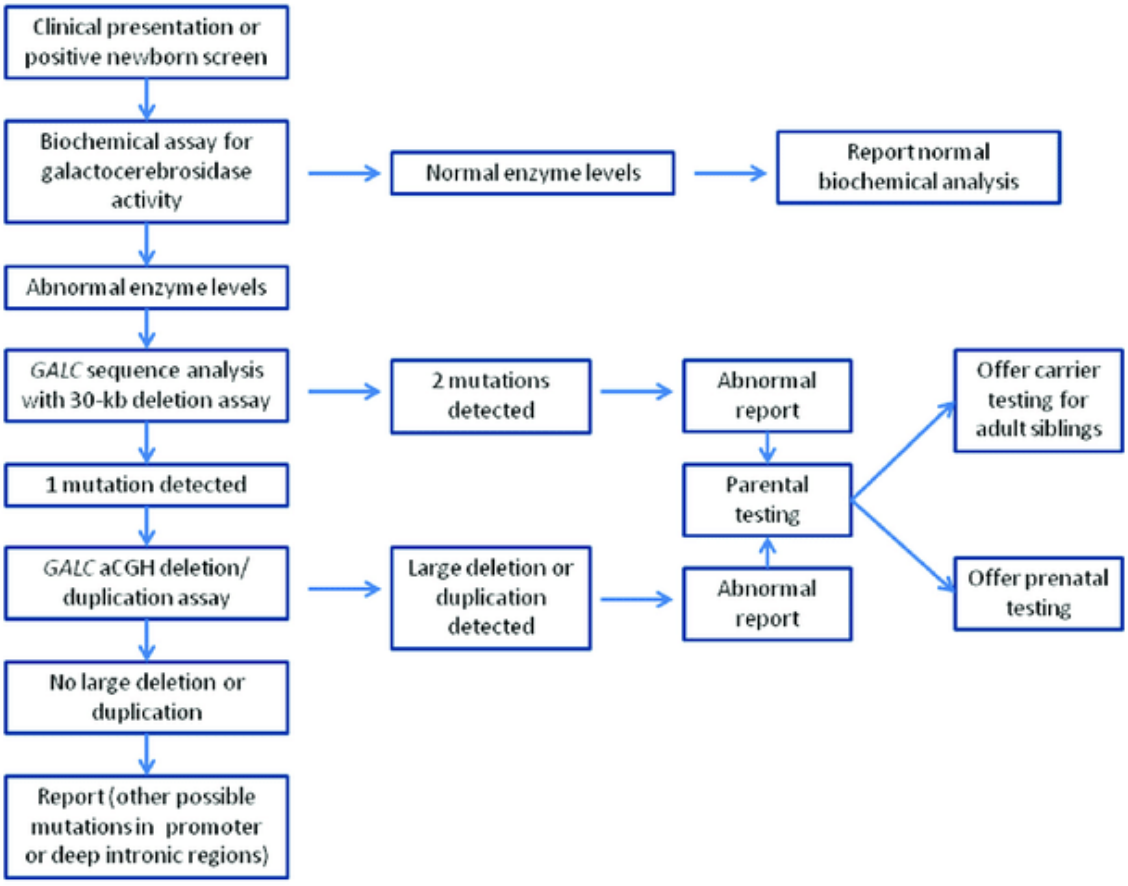

Figure 1: Testing Algorithm for Krabbe disease (6)

To determine the extent and progression of the disorder as well as the necessity for symptomatic therapy, further diagnostic methods must be conducted. A computed tomographic scan may initially show signs of demyelination (symmetrical hypertense areas). However hypodense areas, as a sign of atrophy, develop later in the progression of the disease. Cerebral MRI can be conducted to determine the disease progression. To provide hearing and vision aids, the child must be assessed by an otolaryngologist and ophthalmologist. The cerebrospinal fluid typically shows an increase in proteins. Protein electrophoresis shows high α-1 globulin concentrations while beta-1 globulin and gamma globulin concentrations are low. The level of proteins in the cerebrospinal fluid also correlates with the survival rate: levels higher than 61.5 mg/dl correlate with a lesser period of survival. Studies of nerve conduction reveal peripheral neuropathy with a slower conduction velocity of motor and sensory nerves. Autopsy specimens show monocytes and multinucleated macrophage clusters (globoid cells) with PAS-positive inclusions in gliotic brain tissue. Furthermore, white matter demyelination, destruction of oligodendrocytes, and regions of atrophy can be found (4).

The disease is incurable. The treatment options for children below 6 months of age with the diagnosis of Stage II or Stage III infantile-onset Krabbe disease are limited to supportive

treatment and avoidance of complications. Muscle spasticity can be reduced by physiotherapy and pharmacological treatment. Pharmacological treatment of spasticity includes baclofen and clonazepam for global spasticity and botox injections for local administration. Sufficient energy and fluid intake must be ensured. To prevent vomiting and gastroesophageal reflux disease an upright body position during and after feeding should be maintained. Also, the administration of proton pump inhibitors can be considered. The insertiont of a gastrostomy or nasogastric tube may be necessary during the disease. Constipation can be treated with osmotic laxatives. Neuropathic pain and seizures can be treated with anti-seizure medication e.g., gabapentin and rectal diazepam. To prevent urinary tract infections, temporary catheterization may be necessary to empty the bladder. Permanent catheterization is contraindicated due to the high risk of infections (5). If the infantile type of the disorder is diagnosed before the symptom onset, a hematopoietic stem cell transplant (HSCT) can be attempted. The transplant helps the population of normal functioning microglia cells in the brain and therefore increases the GALC enzyme activity. This treatment option may plateau or slow the disease progression including cognitive and motor decline (4).

Several neurodegenerative diseases as a differential diagnosis must be kept in mind in an asymptomatic individual without a definitive diagnosis. Conditions with white matter anomalies and neurodevelopmental delay include GM2 gangliosidosis,, Canavan disease, metachromatic leukodystrophy, Alexander disease, and sphingomyelinase deficiency. The quality of life is markedly reduced by an array of complications including hearing and vision loss, rigid posture, cognitive decline, pneumonia, and respiratory failure (4).

2.2.**Maple Syrup Urine Disease (MSUD)**

Maple Syrup Urine Disease originates from an abnormal function of the branched-chain α-ketoacid dehydrogenase (BCKAD) complex. The breakdown of the branched-chain amino acids isoleucine, leucine, and valine are carried out by this complex. A disrupted metabolism of these amino acids leads to their accumulation in the plasma and consequently in the form of ketoacids in the urine. The disorder is inherited autosomal recessively (7).

The worldwide incidence of MSUD is 1:185,000 live birth, with girls and boys being equally affected. Higher incidence rates have been found in areas with a high amount of consanguinity. The incidence in the Ashkenazi Jewish community is 1:26,000 live birth, in Mennonites 1:380 live births, and in Portuguese gypsies 1:71 live births. The BCKAD multienzyme complex consists of 4 subunits. BCKAD (E1 subunit) is bound to dihydro-lipoyl acyltransferase (E2 subunit) which is further bound to dihydrolipoamide dehydrogenase (E3

subunit). The subunit E1 consists of E1alpha and E1beta subunits. Also, two regulatory enzymes are associated with the complex (BCKAD kinase and BCKAD phosphatase). The BSKAD complex can be found in the inner membrane of mitochondria of liver, kidney, skeletal muscle and cerebral tissue. The pattern of inheritance is autosomal recessive (8). Currently, there are three known genes whose mutation leads to the disease manifestation. Depending on the gene defect we can distinguish between type Ia, type Ib, type II, and type III. Alteration in the BCKDHA gene found on chromosome 19 leads to type Ia while alteration in the BCKDHB gene found on chromosome 6 leads to type Ib. A mutation in the DBT gene causes type II. If dihydrolipoamide dehydrogenase (DLD) is defective it causes serious type III disease. Here the defect can be found on chromosome 7 (7q31) (9). As seen in Figure 2, branched-chain aminotransferase (BCAT) catalyzes the transamination of BCAAs into their respective α-ketoacids. This process requires the presence of α- ketoglutarate which results in the production of α-ketoisovaleric acid (KIV), α-ketoisocaproic acid (KIC), and α-keto-β-methyl valeric acid (KMV). BCKAD complex then catalyzes these intermediates by oxidative decarboxylation. α-ketoacids are broken down to isovaleryl-coenzyme A, *α*-methyl butyryl-CoA, as well as isobutyl-CoA which are further metabolized into acetyl-CoA, acetoacetate, and succinyl-CoA (7). Most of the catabolism of BCAA occurs in the skeletal muscles while the liver accounts only for 10% to 15% of the BCAA catabolism. The accumulation of BCAA and α-ketoacids can present a variety of clinical symptoms. Glutamate levels are maintained by the BCAA metabolism. Disorders in glutamate synthesis can lead to neurological problems. The accumulation of leucine causes cerebral edema due to decreased blood osmolarity, sodium concentration, and an increase in intracellular water within the subcortical gray matter (8). Further glutamate depletion is caused by altered nitrogen homeostasis, which further increases oxidative stress (7). Large neutral amino acids are reduced due to elevated leucine levels. This results in reduced brain growth, myelin synthesis, and neurotransmitters (8).

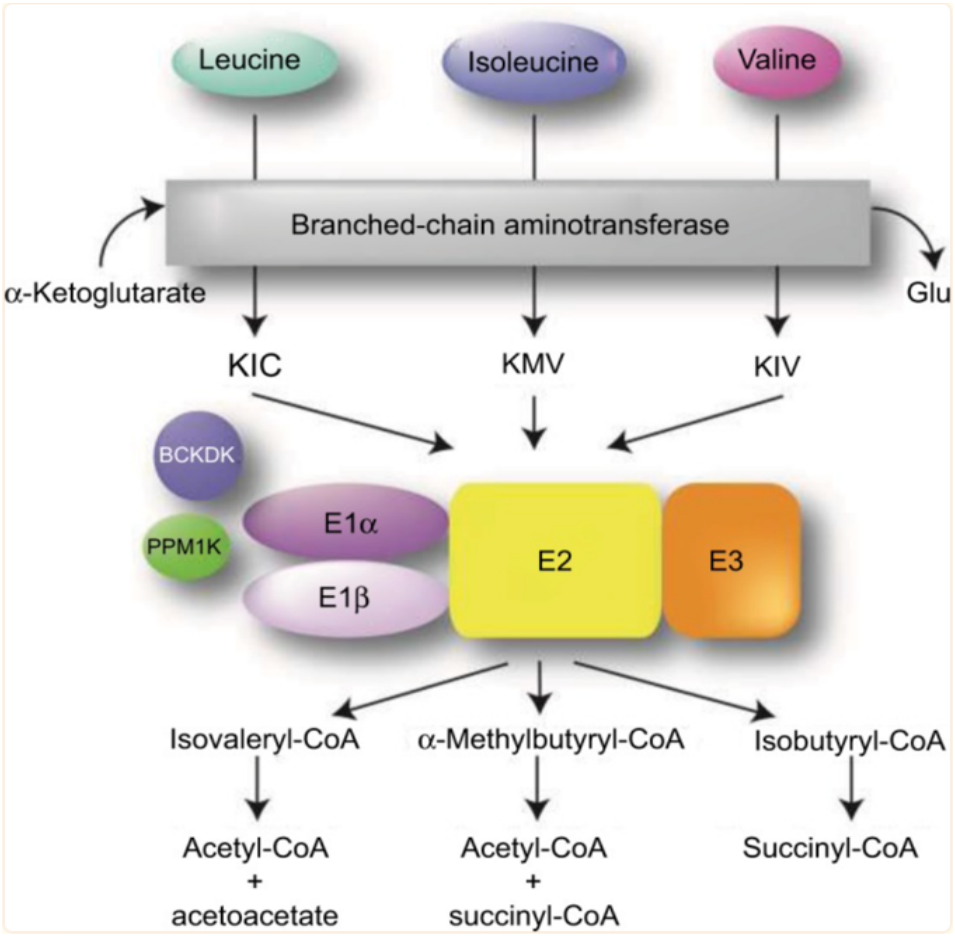

Figure 2: BCAA catabolic pathway (7)

Five clinical phenotypes of the disease can be distinguished: classic, intermediate, intermittent, thiamine responsive, and E3 insufficient subtype. Table 1 differentiates the 5 subtypes according to their age of onset, affected genes, affected BCKAD unit, biochemical characteristics, and clinical characteristics (7).

Table 1: Clinical Phenotypes of Maple Syrup Urine Disease (7)

MSUD subtype	Age of onset	Genetic component	BCKAD unit	Biochemical Characteristics	Clinical Characteristics
Classic (<2% of BCKAD enzymatic activity)	Neonatal	BCKDHA; BCKDHB; DBT	E1 alpha; E1 beta; E2	Increased alloisoleucine and BCAAs (blood); increased branched chain ketoacids (urine)	Neonatal phase: - Maple syrup smell (cerebrum, urine) - Inadequate eating - Apathy - Periodic breathing pauses - Opisthotonos - Brain edema - "bicycling" movements Infant and toddler: - Weight loss - Movement disorders - Vomiting Older - Cognitive deterioration - Hyperactivity - Sleeplessness - Delusions - Movement disorders

Intermediate (max. 30% BCKAD residual activity)	Variable	BCKDHA; BCKDHB; DBT	E1 alpha; E1 beta; E2	Similar as classic form but less severe	Neonatal phase: - Maple syrup smell (Cerumen, urine) Older age: - Low height - Cognitive disability - Impaired eating
Intermittent	Variable	BCKDHA; BCKDHB; DBT	E1 alpha; E1 beta; E2	Similar to the classic type during illness; In asymptomatic phase normal BCAAs	General - Regular growth and neurological development During periods of stress - Encephalopathy
Thiamine-responsive	Variable	DBT	E2	Upon thiamine supplementation, enhanced levels of BCAAs and leucine tolerance	Similar to the intermediate form
E3-insufficient	Variable	DLD	E3		Early-onset neurologic phenotype - Reduced muscle tone - Enlarged Liver - Cognitive disability - Vomiting

					- Apathy - Convolutions - Spasticity - Leigh syndrome Liver Phenotype - Vomiting - Encephalopathy - Enlarged Liver

In prenatal diagnosis, the BCKAD activity is measured in chorion villus or amniotic fluid (8). Since the introduction of the Guthrie test in the 1960s, MSUD screening has been included into NBS in the USA, 5 Canadian territories, 22 European states, 2 Latin American states, and eight states in the Asia Pacific area (7). The algorithm in Figure 3 depicts the process of diagnosing a child with MSUD. Today, in the NBS for MSUD MS/MS is used to quantitatively determine the level of plasma BCAAs. Further studies include dinitrophenylhydrazine (DNPH) test, urine organic acid analysis using gas chromatography (GC)-MS/MS, molecular testing, and quantitative plasma amino acids by liquid chromatography (LC)-MS/MS. MS/MS investigates the leucine-isoleucine concentration as well as their ratio to other amino acids. However, this process is unable to differentiate amino acids with identical mass. This requires further investigation in the form of a second-tier test, such as quantitative levels of plasma amino acids by (LC)-MS/MS, to help differentiate MSUD from hydroxyprolinemia. Furthermore, NBS may not be able to expose slighter forms of the disease because of leucine levels within the normal area in the neonatal period (7-8) The definite diagnosis of MSUD is based on biochemical, clinical, and molecular indicators (7). Molecular tests can be used to determine a prognosis, plan individualized therapies, and for family counseling (8).

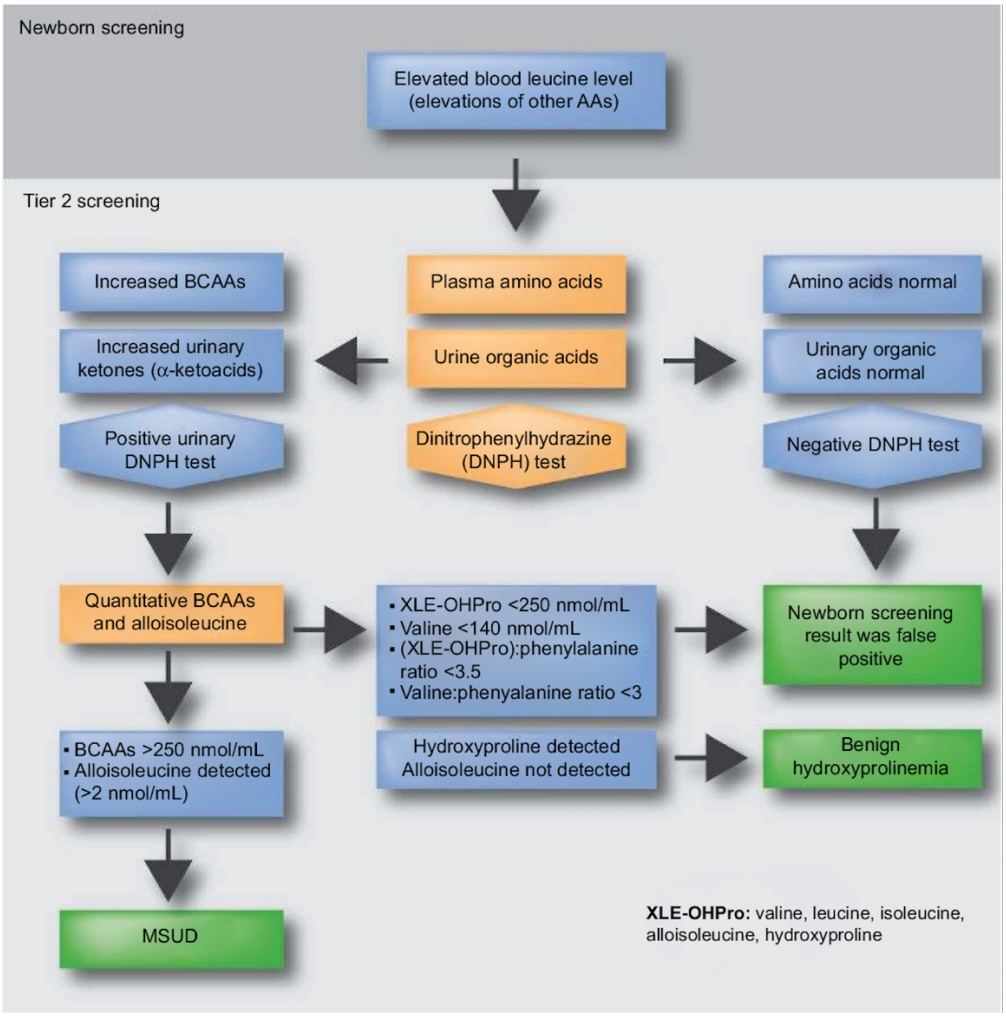

Figure 3: MSUD testing algorithm in NBS (7)

After a positive NBS test and the clinical confirmation of the MSUD nutritional therapy must be initiated. The main part is the restriction of branched-chain amino acids. Through close monitoring of biochemical values and growth measurements, the amounts of BCAAs can be titrated into the diet. The goal is to promote anabolism and prevent catabolism. Desired leucine concentrations to promote normal intellectual development of the child should be between 75 to 300 micromol/L. Recommended reference range of isoleucine and valine levels are 200 and 400 micromol/L. Furthermore, according to recommendations, thiamine should be added to the therapy for four weeks in every patient with MSUD, regardless of the subtype. If the patient belongs to the category of thiamine-responsive patients, the supplementation should be continued. Acute metabolic decompensation is defined as a plasma leucine level over 380 micromol/L. The cause of this decompensation is usually a lack of compliance to dietary recommendations and/or infection. Non-adherence to the dietary regulations raises the BCAA level but rarely leads to decompensation or even encephalopathy. On the other hand, trauma and infection lead to the catabolism of large proteins and consequently to a metabolic crisis.

The goal of the therapy is to reduce protein catabolism. At home, a dinitro-phenylhydrazine reagent can be used to track BCKAs in the urine (8). Patients and their families at home can follow the guidelines of a so-called sick day protocol. This guideline can be used for mild signs of the disease at home (7-8). For severe cases, a more aggressive procedure in the hospital must be initiated (e.g., dialysis, hemofiltration, parenteral nutrition, tube feeding) (7). The reduction of leucine to the ideal range can be achieved with insulin and glucose infusions. Further treatment measurements that can be taken include the treatment of the underlying stressors, nausea and vomiting control, isoleucine and valine supplementation, tyrosine supplementation in case of dystonia, glutamine, and alanine supplementation, BCAA-free amino acids supplementation, maintenance of a physiological sodium level, correction of acid-base disturbances, avoidance of osmolarity fluctuations >5mosm/L, maintain urine output and prevent electrolyte disturbances associated with glucose and insulin infusions. An orthotopic liver transplantation can be indicated in the case of psychomotor disorders, deficient metabolic control, and/or recurrent phases of metabolic decompensations. The method of choice is to use the liver from an unrelated deceased person, however, living donor livers can be used as well. Due to the fact, that the liver is in control of 10% of BCKAD activity, the residual BCKAD activity can rise after the transplantation to the level of a mild MSUD. Following, liver transplantation can increase enzyme activity, and reduce the need for dietary restrictions and episodes of metabolic decompensation (8).

The differential diagnoses of MSUD, that must be kept in mind, include low blood sugar levels, meningitis, status epilepticus, kernicterus, encephalitis, birth asphyxia, organic acidopathies, beta-keto thiolase deficiency, HMG-CoA lyase deficiency, urea cycle disorders, and non-ketotic hyperglycemia. The prognosis depends on the beginning of therapy. If the therapy started ahead of or directly after the development of symptoms, the prognosis is good. Cerebral palsy and learning disability can occur in cases of a late diagnosis (>7-14 days) in classic MSUD. If the disorder is not diagnosed or treated early, serious consequences can influence the quality of life. Consequences include convolutions, metabolic acidosis, brain edema, cerebrovascular ischemia, cognitive disabilities, loss of vision, irreperable neurological damage, muscles spasticity, acute pancreatitis, osteoporosis, chronic esophageal candidiasis, anemia, hair loss, growth failure and acrodermatitis (8).

2.3.Fabry disease

Fabry disease is an infrequent, congenital, monogenic, X-linked, progressive metabolic disease belonging to the class of lysosomal storage. Fabry disease is a multisystem disease that can affect a variety of organs. Depending on the organ system involved, very different symptoms can occur. Due to the different disease manifestations and its rarity, establishing a diagnosis and prevalence can be very difficult (10-11).

In the average population, incidences vary from 1:117,000 to 1:476,000. However, the true prevalence might be underestimated and data from NBS initiatives indicated higher frequencies of Fabry disease. In northern Italy, an incidence of 1:3,100 has been found and NBS initiatives in Taiwan have estimated a prevalence of 1:1,500 male live births (10).

Fabry disease is a recessively inherited disorder based on a genetic defect on the female sex chromosome. The alteration affects the GLA gene which is responsible for the production of the α-GAL enzyme. The α-GAL enzyme breaks globotriaosylceramide (Gb3) into lactosylceramide and galactose inside the lysosomes leading to the accumulation of Gb3 in various tissue, with a preference for the endothelium and smooth muscle cells. This leads to the narrowing and occlusion of vessels resulting in ischemia and infarction. There is a complicated correlation between phenotype and genotype. However, patients with the blood group AB or B show severer clinical presentation as glycosphingolipids accumulate in the membrane of red blood cells of type B. An affected father inherits the disease to every daughter, while a son remains unaffected. A sick mother has a 50% risk of inheriting the disease, regardless of the gender of the child (11).

Two types of Fabry disease can be differentiated. In male patients presenting with the classic form of Fabry disease the aforementioned enzyme has no or very little (<1%) activity, whereas in the atypical type of disease the enzyme still has residual activity (2-20% of normal). Therefore, the classic phenotype usually presents in childhood with cornea verticillate, neuropathic pain, and angiokeratoma and shows permanent complications such as arrhythmias, hypertrophic cardiomyopathy, stroke, and progressive kidney failure. In atypical Fabry disease, which is also called late-onset Fabry disease, symptoms are milder and even restricted to a particular organ system (10).

Table 2: Symptoms of Classic Fabry Disease (10)

Organ System	Symptoms
Nervous System	- Auditory neuropathy - Acroparesthesias

	- Heat intolerance - Hearing loss -
Alimentary Tract	- Diarrhea - Bloating - Feeding Difficulties - Underweight - Vomiting
Dermal Symptoms	- Reduced sweating - Angiokeratomas
Ocular Symptoms	- Vasculopathy - Ocular opacities
Renal Symptoms	- Proteinuria, Microalbuminuria - Impaired concentration ability - Expanded filtration - Increased urinary elimination of Gb3
Cardiac Symptoms	- Valvular insufficiencies - Arrhythmias

Male patients usually exhibit the classic phenotype at the age of three to five. The heterozygous female phenotype may range from asymptomatic to acute presentations similar to male patients. This variation in phenotype is caused by random X-chromosome inactivation which means, that highly affected females express the mutated X chromosome. Like most symptoms of Fabry disease, damage to the kidney is progressive. It leads to end-stage renal failure and a significantly reduced expectancy of lfe. In the classic subtype of Fabry disease, kidney damage starts during 2nd to 3rd decade of life. First microalbuminuria develops, followed by proteinuria leading to Fabry nephropathy. The proteinuria becomes more severe with advancing age. As the disease progresses, isosthenuria develops which is accompanied by changed tubular reabsorption, secretion, and excretion. Initially, the damage is masked by glomerular hyperfiltration. Eventually, a critical number of nephrons are impaired, kidney function successively decreases. As renal function deteriorates renal azotemia occurs. Fibrosis, sclerosis, and tubular atrophy finally lead to end-stage kidney disease, a crucial factor of mortality and morbidity. As mentioned in Table 2, progressive myocardial ischemia leads to irreversible myocardial scarring and congestive heart failure. Early symptoms of peripheral neuropathies

are accompanied by cerebrovascular diseases and autonomic dysfunctions in adults. Among the most unfavorable neurological characteristics of this disease is multifocal circulatory disorders in the small blood vessels resulting in a spectrum of signs and symptoms ranging from headache, dizziness, and TIA to ischemic strokes and vascular dementia (10-11). Late-onset variant (fourth to sixth decade) of Fabry disease may show none or a few of the hallmark symptoms mentioned in Table 2. However, symptoms are predominantly affecting one organ system, therefore the commonly used subdivision into "cardiac variant" and "renal variant" is used (10).

Table 3: Late-Onset Variant of Fabry Disease (10)

Cardiac Variant (more common)	- Megalocardia - Electrocardiographic changes indicating cardiomyopathy - Cardiac infarction
Renal Variant	- Chronic Kidney Disease - Microalbuminuria and Proteinuria - End-Stage Kidney Disease

Diagnosing Fabry disease as early as possible is crucial to significantly improve the quality of life and reduce or delay organ damage. In the classic form of Fabry disease, the special clinical presentation already gives clues to the diagnosis. In male patients, the activity of α-galactosidase A in leukocytes and plasma can be determined. The proof of an α-galactosidase A deficiency confirms the diagnosis in male patients. This method, unfortunately, cannot be used in female patients. The residual activity of the enzyme is too high leading to a result that falls in the normal limits. In these cases, patients should be diagnosed by genotyping. Urinary Gb3 can be used as a marker for diagnosis in all patients. Nevertheless, urinary Gb3 may not be increased in some cases of late-onset variants or specific mutations (10).

The therapy of Fabry disease focuses on controlling the symptoms of the affected organ as well as replacing the absent enzyme.

Table 4: Treatment of Manifestation (12)

Affected Organ System/ Symptom	Treatment
Acroparesthesia	- Diphenylhydantoin - Carbamazepine

	- Gabapentin
Cardiovascular disease	- Acetylsalicylic acid - Lipid-lowering agents - Blood pressure regulation
Neurovascular disease	- Acetylsalicylic acid or other agents for prophylaxis
Kidney disease	- ACE inhibitors or ARBs - Blood pressure regulation - Hemodialysis - Renal transplantation
Hearing impairment	- Rehabilitation - Hearing aid
Psychiatric manifestation	- specific therapy
Skin lesions	- Laser methods (just cosmetic purpose)

So far, the treatment options were just symptomatic but not causal. In 2001 ERT has been introduced into the therapy plan. ERT uses a recombinant human α-galactosidase A (12). Current recommendations according to Eng et. al. can be seen in Table 5 (2006). Currently, 2 enzyme compositions (Agalsidase alfa and beta) for Fabry Disease are available in Europe (10). Migalast, a chaperone therapy, has been approved in the EU in 2016 and in the US in 2018. The goal of this therapy is to increase residual enzyme activity by saving the modified enzyme from misshaping and catabolism inside the cell (12).

Table 5: Guidelines for the onset of Enzyme Replacement Therapy in Fabry disease (13)

Subpopulation	Guidelines for onset of ERT
Males (> 16 years)	After confirming the diagnosis
Males (< 16 years)	After the occurrence of notable symptoms or in case of no symptoms, consider at 7-10 years
Females (all ages)	Signs or proof of advancement of organ damage

Due to its variety in symptoms, Fabry disease is commonly misdiagnosed with growing pain, early-onset stroke, multiple sclerosis, juvenile arthritis, petechiae, rheumatic fever, Raynaud syndrome, SLE, rheumatoid arthritis, neurosis, erythromelalgia, rheumatic fever, cardiomyopathy, end-stage kidney disease or familial Mediterranean fever (12).

According to the Fabry Register, 75 (out of 1,422) male patients and 12 (out of 1,426) female patients have died. The diagnosis in their cases had been established later than other patients in the register. The longevity of male patients is 58.2 years, in comparison to 74.7 years in the US and the longevity of female patients is 75.4 years, in comparison to 80.0 years in the US. Cardiovascular diseases are the most common cause of death in male and female patients. However, 57% of these patients received renal replacement therapy before their death (12).

The quality of life is particularly reduced in males. The quality of life in these patients is similar to that in patients with MS or rheumatoid arthritis. Furthermore, the disease has a negative influence on the psychosocial development of the patients (14).

2.4.Gaucher Disease

Gaucher disease is a rare, hereditary, and progressive metabolic disease that is inherited autosomal recessively (15). Gaucher Disease is the most frequent LSD (16). The condition is named after Philippe Gaucher, who firstly reported the storage cells in the spleen in 1982 (15-16).

The incidence varies between 1:40,000 and 1:60,000 live births. In the Ashkenazi Jewish population, it can reach up to 1:800 births. Out of three defined subtypes, Type-1 Gaucher disease is the most frequent. A mutation in the GBA1 gene causes a defective function of the enzyme β-glucocerebrosidase. The gene is located on Chromosome 1 on Genlocus 1q21 (15). This enzyme is responsible for the catabolism of glucosylceramide (GlcCer). Following this, the defective catabolism leads to a toxic accumulation of glucocerebroside lipids inside the mononuclear phagocyte system, which further leads to their conversion into Gaucher cells (16). Heterozygotes with a specific alteration in the GBA1 gene have a higher risk for Parkinson's disease. Additionally, to the catabolism of glucosylceramide, glucocerebrosidase also facilitates with catabolism of α- synuclein. Mutated GCase causes the buildup of α- synuclein and an accumulation of GlcCer. These two bind to form oligomers and fibrils further decreasing the activity of GCase by binding to the enzyme. These insoluble aggregates in the cytoplasm form Lewy bodies. There is also a relationship between Gaucher disease and cancer, particularly multiple myeloma. Also, the incidences of lymphomas and several solid cancers (hepatocellular carcinoma, melanoma, pancreatic cancer) are higher in patients with Gaucher disease (15).

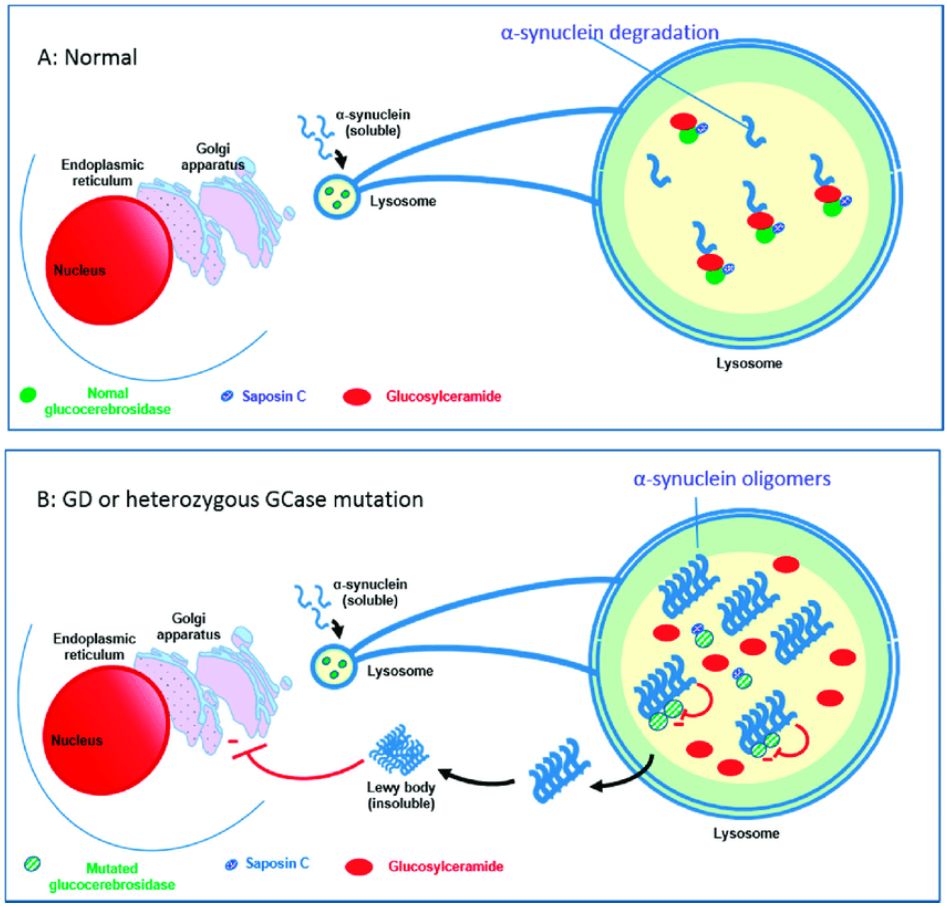

Figure 4: Relationship of Gaucher Disease with Parkinson's Disease (15)

Table 6: Clinical Signs and Symptoms of Gaucher Type I-III (15, 17-18)

Gaucher Types	Prevalence	Onset	Symptoms (% of Gaucher patients showing sign/symptom)	Involvement of Nervous System	Life Expectancy
Type-1 Gaucher Disease/ Non-neuropathic Gaucher disease	90-95% High prevalence in Ashkenazi Jews	Any age	General - Fatigue (50%) - Growth retardation (34% <5th percentile) - Delayed puberty Visceral - Splenomegaly (>90%) - Hepatomegaly (60-90%) - Focal hepatic or splenic like Gaucheroma, HCC, and Lymphoma (40%) - Cholelithiasis (32%) Hematological - Bleeding phenomena - Anemia (20-50%) Skeletal - Acute/Chronic Pain - Painful Bone Crises (30% of children) - Osteopenia and Osteoporosis	No	Reduced

			- Avascular Necrosis (15%) - Secondary bone tumors like osteosarcoma or osteoblastomas (rarely) Other - Lung Fibrosis, Restrictive Lung Disease due to vertebral deformity, pulmonary hypertension (rare) - Proteinuria and hematuria (rare) - Skin Hyperpigmentation - Ocular manifestation (rare) - Myocardial or valvular involvement (rare) - Insulin resistance (rare) - Amyloidosis (rare)		
Type-2 Gaucher Disease/ Acute Neuronopathic Gaucher Disease	<5%	Childhood (3-6 months)	General - Growth retardation (30%) Neurological - Opisthotonos - Bulbar symptoms (especially severe dysphagia) - Oculomotor palsy - Trismus	Yes	Death usually before age 3

			- Hypertonia with pyramidal and extrapyramidal rigidity - Seizures Visceral - Hepatosplenomegaly - Apnea associated with laryngeal spasm Hematological - Thrombocytopenia (60%) Skeletal - No bone involvement Other - Lung lesions due to repeated aspiration and infiltration with Gaucher cells		
Type-3 Gaucher Disease/ Chronic Neuronopathic Gaucher Disease	5% High prevalence in the Swedish province of Norrbotten	Childhood-Adolescents (before 20 years of age)	Visceral - Visceral manifestation as in Type-1 Gaucher Disease Neurological - Horizontal ophthalmoplegia - Progressive myoclonus seizures - Cerebellar ataxia/spasticity - Dementia	Yes	Mid to early adulthood death

			Skeletal - Kyphosis Other - Cardiac involvement (valve calcification) - Corneal involvement - hydrocephalus		

Testing for Gaucher disease is usually initiated upon clinical presentation. Unfortunately, it can take years from the onset of symptoms until defining a definitive diagnosis. The initial test, if Gaucher disease is suspected, is to determine the enzyme activity of beta-glucocerebrosidase in leukocytes, mononuclear cells, or cultured fibroblasts. The diagnosis can be confirmed with a residual enzyme activity of 10-15% of the reference value. Additionally, genetic analysis is carried out. As previously mentioned, the gene GBA1 can be found on chromosome 1. Over 400 mutations in this gene have been identified. The c.1226A>& (N370S) mutation accounts for 75%-80% of mutations in the Ashkenazi Jewish community and 30% of the non-jewish community. The presence of this mutation excludes the diagnosis of Type-2 or -3 Gaucher Disease and therefore any neurological involvement. Patients with two null mutations have a total absence of the enzyme activity which causes the fetal form of Gaucher disease and is incompatible with life. Prenatal diagnosis can also be offered if the is a known affected relative. Prenatal diagnosis of Gaucher disease can be done with either genetic analysis or the calculation of glucocerebrosidase activity in chorionic villi or amniotic cells. Laboratory findings are unspecific and additional enzyme and genetic testing must be conducted to confirm the diagnosis. Several biomarkers have been used in the past years. Chitotriosidase, secreted by Gaucher cells, can be used as a biomarker since 1994 to monitor the effectiveness of the therapy. CCL18 is a chemokine produced by macrophages, dendritic cells, and Gaucher cells and high levels are associated with a poorer prognosis. A new biomarker, glucosyl sphingosine, has better sensitivity and specificity than both afromentioned biomarkers and might be a valuable biomarker for patient monitoring in the future. High ferritin levels are associated with the beginning of bone complications and asplenia. Further diagnostic methods like imaging methods can be used to detect organ involvement (15).

There are two types of treatment for Gaucher disease: Specific treatment and symptomatic treatment. In the field of specific treatment, two options are currently available: ERT and SRT. The goal of the ERT is to increase the level of GCase lacking in the cells, especially in the Gaucher cells. The uptake is achieved by the glycosylation of the terminal mannose residue. The enzyme is then preferably taken up in macrophages (mainly Gaucher cells) to then reach the lysosomes and break down the accumulated glucosylceramide. The therapy is usually administered for a lifetime once initiated. The drug reduces thrombocytopenia, improves the quality of life after 1-2 years of ERT, decreases the infiltration of bone marrow, osteopenia, and the occurrence of skeletal events, improves bone pain, and reduces the risk of avascular necrosis. ERT can be contemplated in all individuals with Type-3 Gaucher disease and in Type-1 Gaucher disease if the individuals show clinical or biochemical irregularities. Substrate

reduction therapy is indicated as a second-line treatment when ERT is contraindicated or not well tolerated. The first drug approved as an SRT for the therapy of Gaucher disease is Miglustat. Miglustat is a synthase inhibitor of GlcCer and therefore prevents the biosynthesis of glucosylceramide. Symptomatic therapy includes temporary immobilization and the use of analgesics during painful bone crises, orthopedic surgery to treat avascular necrosis and pathological fractures, liver transplantation in case of severe liver disease, coagulation factor monitoring, and psychological support. Since the introduction of ERT, splenectomies are avoided due to the high risk of complications (15).

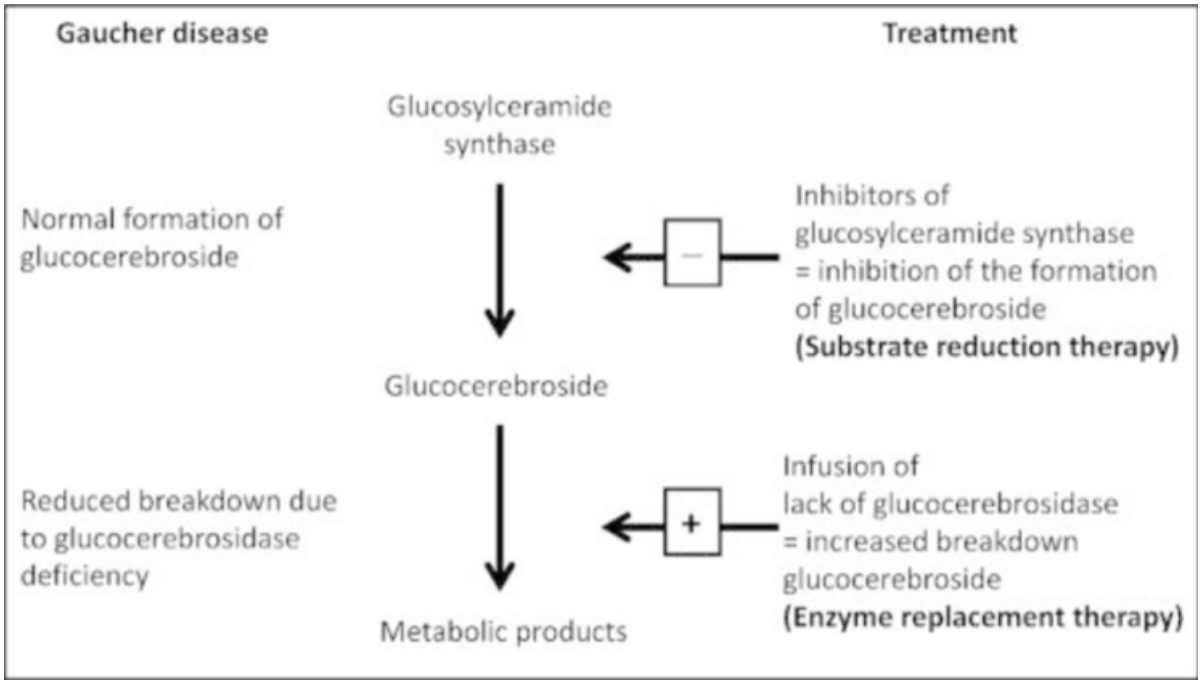

Figure 5: Therapy plans in a patients with Gaucher disease (modified from Claus Niederau C) (18)

The differential diagnoses include NPD, Lewy body dementia, sphingomyelinase deficiency, multiple myeloma, and Parkinson's disease(17). The currently available treatment options reduce hepatosplenomegaly, cytopenia as well as bone manifestations. This leads to a great improvement in the quality of life of the affected individual. However, Parkinson’s disease, persistent bone disease, Lewy body dementia, and the development of hematological disorders and/or malignant tumors reduce the overall quality of life (15).

2.5.Niemann-Pick Disease

Niemann-Pick disease belongs to the group of sphingolipidoses, which in turn belong to the broad group of LSD. It is a rare, hereditary disorder and is inherited in an autosomal recessively (19). The disease is named after the pediatrician Albert Niemann and Ludwig Pick (20).

Niemann-Pick disease can be split into the subcategories A, B, C, and D. Type D is a rare subtype developing in adulthood, which will not be further described in this chapter. In NPD subtype A and B, alterations in the sphingomyelin phosphodiesterase 1 gene lead to a lower activity of ASM which can be mainly found in lysosomes. ASM causes the modification of sphingomyelin to ceramide and phosphocholine (19). Additionally, to sphingomyelin, the elevation of bis(monoacylglycerol)phosphate (BMP) and lysosphingomyelin (sphingosine phosphocholine) can be found (20). The buildup of sphingomyelin and other precursors leads to cellular damage (19). Niemann-Pick disease type C1 arises from a pathogenic mutation in the NPC1 Gene (95% of cases) whereas Niemann-Pick disease type C2 arises from a pathogenic mutation in the NPC2 gene (5% of cases) (21). The encoded proteins by these genes cause the traffic and intracellular mobilization of sterols and cholesterol. Impaired transport due to gene mutations lead to toxic accumulation of cholesterol and later on to cellular and organ damage (19)

Table 7: Comparison of NPD Type A, B and C (19,21)

Subtype	Incidence	Etiology	Clinical Features	Expected Outcome
NPD type A- classic infantile type	1/250,000 in general population 1/40,000 in Ashkenazi Jewish population	Missense mutations in SMPD1 gene (Chromosome 11)	General - irritability - sleep disturbances - failure to thrive Visceral - Hepatosplenomegaly Neurological - Progressive neurodegeneration - Hypotonia/Hyporeflexia - loss of deep tendon reflexes - Ataxia - Dystonia - Dysphagia, Dysphonia - Peripheral neuropathy - hydrocephalus Eye - Cherry-red spot-on macula - Corneal Obscuring	Usually, fatal <4 years

			- Brown staining of the anterior lens capsule Pulmonary - Interstitial lung disease - Recurrent Respiratory infections - Respiratory failure Hematological - High liver enzymes - Hypercholesterolemia - Decrease in hemoglobin - Cytopenias Skeletal - Coxa vara - Impaired growth - Slow mineralization of long bones	
NPD type B-visceral type	1/250,00 In Ashkenazi Jewish population 1/40,000	Missense mutations in SMPD1 gene (Chromosome 11)	General - Bone and joint pain - Growth retardation - Delayed puberty - Fatigue - osteopenia	Death in late childhood or early adulthood

			Visceral - Hepatosplenomegaly - Liver fibrosis Neurological - No overt signs of CNS involvement Eye - Cherry-red spot on macula - Ocular Obscuring - Brown staining of the anterior lens Pulmonary - Interstitial lung disease - Recurrent respiratory infections - Respiratory failure Hematological - Cytopenia - Bleeding - Hypercholesterolemia Skeletal - Coxa vara - Impaired growth - Slow mineralization of long bones	

NPD type C-subacute/juvenile type	1/150,000 with higher incidence in French-Acadian descent	Mutation in NPC1 (Chr. 18) and NPC2 (Chromosome 14)	Early infantile (<2 years) - Hydrops fetalis - Jaundice - Lung infiltrates - Fetal ascites - Neonatal liver disease Late infantile (2 - <6 yeas) - Hypotonia - Developmental delay - Vertical supranuclear saccadic palsy - Clumsiness - Ataxia Juvenile (6 - <15 years) - Spasticity - Clumsiness - Vertical supranuclear gaze palsy - Ataxia - Academic difficulties - Developmental delay and regression - Seizures - Gelastic cataplexy	Depending on time of onset of symptoms

			- Dystonia Adolescent/adult (>15 years) - Clumsiness - Ataxia - Academic difficulties - Developmental delay and regression - Vertical supranuclear gaze palsy - Seizures - Gelastic cataplexy - Dystonia - Spasticity - Early-onset dementia - Depression resistant to treatment - Schizophreniform disease - Bipolar disorder	

Typical clinical picture cannot be solely used to determine a diagnosis. Upon the suspicion of NPD Type A or B, a blood test should be conducted to measure the ASM activity in leukocytes. To confirm the diagnosis genetic testing can be used. Upon suspicion of NPD Type C, a skin biopsy will be obtained, prepared with a specific stain and the enzyme activity can be measured from cultured skin fibroblasts. Low enzyme activity can be determined by genetic analysis and identification of pathogenic variants in the afro mentioned genes (19,22). After confirming the diagnosis of Niemann-Pick disease several organ systems should be evaluated to determine the spread of the disease. These include measuring liver enzymes, spirometry, HRCT to exclude intestinal lung disease, platelet count and size of the spleen, HDL-cholesterol and LDL-cholesterol measurement, ophthalmological and neurological examination, and a pain and fatigue questionnaire. The severity of the disorder can be calculated by measuring the quantity of sphingomyelin, macrophage markers, and oxysterols (19).

Currently, Niemann-Pick disease is incurable. The cornerstone of the therapeutic approach is supportive care. Including mainly the use of statins to keep blood lipids low, monitoring of liver function, physical and occupational therapy, transfusions in case of thrombocytopenia, streptococcus pneumonia vaccination to reduce the risk of pneumonia, pain management, and oxygen administration in case of intestinal lung disease (19,23). In 2022 Japan approved the first ASMD-specific therapy. The ERT with olipudase alfa was introduced in the treatment of NPD Type A and B. Studies with mice showed, that the recombinant human ASM (rhASM) lowered the lipid storage in reticuloendothelial organs. The therapy is administered by biweekly infusions. However, the therapy with rhASM is ineffective in the progression of neurological symptoms (20,24). There are several research approaches to be studied in the future including the enhancement of neutral sphingomyelinase activity, anti-inflammatory therapies, and chaperone therapies (20). Since 2009 Miglustat is authorized for the therapy of Niemann-Pick disease Type C (originally developed to treat Type I Gaucher disease). Today, Miglustat is also authorized for the therapy of progressive neurological complications in individuals with NPC. Studies showed an improvement in dystonia, dysmetria, and dysarthria and a reduced rate of disease progression (22).

The differential diagnoses that should be kept in mind include several other LSD including Gaucher disease, metachromatic leukodystrophy, and Tay-Sachs disease. Furthermore, other hepatic and cerebral diseases should be considered, depending on the clinical presentation. The quality of life is impacted by several complications including hepatic failure, pulmonary

insufficiency, progressive neurodegeneration, thrombocytopenia, coronary artery and valvular heart disease, and bone deformities (19).

2.6.Phenylketonuria (PKU)

Phenylketonuria (also called phenylalanine hydroxylase deficiency) belongs to the most common IEMs. It is inherited autosomal recessively and caused by a mutation in the phenylalanine hydroxylase (PAH) gene. Affected patients have a decreased catalytic ability of phenylalanine, which then accumulates in the body and produces phenylpyruvate, phenylacetate, or phenyllactate. If left untreated this accumulation causes severe mental developmental disorders, psychiatric disorders, and epilepsy. The disease can be detected by NBS. If treated early enough with a low-protein diet afro mentioned complications can be prevented (25).

The incidence of PKU varies between ethnicities and geographic locations worldwide. In Europe, the highest incidence can be found in Italy (1:2,700 live birth) and Ireland (1:4,500 live birth), whereas the lowest incidence is in Finland (<1:100,000 live birth). High incidences can also be seen in the Middle East, for example in Turkey (1:4,370 live births), the Fars province of Iran (1:4,698 live births), or the Russian republic of Karachay-Cherkessia (1:850 live births). Particularly high incidences can be attributed to consanguineous marriages. The incidence of PKU in the Asian population is relatively low (e.g., Thailand 1:212,535 live births). However, data on the incidence of the disease are not available from all areas of the world. The combined worldwide prevalence of classic PKU, mild PKU, and mild hyperphenylalaninemia is 1:24,000 live birth (25).

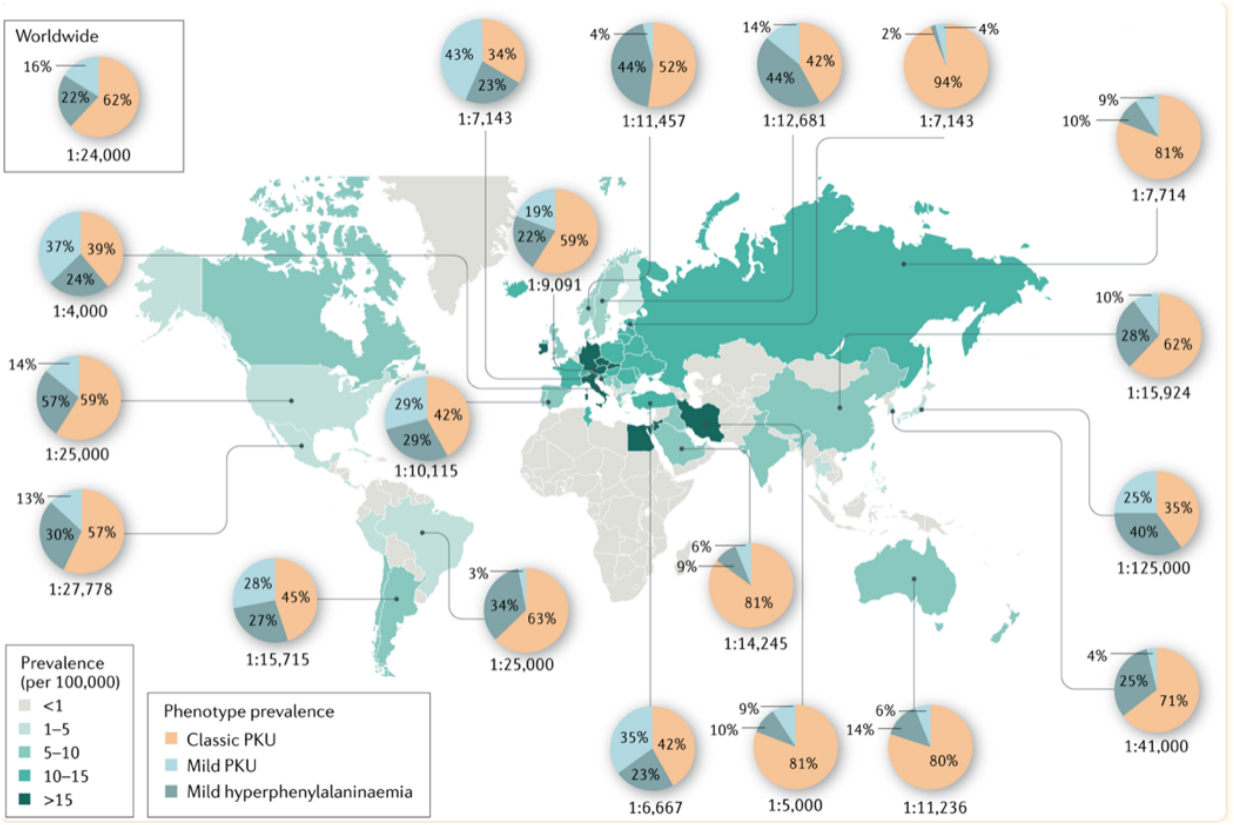

Figure 6: PKU deficiency and different phenotypes worldwide (25)

PKU is caused by a mutation on chromosome 12 (12q22 to 12q24) (33,34). This location codes for the enzyme phenylalanine hydroxylase. Over 1000 different PAH variants have been described, leading to a complex genotype-phenotype prediction. Most PAH variants are in-frame missense amino acid substitutions. Missense variants lead to plenty of hypoactive or inactive PAH monomers. The extent of activity reduction depends on the type of mutation. Therefore, the ability to hydrolyze phenylalanine varies from patient to patient. The hydroxylation reaction of phenylalanine to tyrosine needs molecular oxygen (cofactor) as well as reduced pterin BH4 (co-substrate). Rarely, a PAH deficiency can also be caused by a lack of BH4. BH4 deficiencies can be caused due to errors in the biopterin synthesis (6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency or GTP cyclohydrolase 1 (GTPCH)) or defects in the BH4 recycling mechanisms (pterin-4a-carbinolamine dehydratase (PCD) deficiency or dihydropteridine reductase (DHPR)). HPA can additionally be caused by a pathogenic variant in the DNAJC12 gene. The hydroxylation reaction is a rate-determining step in the break-down of phenylalanine. As a result, tyrosine is required to produce dopamine, adrenaline, norepinephrine, thyroxine, melanin, acetoacetate, and fumarate. The most common clinical manifestation of high levels of phenylalanine is neurological. As seen in Figure 8 large neutral amino acids (LNAAs) can traverse the blood-brain barrier via a LAT1 transporter. However,

high levels of phenylalanine inhibit the transportation of other LNAAs across the blood-brain barrier causing a decreased cerebral protein production. This further leads to decreased levels of monoamine neurotransmitters. The energy-requiring amino acid exporter (EXPORT) may transport some LNAAs leading to a certain degree of homeostasis. Due to this competitive mechanism low levels of dopamine and serotonin may be responsible for mood and anxiety diseases in patients with hyperphenylalaninemia. High cerebral concentrations of phenylalanine have also been linked to amyloid-like plaque formation, epigenetic alteration, impaired glucose metabolism, impaired myelin synthesis, and oxidative stress damage (25-26).

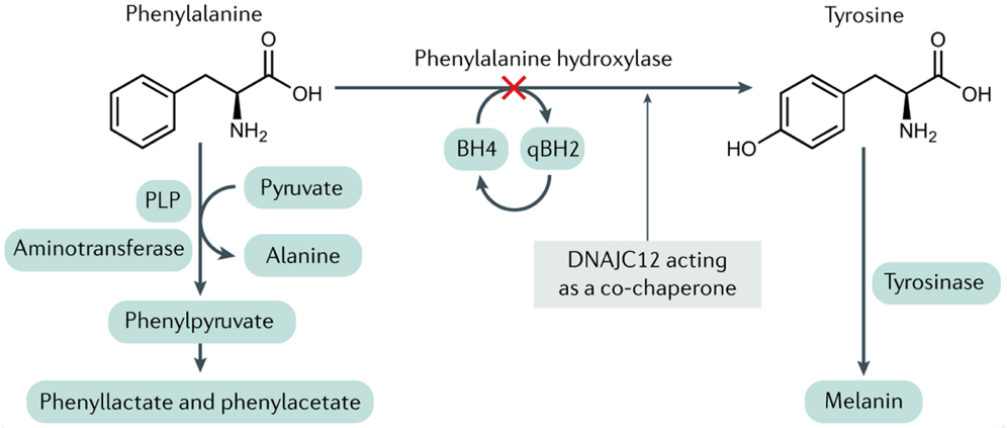

Figure 7: The metabolism of Phenylalanine (25)

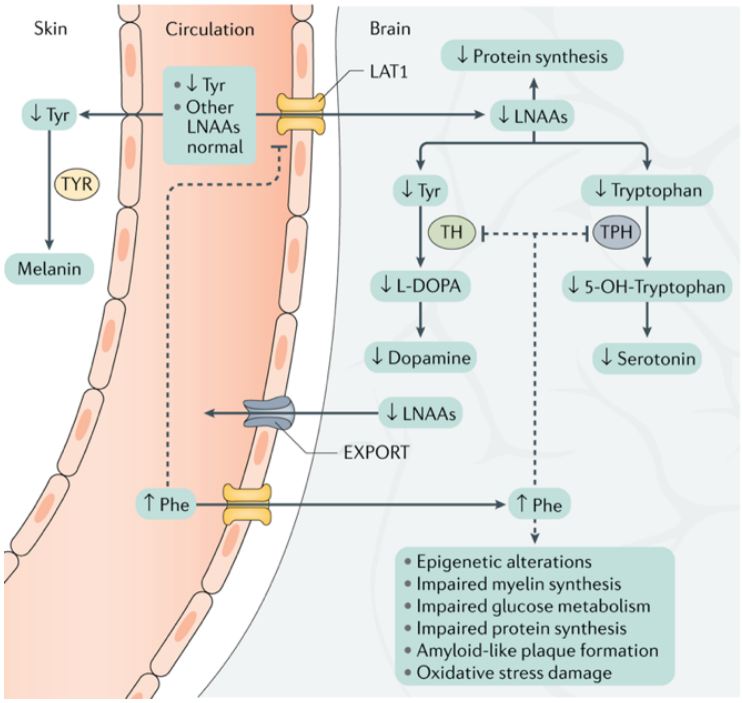

Figure 8: Pathological manifestation in PKU (25)

In the past, the degree of PAH deficiency was categorized by the level of Phe in untreated patients. Since the introduction of NBS, individuals are diagnosed before the peak

concentration of Phe is seized. Currently, PAH deficiency is classified into mild HPA (Phe levels 120-360 μmol/l; no therapy needed) and PKU (Phe levels >360 μmol/l). PKU can be additionally divided into BH4-responsive PKU and BH4-non-responsive PKU. Three biochemical consequences can be described in patients with PAH deficiency: hypotyrosinemia, the buildup of phenylpyruvate and/or associated metabolites, and HPA. Tyrosine levels are usually at the lower normal range as L-Tyrosine is ingested with a normal diet. Organic acids like phenylpyruvate are eliminated via urine and their concentration in tissues is too low to cause clinical effects. High levels are Phenylalanine are considered to be the main neurotoxin causing extensive manifestations of PKU. Patients with untreated PKU develop an intellectual disability, seizures, behavioral, psychiatric, and movement disorders, a musty odor, lighter skin, eye and hair pigmentation, cortical blindness, and dermatitis. Fortunately, immediate treatment initiation after birth can prevent these long-term consequences. Nonetheless, if the patient does not adhere to the treatment plan for a longer period of time, lower limb spasticity, cerebellar ataxia, tremor, brain disorders, and optic disturbances can occur. Despite early treatment initiation and adherence to the treatment plan, the incidence of attention-deficit-hyperactivity disorder and educational problems are higher compared to individuals without PKU. Today, screening for PKU is the prime example of a meaningful and successful newborn screening (25-26).

Therefore, diagnosis usually occurs during the neonatal period. Several laboratory screening methods for the analysis of Phe concentrations are used. BIA and FMA are less expensive methods to screen for only one amino acid. TMS, which is a more expensive approach, allows the concurrent measurement of several amino acids. The use of TMS enables the screening of multiple IMDs from a single drop of blood. The cut-off values for a positive PKU-screening result are a Phe level >120 μmol/l combined with a Phe to Tyr ratio of >1.5. After establishing the diagnosis of HPA, further tests must be conducted to distinguish between the different possible etiologies. With the dried blood spot (DBS) used in the NBS pterins and DHPR activity can be measured (25). PTPS, GTPCH, and PCD can be identified by certain patterns of pterins in urine and/or DBS (26). Alternatively, a 24-hour BH4 loading test can be conducted by giving 20mg/kg of sapropterin dihydrochloride orally. Using a DBS, a baseline Phe concentration is determined, followed by measurements at four, eight, 16, and 24 hours after administration of the loading dose. A decline in Phe concentrations within eight hours is seen in individuals with BH4 defects (PTPS, GTCH, and PCD) and pathogenic variants in DNAJC12. A slower decline in Phe concentrations can be observed in BH4-responsive PKU and DHPR deficiencies. If the Phe concentration is unchanged after the BH4 challenge, the

diagnosis is most likely PAH deficiency. Prenatal testing of BH4 deficiencies can be done by measuring biopterin and neopterin in the amniotic fluid. Currently, the gold standard for the diagnosis of all BH4 deficiencies is molecular analysis (25).

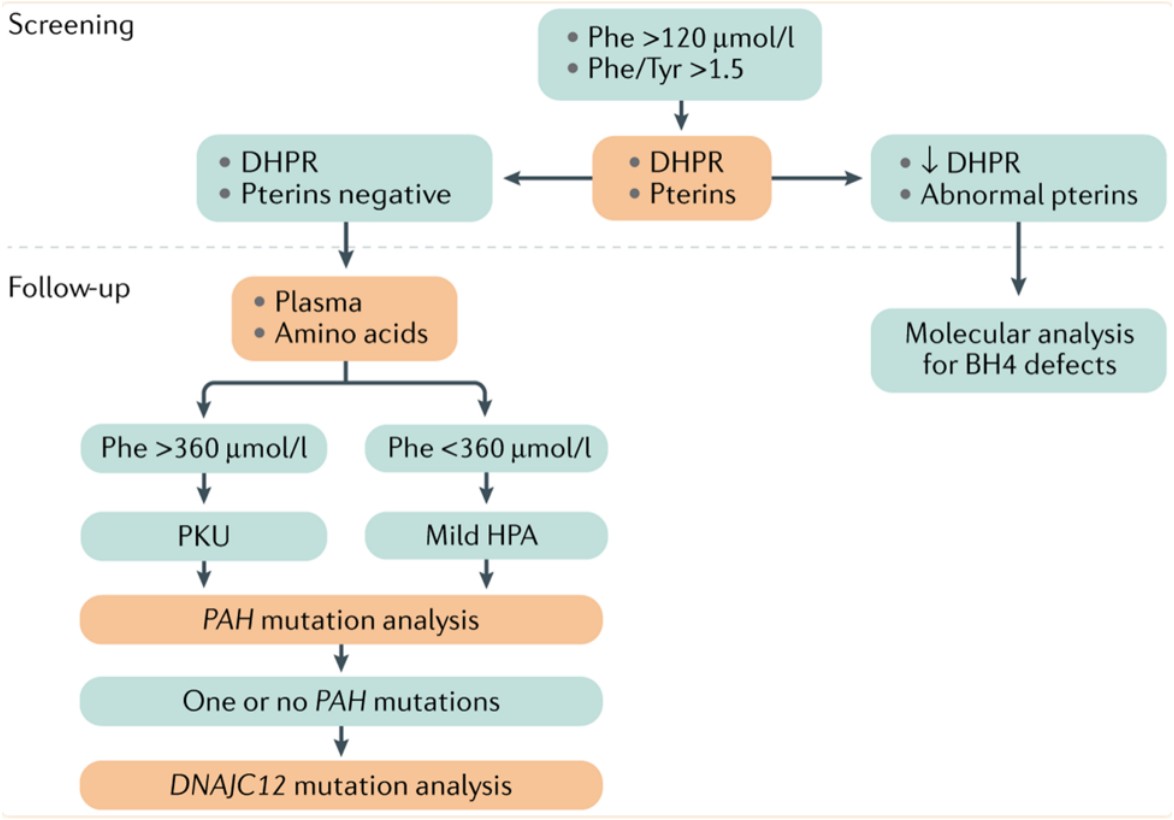

Figure 9: Laboratory diagnosis of BH4 deficiencies and PKU (25)

The mainstay of PKU treatment is dietary management. The fact that Phe is an essential amino acid emphasizes the impact and importance of dietary restriction on the blood Phe concentration. The dietary treatment consists of three main components. Firstly, Phe restriction by reducing the natural protein intake. The effective Phe restriction depends on the need for protein synthesis (depending on age and times of illness) as well as the severity of the enzyme deficiency. Secondly, due to the restricted diet, other amino acids, minerals, vitamins and carnitine are lacking. Therefore, a mixture of amino acids without Phe must be added to the diet. This mixture is especially enriched in micronutrients and Tyr to supplement the Tyr, that would have been produced from Phe. The third and last part of the dietary plan is a low-protein intake. The dietary treatment plan must be tailored to each individual and monitored. Adverse effects of protein and/or Phe restriction include growth retardation, lethargy, alopecia, anorexia, and eczematous lesions(25). The major problems associated with dietary restrictions include the lack of dietary compliance due to unpalatability, persistent neurological and psychosocial problems, nutritional deficiencies, and increased financial burden due to the high cost of food

supplements. Patients with BH4-responsive PKU can be treated with cofactor BH4 supplementation or sapropterin allowing them to loosen their dietary restrictions. Further current and future treatment approaches include large neutral amino acid supplementation, glycomacropeptides, gene therapy, enzyme therapy, and probiotics (27). Since 2018, the FDA approved an injectable pegylated Phe ammonia lyase (pPAL) named pegvaliase. Pegvaliase effectively reduces Phe concentrations, so most patients discontinue dietary restrictions (33).

Untreated or inadequately treated PKU in expecting women shows no risk for the mother but is associated with fetal developmental abnormalities (25). Abnormalities of maternal PKU syndrome include microcephalus, IUGR, hereditary heart defects, facial dysmorphism, and cognitive impairment (27).

The list of differential diagnoses of HPA include increased protein ingestion, prematurity, faulty BH4 metabolism, and hepatic diseases (26).

Early diagnosis and immediate and uninterrupted treatment prevent long-term sequelae. However, the quality of life can be afflicted by the social and psychological burden of being diagnosed with an incurable disease as well as the burden of dietary restriction which affects the patient as well as the family (25).

2.7.**Alpha-1 antitrypsin deficiency (AAT deficiency)**

Alpha-1 antitrypsin deficiency is a rare inherited genetic disorder that is defined by low concentrations of the protein alpha-1 antitrypsin. AAT is made predominantly by hepatocytes and is responsible for the protection of lung tissue by proteolytic enzymes (e.g., neutrophil elastase) (28). AAT deficiency is inherited in an autosomal codominant way and belongs to one of the most common metabolic diseases.

The prevalence in North America is estimated to be 1:5,000 - 7,000 and 1:1,500 – 3,000 in Scandinavian countries (29). Especially in individuals of northern European descent, AATD accounts for one of the leading causes of neonatal hepatitis syndrome (30). SERPINA1 is the gene encoding for the alpha-1 antitrypsin protein and more than 120 mutations have been known at this locus. The normal wild-type allele is M. However, the most frequent forms leading to deficiencies are the S and Z forms (28). S mutations lead to a moderate decrease in alpha-1 antitrypsin whereas Z mutations lead to a severe decrease in the production of alpha-1 antitrypsin. The severity of the disorder depends on the levels of alpha-1-antitrypsin which are, however, affected by the genotype expression. According to the banding pattern, individuals can be classified as PiMM, PiMS, PiSS, PiMZ, PiSZ, or PiZZ. PiMM individuals have normal protein production leading to normal serum concentrations of AAT. PiMS individuals possess

80% of normal serum concentrations. AAT serum levels in patients with PiSS, PiMZ, or PiSZ range from 40-60% of normal serum levels. A severe AAT deficiency can be found in individuals with the genotypic expression PiZZ, which leads to only 10-15 % of normal serum AAT levels (31). Both homozygous and heterozygous forms of the Z allele cause protein misfolding and polymerization which causes accumulation in the ER followed by ER stress, overload response, mitochondrial dysfunction, autophagy, and chronic liver disease. Proteins affected by the S mutation do not form polymers inside the hepatocytes and are associated with intermediate plasma levels and the nonappearance of liver disease. Low levels of AAT lead to the inability to adequately inhibit NE leading to damage to the lung parenchyma and COPD. Symptoms initially mirror other respiratory diseases leading to a high rate of underdiagnosed cases (28).

The most frequent clinical feature in neonates is neonatal hepatitis syndrome, characterized by signs of hepatitis like scleral icterus, jaundice, and enlarged liver and spleen. Laboratory results are highly variable with ALT and AST elevations, normal or high gamma-glutamyl transpeptidase (GGT) and increased conjugated serum bilirubin. In older children, the clinical presentation is very variable including failure to thrive, signs of liver disease, or asymptomatic hepatosplenomegaly. Rarely signs of portal hypertension or acute liver failure can be seen (30). The onset of liver disease in adults may appear without a history of liver diseases. Individuals with AATD and the genotype PI*ZZ are at a higher risk for the development of hepatocellular carcinoma. The risk is a lot higher than usually connected to liver cirrhosis (29). Lung diseases associated with AATD usually do not appear before the patient's 30s. The initial respiratory presentation includes cough, wheezing, and dyspnea, which are neither specific nor pathognomonic for ATDD leading to a high number of underrecognized cases. Smoking is the major driver for the development of pulmonary diseases in individuals with AATD and therefore associated with increased mortality. The respiratory conditions include emphysema, chronic bronchitis, asthma, or a combination. The major cause of death in patients with AATD is related to respiratory diseases. Other extrapulmonary and extrahepatic symptoms can be seen in individuals affected by AATD including panniculitis, ANCA-associated vasculitis, increased risk of gallstone disease, and aneurysmal diseases. The extent of clinical features and the degree of affected organ systems involvement depend on the genotype (32).

Table 8: Genotype-Phenotype Correlation (29)

SERPINA 1 Genotype	Phenotype
PI*MM	- Normal AAT serum concentrations

	- No increased risk of hepatic or pulmonary disorders
PI*MZ	- Non-smokers are not at risk for pulmonary disease - Smokers and individuals with environmental exposure are at higher risk of developing COPD
PI*SS	- No increased risk for clinical disease
PI*SZ	- Not associated with a higher incidence of hepatic and pulmonary involvement - 11% of individuals have AAT levels below threshold
PI*ZZ	- High risk for pulmonary and hepatic disorders - In 95% of patients with clinical features of AATD
PI*FF	- Increased risk for the development of emphysema
PI*null-null	- Complete lack of AAT synthesis - High incidence of developing pulmonary disorder - No higher risk of developing hepatic disease

Patients presenting with chronic obstructive pulmonary disorder and/or liver diseases, C-ANCA positive vasculitis, and necrotizing panniculitis should raise the suspicion of AATD and a further work-up should be initiated (29).

To establish the diagnosis of AATD reduced serum levels of alpha-1 antitrypsin must be found and a pathogenic variant of SERPINA1 or the observation of a defective AAT protein. The most used technique to measure the concentration of AAT in the serum is nephelometry. A physiological serum level of AAT is 100-220 mg/dl (20-53 µmol/L). In AATD serum levels lie below 57 mg/dl. To determine a pathogenic variant in SERPINA1 either comprehensive genomic testing or gene-targeted testing can be used. Single-gene testing or a multigene panel is used when clinical presentation as well as laboratory results indicate the presence of AATD, whereas comprehensive testing is used when the diagnosis of AATD has not been considered. The detection of inadequate AAT protein variants is conducted with a protease inhibitor typing. Clinical indicators for genetic testing include everyone diagnosed with COPD, patients presenting with unexplained bronchiectasis, chronic liver dysfunction, and necrotizing panniculitis, as well as close relatives of persons with abnormal AATD-related gene results (29). Newborn screening is currently not recommended in most countries (except countries with a high prevalence of AATD) (28). To determine the extent of the disease an individual must

undergo an evaluation procedure following the initial diagnosis. To evaluate the pulmonary involvement pulmonary function tests (Spirometry, lung volumes, oxygenation, diffusing capacity) and a CT of the thorax are conducted. A liver biopsy is done to examine the extent of hepatic injury. Furthermore, the skin must be assessed for panniculitis and genetic counseling must be performed (29).

The patients must be informed to avoid certain toxins including smoking, occupational exposure, and the excessive use of alcohol. Symptomatic treatment of the affected organ system depends on disease manifestation. Patients with COPD should receive the current standard COPD therapy. Patients with emphysema can benefit from augmentation therapy including periodic infusions of healthy donor human serum AAT. End-stage lung disease requires lung transplantation. Patients with liver diseases should receive hepatitis A and B vaccination and in severe cases liver transplantation which will restore the AAT levels. For individuals suffering from panniculitis, dapsone or doxycycline therapy as well as augmentation therapy can be used. Several therapies are currently under investigation e.g., inhaled AAT, recombinant AAT, liquid AAT, different doses of augmentation therapy, and oral neutrophil elastase inhibitors. Diagnosed patients with AATD should undergo surveillance examination every 6-12 months including lung function tests, hepatic function tests, and ultrasound, thrombocyte count as well as elastography and MRI (29).

The spectrum of differential diagnosis is broad including acquired infections, congenital anomalies, or hereditary errors of metabolism. The differential diagnosis of lung diseases includes conditions associated with COPD and bronchiectasis. The differential diagnosis associated with neonatal cholestasis includes gestational alloimmune hepatic disease and extrahepatic biliary atresia. Furthermore, acquired disorders involve chronic viral hepatitis, sclerosing cholangitis, primary biliary cholangitis, and steatohepatitis. Genetic disorders include progressive familial intrahepatic cholestasis, Dubin-Johnson syndrome, Wilson disease, cystic fibrosis, juvenile hereditary hemochromatosis, HFE hemochromatosis, Alagille syndrome, and Rotor syndrome (29).

The prognosis and quality of life are highly variable and depend on deficient alleles, genetic polymorphism, and environmental factors. The mainstay in the improvement of prognosis is the early diagnosis and concurrent therapy. Involvement of the respiratory system is the main prognostic factor for AATD patients. Smoking accounts for the most critical risk for fast-progressive COPD. Smokers have a higher risk of developing emphysema, lower diffusing capacity of carbon dioxide, and increased airway blockage and sputum secretion compared to non-smokers. Also, exposure to inhaled irritants correlates with a higher risk for the

development of lung diseases leading to a poorer lung-related outcome. Individuals with severe form of the disease show a decreased life expectancy. Asymptomatic non-smoking patients diagnosed at an early stage can have a normal life expectancy (28).

2.8.Galactosemia

Galactosemia is defined as a group of hereditary defects involved in the metabolism of galactose. Galactose is a component of dairy products (importantly milk, as the prime energy source for infants). The disease is inherited in an autosomal recessively and can be diagnosed with the NBS program (33).

Four types of galactosemia can be differentiated depending on the gene affected. Type 1 galactosemia, the most common out of the four subtypes, is obtained by a mutation of the GALT gene on the 9p13.3 location causing a lower or absent activity of the GALT enzyme. According to the amount of residual enzyme activity, type 1 galactosemia can be further subclassified into classical galactosemia (GALT activity <1%), clinical variant (GALT activity 10-15%), and biochemical variant (GALT activity <25%). Type 2 galactosemia results from an anomaly in the GALK1 gene positioned on chromosome 17q25.1 causing a deficiency of galactokinase or an anomaly in the GALK2 gene located on chromosome 15q21 coding for N-acetylgalactosamine kinase. Type 3 galactokinase is caused by a mutation in the GALE gene found on chromosome 1p36 generating a deficiency of UDP-galactose 4'-epimerase. The very rare type 4 galactokinase has been recently identified in Japan and is caused by a mutation in the GALM gene found on 2p22.1 leading to a deficiency of galactose mutarotase. Galactosemia occurs due to a disturbance in any of the steps during the galactose metabolism by a deficient enzyme. Figure 10 shows the Leloir pathway pointing out the reactions catalyzed by any of the four previously mentioned enzymes. A disruption at any level of the Leloir pathway eventually causes a buildup of galactose intracellularly which further activates alternative pathways of galactose degradation. However, the alternative pathways increase to the assembly of galactitol and D-galactonate. Excess galactose enters the polyol pathway which is then reduced to galactitol. Due to the fact, that galactitol cannot be further metabolized, it accumulates inside the cell and causes hyperosmotic and oxidative stress. D-galactonate can either be eliminated by the kidneys or takes part in the pentose phosphate pathway causing to the production of D-xylose. Finally, GALT deficiency also leads to the accumulation of galactose-1phosphate which activates the pyrophosphorylase pathway. All mentioned alternative pathways lead to an increase in oxidative stress, ER stress, defective glycosylation, and modified signaling pathways. (33)

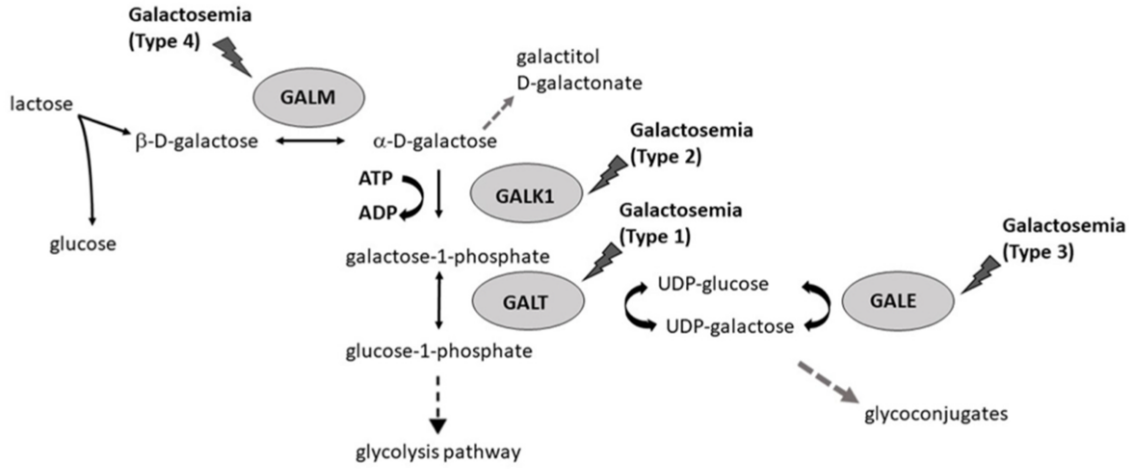

Figure 10: Leloir pathway and an associated reaction that can be disrupted by enzyme deficiencies (33)

The incidence of Type 1 galactosemia is 1:47,000 in the Caucasian population and 1:60,000 in the general population. Type 2 galactosemia has an incidence of 1:100,000 cases in Caucasian people (33). The prevalence of Type 3 Galactosemia is about 1:6,700 in African Americans and 1:70,000 in Americans and Europeans (34). The incidence of the rare Type 4 galactosemia is approximated to be 1:228,411 in the general population, 1:80,747 in the Japanese natives, and 1:10,388 in the African natives (35).

Type 1 galactosemia is the most severe type of galactosemia, whereas the other subtypes have a mild or asymptomatic course of the disease. Symptoms of Type 1 Galactosemia include inadequate feeding, emesis, diarrhea, jaundice, hepatomegaly, cataracts, developmental delay, hypoglycemia, and an increased risk of E. coli sepsis (especially in newborns). The main symptom of Type 2 Galactosemia is cataracts. Type 3 Galactosemia is most commonly asymptomatic or may possibly present with reduced muscle tone, inadequate feeding, emesis, weight reduction, jaundice, increased hepatic size and dysfunction, and/or cataract (34). Due to the fact, that Type 4 Galactosemia has been recently discovered, not much data concerning symptoms are available. However, the only persistent symptom reported has been cataracts. Other complications have not been documented (35).

According to the ‘international clinical guidelines for the management of classic galactosemia’ the diagnosis of Type 1 galactosemia is based on the GALT enzyme activity measured in the erythrocytes and/or the genetic testing of the GALT gene. In case of suspected galactosemia in infants, dietary restrictions should be initiated without waiting for diagnosis confirmation. After establishing the diagnosis, galactose 1-phosphate has to be calculated after 3 and 9 months of treatment initiation. After that, measurements should be taken at yearly

intervals. In many countries, the calculation of galactose and galactose-1-phosphate has been implemented in the NBS program (36). In cases of NBS results of increased total galactose and normal GALT enzyme activity, other types of Galactosemia should be suspected. In this case, the enzyme activity of GALK, GALE, and GALM should be determined (33,36). Further possible diagnostic tests include urine galactose levels (galactosuria) and total serum bilirubin levels (hyperbilirubinemia) (36).

Dietary restrictions are the mainstay of treatment in the cases of classic galactosemia, GALK deficiency, and GALE deficiency (33). However, treatment of classic galactosemia is only recommended in case the GALT enzyme activity inside the erythrocytes is <10% and/or a pathologic variant on two alleles of has been found (36). The goal is to reduce the galactose intake and lactose from dairy products but to have a small intake of galactose from non-milk dietary products. In neonates, it is recommended to discontinue breastfeeding immediately and start a whey-based infant formula to reduce acute neonatal symptoms. Due to these restrictions, a lack of calcium and vitamin D occurs which has to be supplemented. The biochemically variant is commonly not treated with dietary restriction. So far type 4 galactosemia has been reported in 10 individuals which leads to a treatment decision on a case-to-case basis. However, regardless of the dietary approach chosen, individuals with classic galactosemia are nevertheless at risk for long-term complications. Several treatment approaches including gene-based treatment, pharmaceutical chaperones, enzyme inhibitors, and ER stress-reducing substances are under investigation to decrease the risk of long-term complications (33).

The list of differential diagnoses includes hepatic dysfunction and failure, Fanconi-Bickel syndrome, portosystemic venous shunting, hepatic arteriovenous shunting, and congenital disorders of glycosylation type 1T (34). Galactosemia, especially Type 1, is commonly associated with long-term complications, even with dietary restrictions and early diagnosis. Long-term impacts include cognitive disability, delayed speech, motor impairment, emotional disorders, fertility issues, cataracts, and bone diseases. (33)

2.9.Von Gierke Disease

Von Gierke disease belongs to the class of glycogen storage disorders which impact glycogen metabolism. Over 12 subtypes are known, out of which, von Gierke disease is the most common subtype. Other names for this disorder are glycogen storage disease type I (GSD-I), Glucose-6-phosphatase deficiency, and hepatorenal glycogenosis. According to the irregularity in the G6Pase system, von Gierke disease can be further divided into 4 types (Ia,

Ib,Ic,Id). Defects in the catalytic unit of the G6Pase system in the endoplasmic reticulum cause type Ia. A deficiency in the G6P transporter leads to type Ib. Defects in the liver microsomal transport of phosphate cause type Ic and defects in the liver microsomal transport of glucose cause subtype Id (37). Due to the fact, that over 80% of the cases account for a glucose-6-phosphatase deficiency (type Ia) this section will focus on GSD-Ia (38).

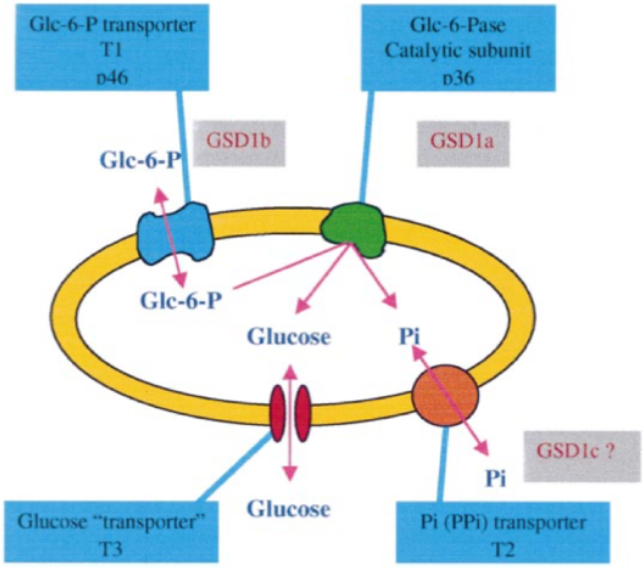

Figure 11: Substrate-transport model (Arion's model) (39)

The worldwide incidence of glycogen storage diseases accounts for 1:20,000 – 30,000 live births. The prevalence of von Gierke disease is between 1:100,000 and 1:400,000 live birth in the Caucasian population and a prevalence of 1:20,000 in the Ashkenazi Jews population. The age of onset is usually during infancy or childhood (37). GSD-Ia results from a mutation in the G6PC gene located on 17q21. This gene is encoding the catalytic unit of the G6Pase system. Glucose-6-phosphate translocase (G6Pase) is mostly found in the kidneys, liver, and alimentary tract and is responsible for the transport of glucose-6-phosphate into the ER. This represents the last step of glycogenolysis and gluconeogenesis. Failure of this process leads to glycogen accumulation in the kidneys, liver, and intestinal mucosa (40).

In newborns, the initial symptoms include hypoglycemia unresponsive to glycogen administration, irritability, hyperventilation, tremors, apnea, convolutions, cyanosis, brain edema/dysfunction, sweating, coma, and death. Later on, patients show doll-like facial characteristics, apathy, difficulty awakening from sleep, devastating hunger, tremors, growth restriction, protrusive abdomen, diarrhea, and lean extremities. An impaired platelet function leads to a bleeding tendency, commonly seen as nose bleeding. Rickets and anemia can

manifest during middle childhood. On physical examination, the examiner may find an abdominal protuberance caused by massive hepatomegaly, renomegaly, poor growth, short stature, and rachitic changes. Hepatomegaly and renomegaly account for the accumulation of glycogen in the organs. On laboratory analysis hypoglycemia, lactic acidosis, hyperlipidemia (especially triglycerides leading to doll-like facies), hyperuricemia, and slightly elevated transaminases can be seen. Upon clinical and biochemical suspicion of von Gierke disease, the definitive diagnosis can be made by a hepatic biopsy, enzyme assay, or mutation testing. A biomarker is plasma α-hydroxyisobutyrate, which cannot be found in healthy individuals (37). Upon a liver biopsy, the hepatic activity of glucose-6-phosphatase can be determined. Genetic testing includes the identification of pathogenic variants in G6PC1 (40).

The treatment aims to avoid phases of hypoglycemia. Nutritional measures include the intake of glucose or frequent consumption of uncooked cornstarch (UCCS) as well as nocturnal intragastric feeding. The intake of lactose, fructose, and sucrose should be minimized. Adherence to nutritional measures reduces the risk of the development of long-term complications (37). Calcium, Vitamin D, and minerals including iron and zinc have to be supplemented due to lack of quantity in cornstarch and further dietary restrictions (41). Medical therapy includes allopurinol in cases of hyperuricemia, bicarbonate or potassium citrate in acidosis, angiotensin-converting enzyme inhibitors can be used to prevent renal function deterioration, triglyceride-lowering drugs in cases of high triglyceride levels, and statins to reduce the levels of cholesterol (37). Percutaneous ethanol injection, radiofrequency ablation, or surgery can be initially used in the treatment of adenomas (41). Liver and renal transplantation correct liver and kidney-related abnormalities, respectively. Hepatocyte transplantation and G6Pase in viral vectors are treatment options under investigation (37).

The list of differential diagnoses includes debranching enzyme deficiencies, Glycerol kinase deficiency, fructose-1,6-bisphosphatase deficiency, Gaucher disease, chronic visceral ASMD (Niemann-Pick disease type B), Hepatic glycogen synthase deficiency (GSD 0), Liver phosphorylase kinase deficiency (GSD IX), and GLUT2 deficiency (GSD XI) (41).

Long-term sequela of ineffectively treated GSD-Ia include liver adenomas, kidney dysfunction, nephrolithiasis, osteoporosis, urarthritis, xanthomas, pancreatitis, and gallstones. Renal disturbances can advance to end-stage renal disease. Hepatic adenomas have the potential to malignant transformation. Repetitive episodes of hypoglycemia may also lead to brain damage. However, early diagnosis has improved the prognosis (37).

2.10. Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency

MCAD deficiency belongs to the commonest mitochondrial fatty acid β-oxidation diseases. The deficiency leads to an impaired catabolism of medium-chain fatty acids. Consequently, fatty acids cannot be used as an alternative pathway for obtaining energy. The disorder is inherited in an autosomal recessively (42).

The prevalence in North America and Northern Europe varies from 1:5,000 to 1:20,000. However, depending on location, disease prevalence can vary. In 80% of the cases the disease is due to a mutation (985 A→G) in the ACADM gene (42). During a period of long fasting and/or increased energy needs, energy can be acquired by fatty acid oxygenation to provide glucose for the brain. MCAD is an enzyme of the mitochondrial fatty acids β-oxidation required for the production of energy and acetyl-CoA. The lack of the aforementioned enzyme results in a deteriorated ketogenesis leading to the appearance of symptoms and finally death upon depletion of glycogen storage (43).

In phases of acute stress, individuals with MCAD deficiency are unable to produce ketone bodies as a source of energy leading to hypoketotic hypoglycemia. Due to a lack of MCAD, medium-chain fatty acids cannot be broken down to acetyl-CoA leading to an buildup of fatty acyl-CoA (42).

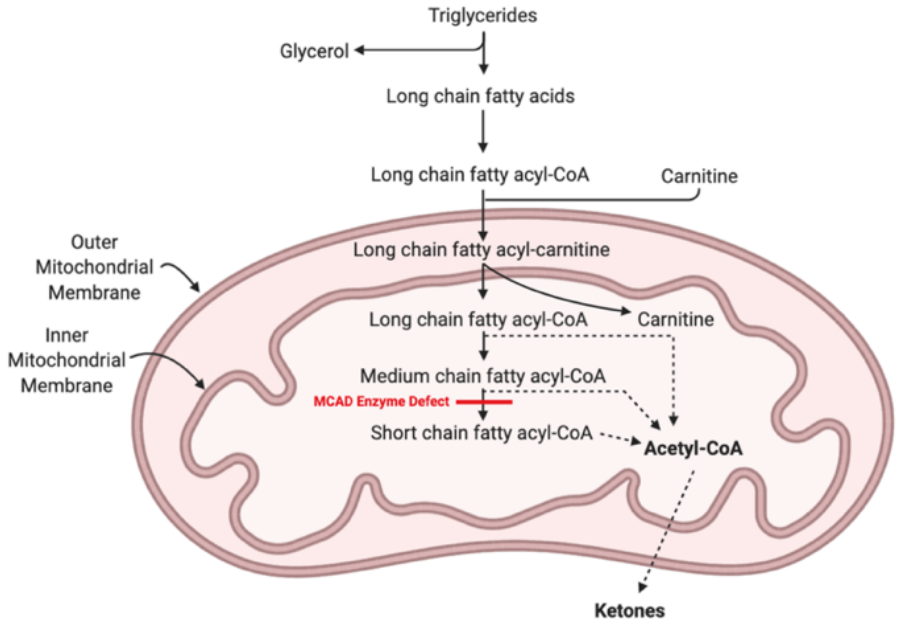

Figure 12: Fatty acid β-oxidation metabolic pathway with MCAD enzyme defect (44)

Symptoms usually occur during the 3rd and 15th month of life although the occurrence of acute metabolic crisis has decreased due to established newborn screening. The symptoms

include dehydration, poor feeding, vomiting, and an altered mental status. CNS symptoms include seizures, lethargy, coma, and hypotonia. An acute initial crisis can lead to death in about 20% of affected individuals (42). Liver diseases are commonly associated with MCADD ranging from periods of hypoketotic hypoglycemia up to Reye-like symptoms (hypoketotic hypoglycemia, liver encephalopathy, enlarged liver, hyperammonemia, microvascular hepatic steatosis, liver failure) (45). Hypoketotic hypoglycemia commonly occurs after prolonged fasting or infections which lead to decreased appetite and higher energy needs (49). Upon physical examination, hepatomegaly may be seen (42). Hepatic disorders can be further seen by the presentation of jaundice, pale stools, and cholestasis (45).

MCAD is included in the newborn screening. Further evaluation usually occurs after a positive screening result by showing increased levels of C6-, C8- and C10-acylcarnitine values with C8 being predominately elevated in 985A→G mutations. Further evaluation includes urine organic acid analysis, plasma acylcarnitine profiling, plasma free and total carnitine levels, and genetic testing of the ACADM gene mutations (42-43). Typically, hexanoyl glycine is increased to a greater degree than octanoyl glycine which is increased to a greater degree than decanoyl glycine. Suberyl glycine and dicarboxylic acids might be increased in acute events and act as a further biomarker of MCAD deficiency. The second indication for MCAD deficiency testing is in initially healthy patients who show clinical and laboratory findings indicative of MCAD deficiency. Laboratory findings suggestive of MCAD include hypoglycemia, low levels of ketones in urine and blood, increased concentrations of ammonia and uric acid in the blood, metabolic acidosis, and elevated liver enzymes. The last indication for diagnostic evaluation is in patients with a sudden death showing symptoms 2 days before the unexpected death (43).

The mainstay of the treatment protocol for MCAD deficiency is to avoid hypoglycemia and reverse catabolism. This is achieved by administering oral carbohydrates or intravenous fluids. Additionally, every patient should be provided with an emergency letter which includes a detailed protocol of treatment procedure in cases of acute illness. To prevent hypoglycemia the periods of fasting should be reduced. In asymptomatic patients, without any signs of infections or other stressful events, the longest fasting time should not exceed 8 hours in infants age 6 and 12 months, 10 hours from 13 to 24 months, and 12 hours after the age of 24 months. Following, to reduce fasting, children should receive repeated periodic feedings, overnight feedings, evening snacks, or 2g/kg UCCS. Fats as an energy resource should not exceed 30 % of total energy. The use of L-carnitine supplementation has been disputed. In times of acute stress (e.g., infections, vomiting, diarrhea, surgery) the caloric needs are increased whereas the intake is

often limited. During these times, patients should receive more frequent caloric intake. If oral intake is insufficient and/or physical and mental status changes appear intravenous treatment with dextrose should be initiated. Alternatively, glucose can be administered to increase glucose levels above 5 mmol/L (43).

The list of differential diagnoses includes other fatty acid β-oxidation defects, organic acidurias, disorders in ketogenesis, respiratory chain disorders, urea cycle defects and other inherited disorders of carbohydrate metabolism. Diseases of fatty acid β-oxidation include MADD, VLCAD deficiency, SCAD deficiency, LCHAD deficiency and trifunctional protein (TFP) deficiency and disorders belonging to the carnitine transport disorders (systemic primary carnitine deficiency, carnitine palmitoyltransferase 1A/II deficiency, and carnitine-acylcarnitine translocase deficiency) (43).

The disease has a good prognosis if the diagnosis is established early and early treatment initiation. If management has been initiated, the mortality and morbidity rate is decreased to practically zero. However, in patients with undiagnosed disease or disease without initiation or adherence to treatment, the disease ends up lethal in 25% of cases. The quality of life can be impaired by several complications of physical activity, cardiac problems like arrhythmias, neurological complications related to encephalopathy as well as liver-related disorders like steatosis (42,45).

3. Conclusion

This paper gives an overview on the most common inherited metabolic diseases. The introduction of the NBS program in the 1960s set a big step in the diagnostic process, however, there is still potential for improvement of diagnostic and therapeutic possibilities. Furthermore, the presence of adequate treatment options and presence of a diagnostic tool has an impact on the implementation of disorders into national screening programs and therefore the early recognition of a disease. In the appendix, the reader may find tables categorizing and summarizing other rare inherited metabolic diseases caused by enzyme deficiencies.

All in all, this overview on the IEMs caused by enzyme deficiencies depicts

a. The importance of the introduction of NBS and the associated early therapy in order to prevent long-term sequela.
b. The variety of diseases with the same/similar symptoms.
c. A list of differential diagnoses, which should be considered in case of non-specific symptoms.

Due to the rarity of many diseases, this area still has the potential for further research and the development of new treatment options.

4. Summary

Inherited metabolic diseases are rare and enzyme-dependent conditions, mostly passed on in an autosomal-recessive manner, and are based on genetic mutations. Each country has its own spectrum of diseases that can/must be tested before and/or after birth. Additionally to metabolic conditions, newborn screening programs might also include e.g., testing for other conditions like endocrine disorders, blood diseases, hearing loss, and/or cystic fibrosis. Out of the over 500 known diseases, 91 are currently treatable. The variety of possible diseases, their rarity, as well as the non-specific symptoms often pose a challenge for medical staff to make a diagnosis. Sensitization of the medical staff to the possible occurrence of such a disease is important. The geographical and ethical distribution can vary greatly. Therapy includes symptomatic treatment, changes in diet, as well as medical and/or interventional procedures. unfortunately, the diseases are mostly not curable, the therapy options are limited and therefore the overall quality of life is often reduced.

Keywords: Autosomal-Recessive, Inherited metabolic diseases, Newborn Screening Program

5. List of rare inherited metabolic diseases

5.1. Amino Acid Disorders

In this chapter conditions belonging to the group of amino acid disorders are listed. Table 9 includes the deficient enzyme, clinical presentation, frequency, and treatment options for each condition. As Maple Syrup Urine disease and Phenylketonuria belong to the more common metabolic diseases caused by enzyme deficiencies, they are discussed in more detail in chapters 2.2 and 2.6 respectively.

Table 9: Amino Acid Disorders

Condition	Deficient Enzyme	Clinical Presentation	Frequency	Treatment Options
Maple Syrup Urine disease				
Phenylketonuria (PKU)				
Homocystinuria/ Methylene Tetrahydrofolate Reductase (MTHFR) deficiency (1,2)	Cystathionine beta-synthase	- Dislocation of lens - Thrombophilia - Osteoporosis - Marfan-like appearance - Developmental Delay	1:200,000	- Methionine restriction - Vitamin B6 and CBS gene therapy
Tyrosinemia type II (2)	Tyrosine Aminotransferase	- Developmental delay - Intellectual disability	1:250,000	- Omega-3 fatty acid supplementation

Primary Pyruvate Dehydrogenase (PDH) Complex Deficiency (2,46)	Pyruvate dehydrogenase E1-alpha (76% - 85%)	Neurological symptoms - Developmental delay - Hypotonia (axial) - Epilepsy - Hypertonia (appendicular) - Ataxia - Peripheral neuropathy - Dystonia - Spasticity - Dyskinesia - Hemiplegia or episodic limb paralysis Facial symptoms - Elongated philtrum - Lean upper lip - Low ears Ophthalmologic findings - Optic atrophy - Nystagmus	Incidence unknown	- Ketogenic diet during - Thiamine supplementation - Physical therapy - Occupational therapy - Anti-seizure medication

		- Ptosis or ophthalmoplegia - Strabismus Growth - IUGR - Reduced length of long bones - Microcephaly Musculo-skeletal Symptoms - Hip dysplasia Psychological symptoms - Acoustic hallucinations - Illusory thoughts		

5.2.Fatty Acid Oxidation Disorders (FAOD)

In this chapter conditions belonging to the group of Fatty Acid Oxidation Disorders are listed. Table 10 includes the deficient enzyme, clinical presentation, frequency, and treatment options for each condition. As MCAD deficiency belongs to the more frequent inherited metabolic diseases caused by enzyme deficiencies, this condition is discussed in more detail in Chapter 2.10.

Table 10: Fatty acid oxidization disorders

Condition	Deficient Enzyme	Clinical Presentation	Frequency	Treatment Options
Carnitine Transport System Disorders				
1) Carnitine-Acylcarnitine translocase (CACT) deficiency (45,47)	Carnitine-Acylcarnitine Translocase	Severe Neonatal Form - Feeding difficulties - Hypotonia - Lethargy - Cardiac arrhythmias - Cardiomyopathy - Hypoketotic hypoglycemia - Hyperammonemia - Transaminitis - Liver dysfunction and hepatomegaly - Rhabdomyolysis - Seizures - Renal abnormalities - Developmental delay	1:750,000 – 1:2,000,000	Daily treatment - High carbohydrate intake - Fat restriction (30% or less than total caloric value) - Avoidance of fasting - MCT oil or triheptanoin - Carnitine supplementation - Physical and occupational therapy Emergency treatment - High carbohydrate feeding - Reduced fasting times - High-energy fluids with electrolytes - Treatment of cardiac and renal complications

		- Intellectual disability Later-Onset Form - Hypoketotic Hypoglycemia - Cardiac problems - Respiratory problems - Hyperammonemia - Elevated transaminases - HyperCKemia - Metabolic acidosis &/or lactic acidosis		
2) Carnitine palmitoyl transferase (CPT) I/ II deficiency (45,48,49)	Carnitine palmitoyl transferase I/ II	<u>CPT I</u> Fetal CPT1A deficiency - Underlying febrile or gastrointestinal illness - Acute fatty liver of pregnancy - Obstetric complications	1:750,000 – 1:2,000,000	CPT I and II - High carbohydrate and low-fat diet - Carnitine substitution - Glucose infusion during phases of stress - Frequent meals - Hydration

		Hepatic encephalopathy - hepatic encephalopathy - hypoglycemia - rapid-onset hepatic failure <u>CPT II</u> Lethal neonatal form - Episodic hepatic failure - Arrhythmias - Convulsions or coma subsequent to stress/ disease - Facial/anatomical anomalies - Cardiomyopathy Severe infantile hepatocardiomuscular form - Hepatic deterioration - Myocardiopathy		- Obviate general anesthesia, valproic acid, diazepam and ibuprofen (hepatotoxic agents)

		- Convolutions - Hypoketotic hypoglycemia - Peripheral myopathy - Enteralgia - Cephalgia Myopathic form - recurrent myalgia and myoglobinuria after exercise, fasting or other stressors - weakness - absence of myopathy		
Short-chain acyl-CoA dehydrogenase deficiency (50)	Short-chain acyl-CoA dehydrogenase (SCAD)	- Biochemical phenotype - Dysmorphic characteristics - Poor feeding - Developmental delay - Metabolic acidosis	1:35,000 – 1:50,000	Mostly no need for treatment or dietary restrictions

		- Ketotic low blood sugar - Lethargy - Convolutions - Decreased muscle tone - Dystonia - Myopathy - Asymptomatic		
Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency				
Long-Chain Fatty Acid Oxygenation Disorders (LC-FAOD)				
1) Very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency (45,51)	Very long-chain acyl-coenzyme A dehydrogenase	- Left ventricular wall hypertrophy - Pericardial Effusion - Reye-like symptoms - Liver Encephalopathy	1:85,000	Daily Management - Formula low in fats - Entire protein intake greater than dietary reference intake at certain age

		- Microvascular hepatic steatosis - Hypoketotic Hypoglycemia - Sudden Death - Hepatic Dysfunction, - Adrenergic signs - Myalgia - Hypotonia - Exercise Intolerance - Myoglobinuria - Rhabdomyolysis - Intellectual Disability - Chronic End-stage kidney disease - Renal Cysts and Fibrosis - Chronic infection - Excessive immune reaction		- Supplementation of MCT oil or triheptanoin, carnitine, arachidonic acid, linoleic acid, docosahexaenoic acid, and α-linolenic acid - Repeated periodic feeding - Bedtime snack - NGT feeding - Avoidance of severe exercise - Address cardiomyopathy and developmental delay Emergency treatment - High carbohydrate feeding - Reduced fasting times - Antipyretics - Antiemetics - High-energy fluids with electrolytes - Avoid L-carnitine and Intravenous lipids - Treatment of cardiac failure

				Rhabdomyolysis - Ample hydration - Urine alkalization
2) Long chain L-3 hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency (45,52)	Long chain L-3 hydroxyacyl-CoA dehydrogenase	- Severe-to-intermediate phenotype - Left ventricular wall hypertrophy - Pericardial Effusion - Reye-like symptoms - Liver Encephalopathy - Microvascular hepatic steatosis - Hypoketotic Hypoglycemia - Liver Dysfunction, - Lethargy - Convolutions - Apnea - Myalgia	1:250,000 – 1:750,000	Daily Treatment - Frequent feeding - Decreased feeding intervals - Higher carbohydrate intake during illness - Overnight feeding - MCT or triheptanoin supplementation - Carnitine supplementation - Low-fat diet - Feeding therapy or gastrostomy Emergency Treatment - Antipyretics - Antiemetics - Intravenous glucose - Bicarbonate therapy - Management of complications

		- Hypotonia - Exercise Intolerance - Myoglobinuria - Rhabdomyolysis - Intellectual Disability - Retinopathy		
3) Tri-Functional Protein (TFP) Deficiency (45,52)	a) Long chain L-3 hydroxyacyl-CoA dehydrogenase b) Long-chain enoyl-CoA hydratase c) Long-chain 3-ketoacyl-CoA thiolase	- Severe-to-mild phenotype - Left ventricular wall hypertrophy - Pericardial Effusion - Reye-like symptoms - Liver Encephalopathy and microvascular steatosis - Hypoketotic Hypoglycemia - Sudden Death - Liver Dysfunction - Lethargy - Convolutions	1:250,000 – 1:750,000	Daily Treatment - Frequent feeding - Decreased feeding intervals - Higher carbohydrate intake during illness - Overnight feeding - MCT or triheptanoin supplementation - Carnitine supplementation - Low-fat diet - Feeding therapy or gastrostomy Emergency Treatment - Antipyretics - Antiemetics - Intravenous glucose

		- Apnea - Myalgia - Hypotonia - Exercise Intolerance - Myoglobinuria - Rhabdomyolysis - Intellectual Disability - Retinopathy - Lund diseases and respiratory distress		- Bicarbonate therapy Management of complications

5.3.Organic Acidemias

In this chapter conditions belonging to the group of Organic Acidemias are listed. Table 11 includes the deficient enzyme, clinical presentation, frequency, and treatment options for each condition.

Table 11: Organic Acidemias

Condition	Deficient Enzyme	Clinical Presentation	Frequency	Treatment Options
Propionic Acidemia (PA) (1,53)	Propionyl-CoA carboxylase	Neonatal-onset PA - Inadequate feeding - Vomiting	Incidence varies worldwide	Dietary treatment - Controlled intake of propiogenic substances

		- Hypotonia - Progressive encephalopathy - Seizures - Lethargy - Coma - Cardiorespiratory failure Late-onset PA - Asymptomatic until metabolic crisis due to stressors - Vomiting - Recurrent alimentary tract disorders - Protein intolerance - Psychosis - Reduced muscle tone - Global developmental dealy	- 1:105,000 – 1:130,000 in the US - 1:166,000 in Italy - 1:250,000 in Germany - 1:20,000 – 1:45,000 in United Arab Emirates - 1:28,000 in Saudi Arabia - 1:2,000-1:5,000 in some Saudi tribes - 1:465,000 in Japan - 1:1,000 among Greenlandic Inuits	- Increased caloric intake during illness - Gastrostomy Tube - Levocarnitine - Antimicrobial therapy - Biotin supplementation Emergency Treatment - Treatment of precipitating factors (e.g., infection dehydration, vomiting, pain) - Intravenous glucose and lipids - Intravenous carnitine - Reduce propiogenic precursors - Pharmacological detoxification (e.g., Nitrogen scavenger) - Extracorporal detoxification Frequent metabolic decompensations - Orthotropic liver transplantation

		Long-term consequences of Neonatal-onset and Late-onset PA - Global developmental dealy - Convolutions - Pancreatitis - Chronic renal failure - Optic atrophy - Hearing loss - Basal ganglia lesions - Premature ovarian insufficiency - Cardiomyopathy		
Isovaleric Acidemia (IVA) (1,54)	Isovaleryl-CoA dehydrogenase	Acute Neonatal Form - Nonspecific symptoms - Poor feeding - Vomiting - Dehydration - Lethargy	Incidence varies worldwide - 1:67,000 in Germany - 1:660,000 in Taiwan	Daily treatment - Protein and leucine intake restriction - L-carnitine and L-glycine supplementation During Intercurrent illness - Anabolizing measures

		- Seizures - Metabolic acidosis - Hyperammonemia - Hyperglycemia or hypoglycemia - "Sweaty feet" odor - Coma - Death Chronic intermittent form - Often associated with precipitating factors (e.g., infections) - Vomiting - Metabolic acidosis - Developmental and cognitive delay - Feeding difficulties - Failure to thrive - Seizures - Pancreatitis - Liver fibrosis	- 1:105,000 in Portugal - 1:775,600 in unscreened population and 1:230,750 in screened population in Australia	- Momentary decrease of protein intake (acute phase) - Increased L-carnitine and L-glycine supplementation Acute neonatal hyperammonemia - N-carbaglutamate

		- Optic nerve atrophy		
(Isolated) Methylmalonic Acidemia (MMA) (1, 55)	Methylmalonyl-CoA mutase or MUT coenzyme adenosylcobalamin	Main Symptoms - Acidosis - Ketosis - Hyperammonemia - Hypoglycemia or hyperglycemia - Neutropenia Secondary Complications - Developmental delay - Tubulointerstitial nephritis - Progressive renal failure - "Metabolic stroke" - Movement disorders (e.g., choreoathetosis, dystonia, para/quadriparesis) - Pancreatitis - Growth failure	Incidence varies worldwide - 1:50,000 in Japan - 1:250,000 in Germany - 1:85,000 in Taiwan	Initial Treatment - Reduce protein intake - Intravenous glucose - L-carnitine, hydroxocobalamin, biotin, sodium phenylbutyrate, L-arginine-Hcl and N-carbamyl-glutamate supplementation depending on case Long-term management - L-carnitine supplementation - Antibiotics - Vitamin B12 (in responsive patients) - Reduced protein intake - Precursor-free amino acid supplementation - Valine and Isoleucine supplementation - Mineral and vitamin supplementation

		- Functional immune impairment - Optic nerve atrophy		- Use of certain amino acid formulas - Liver and/or kidney transplantation - Viral gene therapy (under investigation)
Holocarboxylase Synthetase (HCLS) Deficiency (1,56)	Holocarboxylase synthetase	- Vomiting - Convolutions - Hyperammonemia - Failure to thrive - Dermatitis - Metabolic ketolactic acidosis - Baldness - Reduced muscle tone - Brain edema - Coma - death	1:200,000	- free biotin supplementation
Glutaric Acidemia Type I (GA-1) (1,57)	Glutaryl-CoA dehydrogenase	Infantile-onset GA-1 - Macrocephaly	1:30,000 – 1:110,000	- Diet low in lysine - Supplementation with carnitine

		- Acute encephalopathic crisis - Progressive neurological movement disorders - Subdural hemorrhage - Seizures - Infantile spasm Late-onset GA-1 - Chronic headache - Macrocephaly - Seizures - Tremor - Dementia - Peripheral neuropathy - Brain neoplasm Non-neurological features regardless of age of onset - Chronic kidney disease		- Emergency treatment during encephalopathic crisis

3-methylcrotonyl-CoA carboxylase deficiency (1,58,59)	3-methylcrotonyl-CoA carboxylase	- Very heterogenic phenotype - <10% of affected patients Neonatal onset - Global developmental delay - Hypotonia - Seizures - Poor feeding - Emesis - Dysentery - Dyskinesia - Apnea - Increased reflexes - Acute metabolic crisis Asymptomatic adult form	1:2,400 – 1:68,000 (Most frequent organic acidemia)	- Oral L-carnitine supplements - Modest leucine restriction
Beta-ketothiolase deficiency (1, 60)	2-methylacetoacetyl-coenzyme A	- Asymptomatic Acute metabolic decompensation	250 confirmed cases worldwide	Dietary treatment - Low isoleucine diet - Low-protein diet - Avoidance of fasting

	thiolase (beta-kethothiolase)	- Severe metabolic acidosis - Ketosis - Impaired vigilance - Metabolic stroke - Hypo- or hyperglycemia - Increased transaminases - Secondary carnitine deficiency - Hyperammonemia Chronic neurological symptoms - Developmental Delay - Convolutions - Hyporeflexia - Movement disorders and diminished motor skills - Hypotonia		- Oral carnitine supplementation

		- Nystagmus		

5.4.Urea Cycle Disorders

In this chapter conditions belonging to the group of Urea Cycle Disorders are listed. Table 12 includes the deficient enzyme, clinical presentation, frequency, and treatment options for each condition.

Table 12: Urea Cycle Disorders

Condition	Deficient Enzyme	Clinical Presentation	Frequency	Treatment Options
N-acetylglutamate synthase (NAGS) deficiency (61,62)	N-acetyl glutamate synthetase	- Asymptomatic - Poor feeding - Tachypnea - Changed level of consciousness - Seizures - Diarrhea - Vomiting - Lethargy - Hypotonia - Hepatomegaly - Coma - Anorexia - Respiratory distress	<1:2,000,000	ERT

		- Learning difficulties - Attention deficit - Headache		
Carbamoylphosphate synthetase (CPS) I deficiency (61)	Carbamoylphosphate synthetase I	- Poor feeding - Hypothermia - Changed level of consciousness (somnolence, lethargy, coma) - Encephalopathy (cerebral edema) - Abnormal posture - Seizures - Hyperventilation leading to respiratory alkalosis - Hypoventilation (later stage)	1:1,300,000	ERT with N-carbamylglutamate

Ornithine transcarbamylase (OTC) deficiency (61,63)	Ornithine carbamoyltransferase	Newborn (male) - Poor feeding - Acute neonatal encephalopathy (brain edema) - Hypothermia - Hyperventilation leading to respiratory alkalosis - Neuropsychological complications Child, adolescent, or adult (both genders) - Encephalopathic or psychotic episodes - Disease exacerbation after stressor - Recurrent vomiting - Reye-like symptoms - Migraine headache - Seizures	1:56,500	Acute Phase - Ammonia scavenger - Lowering of plasma ammonia levels - Reversal of catabolism - EEG surveillance Long-Term Treatment - Protein restriction - Nitrogen scavengers - Liver Transplantation - Management of developmental delay - Anti-seizure medication

		- Protein avoidance - Cerebral palsy - Neuropsychological complications		
Citrullinemia type I (ASS1) deficiency (61,64)	Argininosuccinic acid synthetase	Neonatal "classic" Form - Changed level of consciousness - Poor feeding - Emesis - Cerebral ischemic attack - Convolutions - Tachypnea - Increased intracranial pressure - Hypotonia - Neuropsychiatric deficits - Hypertrophic cardiomyopathy (long-term complication)	1:250,000	Supportive Measures Curative Treatment - Liver Transplantation Dietary Treatment - Protein restriction - Natural protein intake - Feeding tube Medication - Nitrogen scavenger therapy - Arginine supplementation - Carnitine supplementation

		- Bilateral cataract (long-term complication) Late-onset “Non-classic” Form - Similar but less severe symptoms as in neonatal form - Changed level of consciousness - Intensive headache - Scotomas - Ataxia - Slurred speech - Hyperventilation and respiratory alkalosis - Abnormal posturing - Liver failure Pregnancy or postpartum related symptoms - Acute hepatic decompensation - Postpartum psychosis		

		Asymptomatic form		
Argininosuccinic (ASL) aciduria (61,65)	Argininosuccinic acid lyase	Neonatal-onset form - Changed level of consciousness - Vomiting - Poor feeding - Hyperventilation and respiratory alkalosis - Seizures - Hepatomegaly - Trichorrhexis nodosa Late-Onset-form - Episodic exacerbation (triggered) - Hepatomegaly, liver fibrosis/cirrhosis - Trichorrhexis nodosa - Hypertension - Hypokalemia - Cognitive impairment	1:218,750	Supportive measures Dietary Treatment - Protein restriction - Salt restriction Medication - Arginine base supplementation - Electrolyte supplementation - Nitrogen scavengers (acute and long-term treatment) - Anti-hypertensives - Dialysis (acute therapy) Surgical Treatment - Liver Transplantation

		- Behavioral problems - Learning disabilities		
Arginase (ARG1) deficiency (61,66)	Arginase-1	- Slow growth (from 1 to 3 years of age) - Microcephaly - Poor feeding - Cognitive Impairment - Not reaching developmental milestones - Seizures - Episodes of hyperammonemia - Postoperative encephalopathy - Liver dysfunction	1:950,000	Supportive Measures Dietary Treatment - Protein restriction - Natural protein intake - Feeding tube Medication - Nitrogen Scavengers - Dialysis - Anti-seizure medication Surgical Treatment - Liver Transplantation
Ornithine translocase (ORNT) deficiency (61,67)	Ornithine translocase	Neonatal form - 8% of cases - Changed level of consciousness	Unknown	Supportive Measures Dietary Treatment - Protein restriction - Natural protein intake

		- Poor feeding - Vomiting - Hyperventilation - Respiratory alkalosis - seizures Infantile, childhood, and adult form - 92% of cases - Neurocognitive problems - Encephalopathy - Chronic liver dysfunction		- Intravenous fluids with dextrose and intralipids Medication - Nitrogen Scavengers - Arginine Supplementation - Citrulline, lysine, creatine, carnitine, supplementation - Anti-seizure medication - Dialysis Surgical Treatment - Liver Transplantation
Citrin deficiency (61,68)	Citrin	Neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD) - Reduced birth weight - Transient intrahepatic cholestasis - Increased liver size	Japan: 1:100,000 – 1:230,000	NICCD - Addition of Vitamin A,D,E and K - Non-dairy formula - MCT-enhanced formula - Zinc supplementation - Liver transplantation

		- Liver dysfunction - Growth restriction - Hemolytic anemia - hypoglycemia Failure to thrive and dyslipidemia caused by citrin deficiency - protein-rich and/or lipid-rich food predilection - carbohydrate-rich food disinclination - growth retardation - low blood sugar levels - pancreatitis - Lethargy - Food aversion - reduced QoL Citrullinemia Type II - recurrent hyperammonemia		FTTDCD - Feeding according to patients' preferences - Sodium pyruvate CTLN2 - Arginine supplementation - sodium pyruvate - Medium chain triglyceride oil - Reduced carbohydrate intake - Increased protein intake - Liver transplantation

		- neuropsychiatric symptoms - history of NICCD or FTTDCD		

5.5.Lysosomal Storage Diseases

In this chapter conditions belonging to the group of LSD are listed. Table 13 includes the deficient enzyme, clinical presentation, frequency, and treatment options for each condition. As Fabry disease, Krabbe disease, Gaucher disease, and Niemann-Pick disease belongs to the more frequent IEM caused by enzyme deficiencies, these conditions are discussed in more detail in chapter 2.1,2.2, 2.4, and 2.5 respectively.

Table 13: Lysosomal Storage Diseases

Condition	Deficient Enzyme	Clinical Presentation	Frequency	Treatment Options
Muccopolysaccharidoses				
1) Hurler Syndrome (MPS I) (69,70)	α-L-Iduronidase	Classic, severe presentation - Failure to thrive - Small statue - Recurring ear and pulmonary infections - Enlarged liver/spleen - Roughening of facial features	1:100,000 (classic, severe presentation 1:500,000 (Mild presentation)	Enzyme Replacement Treatment - Laronidase - No effect on neurological involvement HSCT - In patients <2 years - Preserves neurocognitive function

		- Loss of hearing - Heart valve impairment - Contractures - Specific facial features - Intellectual disability - Corneal obscuring - Median nerve compression - Hydrocephalus - Glaucoma - Airway obstruction - Heart arrhythmias - Cervical weakness - Vertebral compression - Dystosis multiplex Mild presentation - Less pronounced somatic findings - Lack of central nervous system involvement		Treatment of complications - Tonsilloadenoidectomy - Regular cardiac function monitoring - MRI - Adherence to the guidelines for MPS I

2) Hunter Syndrome (MPS II) (69,71)	Iduronate-2-sulfatase	Classic, severe presentation - Failure to thrive - Small statue - Recurring ear and pulmonary infections - Enlarged liver/spleen - Roughening facial features - Hearing impairment - Heart valve disorders - Airway blockage - Contractures - Facial Dysmorphism - Intellectual disability - Corneal obscuring - Median nerve compression - Hydrocephalus - Glaucoma - Heart arrhythmias - Cervical weakness	1:100,000 – 1:170,000 males	ERT - Idursulfase - No effect on neurological involvement Treatment of complications - Tonsilloadenoidectomy - Regular cardiac function monitoring - MRI - Adherence to the guidelines for MPS II

		- Vertebral compression - Dystosis multiplex Mild presentation - Less pronounced somatic findings Lack of central nervous system involvement		
3) Sanfilippo Syndrome (MPS III A, B, C, D) (69,72)	MPS IIIA: Heparan-N-sulfatase MPS IIIB: N-acetylglucosaminidase MPS IIIC: Acetyl CoA glucosamine N-acetyltransferase MPS IIID: N-acetyl-glucosamine-6-sulfatase	Neuropsychiatric disorders - Global developmental delay - Sleep disorders - Seizures - Spasticity - Feeding difficulties - Vegetative state Somatic disorders - Hepatosplenomegaly - Cardiac valve thickening - Mild features of dysostosis multiplex	Overall - 1:50,000 – 1:250,000 MPSIIIA and MPSIIIB - 1:100,000 – 1:200,000 MPSIIIC and MPSIIID - 1:500,000 – 1:1,000,000	No treatment available

		- Mild Facial coarsening		
4) Morquio Syndrome (MPS IV A, B) (69)	MPS IVA: N-acetylgalactosamine-6-sulfate sulfatase MPS IVB: beta-galactosidase	Skeletal Abnormalities - Short statue - Pigeon chest - Forearm malformation - Knock-knees - Scoliosis - Hip dysplasia - Odontoid hypoplasia and atlantoaxial weakness - Teeth abnormalities Other features - Corneal obscuring - Hearing impairment - Restrictive/obstructive pulmonary diseases - Heart abnormalities	Unknown	MPS IVA - ERT with Elosulfase alfa
5) Maroteaux-Lamy syndrome (MPS VI)	Arylsulfatase B	- Short statue - Rough facial characteristics	0.36-1.30:100,000	ERT with Galsulfase

(69)		- Corneal obscuring - Airway blockage - Heart valve problems - Enlarged liver/spleen - Herniation - Dysostosis multiplex - Joint contractures - Median nerve compression - Hip dysplasia		
6) Sly Syndrome (MPS VII) (69)	Beta-glucuronidase	Prenatal - Hydrops fetalis Early age - Intellectual disability - Rough facial characteristics - Joint contractures - Enlarged liver/spleen - Scoliosis - Ocular obscuring - Airway disorder	0.05-0.26:100,000	ERT with Vestronidase alfa

		- Heart valve abnormalities - Cardiomyopathies - Dysostosis multiplex - Somatic symptoms as in MPS I and II		
Sphingolipidoses				
1) Fabry disease				
2) Krabbe disease				
3) Gaucher Disease				
4) Tay-Sachs Disease (73)	Hexoaminidase-A	<u>Infantile Form</u> Initial Symptoms - Nonhydrops fetalis - Motor retardation - Sensitivity to external stimuli - Exaggerated startle - Doll-like facies Ophthalmological Symptoms - Cherry-red spot (retina) - Blindness	1:100,000	Supportive Therapy - Nutrition - Seizure control - Therapy and prevention of infections - Airway protection - Physical and occupational therapy - Bowel management ERT

		- Narrowing of retinal vessels - Nystagmus - Optic Atrophy Neurological Symptoms - Hypotonia - Dysphagia - Developmental Delay/Regression - Seizures - Spasticity - Ataxia - Unresponsive and vegetative state - Dyskinesia - Sleep disturbances - Screaming and irritability - Decerebrate posturing - Macrocephalus Cardiovascular Symptoms		- Impossible to cross the blood-brain-barrier SRT Enzyme enhancing therapy Gene therapy Cell transplant

		- QT elongation - T wave changes <u>Juvenile Form</u> Initial Symptoms - Incoordination - Clumsiness - Muscles weakness Neurological Symptoms - Ataxia - Dysarthria - Dysphagia - Spasticity - Vegetative state - Decerebrate postureing Ophthalmological Symptoms - Cherry red spot (retina) - Optic atrophy - Retinitis pigmentosa <u>Adult Form</u> Neurological Symptoms		

		- Progressive motor neuron disease - Dystonia - Spinocerebellar degeneration - Developmental regression Psychiatric Symptoms - Psychotic depression - Hebephrenic schizophrenia		
5) Metachromatic Leukodystrophy (74)	Arylsulfatase	Late infantile form - Progressive loss of motor abilities - Movement Disorders - Hypotonia - Muscle rigidity - Reduced reflexes - Extensor plantar posturing - Optic atrophy	1:40,000 – 1:100,000	- Supportive Therapy - Genetic Counseling - Gene therapy and HSCT - ERT

		Juvenile form - Psychomotor regression - Intellectual decline - Peripheral neuropathy - Behavioral difficulties - Changes in personality - Ataxia - Convolutions - Mental disorders - Decreased motor function - Optic atrophy - Upper motor neuron signs Adult form - Dysesthesias - Psychosis - Schizophrenia - seizures		
6) Niemann-Pick disease				

5.6.Carbohydrate Metabolism Disorders

In this chapter conditions belonging to the group of Carbhydrate Metabolism Disorders are listed. Table 14 includes the deficient enzyme, clinical presentation, frequency, and treatment options for each condition. As Von Gierke disease and Galactosemia belong to the more frequent IEM, these conditions are discussed in more detail in chapters 2.9 and 2.8 respectively.

Table 14: Carbohydrate Metabolism Disorders

Condition	Deficient Enzyme	Clinical Presentation	Frequency	Treatment Options
Glycogen Storage Disease				
1) Von Gierke disease (GSD Type I)				
2) Pompe disease (GSD Type II) (37,75)	Acid maltase deficiency	Classic infantile onset Pompe disease (IOPD) - Symptoms appear within first year of life - Structural cardiac obnormalities	1:40,000	Dietary Treatment - High protein diet - Low carbohydrate diet ERT - α-glucosidase

		- Respiratory distress and continuous loss of independent ventilation - Poor feeding - Macroglossia - Hypotonia - Developmental delay Nonclassic infantile onset Pompe disease (IOPD) - Symptoms appear in the first year - Similar presentation as classic IOPD - Less severe structural cardiac abnormalities LOPD - Symptoms appear after first year - Speech disorders - Swallowing difficulties - Osteoporosis		

		- Scoliosis - Apnea - Neuropathy - Hearing impairment - Incontinence - Pain and fatigue - Arrhythmias - Intracranial aneurysm - No significant cardiac involvement - Proximal limb-girdle myopathy - Respiratory failure		
3) Cori Disease (GSD Type III) (37)	Glycogen debrancher deficiency - Oligo-1,4-1,4-glucantransferase Amylo-1,6-glucosidase	Both subtypes (GSD IIIa &b) - Hepatomegaly - Hypoglycemia - Short statue - Dyslipidemia - Mental retardation - Facial abnormalities - Osteoporosis	1:83,000 (Europe) 1:100,000 (North America) 1:3,600 (Faroe Islands)	Dietary Treatment - Frequent meals - High carbohydrate and cornstarch supplementation - High protein diet (in case of myopathy) Liver Transplantation

		- Liver cirrhosis - Hepatocellular carcinoma GSD IIIa - Myopathy - Cardiac symptoms		
4) Andersen disease (GSD Type IV) (37,76)	Amylo-1,4 to 1,6-transglucosidase	Fatal perinatal neuromuscular subtype - Fetal akinesia deformation sequence - Arthrogryposis - Severe hypotonia - Muscular atrophy - Fetal Congenital neuromuscular Subtype - Hypotonia - Pulmonary distress - Cardiomyopathy - Fetal Hepatic subtype	1:600,000 – 1:800,000	Liver Transplantation

		a) Progressive - Increased liver size - Elevated liver enzymes - Hepatic cirrhosis - Failure to thrive b) Non-Progressive - Hepatomegaly and hepatic dysfunction - Myopathy - Hypotonia Childhood neuromuscular subtype - Cardiomyopathy - Mild-to-severe myopathy		
5) McArdle disease (GSD Type V) (77)	Glycogen Phosphorylase	- Muscle fatigue and pain - Physical activity intolerance - Rhabdomyolysis	1:100,000 (Specific areas in the USA) 1:139,543 (Spain)	- Supportive Therapy - Physical activity - Sucrose supplementation before exercise - Hydration - Pain medication

				- Carbohydrate-rich diet
6) Hers disease (GSD Type VI) (37,78)	Liver phosphorylase	- Hepatomegaly - Growth retardation - Mild-to-moderate hypoglycemia - Mild ketosis - Elevated hepatic transaminases - Hyperlipidemia	1:65,000 – 1:85,000	Dietary Treatment - Frequent meals - Uncooked cornstarch - High protein intake - Limitation of simple sugars
7) Tarui disease (GSD Type VII) (77)	Phosphofructokinase	- Muscle fatigue and pain - Emesis - Elevated CK - Hyperuricemia - Reticulocytosis - Hyperbilirubinemia - Anemia - Jaundice - Rhabdomyolysis - Physical activity intolerance	100-200 confirmed cases worldwide	- Supportive Therapy - Pain medication - Hydration

Galactosemia				
Disorders of fructose metabolism (78)				
1) Essential Fructosuria	Fructokinase	- asymptomatic	Unknown	- Not necessary
2) Hereditary Fructose Intolerance 3) (HFI)	Aldolase B	- Abdominal ache - Sickness - Low blood sugar levels - Shock-like symptoms after fructose consumption	1:26,100 in Europe	- Fructose avoidance - In case of hypoglycemia intravenous glucose - Folate and vitamin C supplementation
4) Fructose-1,6-bisphosphatase deficiency	FBPase deficiency	- Malignant episodes of hypoglycemia - Coma (triggered)	1-9:100,000	- Avoidance of triggers - Frequent feeding - In case of hypoglycemia intravenous/oral glucose - Fructose and sucrose restriction

5.7.Other

In this chapter other conditions not classified in any of the aforementioned groups are listed. Table 15 includes the deficient enzyme, clinical presentation, frequency, and treatment options for each condition. As Alpha-1 antitrypsin (AAT) deficiency belongs to the more frequent IEM, this condition is discussed in more detail in chapter 2.7.

Table 15: Other disorders

Condition	Deficient Enzyme	Clinical Presentation	Frequency	Treatment Options
Biotinidase deficiency (1,79)	Biotinidase	Profound Biotinidase Deficiency - Seizures - Hypotonia - Ataxia - Visual impairments - Sensorineural hearing loss - Developmental delay - Spastic paresis - Changed level of consciousness - Death - Skin rash - Alopecia - Conjunctivitis - Seborrheic dermatitis	Overall 1:40,000 – 1:60,000 Profound Biotinidase deficiency 1:80,000 Partial Biotinidase deficiency 1:31,000 – 1:40,000	- Biotin Replacement Therapy - Supportive Measures

		- Recurrent viral and fungal infections - Apnea, tachypnea, stridor - Metabolic disturbances Partial Biotinidase Deficiency - Can be asymptomatic - Symptoms as in profound form but differ in severity - Symptoms at times of stress		
Lesch-Nyhan Syndrome (80)	hypoxanthine-guanine phosphoribosyltransferase (HPRT)	- Asymptomatic at birth - Crystalluria - Urolithiasis - Nephrolithiasis - Gout - Juvenile arthritis - Developmental delay - Vomiting - Hypotonia	1:235,000 – 1:380,000	- Allopurinol - Supportive Measures

		- Extrapyramidal symptoms (Dystonia) - Pyramidal Symptoms - Involuntary movements - Dysarthria and dysphagia - Opisthotonos - Cognitive Impairment - Self-injurious behavior - Megaloblastic Anemia		
Alpha-1 antitrypsin (AAT) deficiency				
Adenosine deaminase deficiency (81)	Adenosine deaminase	Immune System - Severe infections - Failure to thrive - ADA-deficient SCID - Absent thymus - Absent lymphoid tissue Non-Immune manifestations - Behavioral problems	Europe - 1:375,000 – 1:660,000	ERT - Polyethylene glycol-conjugated adenosine deaminase (PEG-ADA) HSCT Gene Therapy

		- Intellectual disability - Cognitive Impairment - Bilateral sensorineural hearing loss - Non-infectious pulmonary diseases - Skeletal abnormalities - Hepatic involvement - Renal involvement - Atypical hemolytic urinemic syndrome - Dermatofibrosarcoma		

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7. CV

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