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Inborn errors of Carbohydrates metabolism

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The Glycogen Storage Diseases and Related Disorders

- **The glycogen storage diseases (GSDs) and related disorders (Glycogenoses) are caused by defects of glycogen degradation, glycolysis and, glycogen synthesis.**
- **the GSDs can be divided in three main groups: those affecting liver, those affecting muscle, and those which are generalized**

- **GSDs are denoted by a Roman numeral that reflects the historical sequence of their discovery, by the deficient enzyme, or by the name of the author of the first description.**

The Liver Glycogenoses

- **The liver GSDs comprise GSD I, the hepatic presentations of GSD III, GSD IV, GSD VI, the liver forms of GSD IX, and GSD 0. GSD I, III, VI, and IX present with similar symptoms during infancy, with hypoglycemia, marked hepatomegaly, and retarded growth.**
- **GSD I is the most severe because not only is glycogen breakdown impaired, but also gluconeogenesis.**

- **GSD III patients have a syndrome that includes hepatopathy, myopathy, and often cardiomyopathy.**
- **GSD IV manifests in most patients in infancy or childhood as hepatic failure with cirrhosis leading to end-stage liver disease.**
- **GSD VI and the hepatic forms of GSD IX are the mildest forms: there is only a mild tendency to fasting hypoglycemia, liver size normalizes with age, and patients reach normal adult height**

- **GSD 0 presents in infancy or early childhood with fasting hypoglycemia and ketosis contrasting with postprandial hyperglycemia and hyperlactatemia.**

Glycogen Storage Disease Type I (Glucose-6-Phosphatase of Translocase Deficiency)

- **GSD I, comprises GSD Ia caused by deficiency of the catalytic subunit of glucose-6- phosphatase (G6Pase), and GSD Ib, due to deficiency of the endoplasmic reticulum (ER) glucose-6-phosphate (G6P) translocase.**

Genetics

- **Both GSD Ia and Ib are autosomal recessive disorders.**
- **The gene encoding G6Pase (G6PC) was identified on chromosome 17q21.**
- **More than 75 different mutations have been reported.**
- **The gene encoding the G6P transporter (G6PT) was identified on chromosome 11q23.**
- **More than 65 different mutations have been reported.**
- **Patients diagnosed by enzyme studies as GSD Ib, Ic and Id shared the same mutations in G6PT.**

Metabolic Defects

- **The catalytic site of G6Pase is situated inside the lumen of the ER (its substrate, G6P, must cross the ER membrane and requires a transporter).**
- **There are different proposed models of G6Pase, over the existence of additional transporters forn its products, phosphate and glucose and over the existence of GSD Ic (putative ER phosphate/pyrophosphate transporter deficiency), and GSD Id (putative ER glucose transporter deficiency).**
- **Patients diagnosed by enzyme studies as GSD Ic have been found to have the same mutations in the G6P translocase gene as in GSD Ib.**

- **Hypoglycemia occurs during fasting as soon as exogenous sources of glucose are exhausted, since the final steps in both glycogenolysis and gluconeogenesis are blocked. However, there is evidence that GSD I patients are capable of some endogenous hepatic glucose production, although the mechanism is still unclear. Residual G6Pase activity or the activity of non specific phosphatases may result in hydrolysis of G6P to glucose; glycogen may be degraded into glucose by amylo-1,6-glucosidase, or lysosomal acid maltase.**

- **Hyperlactatemia is a consequence of excess G6P that cannot be hydrolysed to glucose and is further metabolized in the glycolytic pathway, ultimately generating pyruvate and lactate. This process is intensified under hormonal stimulation as soon as the exogenous provision of glucose fails. Substrates such as galactose, fructose and glycerol need liver G6Pase to be metabolised to glucose. Consequently ingestion of sucrose and lactose results in hyperlactatemia, with only a small rise in blood glucose.**

- **The serum of untreated patients has a milky appearance due to hyperlipidemia, primarily from increased triglycerides with cholesterol and phospholipids less elevated. The hyperlipidemia only partially responds to intensive dietary treatment. The increased concentrations of triglycerides and cholesterol are reflected in increased numbers of VLDL and LDL particles, whereas the HDL particles are decreased. VLDL particles are also increased in size due to the accumulation of triglycerides. Hyperlipidemia is a result of both increased synthesis from excess of acetyl coenzyme A (CoA) via malonyl-CoA, and decreased serum lipid clearance.**

- **Elevated hepatic G6P levels may also play a role via activation of transcription of lipogenic genes. Decreased plasma clearance is a result of impaired uptake and impaired lipolysis of circulating lipoproteins. Reduced ketone production during fasting is a consequence of the increased malonyl-CoA levels, which inhibit mitochondrial β-oxidation.**

- **Hyperuricemia is a result of both increased production and decreased renal clearance. Increased production is caused by increased degradation of adenine nucleotides to uric acid, associated with decreased intra-hepatic phosphate concentration and ATP depletion. Decreased renal clearance is caused by competitive inhibition of uric acid excretion by lactate.**

Glycogen Storage Disease Type III (Debranching Enzyme Deficiency)

- The release of glucose from glycogen requires the activity of both phosphorylase and glycogen debranching enzyme (GDE).
- GSD III, also known as Cori or Forbes disease, is an autosomal recessive disorder due to deficiency of GDE which causes storage of glycogen with an abnormally compact structure, known as phosphorylase limit dextrin.
- Differences in tissue expression of the deficient GDE explain the existence of various subtypes of GDS III.

- **Most patients with GSD III have a generalized defect in which enzyme activity is deficient in liver, muscle, heart, leukocytes and cultured fibroblasts, and have a syndrome that includes both hepatic and myopathic symptoms, and often cardiomyopathy (GSD IIIa). About 15% of patients only have symptoms of liver disease and are classified as GSD IIIb. Subgroups due to the selective deficiency of either the glucosidase activity (GSD IIIc) or of the transferase activity (GSD IIId) are very rare.**

Genetics

- **The gene for GDE (GDE) is located on chromosome 1p21.**
- **48 different mutations in the GDE gene have been associated with GSD III. GSD IIIb is associated with mutations in exon 3, while mutations beyond exon 3 are associated with GSD IIIa.**

Metabolic defects

GDE is a bifunctional enzyme, with two catalytic activities, oligo-1,4→1,4-glucantransferase and amylo-1,6-glucosidase. After phosphorylase has shortened the peripheral chains of glycogen to about four glycosyl units, these residual stubs are removed by GDE in two steps. A maltotriosyl unit is transferred from a donor to an acceptor chain (transferase activity), leaving behind a single glucosyl unit, which is hydrolysed.

- **During infancy and childhood patients suffer from fasting hypoglycemia, associated with ketosis and hyperlipidemia. Serum transaminases are also increased in childhood but decrease to (almost) normal values with increasing age. In contrast to GSD I, blood lactate concentration is normal. Elevated levels of serum creatine kinase (CK) and aldolase suggest muscle involvement, but normal values do not exclude the future development of myopathy.**

Glycogen Storage Disease Type IV (Branching Enzyme Deficiency)

- **GSD IV, or Andersen Disease, is an autosomal recessive disorder due to a deficiency of glycogen branching enzyme (GBE).**
- **Deficiency of GBE results in the formation of an amylopectin-like compact glycogen molecule with fewer branching points and longer outer chains.**
- **Patients with the classical form of GSD IV develop progressive liver disease early in life.**

- **The non-progressive hepatic variant of GSD IV is less frequent and these patients usually survive into adulthood. Besides these liver related presentations, there are rare neuro muscular forms of GSD IV.**

Genetics

- The GBE gene has been mapped to chromosome 3p14.
- Three important point mutations, R515C, F257L and R524X were found in patients with the classical progressive liver cirrhosis form.
- In patients with the non-progressive liver form, the Y329S mutation has been reported. This
- mutation results in a significant preservation of GBE activity, thereby explaining the milder course of the disease.
- The mutation found in patients with APBD also appears to be relatively mild which may explain the late onset of this disorder.

Metabolic Disorders

- **Hypoglycemia is rarely seen, and only in the classical hepatic form, when liver cirrhosis is advanced, and detoxification and synthesis functions become impaired.**
- **The clinical and biochemical findings under these circumstances are identical to those typical of other causes of cirrhosis, with elevated liver transaminases and abnormal values for blood clotting factors, including prothrombin and thromboplastin generation time.**

Glycogen Storage Disease Type VI (Glycogen Phosphorylase Deficiency)

- **GSD VI or Hers disease is an autosomal recessive disorder due to a deficiency of the liver isoform of glycogen phosphorylase.**
- **Phosphorylase breaks the straight chains of glycogen down to glucose-1-phosphate in a concerted action with debranching enzyme. Glucose-1-phosphate in turn is converted into glucose-6-phosphate and then into free glucose.**

Genetics

- **Three isoforms of phosphorylase are known, encoded by three different genes. The gene encoding the liver isoform, PYGL, is on chromosome 14q21-q22, and mutations have been described.**

Metabolic Disorders

- **The tendency towards hypoglycemia is not as severe as seen in GSD I or GSD III and usually appears only after prolonged fasting in infancy. Hyperlipidemia and hyperketosis are usually mild. Lactic acid and uric acid are within normal limits.**

Glycogen Storage Disease Type IX (Phosphorylase Kinase Deficiency)

- GSD IX, or phosphorylase kinase (PHK) deficiency, is the most frequent glycogen storage disease. According to the mode of inheritance and clinical presentation six different subtypes are distinguished: (1) X-linked liver glycogenosis (XLG or GSD IXa), by far the most frequent subtype; (2) combined liver and muscle PHK deficiency (GSD IXb); (3) autosomal liver PHK deficiency (GSD IXc);

(4) X-linked muscle glycogenosis (GSD IXd); (5) autosomal muscle PHK deficiency (GSD IXe); and (6) heart PHK deficiency (GSD IXf) with the mode of inheritance not clear yet, but probably due to AMP kinase mutations.

Genetics

- Two different isoforms of the α subunit (α_L for liver and α_M for muscle) are encoded by two different genes on the X chromosome (PHKA2 and PHKA1 respectively), while
- the β subunit (encoded by PHKB), two different isoforms of the γ subunit (γ_T for testis/liver and γ_M for muscle, encoded by PKHG2 and PKHG1, respectively), and three isoforms of calmodulin (CALM1, CALM2, CALM3) are encoded by autosomal genes.
- The PHKA2 gene has been mapped to chromosome Xp22.2-p22.1, the PHKB gene to chromosome 16q12-q13, and the PKHG2 gene to chromosome 16p12-p11.

- **The most common hepatic variant, XLG or GSD Ixa (resulting from PHKA2 mutations), comprises two different entities: XLG 1, the classical type, and XLG 2, the less common variant.**
- **In XLG 1 the PHK activity is deficient in liver and decreased in blood cells.**
- **In XLG 2, PHK activity is normal in liver, erythrocytes and leukocytes. Therefore, normal PHK activity in erythrocytes or even liver tissue does not exclude XLG.**

- **The predominance of affected men with the myopathic presentation suggested that the X-linked α M isoform may be involved predominantly, a concept bolstered by reports of mutations in the PHKA1 gene in two patients.**
- **The molecular study of six myopathic patients, five men and one woman, revealed only one novel mutation in PHKA1, whereas no pathogenic mutations were found in any of the six genes (PHKA1, PHKB, PHKG1, CALM1, CALM2, CALM3) encoding muscle subunits of PHK in the other five patients.**

Metabolic Disorders

- **The degradation of glycogen is controlled both in liver and in muscle by a cascade of reactions resulting in the activation of phosphorylase. This cascade involves the enzymes adenylate cyclase and PHK. PHK is a decahexameric protein composed of four subunits, α, β, γ, and δ: the α and β subunits are regulatory, the □ subunit is catalytic, and the δ subunit is a calmodulin and confers calcium sensitivity to the enzyme.**

- **The hormonal activating signals for glycogenolysis are glucagon for the liver and adrenaline for muscle. Glucagon and adrenaline activate the membrane-bound adenylate cyclase, which transforms ATP into cyclic AMP (cAMP) and interacts with the regulatory subunit of the cAMP-dependent protein kinase, resulting in phosphorylation of PHK. Ultimately, this activated PHK transforms glycogen phosphorylase into its active conformation, a process which is defective in GSD type IX.**

Glycogen Storage Disease Type 0 (Glycogen Synthase Deficiency)

Although this rarely diagnosed enzyme defect leads to decreased rather than increased liver glycogen, it causes symptoms that resemble hepatic glycogenosis.

Genetics

The gene that encodes GS, GYS2, is located on chromosome 12p12.2, and several mutations are known.

Metabolic Disorders

- **GSD 0 is caused by a deficiency of glycogen synthase (GS), a key-enzyme of glycogen synthesis. Consequently, patients with GS deficiency have decreased liver glycogen concentration, resulting in fasting hypoglycemia. This is associated with ketonemia, low blood lactate concentrations, and mild hyperlipidemia.**
- **Post-prandially, there is often a characteristic reversed metabolic profile, with hyperglycemia and elevated blood lactate.**

The Muscle Glycogenoses

- **At rest, muscle utilizes fatty acids.**
- **During submaximal exercise, it additionally uses energy from blood glucose, mostly derived from liver glycogen.**
- **During very intense exercise, the main source of energy is anaerobic glycolysis following breakdown of muscle glycogen. When the latter is exhausted, fatigue ensues. Enzyme defects within the pathway affect muscle function**

Glycogen Storage Disease Type V (Myophosphorylase Deficiency)

Genetics

- **GSD V is an autosomal recessive disorder. The gene for the muscle isoform (PYGM) has been mapped to chromosome 11q13. The number of known pathogenic mutations has increased to over 40.**
- **The most common mutation in Caucasians is the R49X mutation, which accounts for 81% of the alleles in British patients and 63% of alleles in U.S. patients.**
- **This mutation, however, has never been described in Japan, where a single codon deletion 708/709 seems to prevail.**

- **A study of 47 patients with GSD V for associated insertion/deletion polymorphism in the angiotensin-converting enzyme (ACE) revealed a good correlation between clinical severity and number of ACE genes harbouring a deletion.**

Metabolic Disorders

- There are three isoforms of glycogen phosphorylase: brain/heart, liver, and muscle, all encoded by different genes.
- GSD V is caused by deficient myophosphorylase activity.

(reaction catalyzed by myophosphorylase)

Glycogen Storage Disease Type VII (Phosphofructokinase Deficiency)

Metabolic Derangement and Genetics

- **PFK is a tetrameric enzyme under the control of three autosomal genes.**
- **A gene (PFK-M) on chromosome 12 encodes the muscle subunit; a gene (PFK-L) on chromosome 21 encodes the liver subunit; and a gene (PFK-P) on chromosome 10 encodes the platelet subunit.**

- **Mature human muscle expresses only the M subunit and contains exclusively the M homotetramer (M4), whereas erythrocytes, which contain both the M and the L subunits, contain five isozymes: the two homotetramers (M4 and L4) plus three hybrid forms (M1L3; M2L2; M3L1).**
- **In patients with typical PFK deficiency, mutations in PFK-M cause total lack of activity in muscle but only partial PFK deficiency in red blood cells, where the residual activity approximates 50% and is accounted for by the L4 isozyme. At least 15 mutations have been reported in the PFK-M gene of patients with typical PFK deficiency.**

Phosphoglycerate Kinase Deficiency

- **Phosphoglycerate kinase (PGK) is a single polypeptide encoded by a gene (PGK1) on Xq13 for all tissues except spermatogenic cells.**
- **Although this enzyme is virtually ubiquitous, clinical presentations depend on the isolated or associated involvement of three tissues, erythrocytes (hemolytic anemia), central nervous system (CNS, with seizures, mental retardation, stroke), and skeletal muscle (exercise intolerance, cramps, myoglobinuria).**

Glycogen Storage Disease Type X (Phosphoglycerate Mutase Deficiency)

- **GSD X or phosphoglycerate mutase (PGAM) deficiency is an autosomal recessive disorder. Phosphoglycerate mutase is a dimeric enzyme: different tissues contain various proportions of a muscle (MM) isozyme, a brain (BB) isozyme, and the hybrid (MB) isoform.**
- **Normal adult human muscle has a marked predominance of the MM isozyme, whereas in most other tissues PGAM-BB is the only isozyme demonstrable by electrophoresis.**
- **A gene (PGAMM) on chromosome 7 encodes the M subunit.**

Glycogen Storage Disease Type XII (Aldolase A Deficiency)

- **GSD XII or aldolase A deficiency is an autosomal recessive disorder.**
- **Aldolase exists in three isoforms (A, B, and C): skeletal muscle and erythrocytes contain predominantly the A isoform, which is encoded by a gene (ALDOA) on chromosome 16.**

Glycogen Storage Disease Type XIII (β-Enolase Deficiency)

- GSD XIII or β-enolase deficiency is an autosomal recessive disorder.
- β-Enolase is a dimeric enzyme and exists in different isoforms resulting from various combinations of three subunits, α, β, and γ.
- The β subunit is encoded by a gene (ENO3) on chromosome 17.

Glycogen Storage Disease Type XI (Lactate Dehydrogenase Deficiency)

- **GSD XI or lactate dehydrogenase (LDH) deficiency is an autosomal recessive disorder. Lactate dehydrogenase is a tetrameric enzyme composed of two subunits, M (or A) and H (or B) resulting in five isozymes.**
- **The gene for LDH-M (LDHM) is on chromosome 11.**

Muscle Glycogen Storage Disease Type 0 (Glycogen Synthase Deficiency)

- New muscular glycogen storage disease type 0 has been described in a child with hypertrophic cardiomyopathy and myopathy due to a homozygous stop mutation in the muscular glycogen synthase gene GYS1

The Generalized Glycogenoses and Related Disorders

Glycogen Storage Disease Type II (Acid Maltase Deficiency)

GSD II is a lysosomal storage disorder, caused by the generalized deficiency of the lysosomal enzyme, acid maltase or α-glucosidase.

Genetics

- **Acid maltase is encoded by a gene (GAA) on chromosome 17q25. Over 80 pathogenic mutations in GAA are known.**
- **Some degree of genotype:phenotype correlation is becoming apparent, with severe mutations associated with the infantile form and leaky mutations associated with the adult variant.**
- **Prenatal diagnosis is possible by enzyme assay or DNA analysis of chorionic villi.**

Metabolic Defects

- **The enzyme defect results in the accumulation of glycogen within the lysosomes of all tissues, but particularly in muscle and heart, resulting in muscle weakness.**
- **Serum levels of transaminases (ASAT, ALAT), CK and CK-myocardial band (in the infantile form) are elevated.**

Danon Disease

- **Danon Disease or GSD IIb, or pseudo-Pompe disease, is an X-linked dominant lysosomal storage disease due to deficiency of LAMP-2 (lysosomal-associated membrane protein 2).**
- **The disease starts after the first decade, is extremely rare and affects cardiac and skeletal muscle. Acid maltase activity is normal**
- **The gene encoding LAMP2 was mapped to Xq28**

Lafora Disease

- **Linkage analysis localised the gene responsible for Lafora disease (EPM2A) to chromosome 6q24 and about 30 pathogenic mutation have been identified.**
- **The protein encoded by EPM2A, dubbed laforin, may play a role in the cascade of phosphorylation/dephosphorylation reactions controlling glycogen synthesis and degradation.**