

REVIEW

Inherited metabolic disorders of glycoconjugate metabolism

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ABSTRACT

Inherited metabolic disorders of glycoconjugate metabolism include congenital disorders of glycosylation (CDG) - disorders in biosynthesis of glycoconjugates; and some of the lysosomal storage diseases (LSD) – disorders of their degradation. This review summarizes the brief characteristics of metabolic pathways of synthesis and catabolism of glycoconjugates as well as the latest update of relevant enzymatic defects discovered in population. Every year the number of known subtypes of these disorders dramatically increases as a result of high-throughput analytical infrastructure applied. However, due to the broad spectrum of unspecific clinical symptoms, many patients remain undiagnosed or have wrong diagnosis with ineffective treatment. Thus, disorders of glycoconjugate metabolism should be considered and ruled out in any unexplained syndrome. The collaboration between scientists and physicians plays an important role in the progress of such personalized diagnostics, that is essential mainly for rare diseases (Tab. 2, Fig. 1, Ref. 49). Text in PDF www.elis.sk

KEY WORDS: congenital disorders of glycosylation, lysosomal storage disorders.

Introduction

During the last decades, genome and proteome were considered as the major instrument of knowledge of living organisms. Nowadays, science forwarded from genomics and proteomics to glycomics and not only the genetic code and its expression are essential factors of life. Post-translational modifications of proteins, including glycosylation, play a vital role in eukaryotes. Constantly increasing knowledge about pathological changes in glycoprofiles and its integration into genomic and proteomic data opens up new possibilities in the diagnosis, prevention or monitoring of diseases, and also the development of new therapeutic approaches.

Biosynthesis of glycans

Oligosaccharides are bound to protein via serine or threonine (O-linked oligosaccharides) or asparagine (N-linked oligosac-

charides) (Montreuil et al, 1995). O-glycosylation is a sequential process of transmission of single monosaccharide units and N-glycosylation is more complex, including many partial synthetic and trimming reactions. If a mutation in any enzyme involved in glycan biosynthesis occurs, it may lead to the pathway disruption, demonstrated also with altered phenotype. The complete loss of N-glycosylation is lethal (Freeze and Westphal, 2001).

During the last decades, the relationship between aberrant glycosylation and a variety of pathological conditions, including chronic inflammatory diseases (Verhelst et al, 2020), immunodeficiencies (Ravell et al, 2020), diabetes (Rudman et al, 2019), cardiovascular disorders (Gudelj and Lauc, 2018) or cancer (Gao et al, 2020), was observed. Abnormalities in the glycosylation patterns have been discovered also in patients with Alzheimer's disease (Regan et al, 2019). Nowadays primary disorders in the biosynthesis of O-linked oligosaccharides, N-linked oligosaccharides, and glycans present in glyco-phosphatidylinositols and glycosphingolipids are known (Topaz et al, 2004, Freeze and Aebi, 2005; Almeida et al, 2006).

Catabolism of glycoconjugates

Catabolic reactions of glycoproteins and glycoconjugates take place in lysosomes as a part of normal metabolic homeostasis and turnover. Their degradation takes place in two opposite directions. The first is a sequential removal of monosaccharides by specific exoglycosidases and the second direction is proteolytic cleavage of the bond between carbohydrate and protein (Winchester, 2005). The final products of glycoconjugate catabolism (monosaccharides, amino acids and dipeptides) are transported across the membrane into the cytosol. Disorders in degradation pathways occurring in lysosomes are classified as lysosomal storage disorders.

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Congenital disorders of glycosylation

In 1997 only three defects in genes involved in the glycosylation process were known. Nowadays, due to the continuous development of modern analytical methods, more than 130 unique subtypes of these monogenic diseases are known (Post and Lefebvre, 2019). The incidence and prevalence of all types of CDG in aggregate have not been well established yet as it is believed that many cases go unrecognized or misdiagnosed, making it difficult to determine their true frequency. The estimated prevalence in European and African American populations is 1: 10,000 based on carrier frequencies of known pathogenic variants in 53 genes (Chang et al, 2018, Jaeken and Matthijs, 2001, Jaeken and Matthijs, 2007). As the serum glycoproteins contain mostly N-linked complex type oligosaccharides, most of the identified CDG defects were observed in the N-glycosylation pathway (Marquardt and Denecke, 2003). In approximately 20 % of CDG patients the specific enzyme defect is still not described, and these undiagnosed patients are classified as the CDG subtype x. Summary of known CDG subtypes with the list of deficient enzymes/proteins and corresponding OMIM numbers is shown in the Table 1.

Clinical manifestations and diagnostics of CDG

Congenital disorders of glycosylation are a rapidly expanding group of genetic diseases (Grubenmann et al, 2003). This group is characterized by various clinical manifestations with multisystem phenotype that includes disorders in central and peripheral nervous system, often associated with disorders of coagulation, and endocrinologic findings (Peng et al, 2020, Jaeken and Matthijs, 2001). Approximately 20 % of patients do not survive beyond five years of age due to widespread organ dysfunction (Jones et al, 2013). Common clinical manifestations associated with the CDG include delayed development and decreased intellect, ataxia, seizures, retinopathy, growth disorders, cardiomyopathy, pericardial effusions, endocrine abnormalities, renal dysfunction, hepatic failure, disorders of bone development and decreased mineralization, late closure of fontanel, cutis laxa (Morava et al, 2008), skeletal dysplasia (Coman et al, 2007), high frequency of early mortality and typical dysmorphism. Facial dysmorphism is demonstrated by a high forehead, triangular face, large ears, strabismus, and a thin upper lip. Peripheral dysmorphism is manifested by abnormal fat distribution and inverted nipples (Jaeken and Matthijs, 2007).

Wide symptomatology of CDG and structural diversity of glycoconjugates ranks among the diseases as difficult to diagnose (Grubenmann et al, 2004). Currently, as a selective screening test, isoelectric focusing (IEF) of serum transferrin (Tf) is established in many countries (De Jong and Van Eijk, 1988). Its abnormal carbohydrate-deficient isoforms are characteristic biochemical marker for CDG (Stibler, Jaeken, 1990), but this method does not provide sufficient resolution needed to distinguish the specific enzymatic defect. Representative IEF Tf profiles of CDG, compared to the healthy serum, are shown in Figure 1.

To improve the diagnostic possibilities, several methods utilizing mass spectrometry, due to its sensitivity and specificity, were

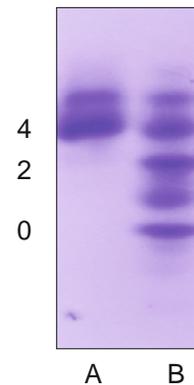


Fig. 1. IEF profiles of serum transferrin isoforms which are divided by the number of sialic acids. A- Negative sample, B- PMM2 CDG sample, 0,2,4- numbers of terminal sialic acids attached. The PMM2-CDG patients present asialo-Tf and in large quantities disialo-Tf; on the other hand, tetrasialo-Tf in PMM2-CDG serum is observed in a lower abundance compared to the healthy serum.

developed. They are widely used to elucidate the structure of the glycans (Barbosa et al, 2019) or glycoproteins. In recent years, broader accessibility and higher rates of conclusive diagnoses have made next-generation sequencing (NGS) one of the preferred approaches for the solving of undiagnosed genetic disorders and the first gene panel targeted for CDGs was released in 2010 (Jones et al, 2013). The advantage of NGS lies in its robust approach, that is usually required in cases where there is no information about what single gene in such complex glycosylation pathway could be defective.

As the advanced methods mentioned above are not suitable for routine diagnostics, comprehensive collaboration between the clinical geneticists, physicians and researchers is essential. In eligible process, after the disorder of glycoconjugate metabolism is suspected, samples of serum or urine are sent to the centers of inherited metabolic disorders where the selective screening is performed. If the result from screening is positive, borderline or ambiguous, samples can be further analyzed by personalized approaches to characterize the specific biomarkers, determine their levels; or to precisely locate the mutations and predict their further impact.

Lysosomal storage disorders

Lysosomal storage disorders (LSDs) are a group of over 50 genetic metabolic diseases, leading to deficiency of a lysosomal enzyme, activator, transport protein; or, in some cases, the non-lysosomal protein included in lysosomal biogenesis. The result of deficient activity of lysosomal catabolic enzymes is the accumulation of metabolites in these organelles (Futerman and Van Meer, 2004). Disruption of one pathway can lead to many clinical symptoms, depending on the location of the disorder. LSDs are classified by the type of metabolite that accumulates: lipidoses, mucopolysaccharidoses, glycoproteinoses, sphingolipidoses, multi-enzymatic deficiencies, disorders of lysosomal transport and

Tab. 1. Summary of the CDG subtypes (edited from Denecke, 2009; Uemura et al, 2008; Chang et al, 2018; Peanne et al, 2018; Sparks et al, 2017).

CDG subtype	Deficient enzyme/protein	OMIM*
ALG1-CDG	GDP-Man:GlcNAc2-PP-dolichol mannosyltransferase	608540
ALG2-CDG	GDP-Man:Man1GlcNAc2-PP-dolichol mannosyltransferase	607906
ALG3-CDG	Dolichyl-P-Man: Man5GlcNAc2-PP-dolichol mannosyltransferase	601110
ALG6-CDG	Dolichyl-P-Glc:Man9GlcNAc2-PP-dolichol glucosyltransferase	603147
ALG8-CDG	Dolichyl-P-Glc:Glc1Man9GlcNAc2-PP-dolichol- α -1,3-glucosyltransferase	608104
ALG9-CDG	Dolichyl-P-Man: α -1,2-mannosyltransferase	608776
ALG11-CDG	Asparagine-linked glycosylation protein 11	613661
ALG12-CDG	Dolichyl-P-Man:Man7GlcNAc2-PP-dolichol mannosyltransferase	607143
ALG13-CDG	ALG13 UDP-N-Acetylglucosaminyltransferase subunit	300884
ALG14-CDG	ALG14 UDP-N-Acetylglucosaminyltransferase subunit	616227
ATP6V0A2-CDG	ATPase, H ⁺ transporting, lysosomal, V0 subunit A2	219200
B3GLCT-CDG	β -3-Glucosyltransferase	261540
B4GALNT1-CDG	β -1,4-N-Acetylgalactosaminyltransferase 1	609195
B4GALT1-CDG	Golgi UDP-Gal:GlcNAc β -1,4-galactosyltransferase	607091
CAD-CDG	Carbamoyl phosphate synthetase/Aspartate transcarbamoylase/Dihydroorotase (CAD trifunctional protein)	616457
CCDC115-CDG	Coiled-coil domain-containing protein 115	616828
COG1-CDG	Golgi conserved oligomeric complex	611209
COG2-CDG	Golgi conserved oligomeric complex	617395
COG4-CDG	Golgi conserved oligomeric complex	613489
COG5-CDG	Golgi conserved oligomeric complex	613612
COG6-CDG	Golgi conserved oligomeric complex	606977
COG7-CDG	Golgi conserved oligomeric complex	608779
COG8-CDG	Golgi conserved oligomeric complex	611182
DDOST-CDG	Dolichyl-diphosphooligosaccharide-protein glycosyltransferase	614507
DHDDS-CDG	Dehydrodolichyl diphosphate synthase	613861
DOLK-CDG	Dolichyl-kinase	610768
DPAGT1-CDG	UDP-GlcNAc:dolicholphosphate N-acetylglucosamine-1-phosphotransferase	608093
DPM1-CDG	Dolichyl-P-mannosyltransferase 1, catalytic subunit	608799
DPM2-CDG	Dolichyl-phosphate mannosyltransferase 2, regulatory subunit	615042
DPM3-CDG	Dolichyl-phosphate mannosyltransferase - polypeptide 3	612937
EXT1-CDG	Exostosin glycosyltransferase I	133700
EXT2-CDG	Exostosin glycosyltransferase II	133701
FCSK-CDG	L-Fucose kinase	618324
FUCT1-CDG	Golgi GDP-fucose transporter	266265
FUT8-CDG	α -1,6-fucosyltransferase	618005
GALNT3-CDG	UDP-N-Acetyl- α -D-Galactosamine:Polypeptide N-Acetylgalactosaminyltransferase 3	211900
GCS1-CDG	Mannosyl oligosaccharide glycosidase (Glucosidase I)	606056
MAGT1-CDG	Magnesium transporter 1	301031
MGAT2-CDG	α -1,6-mannosyl-glycoprotein beta-1,2-GlcNAc-transferase	212066
MPDU1-CDG	Mannose-P-dolichol utilization defect 1	609180
MPI-CDG	Mannosophosphate isomerase	602579
NUS1-CDG	NUS1 dehydrodolichyl diphosphate synthase subunit	617082
PGM1-CDG; also known as GSD XIV	Phosphoglucomutase 1	614921
PIGA-CDG	Phosphatidylinositol glycan anchor biosynthesis class A protein	300868
PIGL-CDG	Phosphatidylinositol glycan anchor biosynthesis class L protein	280000
PIGM-CDG	Phosphatidylinositol glycan anchor biosynthesis class M protein	610293
PMM2-CDG	Phosphomannomutase II	212065
POFUT1-CDG	Protein-O-fucosyltransferase 1	615327
POGLUT1-CDG	Protein-O-glucosyltransferase 1	617232
RFT1-CDG	Flipase	612015
SEC23B-CDG	SEC23 Homolog B, Coat Complex II Component	616858
SLC35A1-CDG	CMP-Sialic acid transporter	603585
SLC35A2-CDG	UDP-Galactose transporter	300896
SLC35C1-CDG	GDP-Fucose transporter	266265

CDG subtype	Deficient enzyme/protein	OMIM*
SLC39A8-CDG	Solute carrier family 39, member 8	616721
SRD5A3-CDG	Steroid 5- α -reductase III	612379
SSR4-CDG	Translocon-associated protein, delta subunit	300934
ST3GAL3-CDG	β -Galactoside α -2,3-sialyltransferase 3	615006
ST3GAL5-CDG	β -Galactoside α -2,3-sialyltransferase 5	609056
STT3A-CDG	Oligosaccharidyltransferase complex, catalytic subunit STT3A	615596
STT3B-CDG	Oligosaccharidyltransferase complex, catalytic subunit STT3B	615597
TMEM165-CDG	Transmembrane protein 165	614727
TMEM199-CDG	Transmembrane protein 199	616829
TUSC3-CDG	Tumor suppressor candidate 3	611093
CDG I/IIx	Still unknown CDG defect	212067

* OMIM – Online Mendelian Inheritance in Man - Phenotype MIM Number (www.ncbi.nlm.nih.gov/omim)

Tab. 2. Summary of the LSDs subtypes (edited from Winchester, 2005, Vellodi, 2005).

LSD type	Deficient enzyme/protein	OMIM*
α -Mannosidose	α -D-mannosidase	248500
β -Mannosidose	β -D-mannosidase	248510
Aspartylglucosaminuria	Aspartylglucosaminidase	208400
Cystinosis	Lysosomal cystin transporter	219800, 219900
Fabry disease	α -D-galactosidase A	301500
Farber disease	Ceramidase	230800
Fucosidose	α -L-fucosidase	230000
Gaucher disease	Glucosylceramid β -galactosidase	230800, 230900
GM1-gangliosidosis	β -D-galactosidase	230500, 230600
Krabbe disease	Galactozylceramide β -galactosidase	245200
Metachromatic leucodystrophy	Arylsulphatase A	250100
MPS I - Hurler - Scheie syndrome	α -l-Iduronidase	607015
MPS I - Hurler syndrome	α -l-Iduronidase	607014
MPS I - Scheie syndrome	α -l-Iduronidase	607016
MPS II	Iduronatesulphate sulphatase	309900
MPS IIIA	Heparan-S-sulphate sulphamidase	252900
MPS IIIB	N-acetyl-D-glucosaminidase	252920
MPS IIIC	Acetyl-CoA-glucosaminid N-acetyltransferase	252930
MPS IIID	N-acetyl-glucosaminine-6-sulphate sulphatase	252940
MPS IVA	Galactosamine-6-sulphate sulphatase	253000
MPS IVB	β -galactosidase	253010
MPS IX	Hyaluronidase	601492
MPS VI	Arylsulphatase B	253200
MPS VII	β -glucuronidase	253220
Mucopolipidose I (sialidose)	Sialidase	256550
Mucopolipidosis II/IIIa,b	N-acetylglucosaminyl-1-phosphotransferase	252500, 252600
Mucopolipidosis IV	Catepsin A	256540, 252650
Neuronal ceroid lipofuscinosis	Palmitoyl protein-thioesterase / tripeptidyl peptidase 1	256730
Niemann–Pick disease A, B	Sphingomyelinase	257200, 607616
Niemann–Pick disease C,D	NPC1, NPC2 protein	257220, 607625
Pompe disease	α -glucosidase	232300
Pyknodysostosis	Catepsin K	265800
Sandhoff disease	β -hexosaminidase B	268800
Schindler disease	α -D-galactosidase B	609241
Tay–Sachs disease	β -hexosaminidase A	272800
Wolman disease	Lysosomal acid lipase	278000

* OMIM – Online Mendelian Inheritance in Man (www.ncbi.nlm.nih.gov/omim)

other diseases related to disorders of lysosomal proteins (Vellodi, 2005, Winchester, 2005).

According to prevalence, LSDs are, as well as CDGs, classified as rare diseases. The numbers of patients are different depending on the individual type, such as 1: 57,000 newborns in Gaucher disease, or about 1: 4.2 million in sialidosis (Meikle et al, 1999). Gaucher disease is the most prevalent inherited disorder among Ashkenazi Jews with carrier frequency of about 6 % (Bronstein et al, 2014). The overall prevalence of LSDs in some regions, according to the available literature, is reaching up to 1: 7,000–8,000 newborns (Meikle et al, 1999; Poorthuis et al, 1999). Overview of LSDs subtypes with the list of defect enzymes/proteins and OMIM numbers is summarized in Table 2.

It is important to mention that not all of the LSDs are involved in the catabolism of glycoconjugates and not all disorders of glycoconjugate catabolism are of lysosomal origin. The first congenital disorder of deglycosylation (CDDG) was described in 2013 (Freeze, 2013), caused by the disruption in *NGLY1* gene (coding peptide N-glycanase), is an enzyme deficiency predicted to cause accumulation of N-glycosylated proteins in the cytoplasm and possible endoplasmic reticulum stress. Accumulation of the undegraded material in the cytoplasm may have additional toxic effects (Enns et al, 2014), comparable to the accumulation of substrates in lysosomes, typical for LSDs. Although this disorder is nowadays considered as CDG, it has typically normal Tf IEF profile and on the other hand, abnormal oligosaccharides present in the urine of patients, that is common for LSDs.

Clinical manifestations and diagnostics of LSDs

Each LSD subtype is characteristic by different clinical and pathological profile that is associated with the accumulated substrate. Some defects may have its different phenotypic variance explained by the residual enzyme activities, but usually patients with the same mutation exhibit widely differing clinical signs; and may even be asymptomatic. Common clinical signs of LSD are abnormalities of bone development, organomegaly and disorders of central nervous system (Mehta et al, 2006). Disorders in glycoconjugate metabolism are characterized by a progressive onset that often led to the early death of the patient.

Based on a wide variety of clinical symptoms, LSDs, as well as CDGs, were characterized as difficult to diagnose. Diagnostics of LSD is usually focused on the identification of key metabolites that may occur in abnormal levels in various body fluids. The first step in diagnostic workup generally consists of urinary analyses of specific undegraded molecules. One of these is thin layer chromatography (TLC) of oligosaccharides present in patient's urine. Another diagnostic approach is based on the determination of enzyme activities in dried blood spots, that can be performed as the selective screening for suspected cases; or as general newborn screening (Gelb et al, 2019). However, enzymatic activity assays are not available for all of LSD types and their significant disadvantage is the fact that carriers of these mutations cannot be determined, because the enzyme activities of carriers correlate with normal subjects (Wang et al, 2011).

As mentioned above, a common feature of all the LSDs is specific metabolite accumulation. Therefore, mass spectrometry and NMR spectroscopy-based methods are a potential tool for fast, accurate and non-invasive diagnosis detecting metabolites excreted in the urine of patients. The last proper step to confirm the diagnosis is analysis of DNA by NGS or simple Sanger sequencing, when there is clear indication for single genetic defect. In addition to diagnostics, advanced analytical techniques may provide subsidiary information about the treatment efficacy through precise monitoring of levels of biomarkers (Pakanova et al, 2018).

Treatment of inherited metabolic disorders of glycoconjugate metabolism

Up to this date, no effective treatments for the majority of CDGs were developed. For some subtypes, dietary supplementation therapies, such as oral administration of mannose for MPI-CDG (Niehues and Hasilik, 2000) and fucose for SLC35C1-CDG (Marquardt et al, 1999); or pharmacological chaperones for CDGs that are classified as misfolding disorders (Andreotti et al, 2015, Brasil et al, 2018), were reported as successful and improving the condition of patients. The discovery of appropriate therapeutic approaches in the treatment of CDGs still remains a major issue, since the prevalence as well as the number of these unique diseases is increasing. Never before have so many disorders from the same family been identified in such short time lapse (Jaeken, 2010). Since the prevalence of individual LSDs is significantly higher than that of CDGs, the number of available and effective therapies is more favorable. Up to this date, twenty-three orphan drugs were FDA-approved for the treatment of 12 LSDs (updated from Garbade et al, 2020). Treatment of LSDs is focused mainly on substrate- or enzyme- replacement therapies, chaperones and small molecules. These data suggest more positive perspective for the development of treatment of disorders in glycoconjugate catabolism than in the case of disorders in their synthesis.

Since the disorders of glycoconjugate metabolism are a group of monogenic diseases, they are potential candidates for gene therapy. Nevertheless, vector-targeted immune responses remain a major limitation of this gene-delivery tool in clinical practice. The reduced number of subjects suitable for clinical trials might also cause the current low number of curative treatments (Brasil et al, 2018).

Conclusion

This review provides a brief summary of knowledge of biosynthesis or degradation of glycoconjugates, known defects in their metabolic pathways and their clinical and biochemical effects in human organism. Nowadays, the amount of glycan structures correlating with various phenotypes is rapidly increasing, and the diagnosis and treatment of these diseases still remain a challenge. Thus, the collaboration between research laboratories, physicians and clinical institutions, where the screening for hereditary metabolic diseases is performed, plays an important role in the progress of diagnostics of CDGs and LSDs subtypes as well as in the development in new therapeutic approaches.

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