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종 설

선천성 당화 장애에 대한 전반적 고찰

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A Comprehensive Review of Congenital Disorders of Glycosylation

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Congenital Disorders of Glycosylation (CDG) represent a complex group of inherited metabolic disorders resulting from defects in multiple pathways of glycosylation, a critical biochemical process for protein functionality and cellular communication. This review provides a comprehensive overview of CDG, including its history, epidemiology, classification, diagnostic complexities, and therapeutic developments. Despite advancements in understanding CDG and identifying over 160 subtypes, challenges remain due to the diverse clinical manifestations and multisystemic involvement. Targeted therapy is available for only a few CDGs, but promising treatments are being investigated. Ongoing research is vital to developing targeted treatments and improving patient outcomes.

Key words: Congenital Disorders of Glycosylation, Glycosylation, Inborn Errors of Metabolism

Introduction

Recent classification of inherited metabolic disorders classified 1450 disorders into 24 categories[1)]. congenital disorders of glycosylation (CDG), a complex group of metabolic disorders that arise from defects in the enzymatic process of glycosylation affecting the synthesis and attachment of glycans in glycoproteins and glycolipids[2)]. The glycosylation process is essential for protein functionality and cell-to-cell communication, occurring in all cells of the body[3)]. Defects in glycosylation can arise in various cell organelles, including the cytosol, endoplasmic reticulum (ER), ER-Golgi intermediate compartment, Golgi apparatus, and the sarcolemma membrane[4)]. This ubiquity explains why defects in glycosylation lead to multi-systemic involvement[5)]. Despite our understanding of these disorders has expanded substantially, new CDG subtypes continue to be reported, and the diversity in clinical manifestations across various organ systems inherent to CDG makes difficulty in identifying CDG and continues to complicate diagnosis and treatment. This review article provides a comprehensive overview of CDG, focusing on their history, pathophysiology, diagnostic complexities, and treatment developments.

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History of CDG

CDG was first recognized in the early 1980s when

Jaak Jaeken and his colleagues described a new type of metabolic disorder characterized by defective glycosylation of serum transferrin[6], which they initially termed "carbohydrate-deficient glycoprotein syndrome." This discovery opened up a new field of study in metabolic and genetic disorders. Through the 1990s and into the 21st century, advances in molecular biology and genetics led to the identification of multiple types f CDG, each associated with defects in different glycosylation pathways. The classification of CDG expanded from just one type (CDG-Ia, caused by a PMM2 gene mutation) to include many distinct disorders, classified as type I and type II CDG based on the characteristic result of serum transferrin (Tf) isoelectric focusing (IEF)[7]. In the 30 years since 1980, 60 CDG have been discovered[8]. After whole exome sequencing found Miller syndrome caused by mutations in DHODH in 2010, the CDG subtypes rapidly increased to 163 CDG[8,9]. As a result of these changes, the nomenclature for CDG has been updated by appending "-CDG" to the name of the affected gene[10]. This historical overview highlights the progression from the discovery of a new group of disorders to an in-depth understanding of their genetic and biochemical foundations, reflecting the ongoing challenges in managing these intricate conditions.

Epidemiology

The incidence and prevalence of CDG have not been well established due to the rarity and diversity of these disorders. However, some epidemiological studies provide insights into their occurrence. The prevalence of CDG in Europe, where screening is most actively conducted, is estimated to be approximately 0.1 to 0.5 per 1,000,000 individuals[11]. A study by Lipinski et al. from 1997 to 2020 estimated the prevalence of CDG in the Polish population at approximately 1 per million, with an annual incidence of CDG at 0.013 per 100,000 people[12]. In a study conducted in southern Brazil by Magalhães et al. from 2008 to 2017, 1546 individuals were investigated using Tf-IEF, and only four individuals were molecularly diagnosed with CDG[13]. The prevalence of PMM2-CDG, the most common type of CDG, could be as high as 1 in 20,000[14]. A review article on epidemiology data of CDG from 165 papers reported prevalence or frequency data based on allele frequency in 17 ethnic group/region or country[15].

Glycosylation and its role

Glycosylation, a biochemical process that involves attaching branched monosaccharide structures known as glycans to proteins or lipids, crucially modulates the functionality and stability of these biomolecules[16]. Monosaccharides used in the human body, including glucose, galactose, N-acetylglucosamine (GlcNAc), N-acetylgalactosamine, glucuronic acid, xylose, mannose, fucose, sialic acid, and ribitol, need be activated to nucleotide sugars, a higher energy state, for incorporation into glycans[17]. Glycosylation significantly affects protein structure, function, and half-life, influencing protein folding, stability, cellular communication, and pathogen interaction[3,16]. It supports structural integrity, cellular trafficking, and modulates protein activity[3]. Glycans contribute to organismal development, differentiation, and environmental interaction, highlighting the essential and complex nature of these carbohydrate modifications in biological systems[3].

Classification of glycosylation defect

CDG can be categorized based on the type of glycosylation affected: defects in N-glycosylation, defects in O-glycosylation, combined N- and O-glycosylation defects, defects in lipid glycosylation, and defects in glycosylphosphatidylinositol synthesis[4,16]. N-linked glycosylation involves attaching GlcNAc to asparagine

residues, essential for protein folding, stability, and cell signaling, starting in the ER and continuing in the Golgi apparatus[4]. O-linked glycosylation occurs on serine or threonine residues, primarily adding N-acetylgalactosamine, and is abundant on mucins that protect epithelial surfaces[4]. Other forms include O-linked fucose and O-linked mannose, often in specific protein domains. O-GlcNAcylation adds GlcNAc to Ser or Thr on intracellular proteins, impacting signaling and metabolism, regulated by O-GlcNAc transferases and O-GlcNAcases. Glycosphingolipids, with glycans attached to lipids, stabilize membranes and aid in signal transduction. Glycosylphosphatidylinositol-anchored glycoproteins link proteins to membranes via glycan-phospholipid bridges, crucial for protein localization and stability[4]. Proteoglycans and glycosaminoglycans, cha racterized by long polysaccharide chains, such as hepa ran sulfate, chondroitin sulfate, keratan sulfate, and hyaluronan, are crucial components of the extracellular matrix and glycocalyx, maintaining cell structure and mediating signaling[4]. Multiple glycosylation pathways can be affected by defect in the synthesis or transport of sugar precursor, defects in the biosynthesis of dolichol-monosaccharides, and defects in Golgi homeostasis[4]. Glycosylation pathways according to cellular location are summarized Table 1.

Clinical manifestations

Although some CDG (~12%) (e.g., EXT2-CDG, DHDDS-CDG) involves only single organ, most CDG (~88%) are usually multi-systemic disease with phenotypic diversity, ranging from prenatal death to mild adult involvement[9]. The most common symptoms of CDG are neurological manifestations and developmental disability, usually exhibit an early-onset neurovisceral signs and symptoms from birth[2]. Neurological symptoms of CDG include psychomotor retardation, hypotonia, microcephaly, seizures, ataxia, peripheral neuropathy, stroke-like episodes, epilepsy, and epileptic encephalopathies (e.g., ALG1-CDG, ALG3-CDG, PIGA-CDG)[2]. In rare cases, CDG can be associated with brain malformations such as lissencephaly and polymicrogyria (e.g., O-glycosylation disorders), involvement of the cerebellum (e.g., PMM2-CDG, dystroglycanopathies, and SRD5A3-CDG), or linked with congenital muscular dystrophy (e.g., PMM2-CDG, dystroglycanopathies)[2]. Since the liver is a major site for the production of glycosylated serum proteins in the body, liver is often involved in CDG (22%). This involvement often manifests early as elevated serum transaminases and can progress to liver fibrosis or cirrhosis, hepatic encephalopathy, bleeding tendency, ascites, and hepatopulmonary syndrome[18]. Heart disease, another significant concern, appears in about 20% of CDG cases, presenting as cardiomyopathy, arrhythmias, or structural defects[19]. The immunodeficiency and skeletal dysplasia are also a notable feature in several CDG types[2]. Moreover, some CDG type may have distinctive clinical features that can expedite recognition and diagnosis, such as specific craniofacial dysmorphia in PMM2-CDG or connective tissue involvement in others (e.g., ATP6V0A2-CDG, COG7-CDG, ATP6AP1-CDG)[2].

Diagnosis

Some CDG with unique manifestations can be suspected based on characteristic symptoms; however, diagnosing many CDG is challenging due to their nonspecific multisystemic involvement. Since Jaeken et al. first utilized it in 1984, Tf-IEF has become the diagnostic method of choice for detecting hypo-N-glycosylation disorders associated with a deficiency in sialic acid. Several laboratory techniques including high-performance liquid chromatography, capillary zone electrophoresis, and mass spectrometry have been used for the separation and quantification of serum Tf isoforms. Like other inborn error metabolic disorders,

Table 1. Glycosylation pathway according to cellular location

Cellular location	Glycosylation pathway
Cytosol	Monosaccharide synthesis and interconversion: MAN2B2, MPI, PMM2
	O-linked glycosylation (via GlcNAc): OGT
	Multiple glycosylation Pathway: FCSK, G6PC3, GNE*, NANS*, PGM1*, PGM3*
	Nucleotide sugar synthesis: CAD, GMPPA, GMPPB
ER	N-linked glycosylation
	N-glycan LLO assembly: ALG1, ALG2, ALG3, ALG6, ALG8, ALG9, ALG11, ALG12, ALG13, ALG14, DPAGT1, RFT1
	N-glycan transfer to protein: DDOST, MAGT1, SSR3, SSR4, STT3A, STT3B, TUSC3
	N-glycan processing: GANAB, JAGN1, MAN1B1, MOGS, PRKCSH
	O-linked glycosylation (via GlcNAc, Glc, Fuc): EOGT, POGLUT1, POFUT1
	Multiple glycosylation pathway (Dolichol synthesis and utilization): DHDDS, DOLK, DPM1*, DPM2*, DPM3*, MPDU1, NUS1, SRD5A3
	GPI anchor biosynthesis: GPAA1, PGAP1, PGAP2, PGAP3, PIGA, PIGB, PIGC, PIGG, PIGH, PIGK, PIGL, PIGM, PIGN, PIGO, PIGP, PIGQ, PIGS, PIGT, PIGU, PIGV, PIGW, PIGY
ER-Golgi intermediate compartment	Transport vesicle and initial processing of glycoproteins
	Nucleotide sugar transport: SLC35A1, SLC35A2, SLC35A3, SLC35C1, SLC35D1
	Vesicular trafficking: COG1*, COG2*, COG4*, COG5*, COG6*, COG7*, COG8*, GORAB, GOSR2, SEC23B, TRAPPC11, TRIP11, VPS13B
Golgi	N-linked glycosylation (N-glycan processing): FUT8, MGAT2
	O-linked glycosylation (via Man, GalNAc, Xyl, Fuc): B3GALNT2, B4GAT1, CRPPA, FKRP, FKTN, LARGE1, C1GALT1C1, GALNT2, GALNT3, B3GALT6, B3GAT3, B4GALT7, CANT1, CSGALNACT1, DSE, EXT1, EXT2, EXTL3, CHSY, XYLT1, XYLT2, B3GALTL, LFNG
	Multiple glycosylation pathway
	Glycosyltransferases: B4GALT1, ST3GAL3, GNPTAB*
	Golgi pH and ion homeostasis: ATP6AP1, ATP6AP2, ATP6V0A2, ATP6V1A, ATP6V1E1, CCDC115, SLC9A7, SLC10A7, SLC39A8, TMEM165*, TMEM199, VMA21
	Lipid glycosylation: A4GALT, B4GALNT1, ST3GAL5

ALG6, Alpha-1,3-Glucosyltransferase; CDG, congenital disorder of glycosylation; COG7, Conserved Oligomeric Golgi Complex Subunit 7; ER, endoplasmic reticulum; Fuc, fucose; GalNAc, N-Acetylgalactosamine; Glc, glucose; GlcNAc, N-Acetylglucosamine; GNPTAB, GlcNAc-1-Phosphotransferase Subunits Alpha/Beta;GPI, glycosylphosphatidylinositol; LLO, lipid-linked oligosaccharides; Man, mannose; MPI, Mannose Phosphate Isomerase; PIGM, Phosphatidylinositol Glycan Anchor Biosynthesis Class M; PMM2, Phosphomannomutase 2; SLC35A2, Solute Carrier Family 35 Member A2; Xyl, xylose.
*CDG subtypes involved in both N-glycosylation and O-glycosylation.

Tf-IEF from dried blood spot samples was recently demonstrated as a reliable method for CDG screening. Lipinski et al. recommend using serum Tf IEF as an initial screening tool in their diagnostic algorithm for CDG, which can differentiate some specific types of CDG by interpreting Tf isoform profile[2]. A type 1 pattern, indicated by decreased tetrasialotransferrin and increased disialo- and asialotransferrin, suggests a defect in glycan assembly or transfer to the peptide chain (CDG-I). In contrast, a type 2 pattern, marked by an increase in trisialo- and monosialotransferrin, points to a glycan remodeling defect (CDG-II)[7]. However, there are some limitations in Tf-IEF. First, normal results do not rule out the possibility of CDG because secondary causes of N-hypoglycosylation, such as galactosemia, may be present. Second, polymorphisms in the transferrin gene can lead to abnormal patterns. Third, some CDG, particularly those not involving defects in N-glycosylation, may exhibit a normal Tf isoform profile. Fourth, many newly discovered CDG lack sufficient information on Tf isoform profiles. Due to these reasons, recent diagnostic approaches have shifted towards using Next Generation Sequencing. Recently, new diagnostic markers have been

proposed for detecting CDG. These include Apolipoprotein C-III for identifying defects in O-glycan biosynthesis, two-dimensional electrophoresis of haptoglobin β glycoforms for diagnosing combined CDG, bikunin analysis by western blot for linkeropathies, and flow injection-electrospray ionization-quadrupole time-of-flight mass spectrometry for enhancing serum N-glycan profiling.

Treatment

Although current therapies for CDG are usually primarily supportive, targeted interventions are available in only a small subset. Nutritional therapies include oral supplementation of monosaccharide sugar, manganese, uridine, or pydidoxine[20]. For instance, oral mannose supplementation in MPI-CDG has shown efficacy in improving endocrine function and coagulation, albeit with limited impact on hepatic issues. Similarly, galactose supplementation in PGM1-CDG has led to improved glycosylation and liver function. There are 7 types of CDG with oral supplementation of monosaccharide serving as an effective method to circumvent enzymatic blocks[4,20]. Transplantation therapies, including liver (e.g., ATP6AP2-CDG) and hematopoietic stem cell transplants (e.g., MAN2B2-CDG), have been applied in severe cases involving multi-organ failure (Table 2). Disease modeling and drug repositioning is also investigated in several CDG [21]. Promising treatments, including pharmacological chaperones (e.g., for PMM2-CDG)[22] and gene therapies (e.g., for PGM1-CDG)[23], are currently being explored in experimental studies.

Conclusion

Recognizing and diagnosing CDG is crucial due to their diverse and multi-systemic manifestations. Despite significant advancements, CDG remains underdiagnosed, highlighting the need for increased awareness and improved diagnostic methods. Future efforts should focus on developing targeted therapies and enhancing collaborative research to address the complexities of CDG, ultimately improving patient outcomes and quality of life.

요 약

선천성 당화장애(CDG)는 당화 과정의 결함으로 인해 발생하는 다양한 유전 대사 장애 질환을 포함한다. 당화는 단백질 접힘, 안정성 및 세포 간 신호전달에 필수적인 생화학적 과정이다. CDG는 1980년대에 처음 발견된 이후로 분자생물학과 유전학의 발전에 따라 현재까지 163개의 아형이 발견되었고 트랜스페린 등전점 전기영동이 선별검사로 사용되고 있으며 유전학적 진단기법의 발달로 CDG의 진단이 확연히 늘었으며, 다양한 선천성 당화장애의 결함에 대한 진단 기법이 연구되고 있다. CDG의 치료는 주로 대증요법에 의존하며, 일부 아형에서 단당

Table 2. Current effective therapies for CDG

Treatment	CDG subtype
Monosaccharide supplementation	
Mannose	MPI[24]
Galactose	PGM1[25], SLC35A2[26], SLC39A8[27], TMEM165[28]
Fucose	SLC35C1[29]
Dietary intervention	
Uridine	SLC39A8[30], CAD[31]
Manganese	SLC39A8[30]
Ketogenic diet	PIGA[32]
Transplantation	
Heart	DOLK[33]
Liver	MPI[34], CCDC115[35]
Hematopoietic stem cells	PGM3[36], MAN2B2[37]
Pharmacologic chaperons	
Multiple chaperone compounds	PMM2[38]
Other	
Acetazolamide	PMM2[39]
Pyridoxine	PIGS[40]
Pyridostigmine	GFPT1[41], ALG2[42], ALG14[42]
Sodium butyrate	PIGM[43]

류, 망간, 우라신, 피리독신 등의 경구 보충요법과 간 이식, 조혈모세포 이식이 사용되고 있으며 약리학적 샤페론, 유전자 치료, 그리고 약물 재배치 연구가 진행되고 있다. CDG 환자들의 진단과 치료에 대한 지속적인 연구와 협력이 필요하다.

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