GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Congenital Disorders of Glycosylation Overview

[*CDG Syndromes, Carbohydrate-Deficient Glycoprotein Syndromes*]

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Initial Posting: August 16, 2005.

Summary

Disease characteristics. Congenital disorders of glycosylation (CDG) are a group of disorders of abnormal glycosylation of N-linked oligosaccharides. Manifestations range from severe developmental delay and hypotonia with multiple organ system involvement to hypoglycemia and protein-losing enteropathy with normal development; the disorders most commonly begin in infancy. Thirteen different enzymes in the N-linked oligosaccharide synthetic pathway are currently recognized to be defective in individual types of CDG. CDG-Ia is the most common form reported and is characterized by cerebellar hypoplasia, facial dysmorphism, psychomotor retardation, and abnormal fat distribution. The clinical course has been divided into an infantile multisystem stage, a late-infantile and childhood ataxia-mental retardation stage, and an adult stable disability stage.

Diagnosis/testing. The diagnostic test for all types of CDG is analysis of serum transferrin glycoforms by isoelectric focusing to determine the number of sialylated N-linked oligosaccharide residues linked to serum transferrin. Such testing is clinically available. Neuroimaging may detect an enlarged cisterna magna and superior cerebellar cistern in early childhood, infratentorial and supratentorial changes, and Dandy-Walker malformations and small white matter cysts. Molecular genetic testing of the *PMM2* gene in the CDG-Ia subtype and the *MPI* gene in the CDG-Ib subtype detects up to 100% of mutations confirmed enzymatically in individuals in research studies.

Management. CDG-Ib, characterized by hepatic-intestinal disease, is the only type of CDG for which therapy exists; mannose normalizes hypoproteinemia and coagulation defects and rapidly improves the protein-losing enteropathy and hypoglycemia. Infants and children with all types of CDG except CDG-IB are nourished with formula for maximal caloric intake; some children require a nasogastric tube or gastrostomy tube. Thickening of feeds, maintenance of an upright position after eating, and antacids prevent gastroesophageal reflux and/or persistent vomiting. Occupational therapy, physical therapy, and speech therapy are instituted with developmental delay. Vision is preserved by use of glasses, patching, or surgery. Thyroid hormone replacement is used to treat elevated TSH and low free T4. Hydration by IV and physical therapy support the individual after stroke-like episodes. Adult treatment of orthopedic issues includes orthopedic and physical medicine, wheel chairs, transfer devices, physical therapy, and surgical treatment of spinal curvature. Acetominophen and other agents metabolized by the liver are used with caution.

Genetic counseling. The CDGs are inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% risk of being affected, a 50% risk of being an asymptomatic carrier, and a 25% risk of being unaffected and not a carrier. Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3. Carrier testing for at-risk family members is available on a clinical basis for some of the CDG subtypes if the mutations have been identified in the proband. Prenatal diagnosis for pregnancies at increased risk for some types of CDG is possible when both disease-causing mutations are known. For other types of CDG, prenatal testing may be available through laboratories offering custom prenatal testing.

Definition

Clinical Manifestations

Congenital disorders of glycosylation (CDG) most commonly begin in infancy. Manifestations range from severe developmental delay and hypotonia with multiple organ system involvement to hypoglycemia and protein-losing enteropathy with normal development.

Establishing the Diagnosis

Congenital disorders of glycosylation are a group of disorders caused by the defective synthesis of N-linked oligosaccharides, sugars linked together in a specific pattern and attached to proteins and lipids (N-linked glycans link to the amide group of asparagine via an N-acetylglucosamine residue) [Jaeken et al 1991, Jaeken & Matthijs 2001, Grunewald et al 2002].

The diagnostic test for all types of CDG is analysis of serum transferrin glycoforms, also called "transferrin isoforms analysis" or "carbohydrate-deficient transferrin analysis," by isoelectric focusing (IEF) or other isoform analysis (i.e., capillary electrophoresis, GC/MS) to determine the number of sialylated N-linked oligosaccharide residues linked to serum transferrin [Stibler & Jaeken 1990, Jaeken & Carchon 2001]. Such testing is clinically available.

- Normal transferrin IEF pattern: Two biantennary glycans linked to asparagine with four sialic acid residues.
- Type I transferrin IEF pattern: A decrease of tetrasialotransferrin and an increase of asialotransferrin and disialotransferrin. The pattern indicates defects in the earliest synthetic steps of the N-linked oligosaccharide synthetic pathway.
- Type II transferrin IEF pattern: An increase of the tri-sialo- and monosialo fractions, most likely because of the incorporation of truncated or monoantennary sugar chains, defects in the terminal portion of the pathway [Jaeken & Matthijs 2001].

Note: (1) The diagnostic validity of analysis of serum transferrin glycoforms before three weeks of age is controversial [Clayton et al 1992, Stibler & Skovby 1994]. (2) On rare occasions, individuals with the diagnosis of PMM enzyme deficiency with normal transferrin glycosylation have been reported [Fletcher et al 2000, Marquardt & Denecke 2003]. (3) Results are expected to be normal in CDG-IIb and CDG-IIc. (4) It is possible that an abnormal transferrin IEF pattern is the result of a transferrin protein variant. IEF of a serum sample from the parents can clarify the result.

Neuroimaging—In CDG-Ia:

- An enlarged cisterna magna and superior cerebellar cistern are observed in late infancy to early childhood.

- Occasionally, both infratentorial and supratentorial changes compatible with atrophy are present.
- Dandy-Walker malformations and small white matter cysts have been reported [Jensen et al 1995, Peters et al 2002].
- Myelination varies from normal to delayed or insufficient [Holzbach et al 1995].

In other types of CDG, MRI may range from normal to non-cerebellar findings.

Differential Diagnosis

Other genetic disorders to consider:

- Prader-Willi syndrome
- Congenital muscular dystrophies including Fukuyama congenital muscular dystrophy (FCMD), caused by mutations in *FCMD;* muscle-eye-brain (MEB) disease, caused by mutations in *POMGNT1* [Yoshida et al 2001, Martin & Freeze 2003]; and Walker-Warburg syndrome, caused by mutations in *POMT1* (see Congenital Muscular Dystrophies Overview).
- Congenital myopathies (such as X-linked myotubular myopathy, multiminicore myopathy)

The following metabolic disorders are in the differential diagnosis of hypotonia, developmental delay, and failure to thrive:

- Mitochondrial disorders (see Mitochondrial Disorders Overview)
- Peroxisome biogenesis disorders, Zellweger syndrome spectrum. Children with peroxisomal disorders are likely to present with seizures and/or hearing loss.
- Urea cycle defects (see Urea Cycle Disorders Overview). Children with urea cycle defects are likely to be ill at presentation.

Prevalence

CDG-Ia is the most common form of CDG reported to date, with more than 400 affected individuals worldwide. The prevalence could be as high as 1:20,000 [Jaeken & Matthijs 2001]. The expected carrier frequency of *PMM2* mutations in the Danish population is 1/60-1/79 [Matthijs et al 2000].

CDG-Ib. At least 20 individuals have been reported.

CDG-Ic. At least 20 individuals have been reported.

All other types of CDG are case reports of a small number of individuals.

Causes

Clinical Findings

Because of the important biologic functions of the oligosaccharides in both glycoproteins and glycolipids, incorrect synthesis of these compounds results in multisystemic clinical manifestations [Varki 1993]. The clinical spectrum of the group of disorders included in congenital disorders of glycosylation is broad. Individual types of CDG are reviewed in Table 1. For many types, only a few individuals have been reported; thus, the phenotype is not completely known.

Table 1. Signs and Symptoms by CDG Subtype

CDG Subtype	CDG-Ia	CDG-Ib	CDG-Ic	CDG-Id	CDG-Ie	CDG-IIa	CDG-IIb	CDG-IIc
# of Affected Individuals	>300	~20	~20	1	4	4	1	3
Sign/Symptom								
Psychomotor retardation	+ →+++	—	+/++	+++	+++	– →+++	+++	+++
Seizures	+ →++	±	+ →+++	+++	+++	+++	+++	—
Axial hypoplasia	+++	±	++/+++		+++	++	++	+++
Strabismus	+++	-	++					
Cerebellar hypoplasia	+++	—	—	—	±	—	—	—
Unusual fat distribution [1]	+ →+++	—	±	±	+	++	+++	+++
Liver disease	+	+++	—	—	+	+	+++	
Coagulopathy	++/+++	+/+++	+++		+	+++	++	
Protein-losing enteropathy	±	+++	+	–	–	–		
Other	Multi-organ involvement			Microcephaly	Microcephaly	Stereotyped behavior	Early death	LAD II Phenotype

From Grunewald et al 2002

1. Fat pads, inverted nipples

CDG-Ia. CDG-Ia, the most common type of CDG, is characterized by inverted nipples, abnormal subcutaneous fat distribution, and cerebellar hypoplasia, in combination with facial dysmorphism and psychomotor retardation. The clinical course has been divided into an infantile multisystem stage, late-infantile and childhood ataxia-mental retardation stage, and adult stable disability stage. (See CDG-Ia.)

CDG-Ib. Cyclic vomiting, profound hypoglycemia, failure to thrive, liver fibrosis, and protein-losing enteropathy, occasionally associated with coagulation disturbances without neurologic involvement, are characteristic [de Koning et al 1998, Jaeken et al 1998, Niehues et al 1998, Babovic-Vuksanovic et al 1999, de Lonlay et al 1999, Adamowicz et al 2000]. The clinical course is variable even within families.

CDG-Ic. Previously classified as CDGS type V [Korner et al 1998], CDG-Ic is characterized by mild to moderate neurologic involvement with hypotonia, poor head control, developmental delay, ataxia, strabismus, and seizures, ranging from febrile convulsions to epilepsy [Grunewald et al 2000; Hanefeld et al 2000; Imbach, Grunewald et al 2000]. The clinical presentation is milder than in CDG-Ia; stroke-like episodes, peripheral neuropathy or skeletal abnormalities have not been reported.

CDG-Id. Two infants were reported with severe psychomotor delay, hypsarrhythmia, postnatal microcephaly, optic atrophy, iris coloboma, and atrophy of the brain and corpus callosum [Stibler et al 1995, Korner et al 1999].

CDG-Ie. Two individuals with severe developmental delay, seizures, and dysmorphic features were reported [Imbach, Schenk et al 2000; Kim et al 2000; Orlean 2000]. They had microcephaly, hypertelorism, a "gothic palate," small hands with dysplastic nails, and knee contractures.

CDG-If. Five individuals with severe psychomotor retardation, generalized scaly, erythematous skin, and attacks of hypertonia have been reported [Jaeken et al 2000, Schenk et al 2001, Kranz et al 2001].

CDG-Ig. One individual with distinctive facial features, generalized hypotonia, feeding difficulties, severe psychomotor retardation, progressive microcephaly, and frequent upper respiratory tract infections was reported [Chantret et al 2002].

CDG-Ih. A four-month-old female with moderate hepatomegaly, severe diarrhea, and hypoalbuminemia from protein-losing enteropathy had normal facial features and normal development [Chantret et al 2003]. She had decreased levels of factor XI, protein C, and antithrombin III.

CDG-Ii. A six-year old had bilateral iris colobomas, a unilateral cataract, infantile spasms beginning at four months of age, and severe developmental delay; coagulation factors were abnormal [Thiel et al 2003].

CDG-IIa. Individuals have facial dysmorphism, stereotypic hand movements, seizures, and varying degrees of psychomotor retardation, but no peripheral neuropathy or cerebellar hypoplasia. A bleeding disorder is caused by diminished platelet aggregation [Van Geet et al 2001].

CDG-IIb. An infant with generalized hypotonia, craniofacial dysmorphism, hypoplastic genitalia, seizures, feeding difficulties, hypoventilation, and generalized edema died at 2.5 months of age [De Praeter 2000].

CDG-IIc. Severe growth and psychomotor retardation, microcephaly, hypotonia, cranofacial dysmorphy, and recurrent bacterial infections with persistent, highly elevated peripheral blood leukocyte count are characteristic [Etzioni 2002].

CDG-IId. Mild psychomotor retardation, Dandy-Walker malformation, progressive hydrocephalus, coagulation abnormalities, and elevated serum creatine kinase concentration have been observed [Peters et al 2002].

Molecular Genetics

Thirteen different enzymes in the N-linked oligosaccharide synthetic pathway are currently recognized to be defective in individual types of CDG (Table 2).

Table 2. CDG Types

CDG Subtype [1]	Gene Symbol	Chromosomal Locus	Protein Name
CDG-Ia	*PMM2*	16p13.3-p13.2	Phosphomannomutase 2
CDG-Ib	*MPI*	15q22-qter	Mannose Phosphate Isomerase
CDG-Ic	*ALG6*	1p22.3	Man(9)GlcNAc(2)-PP-dolichyl -alpha-1,3-glucosyltransferase
CDG-Id	*ALG3*	3q27.3	Dolichyl-P-Man:Man(5)GlcNAc(2)-PP-dolichyl mannosyltransferase
CDG-Ie	*DPM1*	20q13.13	Dolichol-phosphate mannose synthetase I
CDG-If	*MPDU1*	17p13.1-p12	Mannose-P-dolichol utilization defect 1
CDG-Ig	*ALG12*	Chr.22	Dolichyl-P-Man:Man(7)GlcNAc(2)-PP-dolichyl-alpha-1,6-mannosyltransferase
CDG-Ih	*ALG8*	11pter-p15.5	Probable dolichyl pyrophosphate Glc(1)Man(9)GlcNAc(2) alpha-1,3-glucosyltransferase
CDG-Ii	*ALG2*	9q22	Alpha -1,3-mannosyltransferase
CDG-IIa	*MGAT2*	14q21	UDP-N-acetylglucosamine:alpha-1,6-mannosyl-glycoprotein-beta-1,2-N-acetylglucosaminyltransferase II
CDG-IIb	*GCS1*	2p13-p12	Mannosyl-oligosaccharide glucosidase
CDG-IIc	*SLC35C1*	Chr.11	GDP-fucose transporter 1
CDG-IId	*B4GALT1*	9p13	Beta-1,4-galactosyltransferase 1

1. The nomenclature used for CDG subtypes includes a Roman numeral, I or II, and a letter (a-i) [Aebi et al 1999]. The Roman numeral is based on transferrin oligosaccharide analytic pattern: Type I and Type II. Letters are assigned in chronologic order of the date of publication of discovery.

Of the thirteen different defects identified, seven involve N-glycan assembly, three involve N-glycan processing, two involve O-glycan assembly, and one involves N-glycan processing and O-glycan assembly [Jaeken & Carchon 2001, Jaeken & Matthijs 2001, Peters et al 2002].

Evaluation Strategy

An abnormal serum transferrin isoelectric focusing pattern establishes the diagnosis of CDG.

In most CDG types, the enzyme is known but the enzymatic assay has not been developed. Thus, clarification of subtype requires molecular genetic testing. Molecular genetic testing for CGDIa-CGDIi is available clinically (see Table 3).

Table 3. Molecular Genetic Testing Used in Congenital Disorders of Glycosylation

Test Method	Subtype	Mutations Detected	Mutation Detection Rate	Test Availability
Mutation scanning	CDG-Ia	*PMM2*	Up to 100% [1]	Clinical Testing
	CDG-Ib	*MPI*	Up to 100% [1]	Clinical Testing
	CDG-Ic	*ALG6*	Unknown	Clinical Testing
	CDG-Id	*ALG3*	Unknown	Clinical Testing
	CDG-Ie	*DPM1*	Unknown	Clinical Testing
	CDG-If	*MPDU1*	Unknown	Clinical Testing
	CDG-Ig	*ALG12*	Unknown	Clinical Testing
	CDG-Ih	*ALG8*	Unknown	Clinical Testing
	CDG-Ii	*ALG2*	Unknown	Clinical Testing

1. Individuals with enzymatically confirmed diagnosis [G Matthijs, personal communication]

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Congenital disorders of glycosylation are inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of the proband are obligate carriers and therefore carry one mutant allele.
- Carriers are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband

- Adults with CDG, except for CDG-Ib, have not been reported to reproduce.
- The offspring of an individual with CDG-Ib are obligate heterozygotes (carriers). Anecdotally, one woman with CDG-Ib had a child without complications.

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis for some of the CDG subtypes if the mutations have been identified in the proband.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

DNA Banking

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which molecular genetic testing is available on a research basis only or the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk for some types of CDG is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

No laboratories offering molecular genetic testing for prenatal diagnosis for some types of CDG are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutations have been identified in an affected family member in a research or clinical laboratory. For laboratories offering custom prenatal testing, see Testing.

Management

Treatment of Manifestations

For all types except CDG-Ib:

- **Failure to thrive.** Infants and children can be nourished with any type of formula for maximal caloric intake. They can tolerate carbohydrates, fats, and protein. Early in life, children may do better on elemental formulas. Their feeding may be advanced based on their oral motor function. Some children require placement of a nasogastric tube or gastrostomy tube for nutritional support until oral motor skills improve.
- **Oral motor dysfunction with persistent vomiting.** Thickening of feeds, maintenance of an upright position after eating, and antacids can be helpful for children with gastroesophageal reflux and/or persistent vomiting. Consultation with a gastroenterologist and nutritionist is often necessary. Children with a gastrostomy tube should be encouraged to eat by mouth if the risk of aspiration is low. Continued speech and oral motor therapy aids transition to oral feeds and encourages speech when the child is developmentally ready.

- **Developmental delay.** Occupational therapy, physical therapy, and speech therapy should be instituted. As the developmental gap widens between children with CDG and their unaffected peers, parents need continued counseling and support.
- **Abnormal liver function, coagulopathy.** Low levels of factors in the coagulation cascade rarely cause clinical problems in daily activities, but must be acknowledged if an individual with CDG undergoes surgery. Consultation with a hematologist to document the coagulation status and factor levels of the affected individual and discussion with the surgeon is important. When necessary, infusion of fresh frozen plasma corrects the factor deficiency and clinical bleeding.
- **"Infantile catastrophic phase."** Symptomatic treatment may change the clinical course. Parents should also be advised that some infants with CDG-Ia never experience a hospital visit while others may require frequent hospitalization.
- **Strabismus.** Intervention by a pediatric ophthalmologist early in life is important to preserve vision through glasses, patching, or surgery.
- **Hypothyroidism.** Children with CDG who have elevated TSH and low free T4 are treated with thyroid hormone replacement.
- **Stroke-like episodes.** Supportive therapy includes hydration by IV if necessary and physical therapy during the recovery period.

Additional management issues of adults with CDG:

- **Orthopedic issues — thorax shortening, scoliosis/kyphosis.** Management involves appropriate orthopedic and physical medicine management, well-supported wheel chairs, appropriate transfer devices for the home, and physical therapy. Occasionally, surgical treatment of spinal curvature is warranted.
- **Independent living issues.** Young adults with CDG and their parents need to address issues of independent living. Aggressive education throughout the school years in functional life skills and/or vocational training helps the transition when schooling is completed. Independence in self care and the activities of daily living should be encouraged. Support and resources to parents of a disabled adult is an important part of management.

Prevention of Primary Manifestations

CDG-Ib, characterized by hepatic-intestinal disease, is the only type of CDG for which therapy exists. Mannose normalizes hypoproteinemia and coagulation defects and rapidly improves the protein-losing enteropathy and hypoglycemia. One gram of mannose per kg body weight is given per day, divided into five oral doses. Because so few individuals have been treated and the natural history of this disorder is variable, careful monitoring and discussion among physicians treating these individuals are warranted [Jaeken et al 1998, Niehues et al 1998, de Lonlay et al 1999, Hendriksz et al 2001].

Prevention of Secondary Complications

Because infants with CDG have less reserve than their peers, parents should have a low threshold for evaluation by a physician for prolonged fever, vomiting, or diarrhea. Aggressive intervention with antipyretics, antibiotics if warranted, and hydration may prevent the morbidity associated with the "infantile catastrophic phase."

Agents/Circumstances to Avoid

Acetominophen and other agents metabolized by the liver should be used with caution.

Therapies Under Investigation

In one individual with CDG-IIc, fucose improved the fucosylation of glycoproteins and reduced recurrent infections [Marquardt et al 1999].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

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References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

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Revision History

- 15 August 2005 (me) Overview posted to live Web site
- 27 February 2004 (dk) Original submission