

17.1 Introduction

■ Glycerol Kinase Deficiency

Glycerol kinase deficiency (GKD) is the only disorder of glycerol metabolism for which the biochemical defect is known and well-characterized [1]. Glycerol intolerance syndrome (GIS) is poorly characterized and appears to be associated, at least in part, with fructose-1,6-diphosphatase deficiency [2–5]. Among individuals with GKD, there are three distinct clinical phenotypes, the complex form (17.1.1) and two subtypes of the isolated form – symptomatic (juvenile, 17.1.2) and benign (adult, 17.1.3) [1].

The clinical features of a patient with complex glycerol kinase deficiency (17.1.1) will depend on the loci that are involved in this contiguous gene syndrome [1, 6]. Deletion of the adrenal hypoplasia congenita (AHC) locus (*DAX1* gene) results in the cytomegalic form of adrenal hypoplasia [6]. Affected patients exhibit the signs and symptoms of glucocorticoid and mineralocorticoid deficiency, including bronzing of the skin and gums, and inability to respond appropriately to stresses such as intercurrent illnesses, leading to hypoglycemia, hyponatremia and hyperkalemia. Death may occur during these Addisonian crises. Deletion of *DAX1* also is associated with hypogonadotropic hypogonadism [7–10]. Patients with loss of the glycerol kinase (*GK*) gene have episodes of vomiting, acidemia and stupor that seem to be unrelated to adrenal insufficiency and are similar to those observed in patients with the juvenile form of GKD (see below) [1]. Involvement of the Duchenne muscular dystrophy (*DMD*) gene may be associated with severe, progressive muscle weakness as in classical Duchenne muscular dystrophy, but also has been associated with milder muscle disease [11, 12]. All patients with involvement of the AHC, *GK* and *DMD* or *GK* and *DMD* loci, and many but not all with deletion of the AHC and *GK* genes, have been mentally retarded [1]. For those with deletions extending telomeric from *DAX1* the mental retardation may be due to loss of a novel interleukin-1 receptor family member, *IL1RAPL1* [13, 14]. A characteristic facies is seen among patients with deletion of all three loci. They have a triangular face, and a broad nasal bridge and bulbous nasal tip described as an hourglass appearance to the midface [15].

The symptomatic form of isolated glycerol kinase deficiency (Juvenile form, 17.1.2) presents in early childhood. Affected boys have had hypothermia and lethargy beginning in the first week of life, but more generally have episodic vomiting at 2 to 6 years of age associated variably with acidemia, central nervous system depression, including lethargy, somnolence, stupor and unconsciousness, and hypoglycemia, interpreted by some as a Reye-like illness [1].

The benign form (Adult GKD, 17.1.3) of isolated glycerol kinase deficiency is not associated with the episodic metabolic and CNS deteriorations seen with the other forms. Males with this biochemical phenotype are identified incidentally with pseudohypertriglyceridemia, when routine laboratory studies incorrectly identify the elevated free glycerol concentration in their blood as triglycerides [1]. These individuals have increased levels of glycerol in blood and urine and may be at increased risk of type 2 diabetes mellitus [16].

■ Diagnosis

Hyperglycemia and glyceroluria are features of glycerol kinase deficiency [1]. Although glycerol is not an acidic compound, glyceroluria generally comes to attention during evaluation of urine organic acids by gas chromatography/mass spectrometry, if a solvent extraction method is used. The enzyme deficiency can be confirmed by assay in a variety of tissues, including leukocytes, transformed lymphoblastoid cells, cultured fibroblasts, liver, kidney, small intestine and cultured amniocytes [1].

Patients with complex glycerol kinase deficiency will have a deletion of the GK gene that may be large enough to be seen by classical cytogenetic evaluation, but certainly can be identified by molecular genetic and molecular cytogenetic methods, including fluorescence in situ hybridization (FISH) [1, 17].

Because of the importance of recognizing the involvement of contiguous genes for prognosis, counseling and management, it is important to ascertain whether an individual with GKD also has involvement of the AHC and DMD loci. This can readily be accomplished by evaluation of plasma ACTH and serum creatine phosphokinase (CPK) [1, 6]. If either is significantly elevated, then additional studies are indicated. FISH for deletion of the AHC region is now possible [9].

■ Glycerol Intolerance Syndrome (GIS)

Patients with GIS have episodes remarkably similar to those observed among patients with GKD, but patients with GIS have normal GK enzymatic activity [1]. The episodes consist of sweating, irritability, confusion, lethargy and coma, with hypoglycemia and seizures observed on occasion

[2–5, 18]. Episodes have been precipitated by glycerol infusion or ingestion [2–4, 18]. Male and female patients have been described. Several recent reports indicate partial or complete deficiency of fructose-1,6-diphosphatase (FDP) [2–4], though this activity was normal in another patient [18]. One patient with FDP deficiency presented with glycerolemia, hypoglycemia and ketosis, which was at first thought to be GIS [5].

17.2 Nomenclature

No.	Disorder-affected component	Tissue distribution	Chromosomal localisation	McKusick
17.1	Glycerol kinase deficiency (17.1.1, 17.1.2, and 17.1.3)	Leukocytes, lymphoblastoid cells, fibroblasts, liver, kidney, small intestine, adrenal, cultured amniocytes	Xp21	307030

17.3 Metabolic Pathway

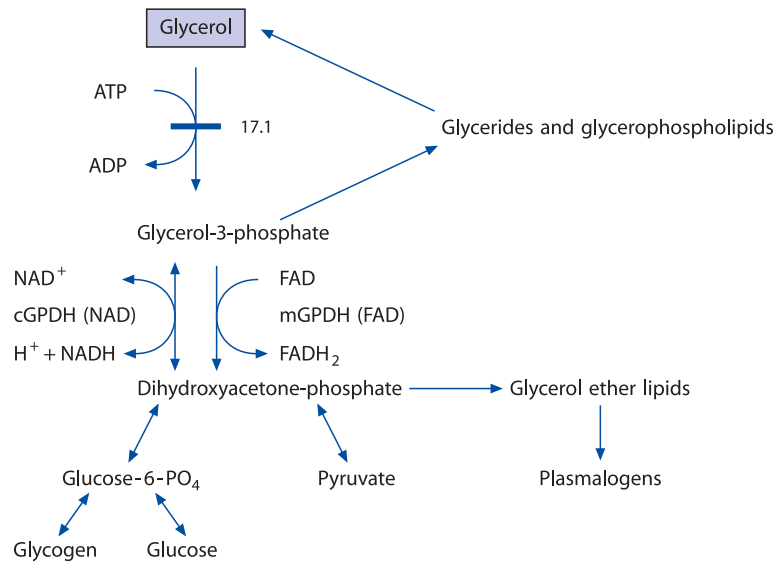


Fig. 17.1. Metabolism of glycerol. 17.1, Glycerol kinase; *cGPDH* (*NAD*), cytoplasmic *NAD*-linked glycerol-3-phosphate dehydrogenase; *mGPDH* (*FAD*), mitochondrial *FAD*-linked glycerol-3-phosphate dehydrogenase. Dihydroxyacetone-phosphate is an intermediate in the glycolytic pathway as well as a precursor for plasmalogens

17.4 Signs and Symptoms

Table 17.1. Complex GKD (1) (>50 Patients)

System	Signs/symptoms	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Dysmorphic	±	±	±	±	±
	Mental retardation	±	±	±	±	±
	Short stature	±	±	±	±	±
Routine laboratory	Triglycerides ^a (s)	↑	↑	↑	↑	↑
	Glucose ^b (s)	↓	↓	↓	↓	?
	pH ^b (B)	↓	↓	↓	↓	↓
Special laboratory	Creatinine kinase(s)	±↑	±↑	±↑	±↑	±↑
	Glycerol (u)	↑	↑	↑	↑	↑
	Glycerol (s)	↑	↑	↑	↑	↑
	ACTH (P)	±↑	±↑	±↑	±↑	±↑
Eye	Strabismus	±	±	±	±	±
	Abnormal ERG	+	+	+	+	+
GI	Vomiting ^b	+	+	+	+	?
Musculoskeletal	Weakness	±	±	±	±	±
	Pseudohypertrophy	±	±	±	±	±
Bone	Osteoporosis	±	±	±	±	±
	Pathological fractures	±	±	±	±	±
Endocrine	Adrenal hypoplasia	±	±	±	±	±
Dermatological	Addisonian pigmentation	±	±	±	±	±
Genitalia	Abnormal ^c	±	±	±	±	±
CNS	Depressed level of consciousness ^b	+	+	+	+	?
	Seizures	±	±	±	±	?

^a Pseudohypertriglyceridemia due to elevated free glycerol.

^b Episodic.

^c Abnormal genitalia include anorchia, cryptorchidism.

^d May improve with decreased glycerol intake.

Table 17.2. Juvenile GKD (6 Patients)

System	Signs/symptoms	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Mental retardation ^d	±	±	±	±	?
	Seizures	±	±	±	±	?
Routine laboratory	Triglycerides ^a (s)	↑	↑	↑	↑	↑
	Glucose ^b (s)	↓	↓	↓	↓	↓
	pH ^b (B)	↓	↓	↓	↓	↓
Special laboratory	Glycerol (u)	↑	↑	↑	↑	↑
	Glycerol (s)	↑	↑	↑	↑	↑
	EEG ^d			±		
GI	Vomiting ^b	+	+	+	+	+
CNS	Depressed level of consciousness ^b	+	+	+	+	+

^a Pseudohypertriglyceridemia due to elevated free glycerol.

^b Episodic.

^c Abnormal genitalia include anorchia, cryptorchidism.

^d May improve with decreased glycerol intake.

Table 17.3. Adult GKD (>25 Patients)

System	Signs/symptoms	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Obesity (↑ Body mass)					↑
Routine laboratory	Triglycerides ^a (s)	?	?	?	↑	↑
Special laboratory	Glycerol (u)	-	-	-	↑	↑
	Glycerol (s)	-	-	-	↑	↑
	Glucose	?	?	?	?	↑ [16]

^a Pseudohypertriglyceridemia due to elevated free glycerol.

17.5 Reference Values

Age	Glycerol (u) (mM)	Glycerol (u) (mmol/mol creat)	Glycerol (s) (mM)
Not specified	≤0.2	not detectable	0.02–0.27

Values taken from McCabe [1].

17.6 Pathological Values/Differential Diagnosis

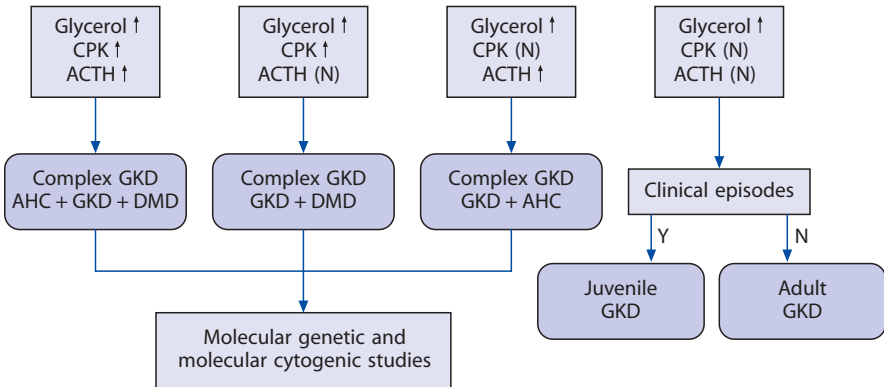
Disorder	Glycerol (u) (mmol/l)	Glycerol (u) (mmol/mol creat)	Glycerol (s) (mmol/l)
17.1 GKD ^a (17.1.1, 17.1.2, and 17.1.3)	41–345	90–193	1.8–8.3

^a Values taken from McCabe [1]. No differences have been noted with the different phenotypes [1].

17.7 Loading Tests

Not indicated – may cause severe CNS symptomatology.

17.8 Diagnostic Flow Chart



* Urine glycerol can be elevated from glycerol-containing emollients applied to perineum or glycerin suppositories contaminating bagged urine specimens

17.9 Specimen Collection

Test	Preconditions	Material	Handling	Pitfalls
Glycerol (u)	None	Random or 24 h	Keep cool or frozen	Contamination by emollients or glycerin suppository
Glycerol (s, p)	None	Serum/plasma	Keep cool or frozen	Some rubber stoppers in vacuum tubes use glycerol as lubricant

17.10 Prenatal Diagnosis

Disorder	Material	Timing, trimester	Ref.
17.1	Amniocytes	II	1

17.11 DNA Analysis

Disorder	Tissue/specimen	Method	Ref.
17.1	WBC, lymphoblastoid cell lines, fibroblasts, amniocytes	PCR and sequencing, FISH	1
			Research testing not clinical

17.12 Initial Treatment (Management while Awaiting Results)

If the patient is acutely ill with vomiting and/or CNS depression, start IV solution containing glucose, evaluate blood pH and serum electrolytes, draw blood for ACTH, and if concerned about adrenal insufficiency consider initiating glucocorticoid and mineralcorticoid treatment.

17.13 Summary/Comments

The differential diagnosis of glycerol kinase deficiency depends on ascertaining whether or not the patient has a contiguous gene syndrome. If the GK gene is deleted by molecular genetic and/or molecular cytogenetic studies, it is important to determine the extent of the deletion, and, particularly, whether the *DAX1* gene is involved, since all deaths have resulted from adrenal insufficiency. If glyceroluria and/or hyperglycerolemia are determined incidentally in a young child without a history of episodic decompensation, it may be difficult to know whether or not he has the symptomatic or benign form of the disorder. Patients with GIS should be tested for FDP deficiency.

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