

15.1 Introduction

This chapter deals with disorders of galactose, fructose and glycogen metabolism. The clinical presentations of these disorders can be mild or severe and life-threatening. The clinical features include failure to thrive, hepatomegaly, hypoglycemia, jaundice, metabolic acidosis, and myopathy including muscle pain and weakness.

A. There are three known disorders of galactose metabolism: galactokinase deficiency (GALK), galactose-1-phosphate uridylyltransferase (GALT) deficiency, (classical galactosemia) and uridine diphosphate galactose-4-epimerase deficiency (GALE). Among these disorders, galactosemia is the most severe and the most common. Several partial forms of transferase deficiency have been reported of which the best known is the Duarte variant. All three disorders can be identified by newborn screening procedures which are based upon detection of increased amounts of galactose and galactose-1-phosphate in the blood.

The clinical manifestations of classical galactosemia occur when galactose is introduced in the diet. The primary source of dietary galactose is lactose, the sugar in milk. It is present in human and cow's milk and in most infant formulae. Individuals with these enzyme defects accumulate metabolites of galactose after ingesting galactose. Galactitol accumulation accounts for cataract formation and galactose-1-phosphate is considered to be responsible for the other clinical manifestations especially liver and kidney problems.

B. There are four disorders of fructose metabolism: fructokinase deficiency (an asymptomatic condition), fructose-1-phosphate aldolase deficiency (hereditary fructose intolerance, HFI), fructose-1,6-diphosphatase deficiency and D-glyceric acidemia. In HFI, symptoms occur after the ingestion of fructose. Affected infants may present clinically with hypoglycemia, vomiting and failure to thrive. Older individuals avoid sweet foods. The dietary sources of fructose are fruits, table sugar (sucrose) as sucrose-containing infant formulae. Fructose-1,6-diphosphatase deficiency, a disorder in gluconeogenesis, is found in children with moderate hepatomegaly, hypoglycemia and lactic acidosis. In the latter two disorders, the diag-

nosis is confirmed by liver enzyme assay. D-glyceric acidemia is associated with a variety of symptoms, mainly neurological. D-glyceric acidemia is also to be regarded as a defect of serine metabolism. A relatively large number of asymptomatic individuals have been identified. Another gluconeogenic disorder is pyruvate carboxylase deficiency. Patients present with lactic acidosis, failure to thrive, hypotonia and anorexia. Some patients were found to have elevated citrulline in blood.

C. Glycogen storage disorders are due to enzymatic blocks in glycogen degradation, with the exception of glycogen synthetase deficiency (GSD 0). Glycogen storage disorders involve primarily liver (GSD 1, 3, 6 and 9), liver, muscle and heart (GSD 3), liver and muscle (GSD 3 and 9) or muscle without liver (GSD 2, 5, 7). GSDs 1, 3, 6 and 9 are similar in physical appearance and are usually detected during infancy or childhood because of failure to thrive, marked hepatomegaly (without splenomegaly) and hypoglycemia. GSD 1 is the most severe of these four conditions. Two forms of GSD 1 can be recognized: GSD 1a and GSD 1 non a (also called GSD1b) both with hepatomegaly and hypoglycemia. Additionally GSD 1 non a may also present with neutrophil dysfunction and inflammatory bowel disease. GSD 2 results in cardiac failure, failure to thrive and death during infancy. Adolescent and adult-onset forms of GSD 2 primarily involve skeletal muscle, and patients with normal lysosomal enzyme activity are reported. GSD 4 manifests as hepatic failure and with cirrhosis by age 4–6 years, some patients may ultimately develop cardiomegaly. GSD 5 and 7 involve skeletal muscle (no liver involvement) and are usually not diagnosed until adolescence or adulthood, when they cause muscle weakness, exercise intolerance and myoglobinuria. Patients with the Fanconi-Bickel form of GSD present with hepatomegaly, hypoglycemia, rickets and tubulopathy.

The reference values for common metabolites in the diagnosis of carbohydrate disorders are shown below. The disorders of carbohydrate and glycogen metabolism are either confirmed by enzyme assay or DNA analysis. Reference values for enzymes have been variable, depending on the assaying conditions; however, the diagnostic value usually falls below 5–10% of normal.

15.2 Nomenclature

No.	Disorders	Enzyme defect	Chromosome localization	MIM
15.1	Galactokinase def.	Galactokinase	17q24	230200
15.2	Galactosemia	Galactose-1-phosphatase uridyltransferase	9p13	230400
15.3	UDPGal-4-epimerase def.	UDPGal-4-epimerase	1p36-p35	230350
15.4	Hereditary fructose intolerance	Fructose-1-phosphatase aldolase	9q22.3	229600
15.5	Fructose-1,6-diphospha- tase def.	Fructose-1,6-diphospha- tase	9q22.2–22.3	229700
15.6	Pyruvate carboxylase def.	Pyruvate carboxylase	11q13.4-q13.5	266150
15.7	D-Glyceric acidemia	D-Glycerate kinase		220120
15.8	GSD 1a	Glucose-6-phosphatase	17q21	232200
15.8a	GSD 1 non a	Glucose-6-phosphate translocase	11q23	232220
15.9	GSD 2 (Pompe)	Lysosomal α -glucosidase	17q25.2-q25.3	232300
15.10	GSD 3 (Forbe, Cori)	Amylo-1,6-glucosidase	1p21	232400
15.11	GSD 4 (Andersen)	Brancher enzyme	3p12	232500
15.12	GSD 5 (McArdle)	Myophosphorylase	11q13	232600
15.13	GSD 6 (Hers)	Liver phosphorylase	14q21-q22	232700
15.14	GSD 7 (Tauri)	Muscle phospho-fructoki- nase	12q13.3	232800
15.15	GSD 9 (GSD 8 by McKusick)	Liver phosphorylase kinase, α -subunit	Xp22.2-p22.1	306000
15.16	GSD 0	Glycogen synthetase	12p12.2	240600
15.17	GSD Fanconi-Bickel type	Glut2	3q26.1-q26.3	227810

15.3 Metabolic Pathway

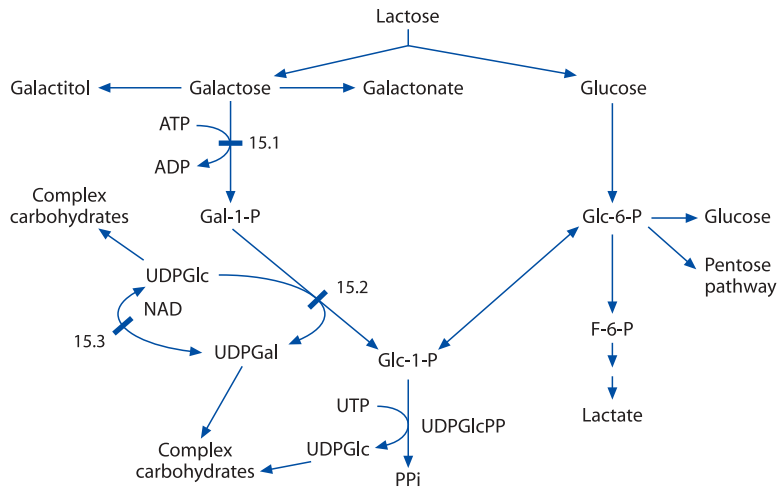


Fig. 15.1. Pathways of galactose metabolism. 15.1, Galactokinase (GALK); 15.2, galactose-1-phosphate uridylyltransferase (GALT); 15.3, uridine diphosphate galactose-4-epimerase (GALE). *Gal-1-P*, Galactose-1-phosphate; *Glc-1-P*, glucose-1-phosphate; *UDPGlc*, uridine diphosphate glucose; *UDPGlcPP*, uridine diphosphate glucose pyrophosphorylase; *UPDGal*, uridine diphosphate galactose; *UTP*, uridine triphosphate; *PPi*, pyrophosphate; *Glc-6-P*, glucose-6-phosphate; *F-6-P*, fructose-6-phosphate

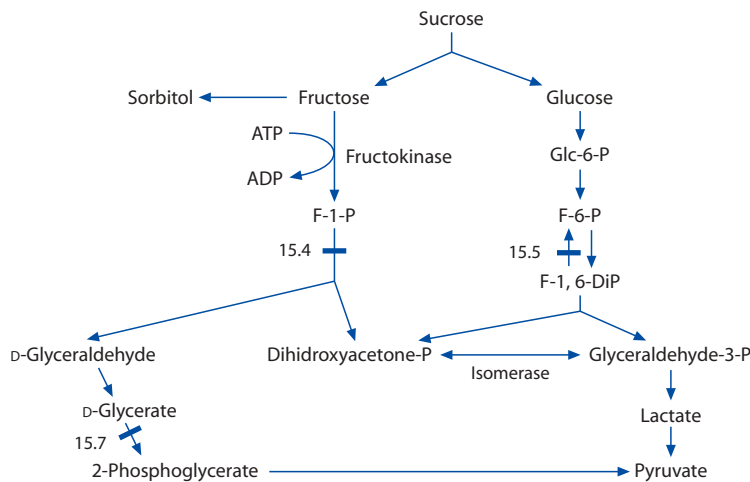


Fig. 15.2. Pathways of fructose metabolism. 15.4, Fructose-1-phosphate aldolase; 15.5, fructose-1,6-diphosphatase; 15.7, D-glycerate kinase. *F-1-P*, Fructose-1-phosphate; *F-6-P*, fructose-6-phosphate; *F-1,6-DiP*, fructose-1,6-diphosphate; *Glc-6-P*, glucose-6-phosphate; *ATP*, adenosine triphosphate; *ADP*, adenosine diphosphate

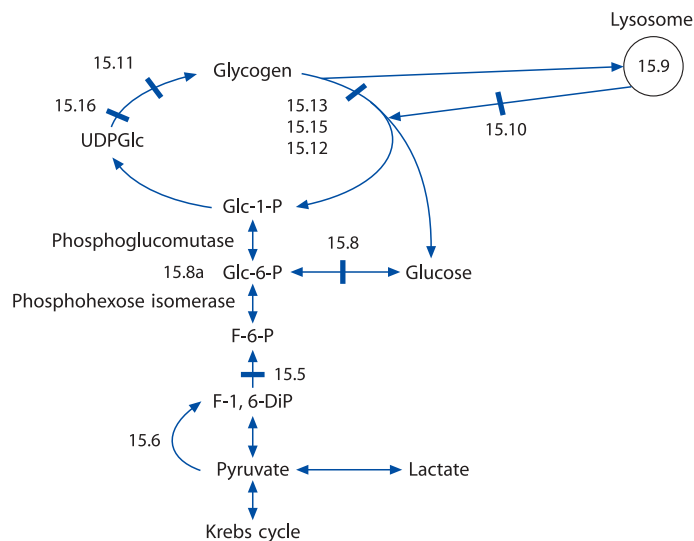


Fig. 15.3. Pathways of glycogen metabolism. 15.16, Glycogen synthetase (liver); 15.11, brancher enzyme; 15.13, phosphorylase (liver); 15.15, phosphorylase kinase (liver); 15.12, phosphorylase (muscle); 15.10, debrancher enzyme (liver + muscle); 15.8, glucose-6-phosphatase (liver); 15.8a, glucose-6-phosphate translocase; 15.5, fructose-1,6-diphosphatase; 15.9, α -glucosidase; UDPGlc, uridine diphosphate glucose; Glc-1-P, glucose-1-phosphate; Glc-6-P, glucose-6-phosphate; F-6-P, fructose-6-phosphate; F-1,6-DiP, fructose-1,6-diphosphate

15.4 Signs and Symptoms

Table 15.1. Galactokinase deficiency

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Unique clinical findings	Cataracts	+	+	+	+	+
	Pseudotumor cerebri	+	+			
Routine laboratory	Reducing substance (U) ^a	+	+	+	+	+
Special laboratory	Galactose (P, U) ^a	↑	↑	↑	↑	↑
	Galactokinase (RBC)	↓	↓	↓	↓	↓
	Galactitol (U)	↑	↑	↑	↑	↑

^a After galactose intake.

Table 15.2. Galactose-1-phosphate uridyltransferase deficiency (classical galactosemia)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Unique clinical findings ^a	Anorexia	+	+			
	Vomiting	+	+			
	'Hepatitis' features	+	+			
	Hepatomegaly	+	+			
	Jaundice	+	+			
	Cataracts	+	+			
	Death	+				
Routine laboratory	Reducing substance (U) ^a	+	+	+	+	+
	Protein (U)	↑	↑	↑		
	Bilirubin (P)	↑	↑	n	n	n
	ASAT/ALAT (P)	↑	↑	n	n	n
	Prothrombin time (P)	↑	↑	n	n	n
Special laboratory	Gal-1-P (RBC)	↑	↑	↑	↑	↑
	Galactose (P, U) ^a	↑	↑	↑	↑	↑
	GALT (RBC)	↓	↓	↓	↓	↓
GI	Vomiting	+	+			
	Weight gain	↓	↓			
Renal	Protein (U)	↑	↑			
Eye	Cataracts ^a	+	+			
Liver	'Hepatitis' features	+	+			
	Jaundice	+	+			
CNS	Seizures	+	+			
	MR	+	+	+	+	+
Endocrine	Ovarian failure	(+)	(+)	(+)	+	+
Infectious	Sepsis	+				

Partial GALT is generally asymptomatic.

^a After galactose intake.

Table 15.3. UPDGal epimerase deficiency

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Severe form						
Unique clinical findings	Similar to classical galactosemia					
Psychomotor retardation		+	+	+	+	+
Routine laboratory	Reducing substance (U) ^a	+	+	+	+	+
Special laboratory	Gal-1-P (RBC)	↑	↑	n-↑	n-↑	n-↑
	Galactose (P) ^a	n-↑	n-↑	n-↑	n-↑	n-↑
	Epimerase (RBC)	↓	↓	↓	↓	↓
Benign form						
Special laboratory	Gal-1-P (RBC)	↑	↑			
	Epimerase (RBC)	↓	↓	↓	↓	↓

^a After galactose intake.

Table 15.4. Hereditary fructose intolerance (fructose-1-phosphate aldolase deficiency)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Unique clinical findings	Anorexia	+	+	+	+	+
	Vomiting	+	+	+	+	
	'Hepatitis' features	+	+			
	Hepatomegaly	+	+	+	±	±
	Proteinuria	+	+			
Routine laboratory	Failure to thrive	+	+	+		
	Reducing substance	+	+	+	+	+
	Protein (U)	+	+			
	ASAT/ALAT (P)	↑	↑			
	Glucose (P)	↓	↓	↓	↓	↓-n
Special laboratory	Uric acid (P, U)	↑	↑	↑	n-↑	n-↑
	Fructose (P)	↑	↑	↑	n-↑	n-↑
	Fru-1-P aldolase (liver)	↓	↓	↓	↓	↓
	Amino acids (U)	↑	↑	↑	↑	↑
GI	Vomiting	+	+	+	+	+
	Abdominal pain	+	+	+	+	+
	Colic	+	+			
Renal	Protein (U)	+	+	+		
	Amino acids (U)	↑	↑	↑	↑	↑

^a Disease features occur following fructose intake.

Table 15.5. Fructose-1,6-diphosphatase deficiency

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Unique clinical findings	Lethargy	+	+	+	+	±
	Irritability	+	+	+	+	
	Hepatomegaly	+	+	±	±	±
	Seizures (hypoglycemia)	+	+	+		
Routine laboratory	Glucose (P)	↓	↓	↓	↓-n	↓-n
	Ketones (U, P)	↑	↑	↑		
	Phosphorus (P)	↓-n	↓-n	↓-n	n	n
	Uric acid (P, U)	n-↑	n-↑	n-↑	n	n
Special laboratory	Lactate (B, P)	↑	↑	↑	↑	
	Alanine (P)	↑	↑	↑	↑	
	Fru-1,6-diphosphatase (L)	↓	↓	↓	↓	↓
	Glycerol (U)	n-↑	n-↑	n-↑		
CNS	Glycerol-3-phosphate (U)	n-↑	n-↑	n-↑		
	Lethargy (hypoglycemia)	+	+	+	+	
	Seizures (hypoglycemia)	+	+	+	+	
	Irritability	+	+	+		
Respiratory tract	Tachypnea (acidosis)	+	+	+		
Growth	Height	n-↓	n-↓	n	n	n

Table 15.6. Pyruvate carboxylase deficiency

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Unique clinical findings	Metabolic acidosis	+	+	+		
	Hypotonia	+	+			
	Seizures	+	+			
	DD	+	+	+		
	Death	+	+	+		
Routine laboratory	Lactate (P, B, U)	↑	↑	↑		
	Ketones (P, U)	↑	↑	↑		
	Glucose (P)	↓-n	↓-n	↓-n		
	Ammonia (B)	n-↑	n-↑	n-↑		
	Renal tubular acidosis	+	+	+		
Special laboratory	Alanine (P, U)	↑	↑	↑		
	Citrulline (P)	↑	↑	↑		
	Pyruvate carboxylase (L, WBC, FB, AFC)	↓	↓	↓		
CNS	Hypotonia	+	+			
	Seizures	+	+			
	DD	+	+			

^a Most die in early infancy or childhood.

Table 15.7. D-Glyceric acidemia (D-glycerate kinase deficiency)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Unique clinical findings	Mental/motor retardation	±	±	±		
	Hypotonia	±	±	±		
	Seizures	±	±	±		
	No symptoms	±	±	±		
Routine laboratory	Acidosis	±	±	±		
Special laboratory	Organic acids	↑	↑	↑		
	D-Glycerate (U)	↑	↑	↑	↑	

Table 15.8. Glycogen storage disease type 1a

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Type 1a (glucose-6-phosphatase deficiency)						
Unique clinical findings	Hepatomegaly	++	++	++	+	+
	Adenomata/carcinoma (L)					+
	Short stature	+	+	+	+	+
	Irritability	+	+			
	Tachypnea (acidosis)	+	+	+		
	Adiposity (doll facies)	+	+	+	+	+
	Enlarged kidneys	+	+	+	+	+
	Nephropathy					+
Routine laboratory	Osteopenia	+	+	+	+	+
	Glucose (P)	↓	↓	↓	↓	↓
	Triglycerides (P)	↑	↑	↑	↑	↑
	Cholesterol (P)	↑	↑	↑	↑	↑
	Uric acid (P, U)	↑	↑	↑	↑	↑
	Lactate (P, B, U)	↑	↑	↑	↑	↑
	Ketones (P)	↓	↓	↓	↓	↓
Special laboratory	Glu-6-phosphatase (L)	↓	↓	↓	↓	↓

Table 15.8a. Glycogen storage disease type 1 non a (also called GSD 1b)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Type 1 non a (glucose-6-translocase deficiency)						
Unique clinical findings	Hepatomegaly	++	++	++	+	+
	Short stature	+	+	+	+	+
	Irritability	+	+			
	Tachypnea (acidosis)	+	+	+		
	Adiposity (doll facies)	±	±	±	±	±
	Infections	+	+	+	+	+
	Inflammatory bowel disease	+	+	+	+	+
Routine laboratory	Glucose (P)	↓	↓	↓	↓	↓
	Triglycerides (P)	↑	↑	↑	↑	↑
	Cholesterol (P)	↑	↑	↑	↑	↑
	Uric acid (P, U)	↑	↑	↑	↑	↑
	Lactate (P, B, U)	↑	↑	↑	↑	↑
	Ketones (P)	↓	↓	↓	↓	↓
	Neutrophil functions	↓	↓	↓	↓	↓
Special laboratory	Glu-6-phosphate translocase (L)	↓	↓	↓	↓	↓

Table 15.9. Glycogen storage disease type 2 (acid α -glucosidase, acid maltase deficiency)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Infantile type	Cardiac failure	+	+			
Unique clinical findings	Cardiomegaly	+	+			
	Hypotonia	+	+			
	Hepatomegaly	+	+			
	Macroglossia	+	+			
	Death	+	+			
Routine laboratory	E.C.G. abn.	+	+			
Special laboratory	Tissue glycogen (all)	↑	↑			
	Acid maltase (L, M, FB, LYM)	↓	↓			
CNS	MR/DD	+	+			
Muscle	Hypotonia	+	+			
Cardiac	Failure	+	+			
Juvenile and adult-onset types						
Unique clinical findings	Walking difficulty			+	+	+
	Muscle dystrophy			+	+	+
	Easy muscle fatigue			+	+	+
	Cardiac function	n	n	n	n	↓-n
	Mental function	n	n	n	n	n
Routine laboratory	EMG			+	+	+
Special laboratory	Acid maltase (M, FB)	↓	↓	↓	↓	↓-±
	Oligosaccharides (U)	↑	↑	↑	↑	↑

Table 15.10. Glycogen storage disease type 3 (debrancher enzyme deficiency)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Unique clinical findings	Hepatomegaly	+	+	+	±	
	Short stature	+	+	+	±	
	Adiposity	+	+	±		
	Hypoglycemia symptoms	+	+			
Routine laboratory	Glucose (P)	↓	↓	↓	n	N
	ASAT/ALAT (P)	↑	↑	↑	↑	↑
	CK (P) ^a	↑	↑	↑	↑	↑
Special laboratory	Glycogen (RBC)	↑	↑	↑	↑	↑
	Lactate, post meal (B, P)	↑	↑	↑	↑	
	Oligosaccharides (U)	↑	↑	↑	↑	↑
	Debrancher enzyme (L, M, FB) ^a	↓	↓	↓	↓	↓
Liver	'Hepatitis' features	+	+	+	±	±
	Cirrhosis					±
Muscle ^a	Myopathy ^a				+	+
Heart	Cardiomyopathy			+	+	+

Creatine kinase is markedly ↑ when debrancher is absent in M.

^a Debrancher enzyme may be absent in L and present in M, or absent in L and M.

Table 15.11. Glycogen storage disease type 4 (branching enzyme deficiency)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Unique clinical findings ^a	Hepatomegaly	+	+	+		
	'Hepatitis' features		+	+		
	Cirrhosis features		+	+		
	Hypotonia		+	+		
	Muscular atrophy		+	+		
	Death			+		
Routine laboratory	Bilirubin (P)	n	↑	↑		
	ASAT/ALAT (P)	n	↑	↑		
	Prothrombin time (P)	n	↑	↑		
Special laboratory	Branching enzyme (L, M, FB, WBC)	↓	↓	↓		
Liver	Hepatomegaly		+	+		
	Splenomegaly		+	+		
	Ascites		+	+		
	Portal hypertension		+	+		
Muscle	Hypotonia		+	+		
Cardiac	Congestive failure			+		

^a Intermediate hepatic variants with juvenile onset exist; a rare fatal neuromuscular form has been described.

Table 15.12. Glycogen storage disease type 5 (muscle phosphorylase deficiency)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Unique clinical findings	Muscle weakness				±	+
	Muscle pain				±	+
	Stiffness				±	+
Routine laboratory	Myoglobin (U)				±	±
	CK (P)				↑	↑
	Uric acid (P)				↑	↑
Special laboratory	Glycogen (M)			↑	↑	↑
	Phosphorylase (M)	↓	↓	↓	↓	↓
	Lactate (B, P) ^a				^a	^a
Muscle	Myalgia after exertion				+	+
	Myoglobin (U)				+	+

^a Lactate (P) fails to rise normally after ischemic exercise.

Table 15.13. Glycogen storage disease type 6 (liver phosphorylase deficiency)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Unique clinical findings	Hepatomegaly	+	+	±		
	Hypoglycemia	+	+	±		
	Small stature	+	+	+	±	
	Hypotonia	±	±	±		
Routine laboratory	Glucose (P)	↓	↓	↓-n	n	n
	Lactate (B, P) ^a	↑	↑	↑	↑	
	ASAT/ALAT (P)	↑	↑	↑	↑	
	Fasting ketone bodies (P, U)	↑	↑	↑	n-↑	
	Cholesterol	↑	↑	↑	↑	↑
	Triglycerides	↑	↑	↑	↑	↑
Special laboratory	Glycogen (L)	↑	↑	↑	↑	n-↑
	Phosphorylase (L)	↓	↓	↓	↓	↓
Liver	Hepatomegaly	+	+	±		

^a Lactate (B, P) increases moderately after meal or carbohydrate loading.

Table 15.14. Glycogen storage disease type 7 (muscle phosphofructokinase deficiency)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Unique clinical findings	Muscle pain/weakness			±	+	+
	Stiffness				+	+
	Exercise endurance	n	n	↓-n	↓	↓
	Jaundice	±	±	±	±	±
Routine laboratory	Reticulocyte count			↑	↑	↑
	CK (P)			↑	↑	↑
	Myoglobin (U)				+	+
	Uric acid (P)			↑	↑	↑
Special laboratory	Phosphofructokinase, M	↓	↓	↓	↓	↓
	Isoenzyme (M, RBC, WBC, FB)	↓	↓	↓	↓	↓
	RBC life span	↓	↓	↓	↓	↓
Hematology	Hemolysis			+	+	+
	Jaundice	±	±	±	±	±
Muscle	Muscle fatigue			±	+	+
	Myoglobinuria				+	+

Table 15.15. Glycogen storage disease type 9 (liver phosphorylase kinase deficiency)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Unique clinical findings	Hepatomegaly	+	+	±		
	Hypoglycemia symptoms	+	+	±		
	Small stature	+	+	+	±	
	Hypotonia	±	±	±		
Routine laboratory	Glucose (P)	↓	↓	↓	n	n
	Lactate (B, P) ^a	↑	↑	↑	↑	
	ASAT/ALAT (P)	↑	↑	↑	↑	
	Fasting ketone bodies (P, U)	↑	↑	↑	n-↑	
	Cholesterol	↑	↑	↑	↑	↑
	Triglycerides	↑	↑	↑	↑	↑
Special laboratory	Glycogen					
	Phosphorylase kinase (L, RBC)					
Liver	Hepatomegaly	+	+	±		

^a Lactate (B, P) rises moderately after a meal or carbohydrate loading.

Table 15.16. Glycogen storage disease type 0

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
GSD 0 (Glycogen synthase deficiency)						
Unique clinical findings	Hepatomegaly	±	±			
	Short stature	±				
Routine laboratory	Glucose (P)	↓	↓	↓	n-↓	
	Lactate (P, B, U) ^a	↑	↑	↑	n-↑	n-↑
	Ketones fasting (P)	↑	↑	↑	n-↑	
Special laboratory	Glycogen synthase (L)	↓	↓	↓	↓	↓

^a Postprandial hyperlactacidemia can be observed.

Table 15.17. Hepatorenal GSD with Fanconi-Bickel syndrome

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Unique clinical findings	Hepatomegaly	n-+	++	++	+	+
	Short stature	+	+	+	+	+
	Rickets, osteopenia	+	+	+	+	+
	Polyuria	+	+	+		
	Enlarged kidneys	+	+	+	+	+
	Adiposity (doll facies)	+	+	+	+	+
Routine laboratory	Glucose (P)	↓	↓	↓	n-↓	n-↓
	Triglycerides (P)	↑	↑	↑	↑	↑
	Cholesterol (P)	↑	↑	↑	↑	↑
	Uric acid (P, U)	↑	↑	↑	↑	↑
	Ketones (P, B, U)	↑	↑	↑	↑	↑
	Hyperaminoaciduria, -phosphaturia, -uricosuria, -calciuria, loss of bicarbonate (U)	+	+	+	+	+
Special laboratory	GLUT2 (L)	↓	↓	↓	↓	↓

15.5 Normal and Pathological Values

Metabolite	Normal	Pathological values
Galactose (B)	≤0.05 mmol/l	>0.5 mmol/l
Galactose (U)	4–6 mmol/mol creat	>10 mmol/mol creat
Galactose-1-phosphate (RBC)	≤0.17 μmol/g Hb	>1.70 μmol/g Hb
Galactitol (U)	2–4 mmol/mol creat	>10 mmol/mol creat
Fructose (B)	≤0.16 mmol/l	>0.16 mmol/l
Fructose (U)	10–14 mmol/mol creat	>20 mmol/mol creat
Lactic acid (B)	≤1.8 mol/l	>2.5 mmol/l
Glycogen (liver)	≤5.0 g%	>5.0 g%
Glycogen (muscle)	≤1.0 g%	>1.0 g%
D-Glycerate (U)	n.d.	>5.0 mmol/mol Creat
D-Glycerate (B)	n.d.	0.19–0.32 mmol/l

n.d., not detectable.

15.6 Loading Tests

■ Oral Galactose Loading Test

Indications: diagnosis of GSD types 0, 1, 3, 6 and 9.

Fasting state: overnight or 6 h.

Galactose dose: 2.0 g/kg (with a maximum of 50 g) as 10% solution given by mouth over 5–10 min.

Blood samples: baseline and every 30 min for 3–4 h.

Determinations: glucose and lactic acid (P).

Cautions: contraindicated for galactosemic infants.

Interpretation: increased (P) lactate occurs in GSD types 0, 1, 3, 6 and 9 but not with hepatomegaly of other causes (see Diagnostic Flow Chart).

Galactose loading tests should not be done on infants when galactosemia is the suspected diagnosis. In these infants galactose loading can cause severe, fatal hypoglycemia.

■ Intravenous Fructose Loading Test

Indications: diagnosis of HFI and fructose-1,6-diphosphatase deficiency (fructokinase deficiency).

Preparation: 2 weeks before the test a diet without sucrose and fructose is prescribed:

Fasting state: overnight or 6 h.

Fructose dose: 0.2 g/kg as 10% solution given over 1–3 min.

Blood samples: baseline, 10, 20, 30, 40, 50, 60 and 90 min.

Determinations: glucose, lactic acid, phosphate and uric acid (P).

Caution: watch for hypoglycemia between 20 and 50 min. 25% i.v. glucose solution should be immediately available to abort hypoglycemia as needed. Nausea and abdominal pain are frequent in affected individuals.

Interpretation: decreased glucose and increased lactic acid, and uric acid together with a decrease of phosphate indicate HFI or fructose-1,6-diphosphatase deficiency (in fructokinase deficiency a rise in fructose can be detected).

Oral fructose loading test is not advocated in the case of suspicion of hereditary fructose intolerance since oral administration of fructose may cause severe gastrointestinal symptoms.

Indications: in patients suspected of having D-glycemic acidemia.

Fasting state: overnight or 6 h.

Fructose dose: 1.0 g/kg as 10% solution given over 5–10 min.

Following the load, approximately 4% of the test dose is excreted as D-glycerate in a 24-h urine. A loading test with 200–300 mg/kg of the amino acid L-serine may be equally effective.

■ Subcutaneous Glucagon Test

Indications: diagnosis of GSD 1a, GSD 1 non a, fructose-1,6-diphosphatase deficiency.

Fasting state: overnight or 6 h.

In GSD 1a and GSD 1 non a there is a no (or minimal) rise in blood glucose after glucagon is given. Blood lactate is elevated at the start in all 3 disorders and rises further after glucagon in GSD 1a and non a. In fruc-

tose-1,6-diphosphatase deficiency blood glucose rises and lactate does not after glucagon administration. Children with these disorders usually cannot tolerate fasting more than 3–4 hours without hypoglycemia. For this reason the pre-test fasting period may need to be shortened. Monitoring for, and management of severe hypoglycemia is mandatory to avoid the risk of neurological injury.

The disorders of galactose metabolism are commonly detected by neonatal screening. Symptoms occur following the ingestion of lactose/galactose-containing formulas.

Disorders of fructose metabolism are usually recognized during infancy or childhood when the ingestion of fructose or sucrose-containing foods results in vomiting, growth failure and/or hepatomegaly.

Fructokinase deficiency and D-glycemic acidemia, however, have symptoms which are nonspecific and are often unimpressive.

Glycogen storage diseases primarily involving the liver present during infancy and early childhood with marked hepatomegaly (without splenomegaly), hypoglycemia of variable degree and poor growth. These features and persistent lactic acidosis characterize GSD 1. Frequent infections and inflammatory bowel disease are indicative of GSD 1non a.

The symptoms of carbohydrate disorders involving muscle appear during adolescence or adulthood. The symptoms include exercise intolerance, muscle weakness and myoglobinuria. Several glycogen storage disorders may involve both liver and muscle (GSD 3, GSD 9).

■ Semi-ischemic Forearm Test (Modified McArdle Test)

Indications: diagnosis of GSD types 5 and 7.

Fasting state: not indicated.

A sphygmomanometer placed around the upper arm is inflated at mid systolic-diastolic blood pressure level. After baseline blood sampling a hand manometer is squeezed for 2 min in a frequency of 1 per sec. Immediately after exercise the cuff is released.

Blood samples: baseline and every 2 min for 20 min, and at 30 and 60 min.

Determinations: ammonia (P) and lactic acid (P).

Cautions: muscle cramp, stop exercise immediately.

Interpretation: No increase (P) of lactate occurs in GSD types 5 and 7, in contrast ammonia (P) increases.

15.7 Diagnostic Flow Chart

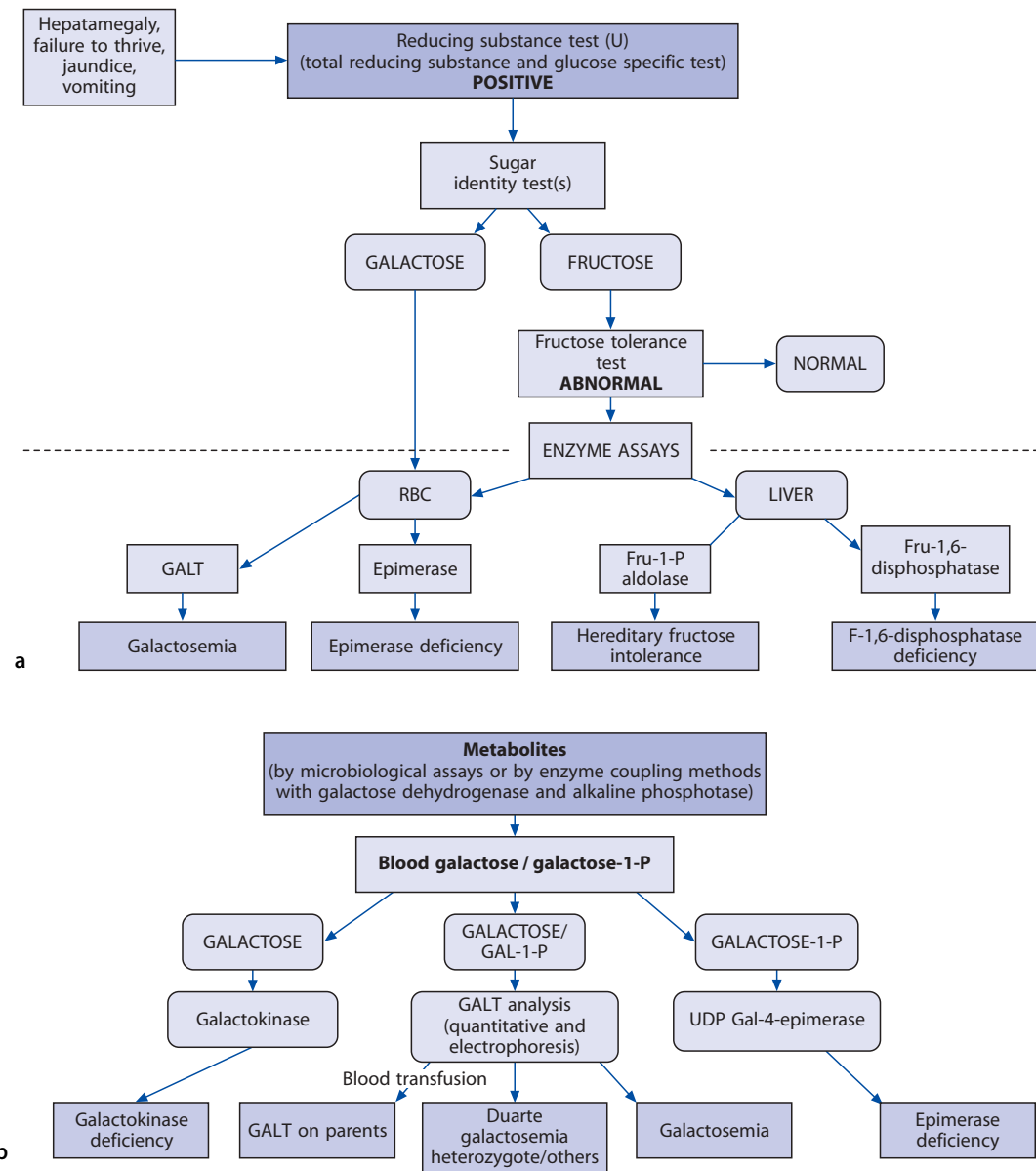


Fig. 15.4. a Diagnostic flow chart on clinical and biochemical findings. **b** Diagnostic flow chart on newborn screening procedures

15.8 Specimen Collection and Storage

Item	Specimen	Process	Storage
Metabolites			
Galactose	P	None	Frozen
Galactose	U	None	Frozen
Gal-1-P	RBC	Washed	Frozen
Glycogen	Liver, muscle, RBC	Quick frozen Washed	-70 °C
Enzymes			
Galactokinase	RBC, LBC	Washed	Frozen
GALT	RBC, LBC, FB	Washed	Room temp.
UDPGal-4-epimerase	RBC, LBC, FB	Washed	Frozen
Enzyme diagnosis GSD, other than glucose-6-phos- phate translocase	Liver, muscle	Quick frozen	-70 °C
Glucose-6-phosphate trans- locase	Liver	Assay unfrozen	None
Enzymes in cultured skin	FB	Assay unfrozen	Room temp.

The requirements for specimen collection are indicated by the laboratory performing the tests.

This can vary from one lab to another. The reference laboratory should be contacted for instructions prior to obtaining specimens for testing.

15.9 Prenatal Diagnosis

Disorder	Enzyme assay		DNA diagnosis
	Amniocytes	Chorionic villi	
15.1 Galactokinase def.	(+)	(+)	(+)
15.2 Galactosemia	+	+	+
15.3 UPDGal epimerase def.	+		+
15.4 Hereditary fructose intolerance			(+)
15.5 Fructose-1,6-diphosphatase def.			+
15.6 Pyruvate carboxylase def.	+	+	+
15.7 D-glycerate kinase def.			
15.8 GSD 1a			+
15.8a GSD 1 non a			+
15.9 GSD 2	+	+	+
15.10 GSD 3	+	+	+
15.11 GSD 4	+	+	+
15.12 GSD 5			(+)
15.13 GSD 6			(+)
15.14 GSD 7			(+)
15.15 GSD 9			(+)
15.16 GSD 0			+
15.17 GSD FBS			+

+, DNA diagnosis feasible; (+); DNA diagnosis feasible, in practical terms regarded unrealistic.

15.10 DNA Diagnosis

Disorder		Material	Gene locus
15.1	Galactokinase def.	WBC, FB, CVCCVS, AFC	17q24
15.2	Galactosemia	WBC, FB, CVCCVS, AFC	9p13
15.3	UPDGal epimerase def.	WBC, FB, CVCCVS, AFC	1p36-p35
15.4	Hereditary fructose intolerance	WBC, FB, CVCCVS, AFC	9q22.3
15.5	Fructose-1,6-diphosphatase def.	WBC, FB, CVCCVS, AFC	9q22.2-22.3
15.6	Pyruvate carboxylase def	WBC, FB, CVCCVS, AFC	11q13.4-q13.5
15.7	D-glycerate kinase def.		
15.8	GSD 1a	WBC, FB, CVCCVS, AFC	17q21
15.8a	GSD 1 non a	WBC, FB, CVCCVS, AFC	11q23
15.9	GSD 2	WBC, FB, CVCCVS, AFC	17q25.2-q25.3
15.10	GSD 3	WBC, FB, CVCCVS, AFC	1p21
15.11	GSD 4	WBC, FB, CVCCVS, AFC	3p12
15.12	GSD 5	WBC, FB, CVCCVS, AFC	11q13
15.13	GSD 6	WBC, FB, CVCCVS, AFC	14q21-q22
15.14	GSD 7	WBC, FB, CVCCVS, AFC	12q13.3
15.15	GSD 9	WBC, FB, CVCCVS, AFC	Xp22.2-p22.1
15.16	GSD 0	WBC, FB, CVCCVS, AFC	12p12.2
15.17	GSD FBS	WBC, FB, CVCCVS, AFC	3q26.1-q26.3

15.11 Initial Treatment

A. When a disorder in galactose metabolism is suspected, especially in GALT and GALE, elimination of dietary lactose/galactose from the diet should be initiated immediately even before the diagnosis is confirmed by enzyme assay and/or DNA analysis.

B. Both initial and follow-up treatment in HFI consists of the prescription of a sucrose/fructose free diet.

In FDPase patients often present with a combination of severe hypoglycemia/lactic acidosis. Initial treatment consists of parenteral administration of adequate amounts of glucose together with sodiumbicarbonate to correct the lactic acidosis. In case of seizures in D-glyceric acidemia not responding to anti-convulsive treatment, attempts to decrease the glycine concentration together with an antagonist of the NMDA (N-methyl-D-aspartate) channel are advised: sodiumbenzoate and dextrometamorphane.

C. In glycogen storage diseases the initial treatment is immediate correction of (severe) hypoglycemia. In GSD 1 the associated severe lactic acidosis requires adequate and repeated administration sodiumbicarbonate.

15.12 Comments

In this chapter metabolic disorders in the metabolism of galactose, fructose and glycogen are described. Often the first clinical presentations may already point in the direction of the definitive disorder. Relative simple routine laboratory analyses indicate the initial emergency treatment. More specific metabolic tests are necessary to confirm the diagnosis on a metabolite level. A definitive diagnosis is established when enzyme assays and DNA analysis are conclusive. It remains a matter of debate whether or not liver-related diagnoses should rely on DNA analysis alone or liver-biopsy-dependent enzyme assays. With increasing knowledge of the genetic basis it is expected that the future diagnosis of liver-related metabolic diseases will be based on clinical symptoms combined with mutation analyses.

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