TABLE 433e-1 FEATURES OF GLYCOGEN STORAGE DISEASES AND GALACTOSE AND FRUCTOSE DISORDERS (*CONTINUED*)

Type/Common Name	Basic Defect	Clinical Features	Comments
Galactose Disorders			
Galactosemia with uridyltransferase deficiency	Galactose 1-phosphate uridyltransferase	Vomiting, hepatomegaly, jaundice, cataracts, amino aciduria, failure to thrive	Long-term complications exist despite early diagnosis and treatment.
Galactokinase deficiency	Galactokinase	Cataracts	Benign
Uridine diphosphate galactose 4-epimerase deficiency	Uridine diphosphate galactose 4-epimerase	Similar to transferase deficiency with additional findings of hypotonia and nerve deafness	Benign variant exists.
Fructose Disorders			
Essential fructosuria	Fructokinase	Asymptomatic, positive urine reducing substance	Benign, autosomal recessive
Hereditary fructose intolerance	Fructose 1,6-bisphosphate aldolase B	Vomiting, lethargy, failure to thrive, hepatic failure, aversion to sweets, severity of symptoms depending on age/quantity of sugar ingested	Prognosis good with early diagnosis and fructose restriction, autosomal recessive.
Fructose 1,6-diphosphatase deficiency	Fructose 1,6-diphosphatase	Episodic hypoglycemia, hyperlactic acidemia, and ketoacidosis usually following illness, hepatomegaly	Avoid fasting, good prognosis

Abbreviations: CK, creatine kinase; CNS, central nervous system; M, muscle.

type Ib, in which the translocase that transports glucose-6-phosphate across the microsomal membrane is defective. The defects in both subtypes lead to inadequate conversion of glucose-6-phosphate to glucose in the liver and thus make affected individuals susceptible to fasting hypoglycemia.

CLINICAL AND LABORATORY FINDINGS Persons with type I GSD may develop hypoglycemia and lactic acidosis during the neonatal period; however, more commonly, they exhibit hepatomegaly at 3–4 months of age. Hypoglycemia, hypoglycemic seizures, and lactic acidosis can develop after a short fast. These children usually have doll-like faces with fat cheeks, relatively thin extremities, short stature, and a protuberant abdomen that is due to massive hepatomegaly. The kidneys are enlarged, but the spleen and heart are of normal size. The hepatocytes are distended by glycogen and fat, with large and prominent lipid vacuoles. Despite hepatomegaly, liver enzyme levels are usually normal or near normal. Easy bruising and epistaxis are associated with a prolonged bleeding time as a result of impaired platelet aggregation/adhesion. Hyperuricemia is present. Hyperlipidemia includes elevation of triglycerides, low-density lipoproteins, and phospholipids. Type Ib patients have additional findings of neutropenia and impaired neutrophil function, which result in recurrent bacterial infections and oral and intestinal mucosal ulceration. GSD I patients may experience intermittent diarrhea, which can worsen with age. In GSD Ib, diarrhea is largely due to loss of mucosal barrier function caused by inflammation.

LONG-TERM COMPLICATIONS Gout usually becomes symptomatic at puberty as a result of long-term hyperuricemia. Puberty is often delayed. Nearly all female patients have ultrasound findings consistent with polycystic ovaries; however, the other clinical features of polycystic ovary syndrome, such as acne and hirsutism, are not seen. Several reports of successful pregnancy in women with GSD I suggest that fertility is not affected. Increased bleeding during menstrual cycles, including life-threatening menorrhagia, has been reported. Secondary to lipid abnormalities, there is an increased risk of pancreatitis. Patients with GSD I may be at increased risk for cardiovascular disease. In adult patients, frequent fractures can occur and radiographic evidence of osteopenia/osteoporosis can be found; in prepubertal patients, radial bone mineral content is significantly reduced. Pulmonary hypertension—although rare—has been reported. By the second or third decade of life, many patients with type I GSD develop hepatic adenomas that can hemorrhage and, in some cases, become malignant. Renal disease is a serious late complication. Almost all patients older than 20 years have proteinuria, and many have hypertension, kidney stones, nephrocalcinosis, and altered creatinine clearance. Laboratory findings include abnormally high levels of blood lactate, triglycerides, cholesterol, and uric acid. In some patients, renal function deteriorates and progresses to complete failure, requiring dialysis or transplantation.

DIAGNOSIS Clinical presentation and abnormal plasma lactate and lipid values suggest that a patient may have GSD I, but gene-based mutation analysis provides a noninvasive means of reaching a definitive diagnosis for most patients with types Ia and Ib disease. Before the glucose-6-phosphatase and glucose-6-phosphate translocase genes were cloned, a definitive diagnosis required a liver biopsy to demonstrate a deficiency.

Type III GSD (Debrancher Deficiency, Limit Dextrinosis) Type III GSD is an autosomal recessive disorder caused by a deficiency of glycogen debranching enzyme. Debranching and phosphorylase enzymes are responsible for complete degradation of glycogen. When the debranching enzyme is defective, glycogen breakdown is incomplete. Abnormal glycogen accumulates with short outer chains and resembles dextrin.

CLINICAL AND LABORATORY FINDINGS Deficiency of glycogen debranching enzyme causes hepatomegaly, hypoglycemia, short stature, variable skeletal myopathy, and cardiomyopathy. The disorder usually involves both liver and muscle and, in such cases, is termed *type IIIa* GSD. However, in ~15% of patients, the disease appears to involve only the liver and is classified as *type IIIb*. Hypoglycemia and hyperlipidemia occur in children. In type III disease (as opposed to type I disease), fasting ketosis can be prominent, aminotransferase levels are elevated, and blood lactate and uric acid concentrations are usually normal. Serum creatine kinase (CK) levels can sometimes be used to identify patients with muscle involvement, but normal levels do not rule out muscle enzyme deficiency. In most patients with type III disease, hepatomegaly improves with age; however, liver cirrhosis and hepatocellular carcinoma may occur in late adulthood. Hepatic adenomas may occur, although less commonly than in GSD I. Left ventricular hypertrophy and life-threatening arrhythmias have been reported. Patients with type IIIa disease may experience muscle weakness in childhood that can become severe after the third or fourth decade of life. Polycystic ovaries are common in GSD III, and some patients develop features of polycystic ovarian syndrome, such as hirsutism and irregular menstrual cycles. Reports of successful pregnancy in women with GSD III suggest that fertility is normal.

DIAGNOSIS In type IIIa GSD, deficient debranching enzyme activity can be demonstrated in liver, skeletal muscle, and heart. In contrast, patients with type IIIb have debranching enzyme deficiency in the liver but not in muscle. The liver has distended hepatocytes due to glycogen buildup; areas of fibrosis are also noted very early in the disease course. In the past, definitive assignment of subtype required enzyme assays in both liver and muscle. DNA-based analyses now provide a noninvasive way of subtyping these disorders in most patients. However, the large size of the gene and the distribution of private mutations across it pose challenges in DNA-based analysis.