Glycogen Storage Disease, Hepatic

KEY FACTS

ETIOLOGY/PATHOGENESIS

- Glycogen storage disease (GSD) refers to group of disorders caused by mutations in genes that control carbohydrate metabolism
  - Hepatic GSD refers to those types that largely or prominently affect liver
- All forms are autosomal recessive, except GSD IXa, which is X-linked

CLINICAL ISSUES

- Most patients present with hepatomegaly and fasting hypoglycemia
- Other features vary by type, including cardiomyopathy, hypotonia, or neutropenia
- Risk of hepatic adenoma or hepatocellular carcinoma in some types
- Prognosis varies based on type and severity
- Treatment for most types is dietary management, symptom control, or liver transplant

MICROSCOPIC

- Most often, liver shows enlarged, pale, swollen hepatocytes with prominent cell membranes causing "mosaic pattern" with steatosis and glycogenated nuclei
- Likelihood of fibrosis and cirrhosis varies by type
- Type IV has characteristic histology with prominent cytoplasmic inclusions

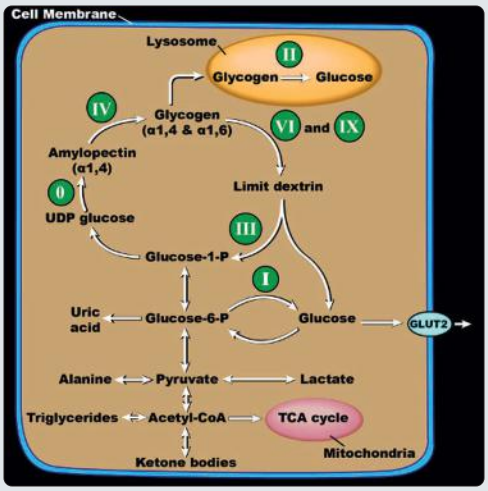
ANCILLARY TESTS

- Electron microscopy shows increased glycogen-displacing organelles
- Genetic testing has supplanted enzymatic activity assay for diagnosis
- PAS- and PAD-D stains can be used to support that the cytoplasmic pallor is due to glycogen

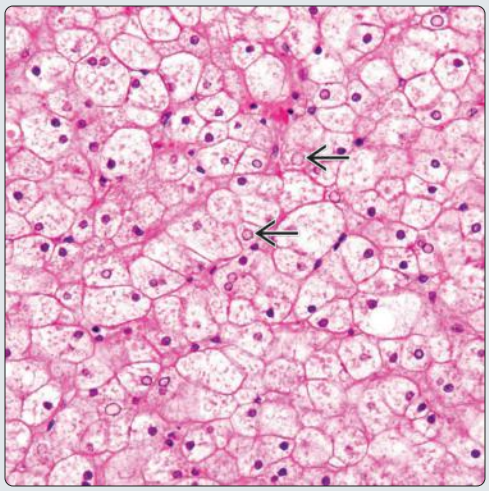
TOP DIFFERENTIAL DIAGNOSES

- Glycogenic hepatopathy in patients with poorly controlled diabetes mellitus

Glycogen Metabolism

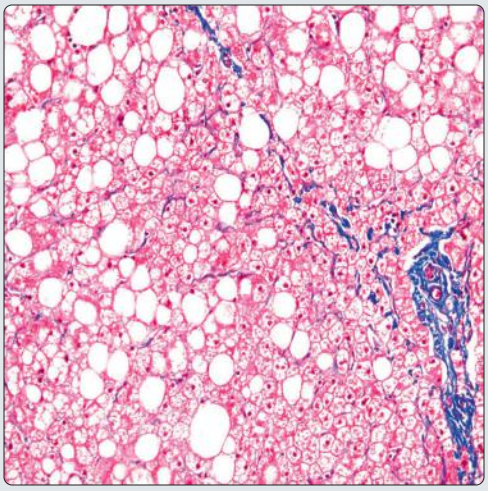


Mosaic Pattern in Glycogen Storage Disease Type Ia

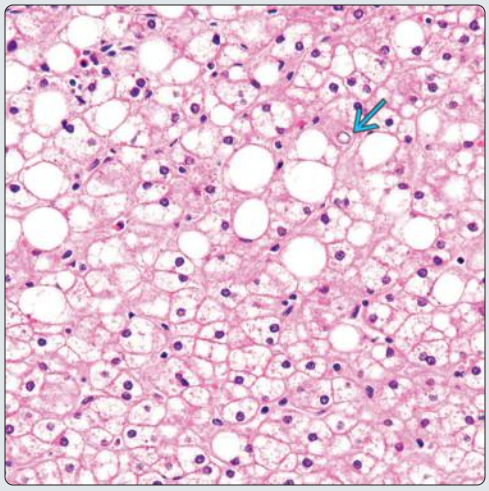


(Left) *Graphic of glycogen metabolism shows the defective enzymes for the major glycogen storage disorders; their subtypes are designated by the included Roman numerals.* **(Right)** *The mosaic pattern shown results from swollen hepatocytes compressing the sinusoids. The cell membranes are accentuated, and prominent glycogenated nuclei ⇨ are seen.*

Steatosis and Fibrosis in Glycogen Storage Disease Type Ia



Enlarged Hepatocytes in Glycogen Storage Disease Type Ib



(Left) *Trichrome stain show prominent large and small droplet fat as well as periportal fibrosis are depicted in this case of glycogen storage disease (GSD) type Ia.* **(Right)** *The findings in this case of GSD type Ib are similar to those observed in GSD type Ia. Pale, enlarged hepatocytes with inconspicuous sinusoids contain only a rare glycogenated nucleus ⇨. Fatty change is more apparent in this focus.*

TERMINOLOGY

Abbreviations

- Glycogen storage disease (GSD)

Synonyms

- Glycogenoses

Definitions

- Group of disorders characterized by inborn errors in carbohydrate metabolism
  - Hepatic glycogenoses are GSDs that primarily or significantly affect liver, including types I, III, IV, VI, IX, and 0

ETIOLOGY/PATHOGENESIS

Genetic Mutation

- Mutations in any one of genes involved in carbohydrate metabolism that results in glycogen accumulation, abnormal glycogen structure, or impaired glycogen/glucose utilization
  - GSD type 0 is no-storage disorder; defect results in inability to produce hepatic glycogen and marked decrease in glycogen
  - Type IX group of disorders is distinguished by which subunit of phosphorylase kinase is affected; type IXa accounts for 75% of cases
- Most forms are autosomal recessive with exception of some subtypes of IX (notably IXa), which are X-linked

CLINICAL ISSUES

Epidemiology

- Incidence
  - Estimated incidence of all GSD is 1 in 20,000-40,000 live births
  - Incidence of specific types varies widely: Type VI is 1:65,000-85,000; types I, III, IX are 1:100,000; type IV is 1:600,000-800,000; type 0 is extraordinarily rare
- Age
  - Most patients diagnosed within 1st decade of life, depending on subtype and its severity
- Sex
  - Type IXa is sex-linked
- Ethnicity
  - Specific subtypes occur in certain populations: Type I in Ashkenazi Jews; type III in non-Ashkenazi Jews of North African descent; type VI in Mennonites

Presentation

- Hepatomegaly
  - Type 0 is exception, presenting with small liver
- Fasting hypoglycemia
  - Severe forms of childhood GSD are associated with seizures induced by hypoglycemia with very short fasting intervals (< 4 hours)
- Failure to thrive, difficulty in settling down, awakening for feeds, short stature, motor delays, muscle weakness, and obesity are other presenting signs, depending on type
- Specific types may have additional characteristic findings
  - Recurrent infections and inflammatory bowel disease due to neutropenia and neutrophil dysfunction characterize type Ib
  - Cardiomyopathy is seen most often in type III, but also IV, VI, XI
  - Liver forms and muscle forms characterize the different subtypes of type IX
- Type IV is multisystem disorder
  - Usually presents as progressive liver disease with hepatomegaly, cirrhosis, and liver failure
  - Can present with nonprogressive liver disease, or with severe myopathy with hypotonia and dilated cardiomyopathy

Laboratory Tests

- Elevated transaminases, hypoglycemia, and hyperlipidemia common
- During fasting, lactic acidosis, ketosis, &/or hyperuricemia characterize the various types
- Elevated serum creatine kinase is seen in some types, including III and IX
- Neutropenia is seen in type Ib
- Hypoalbuminemia and prolonged prothrombin time (PT) and partial thromboplastin time (PTT) are seen when there is liver failure, such as in type IV

Natural History

- Improvement of metabolic parameters results in catch-up growth, symptom improvement, and reduced liver size
- Long-term complications depend on the type: Includes renal damage (type I), inflammatory bowel disease or recurrent infections (type Ib), cardiomyopathy (types III, IV, VI, IX), and cirrhosis
- Cirrhosis develops in 12-15% of patients (types III, IV, IX)
- Increased incidence of hepatocellular neoplasia in some types
  - Hepatic adenoma occurs most often in type I, and less often in types III, VI, IX
    - Regression has been observed with improvement in metabolic hemostasis
    - Malignant transformation has been documented
  - Hepatocellular carcinoma occurs in type I and reported in types III, IV, VI

Treatment

- Dietary therapy, with frequent feeds, avoidance of simple sugars, and use of complex carbohydrates to ensure normoglycemia
  - Uncooked cornstarch is a mainstay of dietary therapy
- Specific therapies targeted to specific complications, such as allopurinol for hyperuricemia or G-CSF for neutropenia
- Liver transplantation for patients with poor metabolic control despite adherence to diet, adenoma with malignant transformation, or cirrhosis

Prognosis

- Variable based on type of GSD
  - Good prognosis for milder types that can be controlled through diet, and, with therapy, most patients survive to adulthood

- Specific types can have additional complications that affect prognosis, such as renal damage (type I), neutropenia (type Ib), cirrhosis (type IV), cardiomyopathy (type III), or hepatocellular carcinoma (types I, III, IV)

IMAGING

Ultrasonographic Findings

- Enlarged, hyperechoic liver is common
- Often used to assess for steatosis, fibrosis (by transient elastography), and liver lesions

MICROSCOPIC

Histologic Features

- Most types show enlarged and pale hepatocytes
  - Due to increased glycogen that displaces cytoplasm
    - This results in thickened cell membrane with mosaic pattern
- Varying degrees of steatosis and glycogenated nuclei
  - More pronounced in type I
- Fibrosis and cirrhosis depend on type
- GSD IV is distinctive
  - Hepatocytes have weakly basophilic cytoplasmic inclusions
  - Inclusions are PAS(+) and partially digested on PAS-D

ANCILLARY TESTS

Histochemistry

- Glycogen is PAS(+) and PAD-D(-)
  - Helps support that intrahepatocytic cytoplasmic pallor is due to accumulated glycogen

Genetic Testing

- Genetic testing has supplanted enzymatic activity assay for diagnosis
  - Single-gene testing or targeted analysis for pathogenic variants may be appropriate in specific populations or when subtype is strongly suspected
  - Multigene panels or comprehensive genomic testing may be necessary to establish diagnosis

Electron Microscopy

- Hepatocytes with increased glycogen often displacing organelles, cytoplasmic lipid, and intranuclear glycogen
- GSD type 0: Sparse hepatocyte glycogen
- GSD type IV: Fibrillary aggregates of electron-dense amylopectin-like material within hepatocytes

Enzyme Activity Assay

- Enzyme activity assays on snap-frozen liver tissue, muscle, or skin fibroblasts were historically performed to establish which enzyme is deficient

DIFFERENTIAL DIAGNOSIS

Glycogenic Hepatopathy

- Resembles GSD, but in patients with poorly controlled type 1 diabetes mellitus

Fanconi-Bickel Syndrome

- Defect in GLUT2, a glucose transporter
- Leads to accumulation of glycogen in liver and kidney, proximal renal tubular dysfunction, and impaired utilization of glucose and galactose
- Sometimes designated GSD type XI
  - This is discouraged because accumulation of glycogen is due to nonfunctional transport issue rather than defect in metabolism

Lafora Disease

- Lafora bodies mimic GSD type IV
- Lafora bodies are more eosinophilic and stain homogeneously with colloidal iron
- Lafora disease is largely neurodegenerative disorder

Fibrinogen Storage Disease or Reactive Fibrinogen Accumulation

- Fibrinogen inclusions in primary storage disorder or as response to injury: Resembles pseudo ground glass inclusions and resembles GSD type IV
- Clinical picture, immunohistochemistry for fibrinogen if available, and EM may help distinguish

Treated Urea Cycle Defects

- Can result in hepatocyte glycogen accumulation, possibly related to therapeutic dietary modification

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Types differ with regard to development of fibrosis or cirrhosis

Pathologic Interpretation Pearls

- The key finding in most hepatic GSD
  - Rarefied and distended hepatocytes with increased glycogen that displace cytoplasm to cell membrane, causing mosaic pattern with variable fat and glycogenated nuclei
- Unique histologic appearance in GSD type IV due to conspicuous cytoplasmic inclusion

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Genetics and Pathogenesis of Hepatic Glycogen Storage Diseases

Type (Eponym)	Enzyme (Gene)	Organ(s) Involved	Mechanism
0	Glycogen synthase (*GYS2*)	Liver	Inability to produce glycogen in liver
Ia (von Gierke)	Glucose-6-phosphatase (*G6PC*)	Liver, kidney	Inability to convert glucose-6-phosphate to glucose, which is final step in glycogenolysis and gluconeogenesis
Ib	Glucose-6-phosphate transporter (*SKC37A4*)	Liver, kidney, leukocytes	Inability to transport glucose-6-phosphate into endoplasmic reticulum for catalytic conversion to glucose
III (Cori or Forbes)	Amylo-1,6-glucosidase (debrancher) (*AGL*)	Type IIIa: Liver, muscle, heart Type IIIb: Liver only	Inability to hydrolyze α-1,6 linkages; accumulation of limit dextrin polysaccharide with numerous branches
IV (Andersen)	Amylo-1,4 to 1,6-transglucosidase (brancher) (*GBE1*)	Liver, muscle, and nervous system	Inability to form branched glycogen; glycogen with abnormally long chains, known as polyglucosan (amylopectin-like polysaccharide)
VI (Hers)	Liver phosphorylase (*PYGL*)	Liver	Rate-limiting enzyme in glycogenolysis; mutations result in inability to break down glycogen into glucose-1-phosphate
IXa	Phosphorylase kinase α subunit (*PHKA2*)	Liver	Phosphorylase kinase activates phosphorylase, rate-limiting enzyme in glycogenolysis; mutations lead to inability to activate phosphorylase
IXb	Phosphorylase kinase β subunit (*PHKB*)	Liver, muscle	Inability to activate phosphorylase
IXc	Phosphorylase kinase γ subunit (*PHKG2*)	Liver	Inability to activate phosphorylase

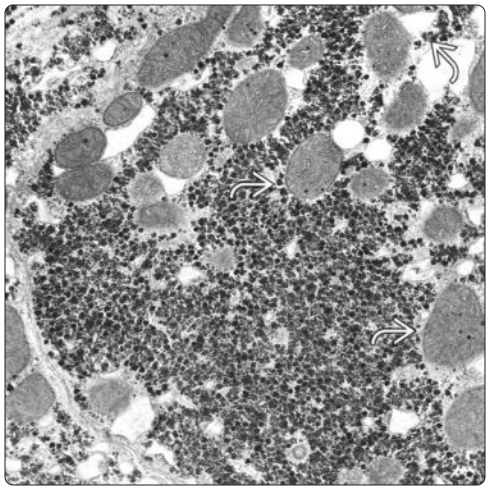
Clinical Features of Hepatic Glycogen Storage Diseases

Type	Clinical Signs and Symptoms	Biochemical Manifestations
I	Severity varies widely; hepatomegaly, renomegaly, growth failure, doll-like face, prone to adiposity Ib: Neutropenia and neutrophil dysfunction with recurrent infections and inflammatory bowel disease	Severe fasting hypoglycemia, lactic acidosis Mild transaminase elevations Long-term metabolic complications: Hyperuricemia, hyperlipidemia, thrombasthenia
III	Hepatomegaly, cirrhosis, splenomegaly IIIa: Hypertrophic cardiomyopathy, muscle weakness	Fasting ketotic hypoglycemia, elevated transaminases, hyperlipidemia, elevated creatine kinase; normal lactic acid and uric acid levels
IV	Variable onset and severity, including congenital, infantile, childhood, or adult patterns; hepatomegaly, failure to thrive, muscle hypotonia, cardiomyopathy	Elevated transaminases and alkaline phosphatase; hypoglycemia is uncommon; normal lactic acid and uric acid levels
VI	Isolated hepatomegaly, short stature; cardiomyopathy reported	Hyperlipidemia; hypoglycemia is uncommon
IX	Hepatomegaly; delayed motor development, delayed growth	Fasting ketosis; hypoglycemia
0	Short stature, lethargy, failure to thrive; absent hepatomegaly	Fasting hypoglycemia and ketonuria; postprandial hyperlactatemia; hyperlipidemia

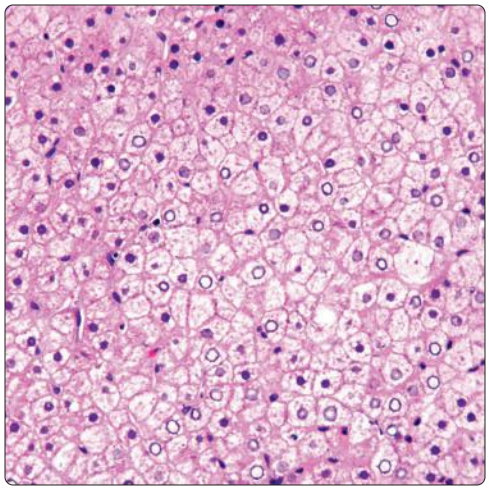
Histologic Findings in Hepatic Glycogen Storage Diseases

Type	Histologic Findings	Fibrosis or Cirrhosis	Hepatic Neoplasms
I	Hepatocyte glycogenation with mosaic pattern, steatosis, glycogenated nuclei	Generally absent	Hepatic adenoma, hepatocellular carcinoma
III	Hepatocyte glycogen with mosaic pattern, variable glycogenated nuclei, and absent steatosis	Yes	Hepatic adenoma, hepatocellular carcinoma
IV	Hepatocytes have slightly basophilic cytoplasmic inclusions	Yes	Hepatocellular carcinoma
VI	Hepatocyte glycogen with mosaic pattern	Fibrosis reported, rarely cirrhosis	Rare hepatic adenoma or hepatocellular carcinoma
IX	Hepatocyte glycogen with mosaic pattern, steatosis, mild portal inflammation	Reported, particularly in type IXc	Rare hepatic adenoma
0	Reduced hepatic glycogen, steatosis	Generally absent	

Glycogen Displaces Mitochondria in Glycogen Storage Disease Type I

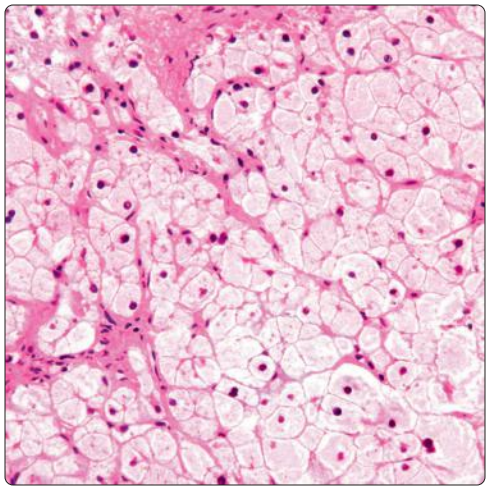


Mosaic Pattern in Glycogen Storage Disease Type III

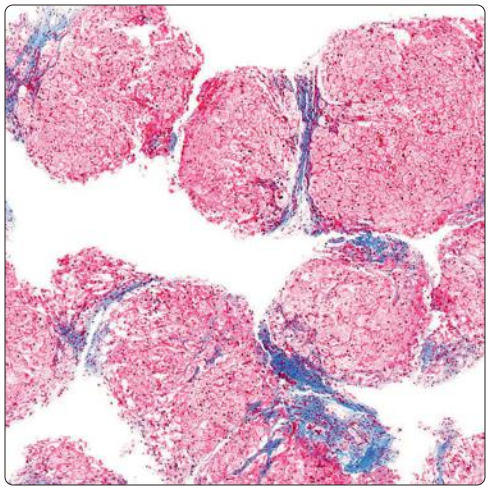


(Left) *In GSD type I shown here, the increased glycogen occupies most of the cytoplasm and causes mitochondrial displacement to the cell margin. A lipid vacuole is also present.* **(Right)** *In GSD type III shown here, the hepatocytes are arranged in a uniform mosaic pattern similar to GSD type I but may reveal less fatty change. This focus has many hepatocytes with intranuclear glycogen, a feature that is more frequently observed in GSD type I.*

Enlarged Hepatocytes, Fibrosis in Glycogen Storage Disease Type III

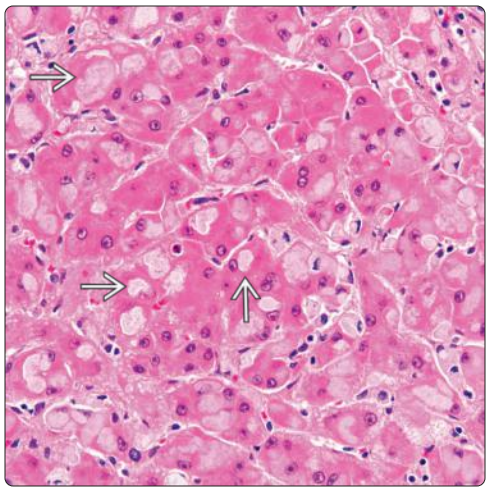


Cirrhosis in Glycogen Storage Disease Type III

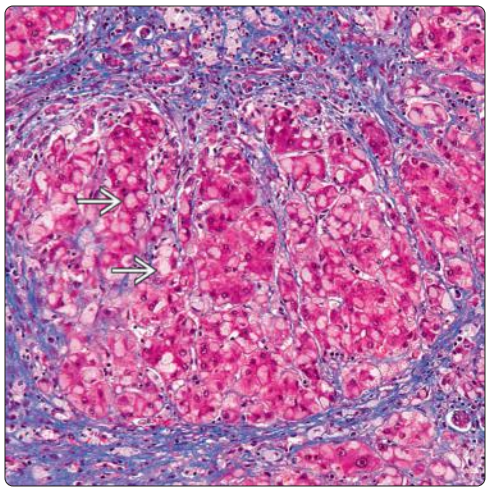


(Left) *The hepatocytes are distended with glycogen and create a mosaic architecture that is interrupted by fibrosis in this case of GSD type III.* **(Right)** *This needle core biopsy with trichrome stain from a patient with GSD type III depicts cirrhosis characterized by nodules of hepatocytes partially surrounded by fibrosis.*

Cytoplasmic Inclusions in Glycogen Storage Disease Type IV

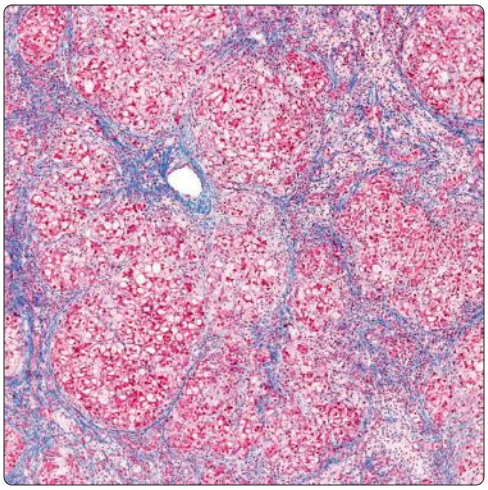


Cirrhosis in Glycogen Storage Disease Type IV

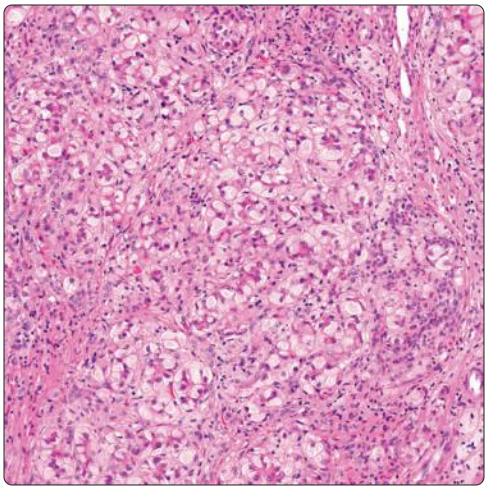


(Left) *GSD type IV demonstrates characteristic cytoplasmic inclusions within hepatocytes (with H&E stain, by light microscopy) that distinguish it from the other types of GSD. In this case, the inclusions are kidney bean-shaped and lightly basophilic.* **(Right)** *Trichrome highlights a small cirrhotic nodule completely surrounded by fibrosis in this case of GSD type IV that has evolved into cirrhosis. The cytoplasmic inclusions of GSD type IV are also apparent.*

Micronodular Cirrhosis in Glycogen Storage Disease Type IV

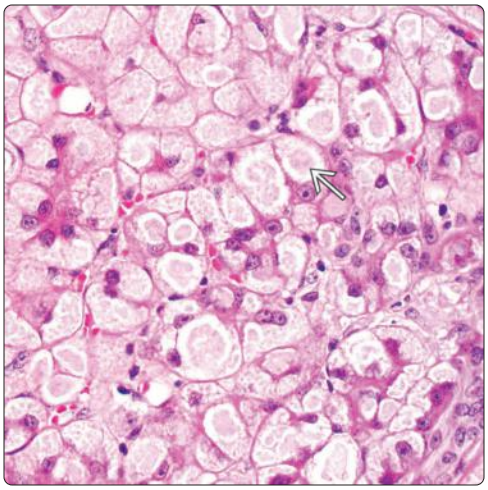


Glycogen Storage Disease Type IV

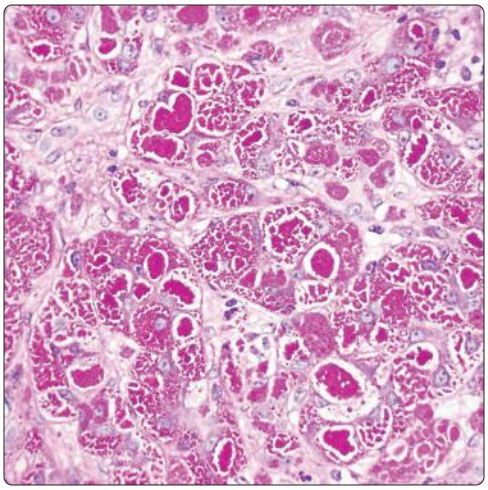


(Left) *In this explant in a child with GSD type IV, a trichrome stain demonstrates micronodular cirrhosis.* **(Right)** *Medium-power view of a liver explant shows a nodule of hepatocytes with conspicuous cytoplasmic inclusions.*

Cytoplasmic Inclusions in Glycogen Storage Disease Type IV

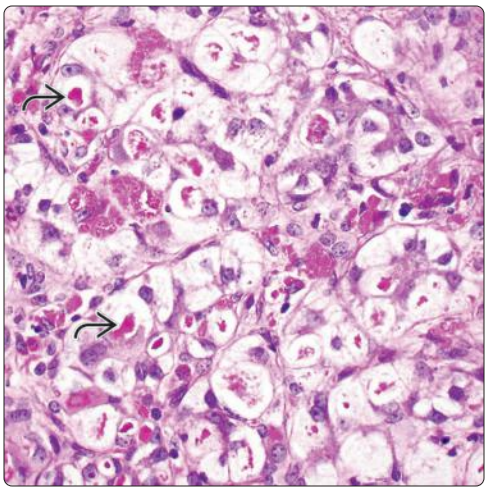


PAS Stain of Glycogen Storage Disease Type IV

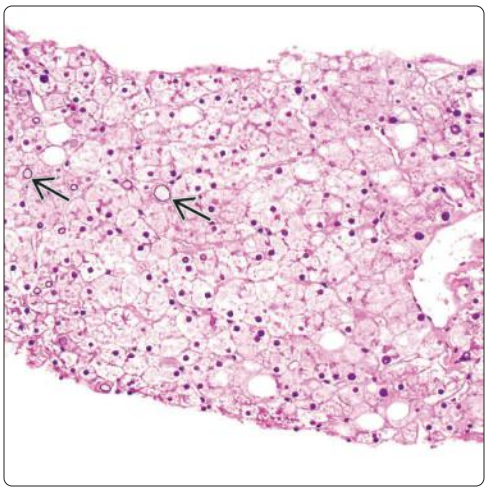


(Left) *High-power view of GSD type IV shows that the hepatocytes have weakly basophilic cytoplasmic inclusions that consist of amylopectin-like polysaccharide* ⇨. **(Right)** *The cytoplasmic inclusions in GSD type IV stain strongly with PAS, consistent with glycogen.*

PAS-D Stain in Glycogen Storage Disease Type IV



Diabetic Glycogenic Hepatopathy



(Left) *A PAS stain after diastase digestions shows that the cytoplasmic inclusions are partially digested with diastase. While most of the material is not staining, minor amounts of residual staining are present* ⇨. *These changes can mimic GSD.* **(Right)** *This liver biopsy from a patient with uncontrolled diabetes shows widespread glycogenation of the hepatocytes, with rarefied cytoplasm. Note also numerous glycogenated inclusions* ⇨.