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Von Gierke's glycogen storage disease

Synonyms: von Gierke's syndrome, glycogen storage disorder type I

What is von Gierke's disease? ^[1]

Von Gierke's disease (described by von Gierke in 1929) represents the largest group of [glycogen storage disorders \(GSDs\)](#).

Glycogen storage disease type Ia (also known as von Gierke disease), is an inborn error of carbohydrate metabolism caused by variants in the glucose-6-phosphatase gene, which accounts for 80% of cases of type I glycogen storage disease.

Cause of von Gierke's disease ^[1]

Glucose-6-phosphatase (G6Pase) is selectively expressed in the liver, kidney and small intestine, where it converts glucose-6-phosphate (G6P) into free glucose, the final common step in gluconeogenesis and glycogenolysis. Glucose-6-phosphate cannot be converted into free glucose but is metabolised to lactic acid or incorporated into glycogen. Large quantities of glycogen are formed and stored in hepatocytes, renal and intestinal mucosa cells. The liver and kidneys become enlarged.

Loss of G6Pase function impairs carbohydrate homeostasis during short-term fasting, causing a risk of severe, life-threatening [hypoglycaemic events](#).

Abnormalities of lipids may lead to xanthoma formation. Uric acid is often elevated and may cause clinical gout. Galactose, fructose, and glycerol are metabolised to lactate. The elevated blood lactate levels cause metabolic acidosis.

Classification of von Gierke's disease

Type I GSD has been divided into subgroups:

- Glucose-6-phosphatase deficiency is the cause of type Ia and should not be confused with [glucose-6-phosphate dehydrogenase deficiency](#).
- There is a specific translocase deficiency in type Ib. Individuals with type Ib also have altered neutrophil function predisposing them to Gram-positive bacterial infections.
- Two other translocase deficiencies have been described to give types Ic and Id.

For practical purposes, there are two major forms. Type Ia has deficient glucose-6-phosphatase in the liver and type Ib has normal activity. The abnormality has been located on gene map locus 17q21 for type Ia and 11q23 for type Ib. Type Ic has been mapped to 11q23-q24.2 and type Id to 11q23-q24. ^[2]

Epidemiology of von Gierke's disease ^[1] ^[3]

- The condition is inherited as an autosomal recessive disorder.
- Prevalence is unknown. Annual incidence is about 1/100,000 births.
- GSD type Ia is the more frequent type, representing about 80% of type I GSD patients.

Presentation of von Gierke's disease ^[1]

Typically presents clinically at a median age of 6 months (range 1 day to 12 years).

- Shortly after birth, hypoglycaemia and lactic acidosis often cause convulsions.
- More moderate hypoglycaemia can cause irritability, pallor, cyanosis, hypotonia, tremors, loss of consciousness, and apnoea.
- Some children have diarrhoea due to pseudo-colitis.
- There is a characteristic rounded 'doll's face' due to deposition of fat.

- During the first weeks of life the liver is normal in size but it enlarges, sometimes very considerably to cause marked abdominal distension.
- Growth is retarded and height is usually below the third centile. Puberty is delayed but mental development is normal.
- Mouth ulcers may develop.
- Skin and mucous membranes may show eruptive xanthomas or gouty tophi on the extensor surfaces of the extremities. Uric acid arthropathy can develop.
- Altered platelet function can cause bleeding, especially epistaxis, and this may result in iron-deficiency anaemia.
- GSD type Ib has the same severity of hypoglycemia as GSD type Ia, but with associated immune disturbance. Infections cause significant mortality in GSD type Ib.^[4]

Investigations

- Blood glucose and pH are usually low with elevated lactate, uric acid, triglyceride and cholesterol.
- Renal function tests: creatinine and urea may be raised if renal function is impaired.
- FBC: anaemia; patients with GSD type Ib may have neutropenia as a result of frequent bacterial infections.
- Lactic acidosis may simply be suggested by a high anion gap when electrolytes are measured.
- Older patients may show anaemia, neutropenia and proteinuria or at least microalbuminuria.

Special tests

- Ultrasound should be used to assess and monitor the size of liver and kidneys and to detect possible hepatic adenomas and nephrocalcinosis.
- Glucagon does not cause a rise in glucose levels, but it does raise lactic acid levels.

- Oral galactose and fructose fail to increase glucose levels but plasma lactic acid levels increase.
- Glucose tolerance test progressively lowers lactic acid levels over several hours.
- A bone density test is highly recommended as soon as possible in childhood.

Tissue diagnosis

- Definitive diagnosis involves assessment of glucose-6-phosphatase activity in fresh and frozen liver tissue specimens.
- Histology shows increased amounts of normal glycogen, as well as fatty infiltration of the liver.
- Kidneys may show glomerular hypertrophy and glomerulosclerosis.

Management of von Gierke's disease^[1] ^[3]

Management is based on individual needs. The cornerstone is medically prescribed dietary treatment, and there are no approved pharmacological therapies that address or correct the underlying cause of disease.

Oral glucose replacement therapy is used, in addition to regular meals and snacks, to manage blood glucose levels.

Additional therapies may be required to treat [hyperuricaemia](#), hyperfiltration, albuminuria, [hyperlipidaemia](#), hypocitraturia, [arterial hypertension](#) and [osteoporosis](#) or to prevent long-term complications, such as hepatocellular adenomas, [hepatocellular carcinoma](#), and [chronic kidney disease and renal failure](#), as well as to normalise growth.

Diet and lifestyle

- The main aim of treatment is to correct hypoglycaemia and maintain normoglycaemia:
 - Young infants require continuous nasogastric tube feeding.
 - Older infants and children are advised to include cornflour in their diet to give slow release of glucose by day but nasogastric feeding by night is still often required to prevent hypoglycaemia and associated metabolic problems.
 - It is thought likely that preventing hypoglycaemia, which is a particular problem at night, will reduce complications.
- Intake of fructose and galactose should be restricted, as they do not increase glucose levels, but do increase lactic acid.
- Restriction of lipids is advised but statins are not used.
- Physical activity does not have to be restricted but rough games and contact sports should be avoided because of the bleeding tendency and the risk of rupture to an enlarged liver.

Drugs and surgery

- [Iron-deficiency anaemia](#) may require oral iron.
- Raised uric acid levels may require allopurinol. Treatment of hyperuricaemia and pyelonephritis protects renal function.
- [Liver transplantation](#) for primary disease or for hepatocellular carcinoma:
 - Liver transplantation improves metabolic control. ^[5]
 - Seems effective, although the immunosuppression may cause deterioration of renal function. ^[6]
- Transplantation of hepatocytes appears to have had only temporary benefit. ^[7]

Complications

- [Acute hypoglycaemia](#) may be fatal or cause brain damage.

- Prolonged hypoglycaemia and metabolic acidosis may cause cerebral oedema.
- Elevated uric acid causes a decrease in the glomerular function with [proteinuria](#), [haematuria](#), [hypertension](#) and [chronic kidney disease](#). Incomplete distal tubular acidosis sometimes causes hypercalciuria, [nephrocalcinosis](#) and [renal stones](#).
- Chronic metabolic lactic acidosis and changes in the proximal renal tubule cells can cause osteopenia and [rickets](#) with severe skeletal deformities or fractures.
- Patients with GSD type Ib are susceptible to bacterial infections, including those of the CNS. Frequent infections in GSD type Ib require intravenous antibiotics to control infections.
- [Short stature](#).
- [Hyperlipidaemia](#).
- Hepatic adenomas usually develop in late teens and require careful follow-up in case of transformation to hepatocellular carcinoma, although some tumours are embryonic hepatoblastomas. Older children and young adults require ultrasound assessment of the liver at least once a year. Although there is substantial morbidity, partial hepatectomy may be an effective intermediate step to prevent hepatocellular carcinoma until definitive treatment with liver transplantation is possible. ^[8]
- Liver transplantation is a final resort when conservative measures have failed or with malignant change of hepatic adenomas. It can improve quality of life with metabolic control and permit a 'catch-up' in growth but it does not prevent renal disease. ^[9] Long-term follow-up after liver transplantation shows excellent graft and patient survival. ^[10]

Prognosis

- Survival to adulthood was previously rare but is now quite frequent. Most affected children now do well and symptoms tend to improve as children progress towards adulthood.
- Adults with GSD type Ib, women, and those with renal complications are more likely to experience a poorer quality of life. ^[11]

- Early death is usually caused by acute metabolic complications of hypoglycaemia or acidosis, bleeding and, in patients with GSD type Ib, infections are a problem. Improving care and treatment have reduced the early mortality.
- Chronic kidney disease, hypertension or malignant change of hepatic adenomas may cause mortality in adolescents and young adults.

Further reading

- [Association for Glycogen Storage Disease UK](#)
- [Beyzaei Z, Geramizadeh B](#); Molecular diagnosis of glycogen storage disease type I: a review. *EXCLI J.* 2019 Jan 30;18:30–46. eCollection 2019.

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