
بسم الله الرحمن الرحيم

In the Name of GOD

Hepatic Manifestations of GSD type I & III

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GSD Type I:

G6PC Deficiency (Von Gierke disease)

GSD I:

- Usual presentation: an infant of a few months with a protuberant abdomen, short stature, and fasting hypoglycemia.
- Median age at presentation:
  - GSD 1a: 6 m/o
  - GSD 1b: 4 m/o
- Dominant features at presentation:
  - protruded abdomen in 83%
  - symptoms of acute metabolic derangement in 71%
  - failure to thrive/growth retardation in 25%.
- The frequent breast or bottle feedings: often protect them from hypoglycemia during early infancy
- Fulminant presentation: in neonatal period with severe metabolic decompensation, hypoglycemia, and lactic acidosis: may be fatal even with aggressive management.

GSD I:

At the time of presentation in infancy:

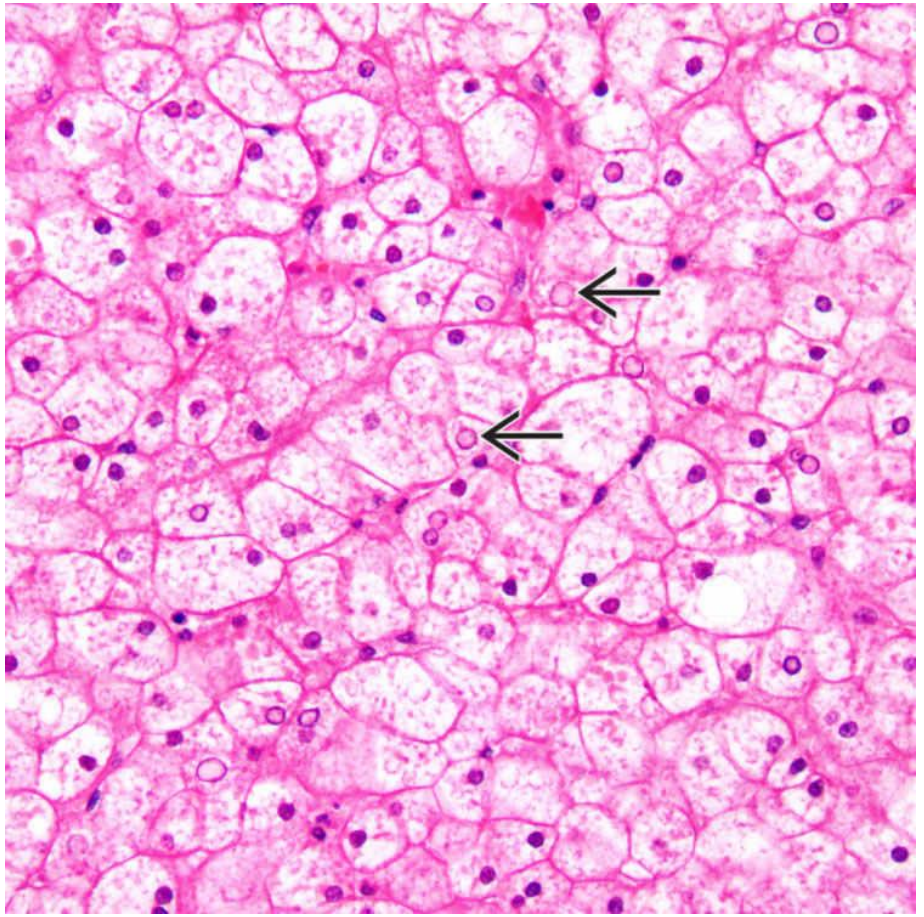
- characteristic “doll's” facies with big cheeks: excessive subcutaneous fat deposition.
- protuberant abdomen: due to massive hepatomegaly, without splenomegaly.
- Kidney enlargement noted only on ultrasonography.

Characteristic features:

- Fasting hypoglycemia (< 60 mg/dL)
- Elevated urate: uric acid > 5 mg/dL
- Hyperlipidemia (triglycerides > 250 mg/dL and cholesterol > 200 mg/dL).
  - Cholesterol is also elevated, but not to the same extent as triglycerides.
- Elevated plasma lactate: greater than 2.5 mmol/L
- Mucosal bleeding or excessive bruising: due to platelet dysfunction as a consequence of hyperlipidemia.

Liver histology

- Swollen hepatocytes, peripheral displacement of organelles by the stored glycogen: appearance likened to plant cells. (Mosaic Pattern)
- The excessive cytoplasmic glycogen stains with periodic acid-Schiff (PAS) and is readily digested by diastase.
- Microvesicular fat is almost invariably seen in the biopsy, but there is little in the way of inflammatory activity or fibrosis.
- These changes, although characteristic, are not pathognomonic, and differentiating the type of GSD on histological criteria is not reliable.



The clinical hepatic consequences:

- Untreated, massive hepatomegaly is the rule through childhood: less significant in adults.
- often a modest increase in transaminases
- Features of chronic liver disease are absent.
- Fibrosis & portal hypertension: unusual
- Hepatic adenomas are very commonly found in adults with GSD I: prone to bleeding and may undergo malignant transformation to hepatocellular carcinoma.

Other complications in untreated pts:

- Recurrent hypoglycemia
- slow linear growth
- pubertal delay and polycystic ovaries in females
- ↑ uric acid: gout
- Hyperlipidemia:
  - Xanthomata and lipemia retinalis
  - atherosclerosis
- Massive hypertriglyceridemia: pancreatitis platelet dysfunction
- Renal dysfunction
- Osteopenia, rickets, and fractures

GSD Ib:

- The metabolic consequences of GSD Ia and Ib are similar with the exception of the neutropenia seen in GSD Ib
- A tendency to recurrent bacterial infections
- Neutropenia in GSD Ib may be cyclical or persistent.
  - reduced numbers of circulating neutrophils
  - impaired neutrophil function
  - defective chemotaxis, phagocytosis, and respiratory burst
- Mucosal inflammation is common:
  - inflammatory bowel disease (IBD)

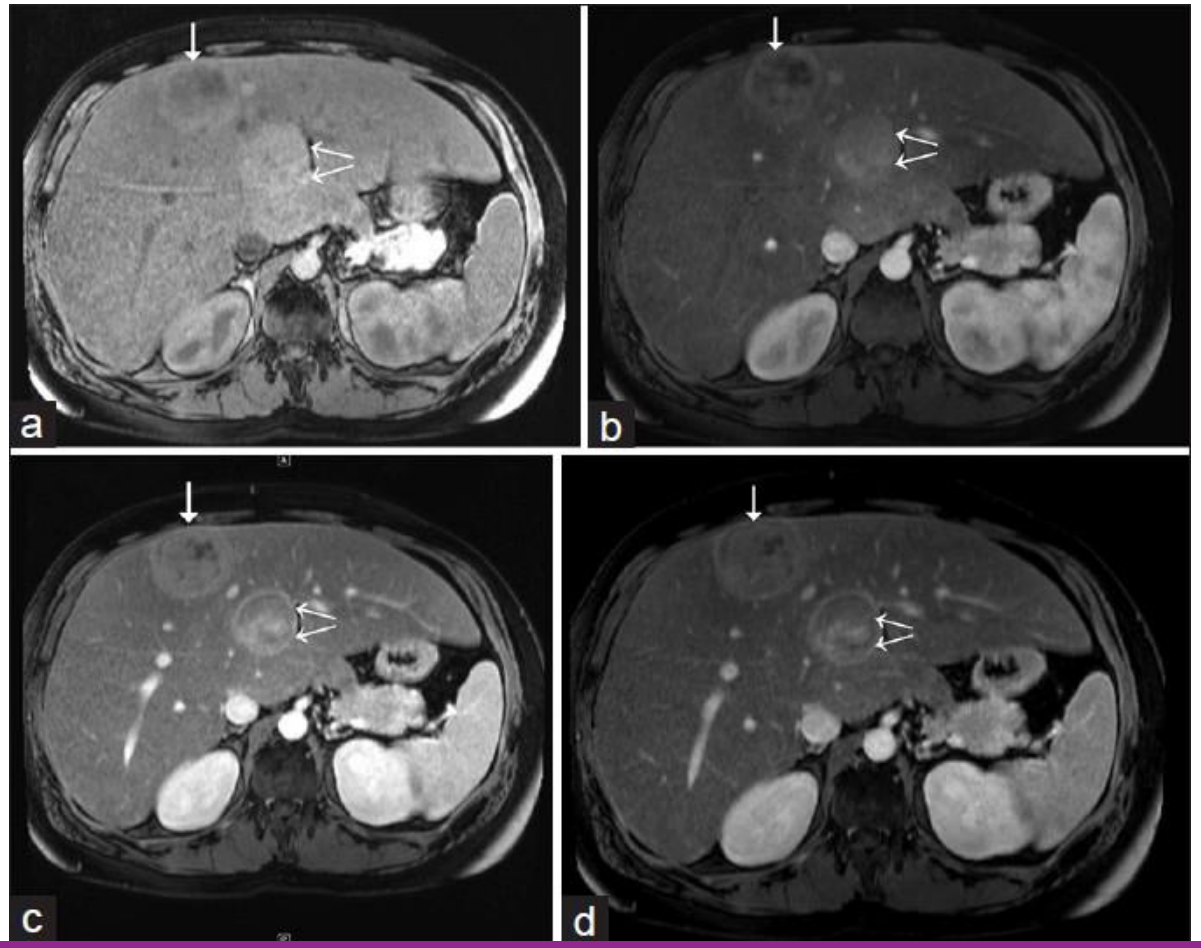
Treatment:

- Avoidance of hypoglycemia and maintenance of normoglycemia improves overall metabolic control.
- The standard approach at diagnosis: continuous overnight nasogastric feeding with glucose polymer solution or a specialized infant formula aiming to supply glucose at rates equivalent to normal hepatic synthesis, which for infants is 8-9 mg/kg/min and for older children is in the range of 5-7 mg/kg/min.
- During the day, frequent feeds are given.
- The diet should avoid galactose and fructose
- In older children, the diet should be rich in complex carbohydrates.
- Uncooked cornstarch given every four hours at a dose of 1-2 gm/kg
- A new, extended release cornstarch made from waxy maize appears to provide longer periods of glycemic control than traditional uncooked cornstarch

Treatment:

- Care needs to be taken when patients with GSD are unwell:
  - IV fluids: always contain glucose, Lactated Ringer's solution should not be used.
- Metabolic control should be strictly maintained prior to surgery to limit bleeding problems.
- Allopurinol is useful in the management of hyperuricemia
- G-CSF: management of neutropenia and recurrent infections in patients with GSD Ib
- Orthotopic liver transplantation: in GSD I: for multiple adenomas and fear of malignant change
  - Hyperuricemia, lactic acidosis, and hypertriglyceridemia clears
  - ?? progression of renal disease.
- Living donor liver transplantation in 4 children with GSD Ib:
  - Hypoglycemia and metabolic control is improved
  - neutropenia and neutrophil dysfunction are unaffected.
- Isolated hepatocyte transplantation

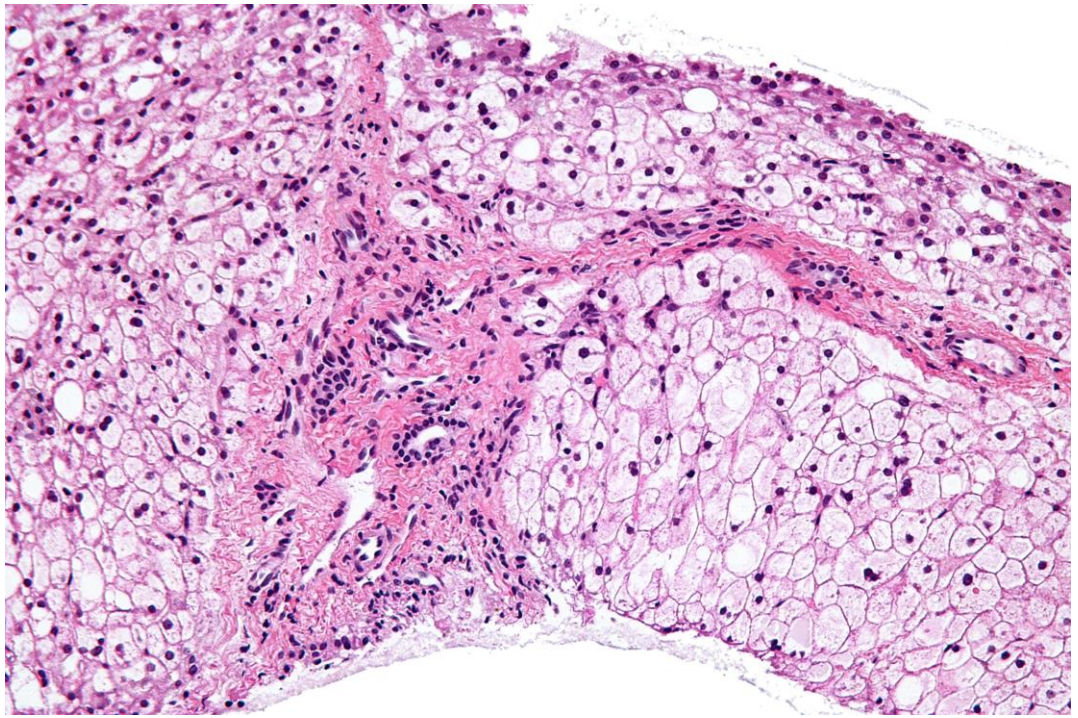
Liver adenomas and malignant transformation to HCC:



GSD III:

Debranching Enzyme Deficiency

(Cori Disease, Forbes Disease, Limit Dextrinosis)



GSD III:

- GSD III, like GSD I, commonly presents in infancy
  - hypoglycemia
  - protuberant abdomen due to hepatomegaly.
  - Growth retardation
  - hyperlipidemia.
- Hypoglycemia and hyperlipidemia are frequently less severe than in GSD I, and occasionally are absent completely.
- In addition, children may present later in childhood with isolated hepatomegaly or abnormal liver enzymes, which in some cases may be very high.
- Liver histology in early childhood tends to show a typical glycogenosis, but is more likely to show diffuse fibbrosis and less steatosis than is seen in GSD I.
- GSD IIIa: typical liver involvement with later muscle involvement
- GSD IIIb: only the liver is affected, accounts for about 15% of cases.

GSD III:

- Fasting hypoglycemia results from incomplete glycogen degradation
- lactic acidosis is not seen because there is no block in gluconeogenesis and ketosis is more apparent during hypoglycemia than in GSD I.
- Although hypoglycemia and hepatomegaly tend to recede with age, hepatic fibrosis and even micronodular cirrhosis can be seen in this condition.
- Adenomas have been reported, but in GSD III hepatocellular carcinoma appears to be associated only with cirrhosis.
- No need to restrict galactose and fructose intake because there is no impairment to their conversion to free glucose, as there is in GSD I.
- Most patients with this condition survive into adulthood, usually with minimal hepatic symptoms and with an ability to tolerate a normal diet.

Take home messages

Clinical presentation	GSD I	GSD III
Onset	3-4 m/o	> 6 m/o
Fasting hypoglycemia	Severe ++++++	Mild ++
General appearance	Doll-like face	-
Growth retardation	+	+
Hepatomegaly	+++	+ (decrease with age)
Splenomegaly	-	+
Lactic acidosis	+	-
Hyperuricemia	+	-
Hyperlipidemia	+	+
Liver transaminases	Mildly ↑	Marked ↑(maybe >500)
Neutropenia	Only in Ib	-
↑bleeding time	+	-
CPK	-	+
Ketoacidosis	-	+ esp. with fasting

Organ involvement	GSD I	GSD III
Kidney	+	-
Cardiomyopathy	-	+
Myopathy	-	+
GI	Intermittent Diarrhea in Ib	-
Osteoporosis	+	+
Fibrosis/Cirrhosis	-	+
PCO	+	+
Liver cell adenoma	+	-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لبیک یا حسین
بازاین چه پوشش است که در خلق عالم است
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