Clinical Presentation and Diagnostic Difficulties of Glycogen Storage Diseases

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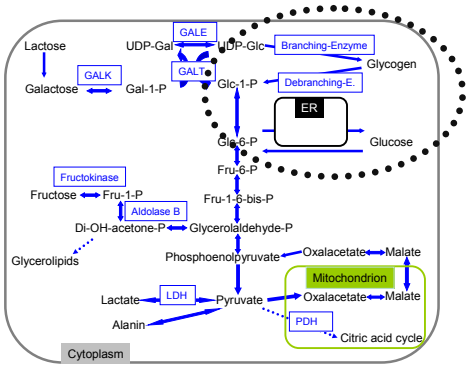
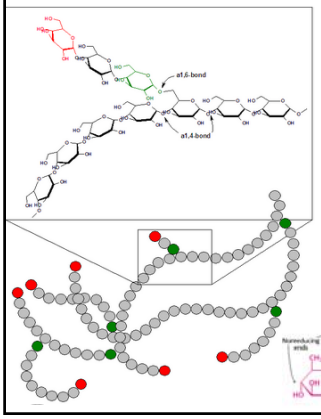
Carbohydrate Metabolism

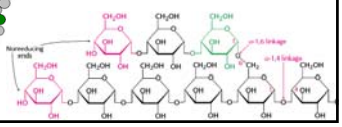


Glycogen Structure

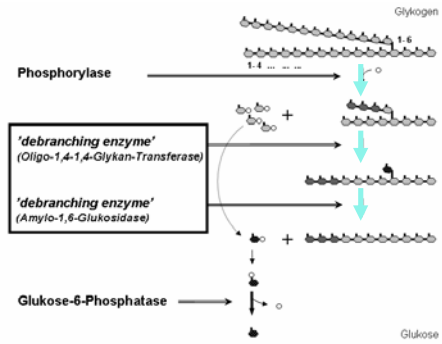


- most of Glc units are linked by α-1,4 glycosidic bonds
- approx 1 in 12 Glc residues -1,6 glycosidic bond with a second Glc → creation of a branch
- glycogen granules contain both glycogen and the enzymes of glycogen synthesis and degradation
- enzymes are nested between the outer branches of the glycogen molecules and act on non-reducing ends

⇒ the many non-reducing end-branches of glycogen facilitate its rapid synthesis and catabolism



Glycogen Catabolism

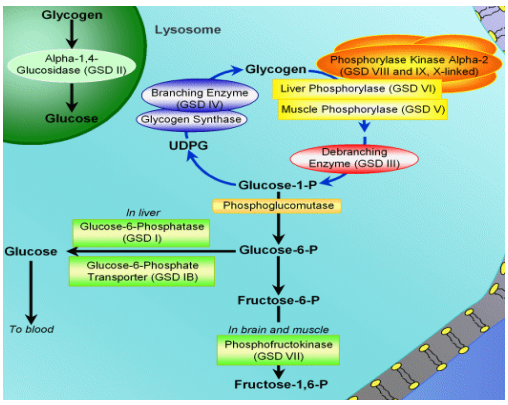


courtesy Prof. R.Santer

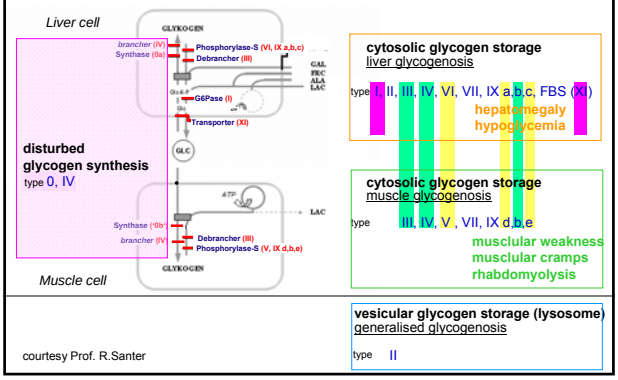
Glycogen Storage Disorders (GSDs)

➢ **Glycogen**	synthesis from G-6-P storage in liver und muscle
➢ **GSDs**	arise in enzymatic defects of
Glycogen synthesis	glycogen synthase „branching enzyme"
Glycogenolysis	tissue specific phosphorylases „debranching enzyme" lysosomal glucosidase
Glycolysis	phosphofructokinase
➢ cumulative **incidence**	1 : 20.000

Glycogen Storage Disorders (GSDs)



Classification of GSDs



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Classification of GSDs

Disturbed Glycogen Synthesis

Main focus → Cytosolic Glycogen Storage in the Liver
"Liver Glycogenosis"

Cytosolic Glycogen Storage in the Muscle
"Muscle Glycogenosis"

Lysosomal Glycogen Storage

Diagnostic Approach to Liver GSDs

isolated hepatomegaly (age 3 -18 months)

additional symptoms und laboratory findings

Disturbed Glycogenolysis **and** Gluconeogenesis	Disturbed Glycogenolysis	Disturbed Glycogenolysis
(symptomatic) hypoglycemia short fasting tolerance (2-4 hrs) urinary ketosis +/ (-) hyperventilation ← lactic acidosis enlarged kidneys upon US	mild hypoglycemia urinary ketosis ++ (*foetor acetonaemicu*) Myopathy ?? (elevated CK ??)	(with abnormal glycogen) no hypoglycemia progressive liver dysfunction cirrhosis
GSD Type I	**GSD Type III, VI, IX**	**GSD Type IV**

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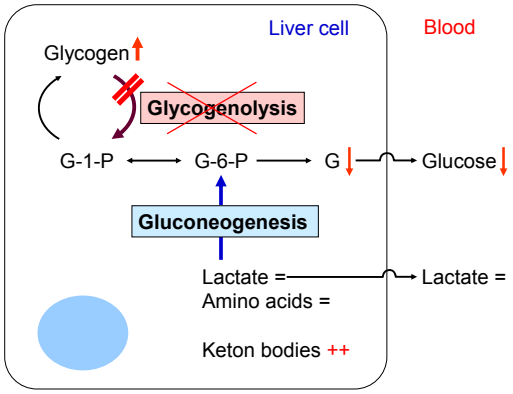
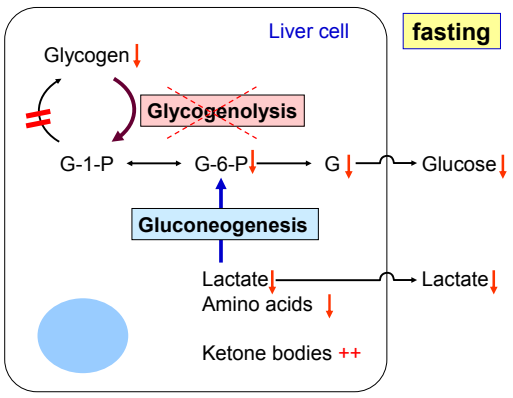
Glycogenolysis defects (GSD III, VI, IX)



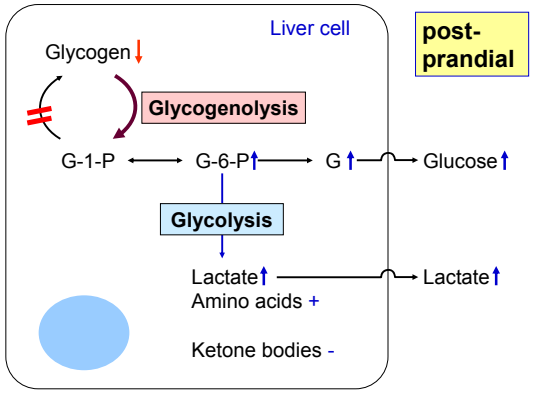
Glycogenolysis defects (GSD III, VI, IX)

- Protruding abdomen (large liver), especially in infants and small children
- Mild hypoglycemia and ketosis when fasting
- „Mild" forms of GSDs
- GSD III and IXb also muscle involvement (CK↑)
- Gene defects
  - Amylo-1,6-Glucosidase (GSD III)
  - Phosphorylase in liver (GSD VI), in muscle (GSD V)
  - Phosphorylase b-kinase (GSD IX)

Glycogen synthase deficiency (GSD 0)



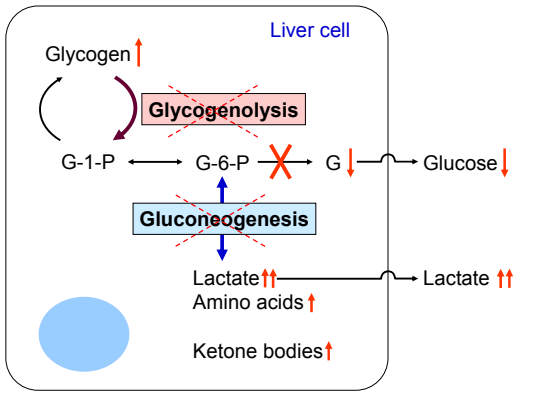
Glycogen synthase deficiency (GSD 0)



Glycogen synthase deficiency (GSD 0)

- ***Fasting***: Hypoglycemia, ketosis und low lactate (and alanine), especially in small children
- ***Postprandial***: Hyperglycemia, paradoxically high lactate (and alanine), no ketosis
- Autosomal-recessive, very rare
- Therapy: frequent meals rich in carbohydrates
- Prognosis: good

Glucose-6-Phosphatase deficiency (GSD I)

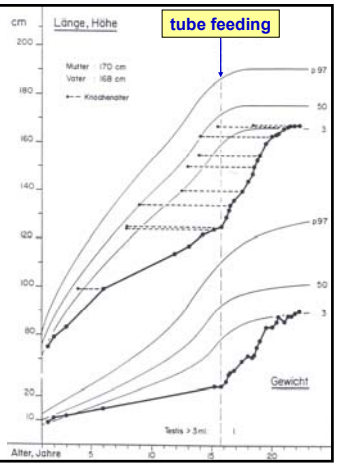


Glucose-6-Phosphatase deficiency (GSD I)

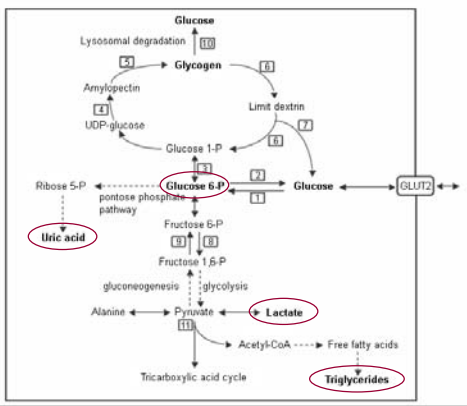
- Combined defect of glycogenolysis and gluconeogenesis
- Most severe form of GSD
- Protruding abdomen, large liver (and kidneys!)
- Failure to thrive, late puberty
- Intolerance to fasting: hypoglycemia, lactic acidosis, hyperlipidemia, hyperuricemia
- Type Ib (transporter in the ER): with neutropenia
- Therapy
  - frequent (every 2-3 hours!) meals rich in carbohydrates
  - uncooked starch
  - tube feeding at night

Glycogenosis type I

Catch up growth thanks to tube feeding at night

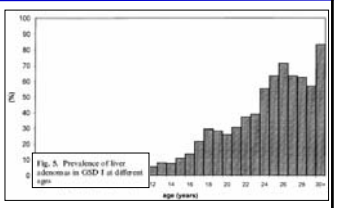


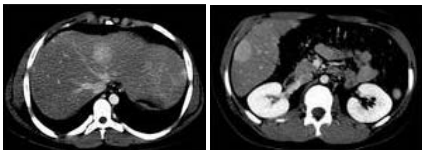
Secondary lab changes in GSDs (mainly GSDI)



Complications in GSDs

- Liver adenoma
→ hepatocellular cancer
- Osteoporosis
- Renal failure
- liver cirrhosis (IV)
- cardiomyopathy (III / IX)





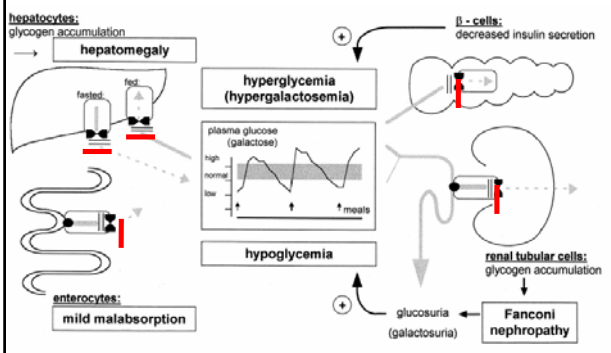
Eur J Pediatr (2002) 161: S29–S34

DD: Fanconi-Bickel-Syndrome (FBS)
→ GLUT2 deficiency

Clinical findings

- normal at birth
- failure to thrive with 3-10 months
- hepato-nephromegaly
- rickets
- growth delay
- rarely cataracts

Fanconi-Bickel-Syndrome (FBS)



Fanconi-Bickel-Syndrome: Diagnosis

1. Fasting hypoglycemia and ketonuria, low lactate
2. Postabsorptive hyperglycemia /-galactosemia, high lactate

Urine
- Glucose ↑↑↑ / Galactose (↑↑↑)
- Phosphate ↑↑
- Calcium ↑
- Amino acids ↑↑
- Uric acid ↑
- Protein ↑

Serum
- Phosphate ↓
- ALP ↑, liver enzymes ↑
- Uric acid ↓
- Bicarbonate ↓
- Lipids ↑

Fanconi-Bickel-Syndrom: Therapy

- Vitamin D
- Calcium
- Fluids
- Frequent meals

- Unooked starch: catch up growth?
- Galactose restriction: avoidance of cataracts?
- Fructose: alternate source of carbohydrates?

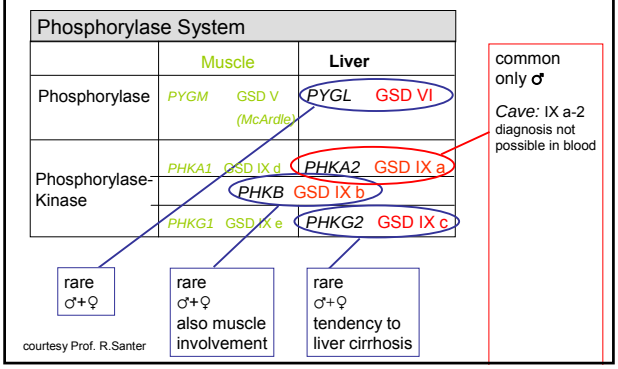
How long and how strict??

Diagnostic Approach to Liver Glycogenosis

	Type I	Type III	Type VI, IX	FBS
Hypoglycemia	+++ - ++	++ - (+)	(+)	+
Lactic acidosis	++	Ø	Ø	(+)
Fasting ketosis	Ø - +	++	+	++
Hyperlipidemia	++	++	+	++
Liver enzymes ↑	Ø - +	++	+	+
CK ↑	Ø	Ø - +	Ø - (+)	Ø
Uric acid ↑	+	Ø	Ø	(+)
Renal tubulopathy	(+)	Ø	Ø	+++
Enlarged kidneys	++	Ø	Ø	+

courtesy Prof. R.Santer

Diagnostic Difficulties in the Phosphorylase System (GSD VI + IX)



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Genetic diagnosis of hepatic GSDs

	Type I		Type III	Type VI, IX	
genes	*G6PC*	*G6PT*	*AGL*	*PYGL* *PHKA2* *PHKB* *PHKG2*	FBS *GLUT2*
number of coding exons	5	8	33	20 33 31 10	11
number of common mutations	1 [p.R83C]	2 [c.1211del CT, p.G339C]	*none*	*none* *none* *none* *none*	*none*

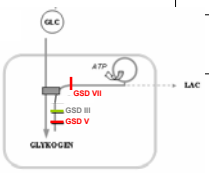
courtesy Prof. R.Santer

As a (first line) diagnostic measure only useful for GSD I

Muscle Glycogenosis

GSD V (McArdle *disease*)	**GSD VII** (Tarui *disease*)
Musclel Phosphorylase diagnosis > 10-20 J	*Phosphofructokinase* symptoms earlier
exercise intolerance muscle pain, muscle stiffness, -cramps acute crises (rhabdomyolysis)	
	hemolysis icterus
CK EMG forearm-ischaemia-test histochemistry molecular genetics	

Muscle cell



courtesy Prof. R.Santer

Diagnostic difficulties in not typical patients…

- SN, female, *02/2003
- healthy, not related Swiss parents
- normal pregancy and birth
- aunt with Crohn's disease

Admission with 18 months because of gastroenteritis

- ASAT 164, ALT 72, γGT 104 U/l
- Hepatomegaly (US) 15 cm in MCL

➔ Parainfectious Hepatopathy

- DD metabolic disease
- Did not show up for follow up

Diagnostic difficulties in not typical patients…

At 5 ¾ years

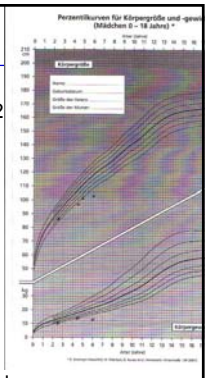
- Abdominal pain
- Diarrhea
- Fever
- Not eating well

At 6 years

- Rotavirus enteritis

Admission at 6 years

- Microcytic anemia: Hb 62, MCV 68.2
- Thrombocytosis 1.014.000
- CRP 20.1 mg/dl
- Weight 13 kg, length 103 cm, BMI 12,3 (all <<P3)
- Glucose 5.3 mmol/l
- ASAT 73 U/l, ALAT 23 U/l γGT 76 U/l



- Endoscopy: Ulcers throughout the colon

➔ chronic infectious bowel disease?

Some findings not fitting and irritating…

- Liver ultrasound: hepatomegaly (18 cm MCL)
  ⇒ storage disorder?

➔ Screening for GSD and lysosomal storage disorders

- Biotinidase: 12.6 mU/ml (N 7.0–10.6)
- Chitotriosidase: not done after asking back
- Phoyphorylase b-Kinase: 7.1 E/g Hb (N 3.5–6.5)
- Amylo-1,6-Glucosidase: 2.3 E/g Hb (N 0.9-4.2)
- Catabolism Limit Dextrin and Glycogen: normal
- Suspicion for GSD, type III and IX ruled out

➔ ask for better history

After asking specifically….

- Discrete enlargements of both kidneys
- Lactic acid 5.1 mmol/l
- Uric acid (↑)
- Triglycerides ↑↑ (8.6 mmol/L)
- Doll face, large abdomen, thin legs

After asking specifically….

Nutritional history

- „the child is always hungry and is eating all the time“
- no defined main meal times
- Small feedings spread over the entire day
- „I can‘t get rid of her demand for milk during the night“

➔ longest fasting time: 4.5 hours

Summary extended history / findings….

- Hepatomegaly, nephromegaly
- Elevated lipids, lactate and uric acid
- Failure to thrive, delayed growth
- Large abdomen, doll face
- Unusual eating habits
- Infectious bowel disease (Crohn‘s disease like)

⇒ Glykogenosis type Ib?
Neutropenia and functional disturbance of neutrophils because of defective glucose transport in ER

But: normal white blood and neutrophils count

Further diagnostic steps

Liver biopsy

- Glycogen content: 10.5g/100g (N 2.4-6.4)
- Glucose-6-Phosphatase: 0.4 U/g liver (N 3.7-9.6)
- Phosphorylase and phosphorylase b-kinase normal

Mutation analysis: *G6PC* D38V / G188R

⇒ GSD Ia

But: how does this fit to infectious bowel disease?

⇒ G188R homozygotes with GSDIb like phenotype have been reported (Weston et al. Ped Res 2000)

Conclusions from this case

- Always ask for a complete history
- Ask the right questions
- Stepwise approach
  - good history
  - basic lab tests including glucose, lactate, uric acid, lipids, CK and transaminases
  → screening test → „easy“ enzymes in blood
  → liver biopsy and/or mutation analysis

⇒ Screening test: biotinidase useful?

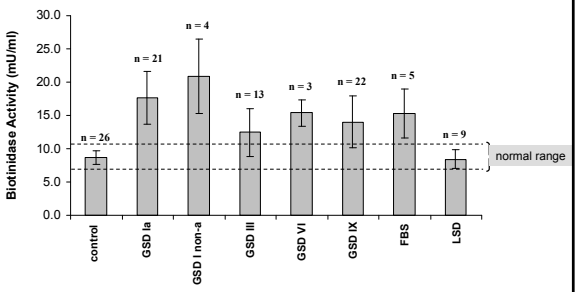
Elevated Serum Biotinidase Activity in Hepatic GSDs: How specific is this phenomenon?

- Elevated serum biotinidase activity in patients with GSD type Ia reported previously
  Wolf et al. (*JIMD* 2003), Burlina et al. (*JIMD* 1996), Saltik et al. (*Am J Gastroent* 2000), Hug et al. (*Ped Res* 1994)

Goals of study

- Expand to other types including GSD type Ib, III, VI and IX
- 68 patients with different GSDs
  - 21 GSD Ia
  - 4 GSD Ib
  - 13 GSD III
  - 3 GSD VI
  - 22 GSD IX
- 5 patients with Fanconi-Bickel Syndrome

Serum Biotinidase Activity in Controls and Patients with Hepatic Storage Disorders



Paesold et al (*JIMD* 2007)

Serum Biotinidase Activity in Controls and GSDs

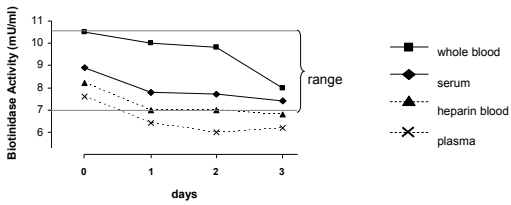
Disorder	n	SD	Range	Sensitivity (%)
control	26	± 1.0	7.0 - 10.6	
GSD Ia	21	± 3.9	11.4 - 24.8	100
GSD I non-a	4	± 5.6	14.6 - 26.0	100
GSD III	13	± 3.6	7.8 - 19.1	62
GSD VI	3	± 2.0	14.1 - 17.7	100
GSD IX	22	± 3.8	7.5 - 21.6	77
Fanconi-Bickel Syndrome	5	± 3.7	11.0 - 19.4	100

Biotinidase activity expressed in mU/ml

Paesold et al (*JIMD* 2007)

pitfall: chronic liver damage
→ false positive case: patient with cystic fibrosis and massive steatosis
→ false negative case: GSD type III patient with massive liver cirrhosis

Influence of Blood Sample Storage on Biotinidase Activity



Blood samples from one healthy control stored at room temperature
Measurements were done in replicates; mean values are shown

Paesold et al (*JIMD* 2007)

Biotinidase Activity in Hepatic GSDs: Conclusions

- Biotinidase activities are significantly elevated in sera from patients with
  - GSD Ia and Ib
  - GSD III
  - GSD VI
  - GSD IX
  - Fanconi-Bickel Syndrome (FBS)
- High sensitivity for GSD type I, VI and FBS
- Somewhat less sensitivity for GSD III and IX

Elevated serum biotinidase activity
⇒ convenient biomarker for hepatic GSDs

Paesold et al (*JIMD* 2007)

Thank You

University of Zurich

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