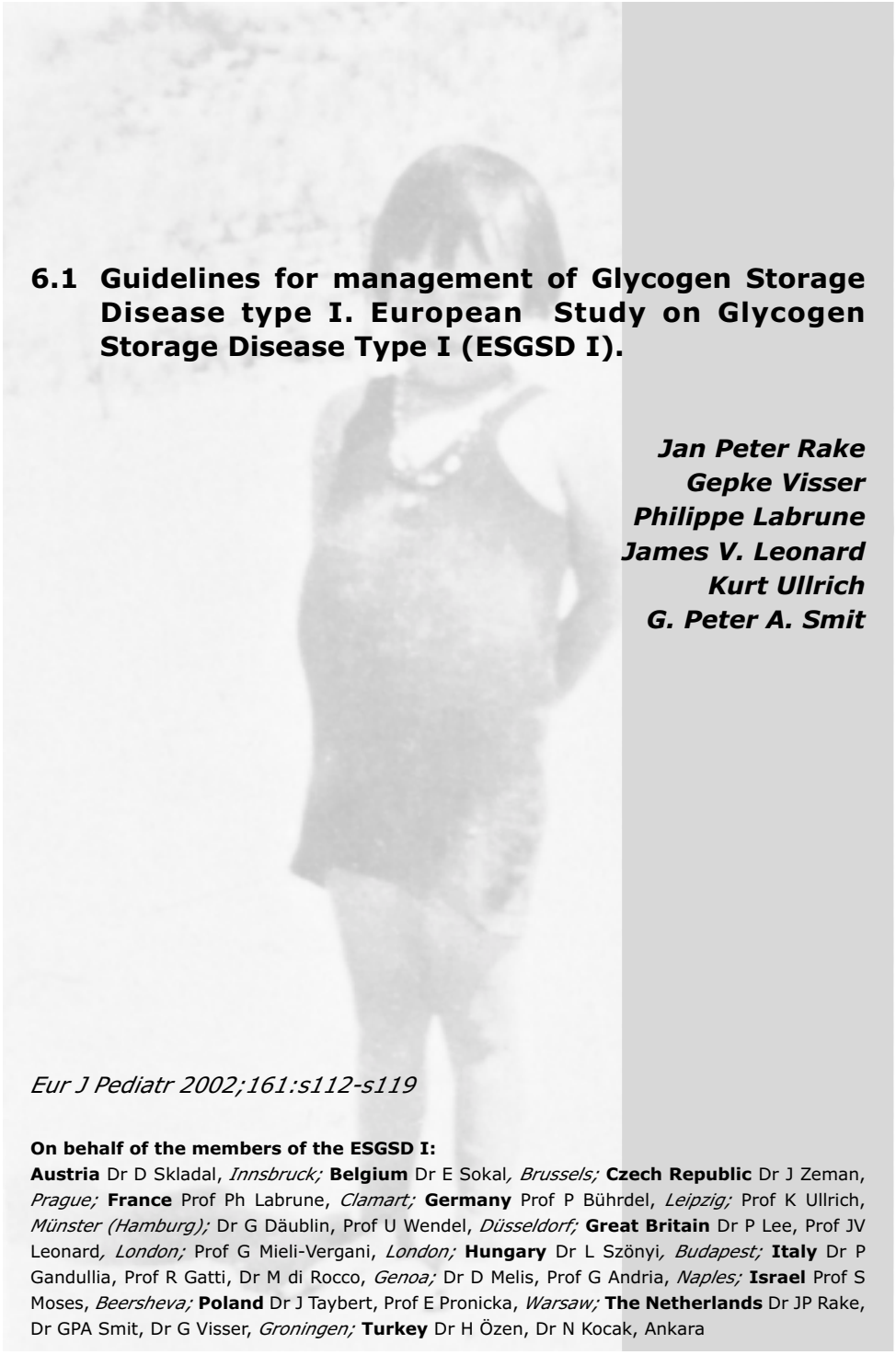
Guidelines for the management of Glycogen Storage Disease type I

Chapter 6

6.1 Guidelines for management of Glycogen Storage Disease type I - European Study on Glycogen Storage Disease Type I (ESGSD I).

6.2 Consensus guidelines for management of Glycogen storage Disease type Ib - European Study on Glycogen Storage Disease Type I (ESGSD I).



6.1 Guidelines for management of Glycogen Storage Disease type I. European Study on Glycogen Storage Disease Type I (ESGSD I).

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Eur J Pediatr 2002;161:s112-s119

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Summary

Life-expectancy in glycogen storage disease type I (GSD I) has improved considerably. Its relative rarity implies that no metabolic centre has experience of large series of patients and experience with long-term management and follow-up at each centre is limited. There is large variation in methods of dietary and pharmacological treatment. Based on the data of the European study on Glycogen Storage Disease type I (ESGSD I), discussions within this study group, discussions with the participants of the international SHS-symposium 'Glycogen Storage Disease type I and II: Recent developments, management and outcome' (Fulda, Germany; 22-25th November 2000) and on data from the literature, guidelines are presented concerning: (1) diagnosis, prenatal diagnosis and carrier detection; (2) (biomedical) targets; (3) recommendations for dietary treatment; (4) recommendations for pharmacological treatment; (5) metabolic decompensation / intercurrent infections / emergency treatment / preparation elective surgery; and (6) management of complications (directly) related to metabolic disturbances and management of complications which may develop with ageing, and their follow-up.

Introduction

Life-expectancy in glycogen storage disease type I (GSD I) has improved considerably. However, its relative rarity implies that experience with long-term management and follow-up at each referral medical centre is limited. In 1996 the European Study on Glycogen Storage Disease type I (ESGSD I) was established. One of the objectives of this collaborative study was to develop guidelines for long-term management and follow-up. The necessity of such guidelines is underlined by the statement of a father of a GSD I patient: 'Hey doctors, we need you to meet all together and define a protocol that would be the best for everybody, if that is possible. I do not know two families who do the same thing!' [gsdnet@maelstrom.stjohns.edu; 7th August 1999]. This was indeed confirmed as the ESGSD I has found that there is a wide variation in long-term management and follow-up[45,58,59].

In this paper, guidelines are presented based on the data of the ESGSD I[45], discussions with the members of the ESGSD I group and participants of the international SHS-symposium 'Glycogen Storage Disease type I and II: recent developments, management and outcome' (Fulda, Germany; 22-25th November 2000) and on data from the literature. However, only very little evidence on long-term management exists and most of the guidelines are so called 'best practice'. Furthermore, in the management of patients with GSD I, both children and adults, one must take in account individual differences and circumstances.

In the present guidelines, deficient activity of the catalytic unit is called GSD Ia and defects of the transporter(s) GSD Ib. The management of the specific GSD Ib complications such as neutropenia, neutrophil dysfunction, recurrent infections and inflammatory bowel disease (IBD) are discussed in chapter 6.2[60].

Guidelines concerning the following subjects are presented: (1) diagnosis, prenatal diagnosis and carrier detection; (2) (biomedical) targets; (3) recommendations for dietary treatment; (4) recommendations for pharmacological treatment; (5) metabolic decompensation / intercurrent infections / emergency treatment / preparation elective surgery; and (6) management of complications (directly) related to metabolic disturbances and those which may develop with ageing, and their follow-up

Diagnosis, prenatal diagnosis, carrier detection

With increased knowledge of the genetic basis of GSD I, the diagnosis GSD Ia and GSD Ib can be based on clinical and biochemical findings (Table 6.1.1) combined with mutation analysis. A flowchart for the diagnosis of GSD I is presented elsewhere (page 99)[44]. If patients have neutropenia,

Table 6.1.1 Findings and complications in GSD I

A findings / complications (directly) related to metabolic disturbances	
hypoglycaemia	paleness, sweating, irritability, convulsions, coma, death, cerebral dysfunction impaired platelet function
G6Pase deficiency (liver)	hepatomegaly (glycogen - and fat storage)
G6Pase deficiency (kidneys)	renomegaly, proximal tubular dysfunction
G6Pase deficiency (intestine)	impaired intestinal function: diarrhoea / loose stools
hyperlactacidaemia	hyperventilation
hyperuricaemia	gout, urolithiasis
hyperlipidaemia	xanthomas, pancreatitis, cholelithiasis
combination/unknown	stunted growth,rounded 'doll face', truncal obesity, hypotrophic muscles
B complications in the (ageing) patient	
hepatic tumours	liver adenomas (mechanical complaints, hemorrhage) liver carcinomas
progressive renal disease	glomerular hyperfiltration, micro-albuminuria, proteinuria, hypertension, decreased renal function, end-stage renal disease
renal distal tubular dysfunction	hypercalciuria, hypocitraturia (urolithiasis)
osteopenia	increased risk of fractures
anaemia	fatigue
ovarian cysts	decreased fertility, mechanical / vascular complaints
vascular abnormalities	(atherosclerosis), pulmonary hypertension
type Ib: neutropenia/ neutrophil dysfunction	recurrent infections, IBD

recurrent infections or IBD, mutation analysis of the glucose-6-phosphate translocase gene (G6PT, 11q23) should be performed first. Otherwise analysis of the glucose-6-phosphatase (G6Pase) gene (G6PC, 17q21) should be performed. If one or two mutations in G6PC or G6PT are identified, enzyme assays in liver tissue obtained by biopsy are no longer necessary to establish the diagnosis. Only if no mutations in neither G6PC nor in G6PT are identified, a glucose tolerance test should be performed. In GSD I, a marked decrease in blood lactate concentration from an elevated level at zero time is observed. This pattern is also observed in fructose-1,6-biphosphatase deficiency. An increase in blood lactate concentration is observed in other glycogen storage diseases[18]. If after a glucose tolerance test the suspicion of GSD I remains, enzyme assays in fresh liver tissue should be performed. In the case of GSD

Ia, G6Pase activity is deficient in both intact and disrupted microsomes; in that of GSD Ib, a combination of deficient G6Pase activity in intact microsomes and (sub)normal G6Pase activity in disrupted microsomes is observed[41].

Identification of mutations on both G6PC or G6PT alleles of a GSD I index case allows reliable prenatal DNA-based diagnosis in chorionic villi samples. Carrier detection in partners of a known mutation carrier is also a reliable option, since a high detection rate of mutations is observed for both G6PC and G6PT[44,56].

Biomedical targets

The following main targets for the management of GSD I should be held in mind: prevention of acute metabolic decompensation, prevention of acute and long-term complications, attainment of normal psychomotor development, and good quality of life. The biomedical targets for patients with GSD I are summarised in Table 6.1.2. Biomedical targets are based on evidence of what levels of abnormality constitute an added health risk. One should attempt to approach these targets as much as closely, without deterioration in quality of life.

Table 6.1.2 Biomedical targets in GSD type I

1	preprandial blood glucose > 3.5 - 4.0 mmol/l (adjusted to target 2)
2	urine lactate/creatinine ratio < 0.06 mmol/mmol
3	serum uric acid concentration in high normal range for age and laboratory
4	venous blood base excess > -5 mmol/l and venous blood bicarbonate >20 mmol/l
5	serum triglyceride concentration < 6.0 mmol/l
6	normal faecal alpha-1-antitrypsin concentration for GSD Ib
7	body mass index between 0.0 SDS and + 2.0 SDS

Single (clinic) blood glucose estimations are not very useful because of the wide variation between days and between times of day. It is preferable to repeat these estimations at home preprandial and in the night over 48 hours. The preprandial blood glucose concentrations should be above 3.5 - 4.0 mmol/l and adjusted to the actual urinary lactate excretion. Lactate/ creatinine ratio in urine should be estimated in portions collected at home and delivered to the laboratory in the frozen state[16,23,35]. Serum uric acid concentration, serum cholesterol and triglyceride concentrations, and venous blood gases should be estimated during each outpatient visit. A good marker for the degree of IBD activity in GSD Ib is faecal alpha-1-antitrypsine[60].

Some evidence exists that long-term optimal metabolic control with

normoglycaemia and (almost) no secondary metabolic disturbances (especially normal blood lactate concentration) reduces the risk of development of the long-term complications[11]. On the other hand, moderate hyperlactacidaemia protects against cerebral symptoms, even when the blood glucose concentration is very low, as lactate serves as an alternate fuel for the brain[16].

Recommendations for dietary treatment

The aim of dietary treatment is to achieve optimal metabolic control by mimicking the demanded endogenous glucose production, in healthy persons a result of glycogenolysis and gluconeogenesis, as closely as possible during day and night, hereby avoiding hypoglycaemia and suppressing secondary metabolic decompensation as much as possible[17,18]. No consensus exists about the extent of avoiding lactate production from galactose, fructose and saccharose.

Provision of exogenous glucose to GSD I patients has altered over the years[1,6,10,12,18,22,36,52,53,66,68]. Methods are frequent feedings, meals and snacks preferably with precooked cornstarch (PCCS), continuous nocturnal gastric drip feeding (CNGDF) and administration of uncooked cornstarch (UCSS). The application of these methods among different age-groups of GSD I patients is shown in Table 6.1.3.

Glucose requirements in mg/kg/min decrease with age. Only the required amount of glucose should be given since larger quantities of exogenous glucose will cause undesired swings in blood glucose. This makes patients more sensitive to rebound hypoglycaemia and will induce peripheral body fat storage.

In infants it is not necessary to replace breast milk for a milk-based formula as long as the biomedical targets are reached. If breast milk is given one should accept a higher urinary lactate excretion.

CNGDF can be introduced already in very young infants. Both a glucose/glucose polymer solution or a sucrose-free, lactose-free/low formula enriched with maltodextrin may be used. There are no studies comparing both methods. CNGDF should be started within 1 hr after the last meal. Otherwise a small oral or bolus feed should be given. Within 15 minutes after the discontinuation of the CNGDF, a feed should be given. CNGDF can be given using a nasogastric tube or by gastrostomy. Gastrostomy is contraindicated in type Ib patients because of the problems that can arise in the case of development of IBD and the risk of local infections. A reliable feeding pump which accurately controls flow rate and has alarms in case of a fault in the system should be used. Parents need thorough teaching with meticulous explanation of technical

Table 6.1.3 Recommendations for dietary therapy GSD I patients

recommendations dietary treatment 0 - 12 months
D breast feeding / formula feeding (lactose free + maltodextrin) 2-3 hrs interval
from 6 months up maltodextrin in formula feeding replaced by rice/corn (up to 6%)
N CNGDF if possible during 12 hours (50 → 35% energy), otherwise frequent feedings
recommendations dietary treatment 1 - 3 years
D 3 meals with PCCS and 2 snacks (preferable PCCS)**;** UCCS (4 hrs interval; 1.0 - 1.5 g/kg)
N CNGDF during 12 hours (35% energy), otherwise UCCS (4 hrs interval; 1.0 - 1.5 g/kg)
recommendations dietary treatment 3 - 6 years
D 3 meals with PCCS and 2 snacks (preferable PCCS); UCCS (4-6 hrs interval; 1.5 - 2.0 g/kg)
N CNGDF during 12 hours (35% energy), otherwise UCCS (4-6 hrs interval; 1.5 - 2.0 g/kg)
recommendations dietary treatment 6 - 12 years
D 3 meals with PCCS and 2 snacks (preferable PCCS); UCCS (6 hrs interval; 1.5 - 2.0 g/kg)
N CNGDF during 10 hours (30% energy), otherwise UCCS (6 hrs interval; 1.5 - 2.0 g/kg)
recommendations dietary treatment adolescents
D 3 meals with PCCS and 2 snacks (preferable PCCS); UCCS (6 hrs interval; 1.5 - 2.0 g/kg)
N CNGDF during 10 hours (30% energy), otherwise UCCS (6 hrs interval; 1.5 - 2.0 g/kg)
recommendations dietary treatment adults
D 3 meals with PCCS and 2 snacks (preferable PCCS); UCCS (6 hrs interval; 1.5 - 2.0 g/kg)
N CNGDF during 8 - 10 hours (25 - 30% energy), otherwise UCCS (6 -8 hrs interval; 2.0 g/kg)
CNGDF and UCCS during night exchangeable (weekends/holidays)

D daytime; **N** overnight

and medical details and should be completely confident with the feeding pump system.

Glucose is slowly released from UCCS and absorbed. During the day it prolongs the fasting period, overnight it may be used in children if CNGDF is not an option. Furthermore it may replace CNGDF in adults. No significant differences in growth and biochemical parameters between the use of CNGDF and UCCS overnight have been found[9,65]. Theoretically pancreatic amylase activity is insufficiently mature in children less than 1 year of age and therefore UCCS should not be started in these patients[25]. However, it may be effective and useful in these younger children. Starting dose is 0.25 g/kg bodyweight and the dose should be increased slowly to prevent side-effects as bowel distension, flatulence and loose stools. The side-effects are usually transient. Precaution is needed in GSD Ib patients since UCCS may exaggerate IBD. UCCS can be mixed in water in a starch/water ratio of 1:2. No glucose should be added to avoid insulin release. Especially if UCCS is used overnight, an UCCS tolerance test should be performed to investigate the possible duration

of the fasting period.

The total dietary plan should provide 60-65% of the total energy intake from carbohydrates, 10-15% from protein, and the reminder from fat (preferably vegetable oils with high linoleic acid content). Lactose, fructose and sucrose should be restricted except for fruits, vegetables and (small amounts of) milk products.

Recommendations for pharmacological treatment

Xanthine-oxidase inhibitor (allopurinol)

Uric acid is a potent radical scavenger and it may be a protective factor in the development of atherosclerosis. Therefore, it is recommendable to accept serum uric acid concentrations in the higher ranges of normal. To prevent for gout and urate nephropathy, allopurinol should be started if serum uric acid concentration exceeds the upper level of normal for age and laboratory despite optimal dietary treatment. Starting dose is 10 mg/kg per day in three doses orally (maximum 900 mg/day).

Bicarbonate / citrate

If, despite optimal dietary treatment, venous blood base excess is below -5 mmol/l or venous blood bicarbonate is below 20 mmol/l, it is recommended to correct lactacidaemia. Until now, (sodium)bicarbonate was advised: starting dose 1-2 mmol (85-170 mg)/kg per day in four doses orally. Apart from correcting lactacidaemia, bicarbonate also induces alkalinasation of urine, hereby diminishing the risk for the development of urolithiasis and nephrocalcinosis[18]. Recently it was found that hypocitraturia, that worsens with age, occurs in patients with GSD Ia[62]. Therefore alkalinasation with citrate may be even more beneficial in preventing or ameliorating urolithiasis and nephrocalcinosis. Starting dose: potassium citrate 10 mEq orally every 8 h (adults), 5-10 mEq every 12 h (children). Check for serum potassium concentration [oral communication DA Weinstein].

Angiotensin converting enzyme inhibitor / additional blood pressure lowering drugs

If persistent microalbuminuria is present a (long-acting) angiotensin converting enzyme (ACE) inhibitor should be started to slow-down or prevent further detoriation of renal function, in analogy to diabetic nephropathy. Starting dose depends on choice of ACE inhibitor. Additional blood pressure lowering drugs should be started if despite the use of a ACE inhibitior, blood pressure remains above p95 for age.

Supplementation of vitamins and minerals

The dietary plan should be carefully designed and followed to provide enough essential nutrients as recommended by the WHO. Otherwise supplementation should be started. Special attention is needed regarding calcium (limited milk intake) and vitamin D. Furthermore, increased carbohydrate metabolism needs sufficient vitamin B1.

Iron

After excluding other causes (vitamin B12 -, folic acid deficiency), in the case of (micro- or normochronic) anaemia, iron can be given. Starting dose 3 mg Fe^{2+}/kg per day orally. After 2-3 months, the effects should be evaluated. Iron given parenterally is more effective in especially some older patients. An iron-refractory anaemia is observed in patients with liver adenomas.

GCSF and prophylactic antibiotics in GSD Ib

See specific recommendations in chapter 6.2[60]

Miscellaneous

To reduce the risk of cholelithiasis and pancreatitis, *triglyceride-lowering drugs* (nicotinic acid, fibrates) in GSD I seems only indicated if serum triglyceride levels remain above 10.0 mmol/l despite optimising dietary treatment.

Life-long hypercholesterolaemia in young adult GSD Ia patients is not associated with the development of premature atherosclerosis[30,55]. Therefore, *cholesterol-lowering drugs* seem not to be indicated in younger GSD I patients. In adult patients however, progressive renal insufficiency may deteriorate hyperlipidaemia. This 'renal' contribution to the hyperlipidaemia may play a more important role in the development of atherosclerosis. Therefore, if in these adults, despite optimising dietary treatment and reducing microalbuminuria/proteinuria (ACE inhibitors), cholesterol remains strongly elevated (> 8 - 10 mmol/l), statins (hydroxymethylglutaryl-coenzyme-A-reductase inhibitors) may be indicated, although no evidence exists.

Fish-oil seems not be indicated since its positive effect on serum triglyceride and cholesterol does not last and it even may lead to increased lipoprotein oxidation hereby increasing atherogenecity[3].

At this moment it is our opinion that there is no place for *growth hormone therapy* in GSD I since it may enhance growth during therapy but does not exert a positive influence on final height. Also *oestrogens and testosterone* to enhance pubertal development seem not be indicated since they have a negative influence on final height.

For recommendations about *oral anticonceptives,* see[38].

Metabolic decompensation/intercurrent infections/emergency treatment/preparation for elective surgery

Parents and patients need to recognise different stages in metabolic decompensation: from the impending metabolic situation with paleness, sweating and abnormal behaviour (irritability), to more serious metabolic decompensation with decreased consciousness and hyperventilation, to severe metabolic crisis with coma, convulsions and ultimately death. Impending metabolic decompensation can be elicited by trivial events such as short delay of a meal, or an intercurrent illness. Parents and patients should respond by giving/taking a glucose drink (low osmolarity), and after recovery more slowly released carbohydrates. If unsuccessful, repetitive small amounts of a glucose solution should be administered by gastrostomy, by nasogastric tube, or orally to overcome the time to intravenous therapy. An emergency protocol in case intravenous therapy is needed is summarised in the emergency letter (Table 6.1.4). Since not all (emergency) doctors are familiar with GSD I, it is advisable for patients to always have an emergency letter with them.

During infections, the frequent supply of exogenous glucose must be maintained. However anorexia, vomiting and diarrhoea do endanger this. Furthermore glucose metabolism is increased in case of fever. Replacement of meals and snacks by glucose polymer drinks is often needed. Nasogastric drip feeding 24 h a day may be necessary. If this is not tolerated a hospital admission is needed for intravenous therapy.

Prior to elective surgery, bleeding time (platelet aggregation) should be normalised by continuous gastric drip feeding during 24 h for 1 week or by intravenous glucose infusion over 24-48 hours[18]. Close peri-operative monitoring of blood glucose and lactate concentration is essential.

Management of complications (directly) related to metabolic disturbances and management of complications that may develop with ageing; follow-up guidelines

By adjusting metabolic control in GSD I patients as optimal as possible, the occurrence of symptoms/complications directly related to metabolic disturbances will diminish: growth improves, liver size decreases, the risk of gout, urolithiasis, xanthomas and pancreatitis decreases, platelet function normalises, and, as long as cerebral symptoms (coma, convulsions) of acute metabolic decompensation can be prevented, cerebral function is preserved[10,18,45]. Optimal metabolic control implies however, that patients are more prone to develop these cerebral symptoms since they become more glucose-dependent and the ability to use lactate as a fuel for the brain reduces.

Table 6.1.4 Emergency letter for patients with GSD I

Glycogen storage disease type I (m. von Gierke) is an inborn error of carbohydrate metabolism. Due to deficient glycogenolysis and gluconeogenesis, patients develop hypoglycaemia and hyperlactacidaemia after a short period of fasting, for instance in case of high fever in combination with vomiting and diarrhoea or at surgical procedures.

Emergency procedure for acute metabolic decompensation in patients with GSD I:

A intravenous glucose solution should be given immediately

initially as bolus injection (in 10 min), followed by
125 - 150% of normal glucose requirement (depending body-temperature) for 12 h
100 - 125% of normal glucose requirement thereafter

age	**bolus**	**normal glucose requirement**
0 - 12 months	500 mg glucose/kg (5 ml gluc 10% / kg)	7 - 9 mg/kg/min
1 - 6 years	400 mg glucose/kg (4 ml gluc 10% / kg)	6 - 8 mg/kg/min
6 - 12 years	350 mg glucose/kg (3.5 ml gluc 10% / kg)	5 - 6 mg/kg/min
adolescents	300 mg glucose/kg (3 ml gluc 10% / kg)	4 - 5 mg/kg/min
adults	250 mg glucose/kg (2.5 ml gluc 10% / kg)	3 - 4 mg/kg/min

B metabolic acidosis should be corrected with intravenous bicarbonate solution

With ageing several complications may develop; these are summarised in Table 6.1.1.

Liver adenoma, single or multiple, may develop in the second or third decade. One should realise that on ultrasound focal fatty sparring may be thought to be adenomas, especially if observed before 10 years of age[31,33]. Adenomas may remain constant during many years of intensive dietary treatment. Also a reduction in size and or number of adenomas has been observed following optimal metabolic control. Liver adenomas may cause mechanical complaints and acute haemorrhage. Furthermore, they may transform into carcinomas. To screen for adenomas and to follow them in size and number, ultrasonography should be performed regularly (Table 6.1.5). Increase in size of nodules or change to poorly defined margins necessitates further investigations such as CT scans or MRI[18]. In addition, serum α-fetoprotein (αFP) and carcino-embryonal antigen (CEA) can be used to screen for malignant transformation. However, both CT and MRI are not highly predictive of malignant transformation[37], and of both tumour markers, false negative results in the case of malignant transformation of adenoma(s) in GSD I have been reported[4]. The management of liver adenomas is either expectant or surgical[37]. In severe cases of adenomas, enucleation or partial

liver resection are therapeutic options. By recurring adenomas or on suspicion of malignant transformation, orthotopic liver transplantation (LT) is a therapeutic options if metastases are not present. LT corrects also glucose homeostasis[29], but it does not prevent for the development of renal failure[40]. Immunosuppression may even worsen renal function.

Progressive renal disease in GSD I starts with a 'silent' period of hyperfiltration already in the first years of life[2]. Microalbuminuria may develop at the end of the first or in the second decade of life and is an early detectable manifestation of the progression of renal disease[8,47,48]. Estimation of urinary albumin excretion should be done regularly (Table 6.1.5). Microalbuminuria observed before 5 years of age must be differentiated from urinary excretion of small proteins caused by proximal tubular dysfunction. Some evidence exists that optimal metabolic control will reduce the incidence and diminish the progression of renal disease[54,38]. In analogy to diabetic nephropathy, an ACE inhibitor should be started if persistent microalbuminuria exists over a period of 3 months. A moderate dietary restriction of protein is recommended. Blood pressure should be below p95 for age and gender and if necessary additional blood pressure lowering drugs should be started. Hemodialysis, continuous ambulatory peritoneal dialysis and renal transplantation are all therapeutic options for end-stage renal disease in GSD I.

In contrast to renal proximal tubular dysfunction that is related to poor metabolic control[7], renal distal tubular dysfunction with hypercalciuria and hypocitraturia is also observed in more optimally controlled patients[49,62]. It contributes to the development of urolithiasis. Alkalinasation of the urine may be protective. Citrate supplementation seems to be most beneficial in preventing or ameliorating urolithiasis and nephrocalcinosis[62]. Regular ultrasonography of the kidneys is recommended (Table 6.1.5).

Osteopenia in GSD I seems to be a result of both decreased bone matrix formation and decreased mineralisation[34,43]. Limited peak bone mass formation increases the risk of fractures later in life. Important for normal bone formation is suppressing secondary metabolic and hormonal disturbances, especially chronic lactacidaemia. Calcium intake and vitamin D intake should be within the ranges recommended by the WHO. Monitoring bone density by quantitative CT or dual-energy X-ray absorptiometry is recommended.

Anaemia in GSD I is observed at all ages. However, especially adolescent and adult patients have complaints[45]. If there are complaints, and after excluding other causes (vitamin B12-, folic acid deficiency), a trial with iron should be started (orally, and if unsuccessful, parenterally). Patients with liver adenomas may have iron-refractory anaemia.

Polycystic ovaries (PCOs) have been observed in adolescent and adult

Table 6.1.5 Follow-up guidelines for patients with GSD I

(for additional guidelines for GSD Ib patients see chapter 6.2 [60])

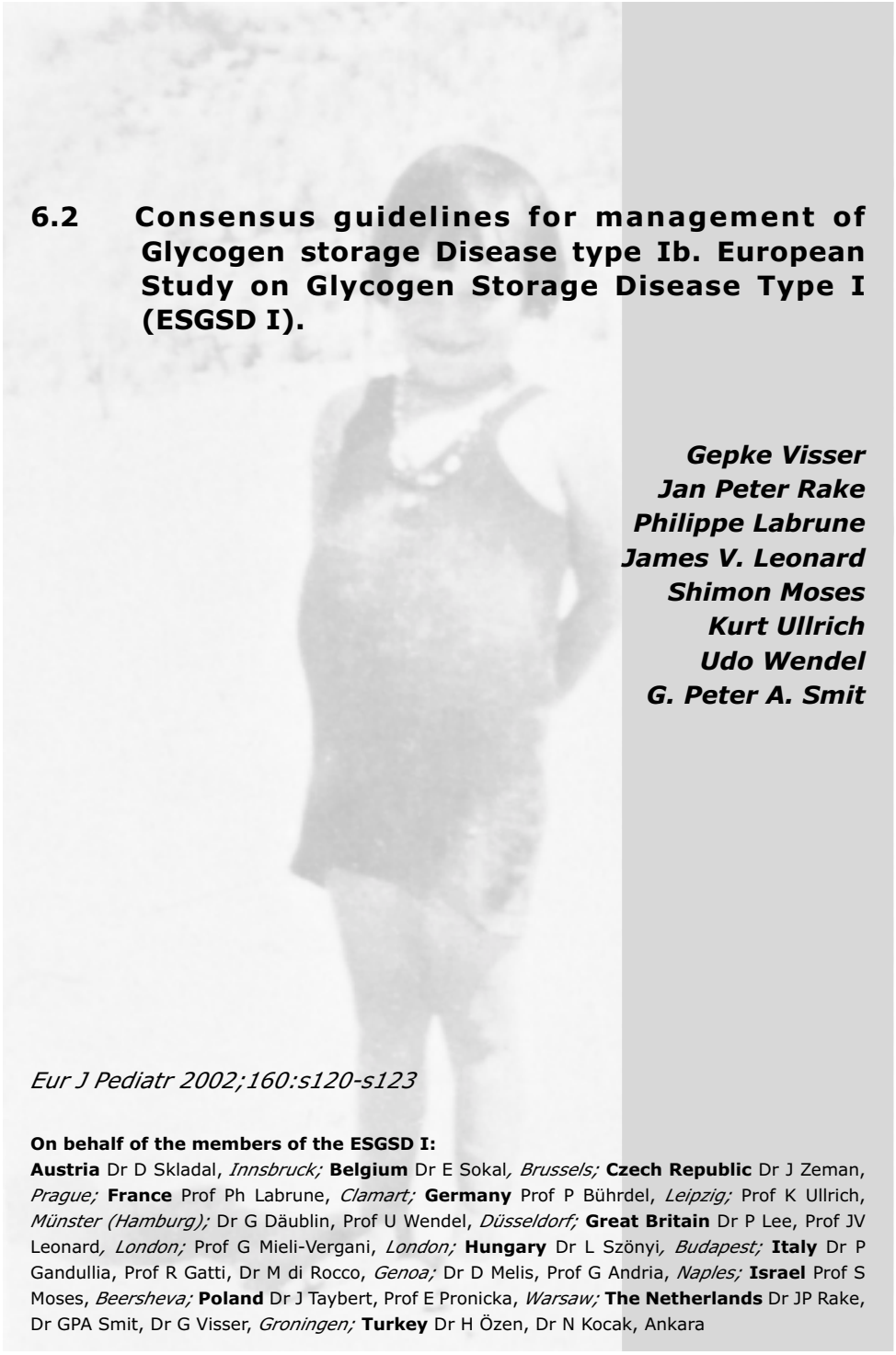
History (*)		
frequency 0 – 3 years every 2 months; 3 – 20 years every 3 months; adults every 6 months		
(a)symptomatic hypoglycaemia; hospitalisation (causes); physical complaints; frequency of infections, epistaxis, bruises, diarrhoea; medicines; social life		
Dietary history		
frequency see history		
cooping & compliance; analysis (carbohydrates, protein, fat, calcium, vitamins) adjustment based on history, physical examination, biochemical results and dietary analysis		
Physical examination (*)		
frequency see history		
height, weight, liver size, spleen size, blood pressure, skin, joints		
Blood glucose 48-h curve		
0 – 20 years every 1 – 2 months; adults every 2 – 3 months		
estimated at home, preprandial and during the night		
Urinary lactate excretion (lactate/creatinine ratio)		
frequency see history		
4 – 8 frozen samples collected at home		
Routine investigations (*)		
frequency see history		
total blood cell count with differential; serum uric acid, cholesterol, triglyceride		
venous blood gas analysis, (platelet aggregation / bleeding time)		
Investigations for detection or follow-up of complications		
serum creatinine, urea, sodium, potassium, calcium, phosphate (*)		every 6 months
serum ASAT, ALAT, AP, _GT, protein, albumin (*)		every 6 months
if renal or hepatic complications are present		on demand
urine sediment (*)		every 6 months
urine microalbumin, protein, creatinine, calcium, citrate (*)	0 – 5 years	every year
	> 5 years	every 6 months
if microalbuminuria/proteinuria is present		every 3 months
if using ACE-inhibitors		every 3 months
creatinine clearance (GFR measurement)	> 5 years	every year
ultrasonography abdomen (*)	0 – 10 years	every year
	>10 years	every 6 months
liver: size, parenchym, adenomas, other focal anomalies kidneys: size, calcifications, stones spleen: size, ovaries: cysts		
if liver adenoma(s) are present:		
ultrasonography and serum αFP, CEA	every 3 months	
CT/MRI	on demand	
X-left hand: bone age	< 20 years	every 1-2 years
ultrasonography heart and ECG	> 10 years	every year
bone densitometry	> 5 years	every 1-2 years
faecal α-1-antitrypsin		on demand
if anaemia is present	iron-status, vit B12- en folic acid status	
if (acute) abdominal pain is present	blood amylase, ERCPG, ultrasonography liver, pancreas, ovaries	
Investigations at diagnosis	- the * marked investigations (if possible before therapy is started) - DNA-analysis G6Pase gene or G6PT gene - (enzyme-activities in fresh liver tissue)	

female patients[32]. The pathophysiology is still unresolved. The effects on reproductive function are also still unclear. In some patients, complaints of enlarged cysts have been reported. PCOs may cause acute abdominal pain in case of vascular disturbances. This abdominal pain should be differentiated from pancreatitis (serum and urine amylase, CT, endoscopic retrograde cholangiopancreatography) and haemorrhage into adenoma (decrease in blood hemoglobin, CT/MRI). In severe cases, surgical resection of PCO(s) may be indicated.

Although GSD I is associated with chronic hyperlipidaemia, atherosclerosis in the ageing GSD I patient is remarkably rare[30,45,55]. A vascular complication that may cause more morbidity and mortality in the ageing patient is pulmonary hypertension followed by progressive heart failure. Its pathophysiology is still unclear. It may develop in the second decade or later. Monitoring by ECG and cardiac ultrasonography is recommended after the first decade.

GSD Ib is associated with neutropenia and neutrophil dysfunction causing recurrent infections and IBD. For additional guidelines for the management of these specific complications in GSD Ib see chapter 6.2[60].

In conclusion, in this chapter guidelines for the management of GSD I are presented.



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Eur J Pediatr 2002;160:s120-s123

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Summary

Life expectancy in glycogen storage disease type I (GSD I) has improved considerably. Its relative rarity implies that no metabolic centre has experience of large series of patients and therefore experience with long-term management and follow-up at each centre is limited. There is wide variation in methods of dietary and pharmacological treatment. Based on data from the European Study on Glycogen Storage Disease Type I, discussions within this study group together with those at the International SHS Symposium 'Glycogen Storage Disease Type 1 and II: Recent Developments, Management and Outcome', Fulda, Germany (2000) and on data from the literature, a series of guidelines were drawn up. The following guidelines for the management of patients with GSD type Ib are in addition to those general guidelines for GSD I and address specific problems related to neutropenia and neutrophil dysfunction.

Introduction

Glycogen storage disease type lb (GSD Ib) is caused by inherited defects in the glucose-6-phosphate transporter. Patients have the clinical features characteristic of GSD I, hepatomegaly, growth retardation, osteopenia, kidney enlargement, hypoglycaemia, hyperlactacidaemia, hyperlipidaemia and hyperuricaemia. In addition most, but not all, patients with GSD Ib have intermittent severe neutropenia and neutrophil dysfunction that predispose to severe infections and to inflammatory bowel disease (IBD)[58,61]. Patients with GSD Ia who are homozygous for the G188R mutation may also have neutropenia and neutrophil dysfunction[64]. The exact pathogenesis of the neutropenia and neutrophil dysfunction in GSD Ib is as yet unknown. The following guidelines (Table 6.2.1) are in addition to the general guidelines for GSD I presented in chapter 6.1[46] and are meant for patients with neutropenia and neutrophil dysfunction.

Haematology

Patients with GSD Ib generally have neutropenia and increased platelet counts. With increasing age, haemoglobin, platelet counts and leucocyte counts decrease whereas neutrophil counts generally remain very low but stable[59]. Neutropenia may develop at a later age[58]. The age of onset of uncommon, serious or frequent infections is related to the age at which the neutropenia develops. IBD is only reported in neutropenic patients. We

Table 6.2.1 Follow-up guidelines for patients with GSD Ib (in addition to the general guidelines for GSD I presented in chapter 6.1[46])

History in GSD Ib *frequency every 3 months*	
infections: frequency, localisation, severity antibiotic use; hospitalisation; diarrhoea, other gastro-intestinal complaints	
Physical examination in GSD Ib *frequency see history*	
peri-oral and peri-anal inflammation, pustulous skin infection	
Other investigations in GSD Ib	
total blood cell count with differential	every 3 months
bone marrow (cellularity, morphology, ME ratio)	on demand
ultrasonography spleen	every year
faecal α-1-antitrypsin	every 6 months
contrast radiology	on demand
colonoscopy with biopsies	on demand

suggest that a full blood count with differential leucocyte count should be done every 3 months and more often if the patient has frequent or serious infections and/or active IBD.

The results of studies of bone marrow in GSD Ib are inconsistent and may be normal but may show myeloid hyperplasia or maturation arrest[21]. Routine bone marrow aspiration is not necessary, but should be done if there is a sudden worsening of neutropenia, abnormal differentiation, unexplained fever, abdominal pain or abnormal skin lesions or progessive lymphadenopathy in order to exclude leukaemia. So far, one patient with GSD Ib and acute myelogenous leukaemia has been reported[51].

Several aspects of neutrophil function are abnormal in GSD Ib, including in vivo mobilisation and motility, in vitro random and direct migration and one or several components of the metabolic burst[21]. In the European Study Group on Glycogen Storage Disease Type I (ESGSD I), in all patients with neutropenia who were studied, neutrophil function was abnormal; especially the respiratory burst[58]. Monitoring neutrophil function is of no clinical value.

Inflammatory bowel disease

In the ESGSD I, up to 77% of the patients had signs of IBD such as perioral and perianal infections and protracted diarrhoea. Some patients also have joint symptoms. Patients with neutropenia and one or more of these problems should be investigated for IBD. A good marker for IBD activity in GSD Ib is faecal α1-anti-trypsin[61]. In blood, CRP is preferred to ESR because in GSD I the ESR is generally increased due to the increased blood lipid fraction and altered erythrocyte membrane fractions[27]. Therefore it has less predictive value. In patients with serious complaints and abnormal laboratory results, abdominal ultrasound, colonoscopy and radiology with contrast should be done to document the severity of the disease and to be able to evaluate treatment. Information on serological markers of IBD in GSD Ib is not yet available.

The disturbed immune response is probably crucial to the pathogenesis of IBD in GSD Ib. Based on case reports, granulocyte colony-stimulating factor (GCSF) (see below) seems to be more effective than conventional treatment for IBD[13,63] although a comparison of several treatment regimens has not been done. In view of the uncertainty, in mild cases conservative treatment with 5-amino-salicylic acid might be considered; however, one has to keep in mind that 5-amino-salicylic acid may produce renal tubular dysfunction[24,50] which might be especially harmful to patients with GSD I. Monitoring kidney function as proposed in the general guidelines is recommended[46].

Spleen

In the ESGSD I, splenomegaly was found in 35% of the GSD Ib patients[45,58]. The splenomegaly is probably the result of extramedullary haematopoiesis and might also be a sign of frequent infections and active IBD. However, hypersplenism has only been reported in patients on GCSF. Monitoring of spleen size by ultrasound at least once per year is advised.

Antibiotics

The benefits of prophylaxis with oral antibiotics in patients with neutropenia have been studied in several groups, but not systematically in GSD Ib. The most frequently reported infections in GSD Ib are ear, nose, throat infections, respiratory tract infections, pyogenous skin infections, urinary tract infections, gastrointestinal tract infections, and deep abscesses[57]. The most common pathogens are Staphylococcus aureus, Streptococcus pneumoniae and Escherichia coli, and prophylaxis with cotrimoxazol is advised in symptomatic patients or those with a neutrophil count < $500x10^6/1$[15,28,39].

Granulocyte colony-stimulating factor

Patients with GSD Ib and neutropenia have been treated with GCSF since 1989. This increases the neutrophil count and it is widely thought that the IBD regresses. However, in the retrospective ESGSD I, no unequivocal improvement in outcome of those GSD Ib patients on GCSF could be established[58,59]. In view of the uncertainty, prospective controlled trials seem warranted to clarify the indication and the value for the use of GCSF in this disease. As at present no other therapy is available, it is advised to limit the use of GCSF to one or more of the following indications (1) a persistent neutrophil count below $200x\ 10^6/1$, (2) a single life threatening infection requiring antibiotics intravenously, (3) serious IBD documented by abnormal colonoscopy and biopsies, or (4) severe diarrhoea requiring hospitalisation or disrupting normal life.

In the reports of Donadieu et al.[13] and Calderwood et al.[5] as well as in the ESGSD I, all patients responded to low doses GCSF, so a starting dose of 2.5 μg/kg every other day is recommended (Table 6.2.2). After reaching a mean neutrophil count just above $1000x10^6/1$, the effect on total blood cell count blood with differential could be monitored and adjusted every month. Dose increments of 5 μg/kg are proposed with a maximum dose of 25 μg/kg per day.

Data on the safety and efficacy of long-term GCSF administration are limited. In several reports intermittent, long-term treatment with low dose GCSF is reported to be successful[13,26,59]. Further investigation with comparison

Table 6.2.2 Guidelines GCSF therapy in patients with GSD Ib

Before initiating therapy:
complete evaluation as outlined in table 6.2.1 including bone marrow and colonoscopy

Start therapy
initial dose 2.5 μg/kg s.c. per day or every other day
measure neutrophils daily for 10 days; aim neutrophil count > 1000 x 10^6/l
adjust dose in steps of 2.5-5.0 μg/kg (max. 25 μg/kg)
stay at dose required to maintain neutrophil count > 1000 x 10^6/l

Follow-up

History *frequency every 3 months*	infections: frequency, localisation, severity; antibiotic use; hospitalisation; diarrhoea, other gastro-intestinal complaints; adv.effects: local redness, bone pain, syst. symptoms	
Physical examination *frequency every 3 months*	peri-oral and peri-anal inflammation; pustulous skin infection; spleen size	
Investigations	total blood cell count with differential	every month
	serological markers of inflammation (CRP, Igs)	every 6 months
	bone marrow (cellularity, morphology, ME ratio)	every year
	ultrasonography abdomen (liver,spleen, kidneys,pancreas)	every 6 months
	faecal α-1-antitrypsin	every 6 months
	contrast radiology	on demand
	colonoscopy with biopsies	on demand
	bone mineral density	every year

of intermittent versus continuous treatment strategies is warranted before advice can be given.

Neupogen (Filgrastim), a recombinant GCSF, has identical biological activity as endogenous GCSF, but contains an N-terminal methionine residue and is not glycosylated. Lenograstim is glycosylated GCSF, and in vitro seems to be more potent and stable than Filgrastim. The clinical significance of these differences still has to be established[19,20]. An advantage of the glycosylated form is the smaller volume to be injected, which makes it less painful.

In the ESGSD I, the most serious complication of treatment with GCSF was splenomegaly, which regressed on reducing the dose. However, some patients are known who had splenomegaly and hypersplenism who did not improve on reduction of the dose and needed splenectomy. (High) dose GCSF might induce an overstimulation of extramedullary haematopoiesis. Careful monitoring of spleen size and total blood cell counts before and

during GCSF treatment seems warranted.

Recently, one patient has been reported who, on GCSF, developed acute myelogenous leukaemia. Acute myelogenous leukaemia has also been described in a GSD Ib patient who did not receive GCSF[51], so leukaemia might be a complication of the disease. However, since the effect of long-term treatment is as yet unknown, we advise bone marrow aspiration with cytogenetic studies before and once per year during GCSF treatment and, if indicated, more often.

One patient with GSD Ib is reported who developed renal carcinoma during long-term use of GCSF[14]. The question whether this is related to the GCSF is still open as GCSF does not only stimulate granulocyte blood precursors, but can also induce proliferation in other tissues. Evaluation for malignancies by abdominal ultrasound twice per year, monitoring liver adenoma, kidney, ovary and pancreas is recommended, as is regular follow-up of serum alpha-fetal protein.

Osteopenia is a well recognised complication of GSD I[34,43]. Significant osteopenia has been described in patients with congenital neutropenia treated with GCSF and there is an increased risk of osteopenia in IBD, so patients with GSD Ib on GCSF may be at particularly high risk of this complication. However, information on osteopenia during treatment with GCSF in GSD Ib is still limited. Monitoring bone density preferably by peripheral quantitative computed tomography, or else by DEXA[42] before and once per year during GCSF is therefore recommended.

In conclusion, in this chapter additional guidelines for the management of specific problems in GSD Ib related to neutropenia and neutrophil dysfunction in are presented.

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