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The Long-term Outcome of Patients with Glycogen Storage Diseases

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Summary: In this retrospective study from five centres, 139 patients over 10 years of age with glycogen storage disease types I, III, VI and IX are described. Almost half of the patients with glycogen storage disease type Ia had retarded growth and most had hyperlipidaemia. One-third of the patients had adenomas, although none of these showed malignant transformations. With increasing age the growth, liver size and hyperlipidaemia of patients with glycogen storage disease type III improve. However, there was a high incidence of myopathy and cardiomyopathy. Patients with glycogen storage disease types VI and IX had a normal growth pattern after childhood. Hepatomegaly and hypercholesterolaemia, however, were still present in half of the patients.

As only limited information is available at present about the long-term outcome of patients with glycogen storage diseases (Huijing and Fernandes, 1969; Fernandes, 1975; Hers *et al.*, 1989) we reviewed all the patients with the more common types of glycogen storage disease who were under our care and over 10 years of age. We studied the growth and the complications in patients with glycogen storage disease type I (glucose-6-phosphatase deficiency), glycogen storage disease type III (debranching enzyme deficiency), glycogen storage disease type VI (phosphorylase deficiency) and glycogen storage disease type IX (phosphorylase-*b*-kinase deficiency).

Since the therapeutic approach to patients with the different types of glycogen storage disease is generally similar in the participating metabolic centres (Fernandes *et al.*, 1988) and specific information on treatment of individuals was not available, treatment is not discussed in detail.

PATIENTS AND METHODS

139 patients over 10 years of age with glycogen storage disease were included in this study: 41 patients with glycogen storage disease type 1a (16 females / 25 males), 5

patients with glycogen storage disease type Ib (4 females / 1 male), 50 patients with glycogen storage disease type III (25 females / 25 males), and 43 patients with glycogen storage disease types VI and IX (6 females / 37 males). Patients were diagnosed by enzyme assay of either liver biopsy or leukocytes. Since the two disorders of the phosphorylase system show very similar clinical and biochemical abnormalities they were combined.

Glycogen storage disease type Ia, glucose-6-phosphatase deficiency: This glycogen storage disease is the most severe type because both gluconeogenesis and glycogenolysis are impaired. Patients with this glycogen storage disease are characterized clinically by short stature, hepatomegaly, and enlarged kidneys. As the patients become older they may develop liver adenoma and glomerular sclerosis. Biochemically the patients often have marked hypoglycaemia together with hyperlactacidaemia, hyperlipidaemia and hyperuricaemia (Hers *et al.*, 1989).

Glycogen storage disease type Ib, glucose-6-phosphatase translocase deficiency: The majority of the clinical and biochemical symptoms of this glycogen storage disease are identical to those of glycogen storage disease type Ia, but the susceptibility to bacterial infections due to neutropenia and impaired neutrophil function reduces the number of patients who survive to older age. From the small number of patients reported in this study it is not possible to assess the long-term outcome which may reflect the poor long-term prognosis of this glycogen storage disease (Schaub and Heyne, 1983; Hers *et al.*, 1989).

Glycogen storage disease type III, debranching enzyme deficiency: Usually the clinical findings in this glycogen storage disease are less severe than in glycogen storage disease type I. Hepatomegaly, growth retardation and the propensity for hypoglycaemia seem to be age-related and become less severe with increasing age. Myopathy and cardiomyopathy, however, may become more clinically apparent (Hers *et al.*, 1989).

Glycogen storage disease types VI and IX, deficiencies of the liver phosphorylase system: Because of the similarity in clinical and biochemical parameters these two glycogen storage diseases were combined. Hepatomegaly and growth retardation usually resolve before puberty. In most patients hypoglycaemia is only seen during infections or prolonged fasting (Huijing and Fernandes, 1969; Fernandes, 1975; Hers *et al.*, 1989).

The definitions used in the study were as follows:

(1) Growth: patients's centiles were calculated for their own country and those below the 3rd centile were considered to have retarded growth.

(2) Hepatomegaly: a liver palpable more than 2 cm below the costal margin in the mid-clavicular line.

(3) Liver adenoma: detected by ultrasound investigation and/or computer tomography.

(4) Myopathy: clinical symptoms of myopathy defined by exercise intolerance and/or muscle wasting.

(5) Cardiomyopathy: defined by either clinical signs and/or abnormal ECG/echocardiogram.

(6) Mental development: regarded as 'normal' when patients were able to attend normal school.

(7) Hypoglycaemia: attacks of drowsiness, excessive sweating, hunger or diminished consciousness, with or without documented hypoglycaemia (blood glucose < 2.0 mmol/L).

(8) Hypercholesterolaemia: blood cholesterol concentration > 5.0 mmol/L.

(9) Hypertriglyceridaemia: blood triglyceride concentration > 2.0 mmol/L.

(10) Hyperuricaemia: when patients were on allopurinol treatment and/or blood uric acid concentration was < 0.36 mmol/L.

RESULTS

Glycogen storage disease type Ia

19 out of the 41 patients (16 females and 25 males) studied were below the 3rd centile and there was no apparent improvement with age (Figure 1). Hypoglycaemia was reported in only 6 out of 41 patients, but hepatomegaly was still present in 39 out of 40 patients on whom information was available, and 11 out of the 27 patients with quantitative measurement had marked hepatomegaly (greater than 10 cm in the mid-clavicular line).

Adenomas were detected in 11 out of 39 patients investigated by ultrasound or computer tomography. α1-Fetoprotein was reported to be within normal limits in a total of 22 patients, of whom 6 had liver adenomas.

Blood cholesterol concentration was elevated in 31 out of 38 reported patients and in 7 of these, the concentration was more than 10.0 mmol/L. Blood triglyceride concentration was also elevated in 29 out of 34 patients, of whom 18 had concentrations $\geqslant 4.0$ mmol/L. Blood uric acid concentration was found to be elevated in 19 out of 35 patients studied, and 12 of these patients were being treated with allopurinol.

Mental development was reported to be normal in 32 out of 37 patients.

Renal function was not investigated systematically in all centres. Unpublished data available from one centre, however, on glomerular filtration rates and renal plasma flow rates showed that virtually all patients had elevated values of both.

Limited information on treatment is available for 39 patients. Of these, 33 have or did receive nocturnal gastric drip feeding; the remaining 6 patients are on a frequent meal regimen. No differences could be detected between the two treatment groups.

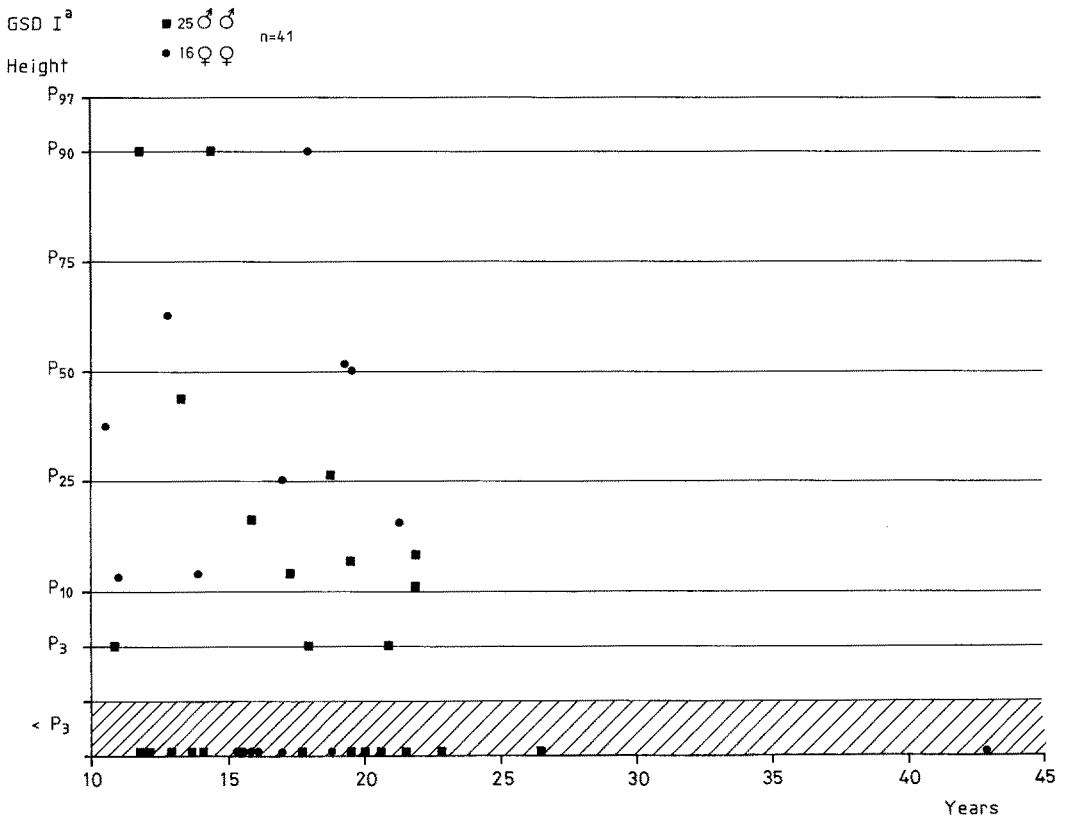

Figure 1 Height in centiles in GSD Ia patients over 10 years of age.

Glycogen storage disease type Ib

Four out of 5 reported patients were below the 3rd centile in height (Figure 2). However, it is not possible from the small number of patients to assess the long-term outcome.

Glycogen storage disease type III

Of the 50 patients (25 females and 25 males) reported, 18 were below the 3rd centile (Figure 3). An improvement in the growth in height with increasing age was apparent.

Hypoglycaemia was reported in only 4 out of the 50 patients.

Hepatomegaly was detected in 34 out of 50 patients, of whom 5 patients had a very large liver ($\geqslant$ 10 cm in the mid-clavicular line). The remaining 16 patients had a normal liver size; these patients were all over 15 years of age. Liver adenomas were reported in 3 out of 30 investigated patients.

Myopathy was diagnosed in 26 out of 41 reported patients and in 17 of these 26 patients cardiomyopathy was also present. Cardiomyopathy was diagnosed in a total

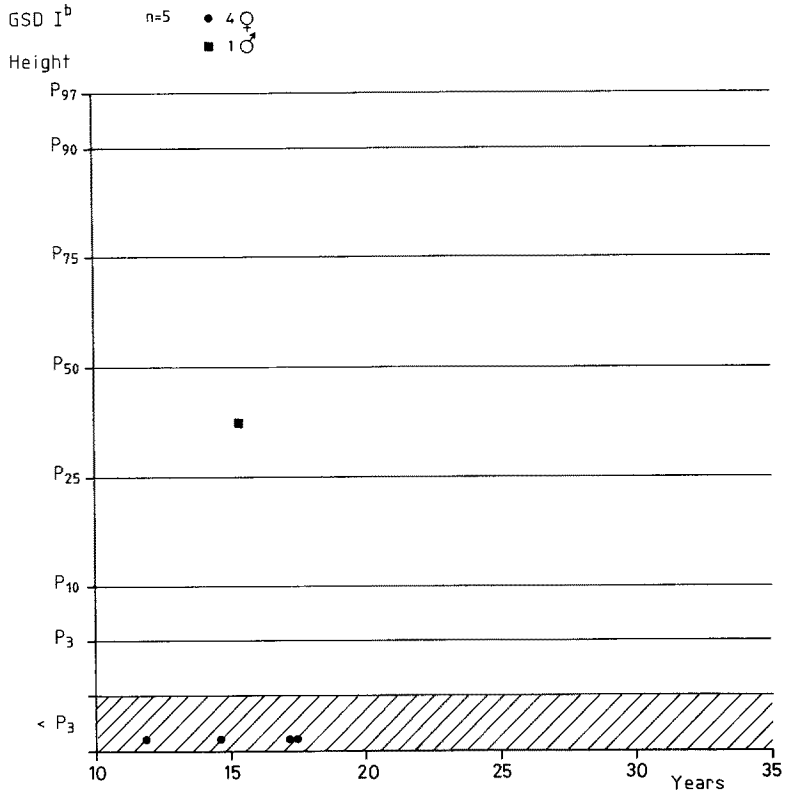

Figure 2 Height in centiles in GSD Ib patients over 10 years of age.

of 22 out of 44 reported patients. There was no correlation with age for either the myopathy or the cardiomyopathy.

Hypercholesterolaemia was present in 17 out of 44 reported patients and was seen mainly in patients below 20 years of age. Hypertriglyceridaemia was present in 14 out of 38 patients but there was no correlation with age. Mental development was reported to be normal in 41 out of 44 patients.

Glycogen storage disease types VI and IX

Four out of the 43 reported patients had growth retardation (Figure 4). The patients in this group had the most pronounced age-related improvement in height of all the types studied.

Hypoglycaemia was not reported. Hepatomegaly was present in 18 of the 43 patients, with no correlation with age.

Hypercholesterolaemia was present in 22 of the reported 41 patients and hypertriglyceridaemia in 7 out of 35. There was no correlation with age for either of the blood lipid concentrations.

Mental development was normal in all 42 reported patients.

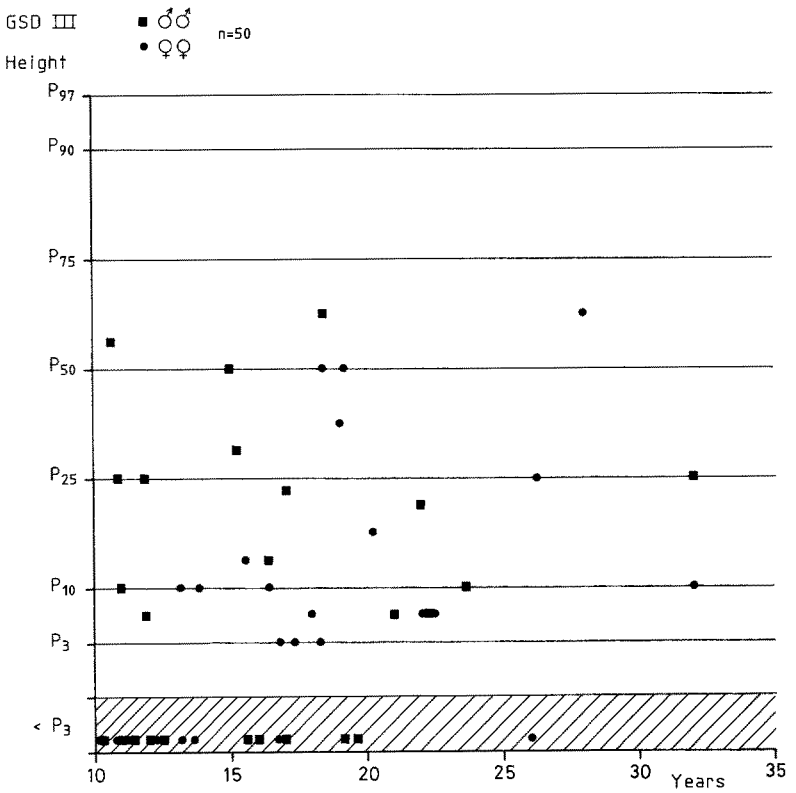

Figure 3 Height in centiles in GSD III patients over 10 years of age.

DISCUSSION

Glycogen storage disease type Ia

With increasing age hypoglycaemia becomes less of a problem. This improvement probably reflects the natural decrease in metabolic rate, and therefore glucose consumption expressed in kg bodyweight, rather than any real improvement in metabolic control. Cholesterol and triglyceride concentrations remain elevated in most patients, and may even become worse with increasing age, which suggests that despite the improvement metabolic control remains unsatisfactory. This is also reflected in the large number of patients who show retarded growth and have developed adenomas. Fortunately none of the patients with adenomas have developed elevated α1-fetoprotein concentrations or hepatocellular carcinoma, although this may still be a possible future threat (Coire *et al.*, 1987).

Another potential problem is the progressive glomerular injury leading to focal glomerulosclerosis (Chen *et al.*, 1988; Baker *et al.*, 1989), the prognosis and treatment of which needs further study in order to identify reliable and predictive indicators of future renal function and to develop possible long-term treatment.

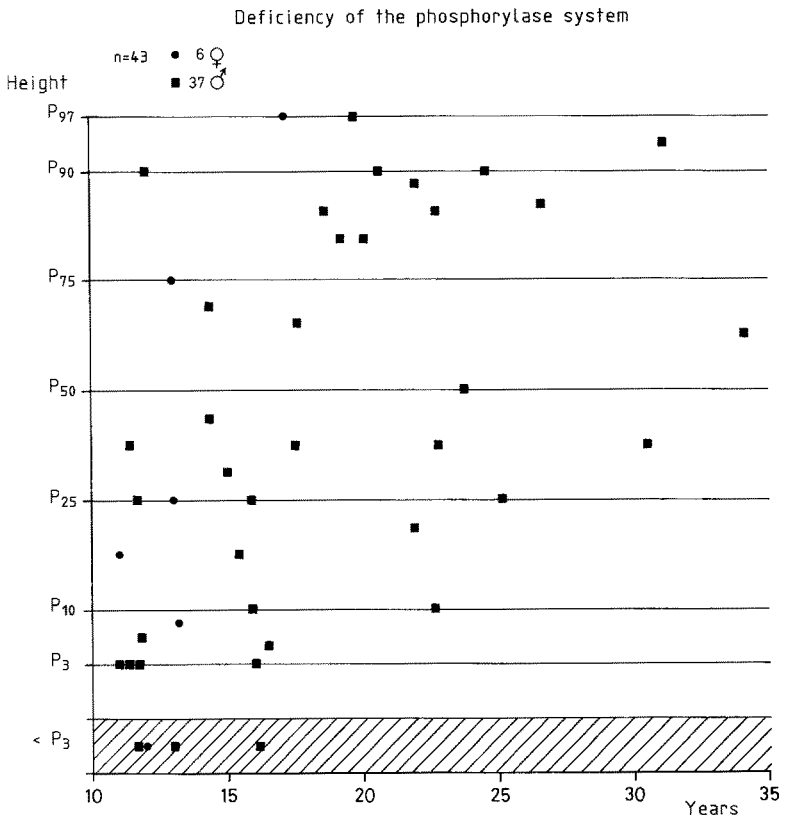

Figure 4 Height in centiles in GSD VI and IX patients over 10 years of age.

Glycogen storage disease type III

An age-related improvement was seen in this glycogen storage disease with respect to height, liver size and cholesterol concentration. However, there is a high incidence of cardiomyopathy, the importance of which in terms of long-term prognosis remains to be determined.

Glycogen storage disease types VI and IX

Virtually all patients with these glycogen storage disease types have normal growth patterns after childhood. Despite this improvement, however, in about half of the patients the liver remains palpable and the serum cholesterol concentration elevated.

CONCLUSION

From this retrospective study glycogen storage disease types VI and IX clearly have the best long-term follow-up results, and patients with glycogen storage disease type

Table 1 Long-term follow-up results for patients with different types of glycogen storage disease

	Type of glycogen storage disease		
	Ia (%)	*III* (%)	*VI/IX* (%)
Height < P3	46	36	9
Hepatomegaly	98	68	42
Hepatomegaly > 10 cm	41	10	0
Adenoma	28	10	0
Hypoglycaemia	15	8	0
Cholesterol > 5.0 mmol/L	82	39	54
Cholesterol > 10.0 mmol/L	18	0	0
Triglycerides > 2.0 mmol/L	85	37	20
Triglycerides > 4.0 mmol/L	53	13	0
Uric acid > 0.36 mmol/L	54		
Normal mental development	85	93	100

1b, as expected, have the worst (Table 1). The high incidences of both adenoma and (probably) hyperfiltration were impressive and unexpected. The long-term prognosis for these types of glycogen storage disease must remain guarded.

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