

Patterns of growth in the hepatic glycogenoses

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SUMMARY Longitudinal growth data from 31 patients with hepatic glycogen storage disease (type I (8 patients), type Ib (three patients), type III (13 patients), and type IX (phosphorylase kinase deficiency) (7 patients)) have been reviewed. All patients were below the mean for height at presentation; the mean height standard deviation scores were -2.13 (type I), -2.0 (type Ib), -2.4 (type III), and -1.6 (type IX). Untreated, most patients with type I and Ib grew slowly with no catch up growth but three patients with mild disease grew normally. Most children with type III disease grew at a normal velocity throughout childhood. Puberty was delayed and final height normal. Some of the children with type III and all of those with type IX had catch up growth throughout childhood. Intensive treatment of patients with severe forms of type I and Ib disease resulted in catch up growth, but this was not complete if the treatment was started late.

Growth delay may occur in all of the common types of hepatic glycogen storage disease¹ (glucose-6-phosphatase deficiency, type I and type Ib;² debrancher deficiency, type III; and phosphorylase kinase deficiency, type IX).³ Fine *et al.*,⁴ in a long term follow up study of four children with type I disease noted severe growth retardation with delayed sexual maturation.

With intensive treatment the growth rate of growth retarded children with type I hepatic glycogen storage disease may increase strikingly.^{5,6} Children with type III and IX disease may also have delayed sexual maturation but growth retardation is less pronounced.¹ As longitudinal growth data are limited, we studied the growth of 31 children with these disorders.

Patients and methods

Between 1952 and 1980 a diagnosis of hepatic glycogen storage disease was made in 40 children admitted to the Hospital for Sick Children, London. Longitudinal growth data suitable for analysis were available in 31 of these patients. Eight had type I, 13 had type III, and 7 had type IX disease. The diagnosis was confirmed at liver biopsy in all the patients with type I, 6 of those with type III, and 6 of the children with type IX disease. The remainder were diagnosed by assay of the appropriate enzyme activities in red and white blood cells. Enzyme activities were determined in the laboratories of Professor A D Patrick (Institute of Child Health,

London) using standard methods.⁷⁻⁹ Three other patients had the clinical features of type I hepatic glycogen storage disease with failure of glycaemic response to both glucagon and galactose, lactic acidemia, increased hepatic glycogen, but normal activities of glucose-6-phosphatase and fructose 1-6 diphosphatase in liver that had been frozen. These have been classified as type Ib.² Two of these patients had neutropenia and a neutrophil mobility defect.¹⁰

Longitudinal growth data were available from the records of attendance in the outpatients department and where the patients had been referred back to the local medical services the relevant paediatrician was asked for details of the patient's growth. These height data were compared with the normal data of Tanner, Whitehouse, and Takaiishi¹¹ and height SD scores were calculated as described by those authors. Bone age maturity scores were calculated by the TW2-RUS method.¹²

During the study 6 of the children with type I and Ib disease were started on treatment with regular drinks of a glucose polymer (Caloreen, Roussel) by day and nasogastric tube feeds of the glucose polymer at night;⁶ they received approximately 0.5 g/kg/hour of glucose throughout the 24 hours (patients A1, A3, A4, A6, B1, and B2). Lactose and sucrose in their diet was restricted. All the children with type IX disease were untreated. Five of those with type III were encouraged to take a high protein diet (patients C1, C2, C3, C11, and C12) with a milk drink at night, but this treatment was not followed consistently.

Results

Height at diagnosis. At the time of diagnosis all of the patients were below the mean for height and some were very short. The mean height SD scores of children with different types of hepatic glycogen storage disease were; type I (mean (SD)) -2.13 (1.45), type Ib -2.0 (1.27), type III -2.4 (1.18), and type IX -1.6 (1.27). Where the bone age data were available (14 patients) maturity was found to be delayed by approximately the same extent as height. The mean bone age SD scores were: type I -2.5 (4 patients), type Ib -1.5 (2), type III -1.3 (5), and type IX -1.3 (5).

Longitudinal growth data. Longitudinal growth data presented as height SD scores in these four types of hepatic glycogen storage disease are shown in Figs. 1 to 4. Untreated, most children with type I and Ib grew slowly, tending to fall further below the mean, with no evidence of catch up growth (Figs. 1 and 2). The oldest child (A1) showed no signs of puberty or catch up growth at the age of 15 years—his bone age being 11 years, height SD score -6.0 , and height velocity SD score -2.8 . There were, however, three exceptions—two girls and one boy with type I disease (A5, A7, and A8) grew normally without any treatment and without any bone age delay. All of the children with type I and Ib disease who were

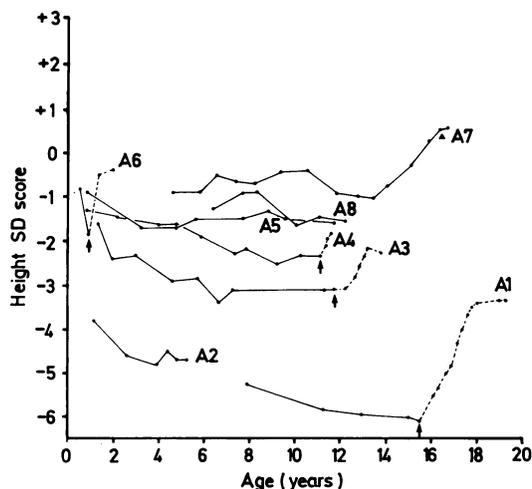


Fig. 1 Longitudinal height data, presented as height standard deviation scores, of patients with hepatic glycogen storage disease, type I. The arrow indicates start of treatment (see text) and the interrupted line the growth thereafter. Onset of menstruation in girls shown by solid triangle (▲).

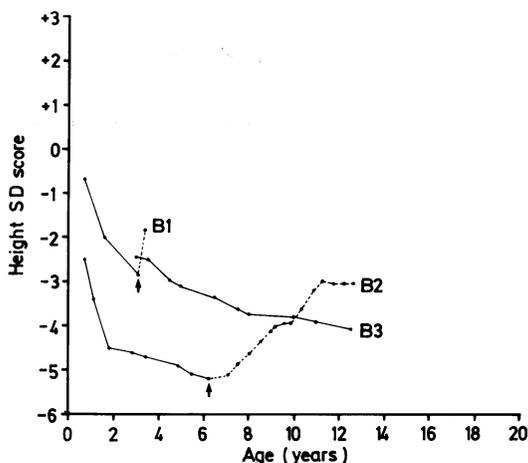


Fig. 2 Longitudinal height data, presented as height standard deviation scores, of patients with hepatic glycogen storage disease, type Ib. The arrow indicates start of treatment (see text) and the interrupted line the growth thereafter.

started on regular glucose drinks by day and nasogastric tube feeds of glucose at night showed accelerated growth (A1, A3, A4, A6, B1, and B2). Four of the children, after an initial period of catch up growth, continued with a normal velocity. Bone age showed corresponding catch up growth but did not accelerate beyond the chronological age. All

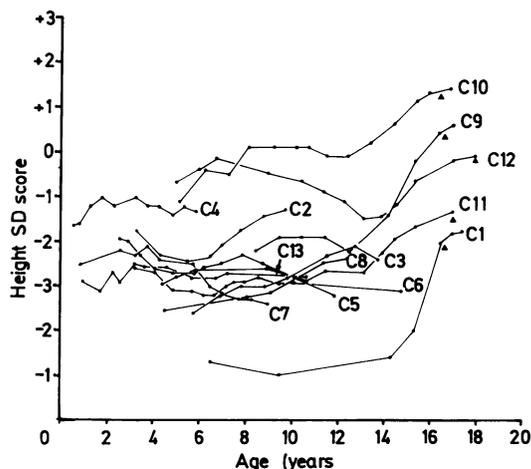


Fig. 3 Longitudinal height data, presented as height standard deviation scores, of patients with hepatic glycogen storage disease, type III. Onset of menstruation in girls shown by solid triangle (▲).

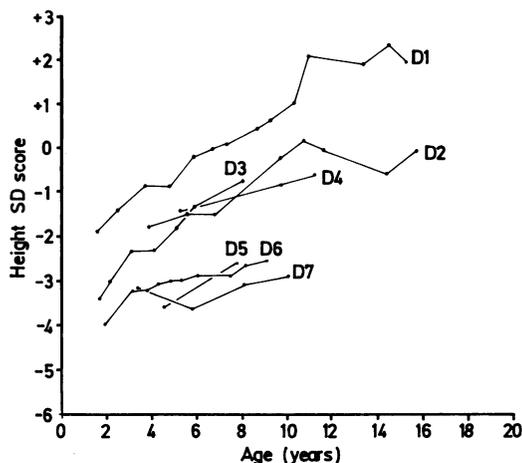


Fig. 4 Longitudinal height data, presented as height standard deviation scores, of patients with hepatic glycogen storage disease, type IX.

children were prepubertal, with the exception of patient A1 who was started on treatment at age 15½ years (bone age 11 years) and started puberty at the age of 16½ years: His final height was 154 cm (limits predicted from parental heights 161 to 178 cm). At the age of 19 years, when growth had ceased, his bone age remained immature at 14 years. One patient (B3) with type Ib disease was treated elsewhere by portal diversion¹³ at the age of 6 years. Growth velocity was unchanged after surgery.

Children with type III hepatic glycogen storage disease also tended to be short at diagnosis but the subsequent pattern of growth differed from children with type I disease (Fig. 3). In many of the children there was catch up growth during childhood or at the time of puberty.

Five of the children have passed through puberty. Final heights in all were within 2 SD of the adult mean and where parental height data were available, heights were well within target limits.¹⁴ The onset of puberty was delayed in these children (onset 14 to 16 years; menarche 16½ to 18 years). A typical example is patient C9 who received no treatment. At the age of 8.5 years her height was 2.5 SD below the mean and her skeletal age was 5 years. Puberty began around 15 years of age (skeletal maturation 13.5 years) and she had a normal growth spurt; her final height was +0.6 SD and menarche occurred at 16½ years.

Children with type IX disease tended to show gradual catch up growth throughout childhood (Fig. 4). The heights of two brothers (D1 and D2) were -0.9 and -1.7 SD respectively at diagnosis.

Gradual catch up growth occurred and by the age of 11 years their heights were +2.1 and +0.3 respectively. Puberty was not delayed and final heights were within parental height targets.

Discussion

We present longitudinal growth data from 31 patients with hepatic glycogen storage disease. The data are not perfect as they were obtained retrospectively from charts and are likely to be subject to observational errors; but despite this limitation, because of the long period and number of patients studied, clear growth patterns emerge. Untreated, most of the patients with type I and Ib disease grew slowly with no catch up growth. There were three exceptions (all with type I disease) who had a mild disease without documented hypoglycaemia and grew normally. The untreated children with type III disease showed growth and pubertal delay but their final heights were normal. Some of the children with type III and all of those with type IX disease showed catch up growth throughout childhood.

Intensive treatment of children with type I and Ib disease resulted in catch up growth and the prognosis for growth was excellent if treatment was started early. Treatment also reverses the endocrine abnormalities¹⁵ and may affect favourably the formation of adenomata,¹⁶ but it is not without dangers as sensitivity to hypoglycaemia is restored.¹⁷ As some children with type I disease will grow normally without treatment it is clearly not indicated for all patients.

The mechanisms governing growth delay in these children are not clear. We have recently shown that the severity of growth delay can be correlated with endocrine change (principally low concentrations of insulin and somatomedin with raised plasma cortisol)¹⁵ and suggested that these changes are part of an overall adaptation to decreased hepatic glucose production. Those children with mild disease tend to have a normal glucose response during the fasting glucagon test¹⁸ and may be more able to maintain glucose output from the liver. In patients with type III and IX disease glucose release from gluconeogenesis may be sufficient to allow for catch up growth during childhood as the requirement for glucose, expressed per kg body weight, declines after the age of 6 years.¹⁹

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