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Treatment with low-dose diazoxide in two growth-retarded prepubertal girls with glycogen storage disease type Ia resulted in catch-up growth

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Summary: Two originally prepubertal girls suffering from glycogen storage disease type Ia and short stature were treated with low-dose diazoxide (3–4.8 mg/kg per day) for 7 and 4 years, respectively. Both showed an impressive catch-up growth following this treatment. This appeared to be due to prolongation of normoglycaemia after meals and reduction of fasting lactic acidosis by diazoxide.

Growth retardation is a well-known complication in patients with glucose-6-phosphatase deficiency (glycogen storage disease (GSD) type Ia; McKusick 232200) (Fernandes and Berger 1987). It is almost universal in infancy but responds variably to different types of therapies for reasons that are not yet clear. Introduction of uncooked cornstarch during night time as well as nocturnal gastric tube feeding partially improved height velocity (Wolfsdorf et al 1990; Chen et al 1993) but not in all patients. The use of diazoxide in patients with GSD type Ia was first described by Rennert and Mukhopadhyay (1968) for the improvement of glucose homeostasis. The treatment was of short-term duration because of skin rashes and was later forgotten. Unaware of this early observation, we started to treat a female patient with diazoxide in 1987. In this paper, we report as a new finding a catch-up growth in two prepubertal female patients with GSD type Ia following prolonged treatment with low doses of diazoxide (3–4.8 mg/kg per day) for 7 and for 4 years, respectively. Since diazoxide therapy prolongs normoglycaemia in the patients, it significantly reduces elevated blood lactate concentrations. We therefore speculate that blood lactic acidosis is a major cause of growth retardation in GSD type Ia and that growth retardation may be alleviated by long-term diazoxide treatment.

Table 1 Effects of diazoxide[a]

	Patient 1					*Patient 2*			
	Before		*On treatment*			*Before*		*On treatment*	
	(*n*)	(*mean* ± *SD*)	(*n*)	(*mean* ± *SD*)	(*p-value*)	(*n*)	(*mean* ± *SD*)	(*n*)	(*mean* ± *SD*)
Lactate (mmol/L)	7	7.73 ± 0.58	9	3.69 ± 1.22	0.018	4	7.89 ± 0.98	3	3.66 ± 0.64
Cholesterol (mmol/L)	8	6.66 ± 0.54	11	6.86 ± 0.49	0.575	5	10.65 ± 5.9	3	9.48 ± 1.03
HDL-cholesterol (mmol/L)	10	0.67 ± 0.11	10	1.11 ± 0.14	0.005	3	0.45 ± 0.28	2	0.79 ± 0.23
Triglycerides (mmol/L)	8	8.01 ± 1.48	11	3.94 ± 1.01	0.011	5	11.87 ± 8.33	3	12.1 ± 2.32
One-year height[b] velocity SDS	7	−2.7, −1.1	10	−1.1, 9.4	0.018	3	−3.5, −1.4	3	−1.9, 5.6

[a] Blood lactate and lipids were determined between 08:00 and 09:00 after 2 h fasting. *p*-Values were calculated with the Wilcoxon signed rank test. Because of the small number of data, no statistics were done on patient 2 data

[b] Growth data are given in one-year height velocity standard deviation scores (Prader et al 1989). Since the distribution of these growth data is not normal we indicate the range, rather than mean and SD

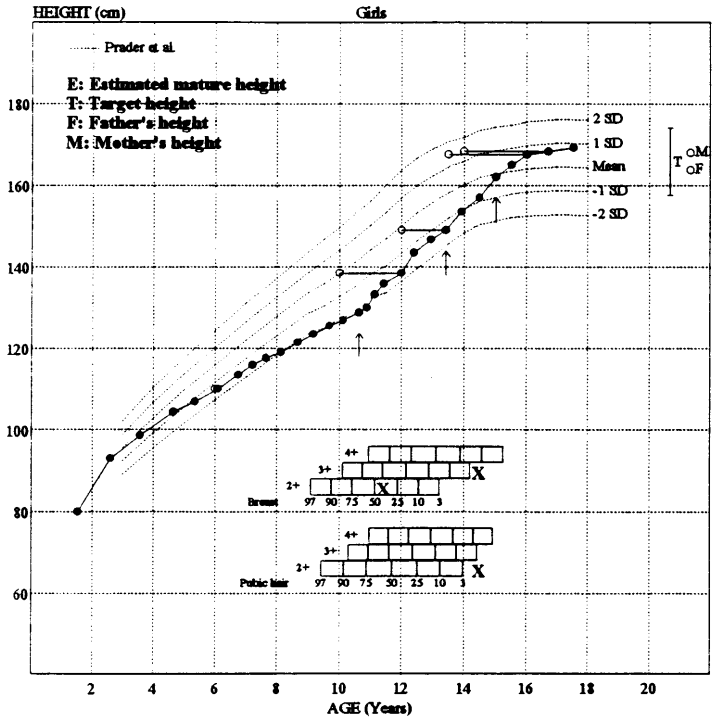

Figure 1 (a) Growth chart (Prader et al 1989) of patient 1. Start of diazoxide therapy and adaptation of dosage for increased weight, on two occasions, are indicated by arrows. A few months after introduction of diazoxide therapy an impressive catch-up growth started. Bone age (○) remained retarded throughout the treatment with diazoxide and, as indicated in the lower part of the chart, there was a delayed pubertal development

CASE REPORTS

The first patient, a girl, was born as the third child to unrelated parents after a 41-week normal pregnancy, birth weight 3920 g (50th–90th centile), length 51 cm (50th–90th centile), head circumference 35 cm (50th centile). At the second day of life, the child was referred to our hospital because of a transient tachypnoea of the newborn (TTN) with metabolic acidosis (pH 7.35, pCO_2 21.3 mmHg, base excess −10). Lactate measured 9 days later was 2.98 mmol/L. In addition a hepatomegaly (5.5 cm below costal margin) and a functional systolic murmur were found. Hyperinsulinism causing hypoglycaemia was excluded. There was no rise in blood glucose concentrations but an increase in lactate after intravenous glucagon. Diagnosis of glucose-6-phosphatase deficiency was established at 4 weeks of age by liver biopsy. A diet consisting of 6–8 meals per day restricted in galactose and fructose but enriched in glucose and polyunsaturated fat was initiated. Uncooked cornstarch was introduced at the age of 3 months (2 g/kg body weight distributed over all meals initially, later during night time). Oral therapy with $NaHCO_3$ was started at 3

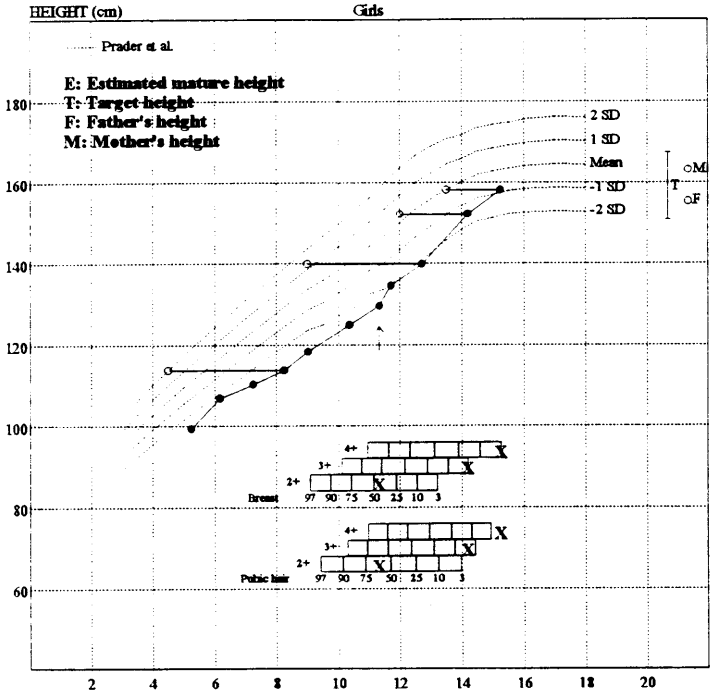

Figure 1 (b) Growth chart (Prader et al 1989) of patient 2. Start of diazoxide therapy is indicated by an arrow. A few months after introduction of diazoxide therapy an impressive catch-up growth started. There was a delayed pubertal development, as indicated in the lower part of the chart, and bone age (○) remained retarded during the first year of catch-up growth. Later, growth and bone age were probably affected by advancing pubertal development

months of age and at 10 months allopurinol was added. This medication has continued up to the present time.

The patient was seen at regular intervals in our outpatient clinic. She was admitted several times to our hospital because of recurrent urinary tract infections with poor control of glycaemia. A malformation of the urinary tract could be excluded. Urinary tract infections subsided after the age of 10 years. Preprandial hyperlacticacidaemia was repeatedly measured at 08:00 to 09:00 (Table 1). It still persisted when uncooked cornstarch was given during night time.

Initially (according to the Swiss growth charts, Prader et al (1989)), the girl grew between -0.3 and -1 SDS. After the age of 5 years, the growth gradually dropped until it was below -2 SDS at 8 years of age (Figure 1a).

At the age of $10\frac{11}{12}$ years a trial with diazoxide (initially 4.8 mg/kg per day divided in three doses) was started. The drug was given with the main meals. Following this treatment a significant reduction of both blood lactate concentrations and hyperlipidaemia was achieved. At the age of $13\frac{4}{12}$ and of 15 years respectively, the dosage of

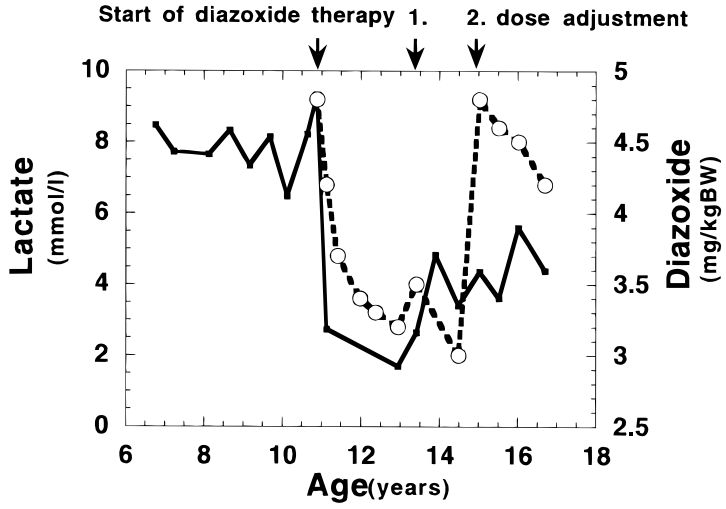

Figure 2 Effects of diazoxide (open circles and broken curve) on blood lactate (solid squares and solid curve) in patient 1. Start of diazoxide therapy is indicated with an arrow. Diazoxide was given in three divided doses with the main meals. The dosage was adapted for increased weight on two occasions because the metabolic parameters (lactate and lipids) again became less favourable. Blood lactate was determined between 08:00 and 09:00 after 2 h fasting

diazoxide was adapted for increased weight, because the metabolic parameters (lactate and lipids) again became less favourable (Figure 2).

Following this observation, we decided to treat another prepubertal Swiss patient with GSD type Ia. Her growth pattern had followed the curve -0.5 to -1 SDS on the Swiss growth chart (Prader et al 1989) until 2 years and dropped below -2 SDS at 3 years of age (Figure 1b). A trial with diazoxide (3.3 mg/kg per day taken in three doses together with the main meals) was started at $11\frac{4}{12}$ years of age. Previous to treatment bone age was retarded by 4 years according to Greulich and Pyle (1959). Since this patient lives in Asia, controls were possible only once a year during vacations in Switzerland. Apart from frequent meals, a special diet was not followed but she had uncooked cornstarch during the night time.

EFFECTS OF DIAZOXIDE TREATMENT

Shortly after the introduction of diazoxide therapy, lactic acidaemia significantly decreased in both patients. Furthermore, after 12 months on treatment an impressive increase in the 1 year height velocity (cm/year) SDS was noted (Figure 3). The difference of height velocities SDS (pretreatment and on treatment) was significant (Table 1). Bone age assessed according to the method by Greulich and Pyle (1959) remained retarded by 2–3 years in the first patient, and her pubertal development was still clearly delayed during the first years of her catch-up growth (Figure 1a). In the meantime, puberty started. In case 2, delay of bone age had lessened at the time

of the last clinical control in our outpatient clinic and pubertal development progressed to maturity. The initial catch-up growth, however, did not occur at the expense of advance in bone age.

As shown in Table 1, there was a significant amelioration of HDL-cholesterol and triglycerides in patient 1, whereas total cholesterol remained elevated. In patient 2, values of blood lipids remained abnormally high despite diazoxide therapy. There were no significant changes of plasma pH and bicarbonate following diazoxide therapy; a reduction of negative base excess in both patients was suggested but not statistically validated.

In both patients, liver size diminished during diazoxide administration. In the first patient, liver size before treatment was 12.3 ± 0.5 cm below costal margin. After 1 year of therapy, the liver size reduced to 8.0 cm and has remained 8.8 ± 1 cm up to the present time. In the second patient, the liver size before treatment was 13.5 ± 0.5 cm; during 3 years of treatment it was 11.5 ± 0.5 cm. Following treatment with diazoxide, a significant weight gain was experienced from initially the 25th to the 97th centile over a period of 7 years in the first case, and from the 25th to the 50th centile over a period of 3 years in the second case.

No significant side-effects, such as hypertrichosis, water retention, change in blood pressure or worsening of hyperuricaemia, were noted in either patient. To monitor the risk of diazoxide administration producing hyperglycaemic insulinopenia in the patients, fructosamine and $HbA1_c$ were measured regularly. These parameters remained normal in both patients.

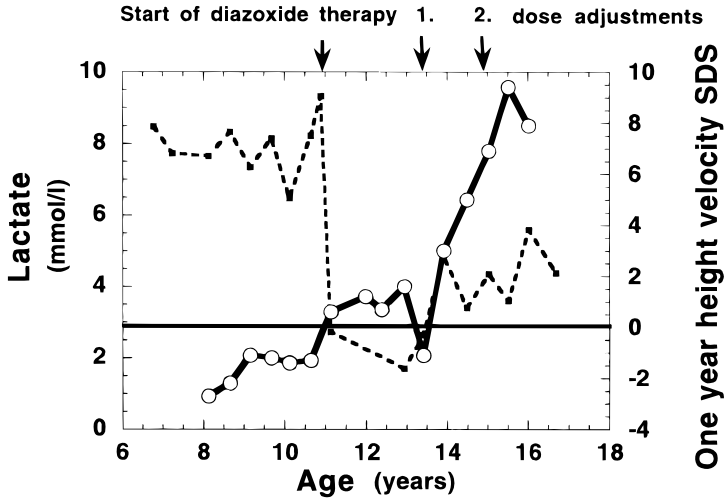

Figure 3 Growth versus blood lactate (patient 1). Blood lactate (broken curve) was determined between 08:00 and 09:00 after 2 h fasting. Growth data are given in one-year height velocity standard deviation scores (open circles, solid curve) (Prader et al 1989). Diazoxide therapy was started at the age of $10\frac{11}{12}$ years. The dosage was adapted for increased weight on two occasions, because the metabolic parameters (lactate and lipids) again became less favourable

In case 1, oral glucose tolerance test (45 g/m^2) was performed after 2 h fasting and administration of 25 mg diazoxide. Blood sugar concentrations prior to the test were 4.92 mmol/L (norm 4.23 $\pm$ 0.49); at 30 min 9.74 mmol/L (norm 7.4 $\pm$ 1.3); at 60 min 8.01 mmol/L (norm 6.4 $\pm$ 1.1); at 120 min 6.88 mmol/L (norm 5.3 $\pm$ 0.8); and at 180 min 3.88 mmol/L (norm 4.0 $\pm$ 0.9), respectively. The corresponding insulin concentrations were at the mean level for healthy controls: at the beginning 13 mU/L (norm 9.5 $\pm$ 7.1); at 30 min 46 mU/L (norm 49 $\pm$ 25.7); at 60 min 53 mU/L (norm 47.7 $\pm$ 36.3); at 120 min 35 mU/L (norm 31.3 $\pm$ 26); and at 180 min 6 mU/L (norm 16.7 $\pm$ 13.5). C-Peptide values remained at the lowest norm throughout the test. Lactate at the beginning of the test was only slightly elevated (2.73 mmol/L).

DISCUSSION

In GSD type Ia the release of free glucose from glucose 6-phosphate from the liver into the blood is greatly impaired, although glycogenolysis and glycogenesis are normal. This results in early hypoglycaema 2–3 h after a meal. Since glycolysis of glucose 6-phosphate is intact or even intensified under hormonal counterregulation similar to a fasting state, production of pyruvate and lactate is increased. Lactic acidosis becomes more severe whenever postabsorptive sources of glucose are exhausted. The resulting chronic acidosis is usually treated by alkalinization with oral doses of $NaHCO_3$.

Chronic metabolic acidosis is an important growth-inhibiting factor as shown by Challa and colleagues (1993) and in clinical studies by Mehls and colleagues (1992). A severe lactic acidaemia exceeding 5 mmol/L seems to impair normal growth (Smit 1993). Therefore, short stature and growth retardation are common features of GSD type Ia, especially in pre- and pubertal patients, although postpubertal catch-up growth seems possible (Smit 1993).

Therapy with diazoxide was started with the idea of avoiding early and prolonged hypoglycaemic states between meals as well as to reduce excessive production of lactate. Diazoxide was introduced for therapy of idiopathic hypoglycaemia in childhood (Goodman et al 1968). It was equally successful in preventing hypoglycaemia in patients affected with hypopituitary dwarfism (Ventura et al 1983). In 1968, Rennert and Mukhopadhyay suggested treatment with diazoxide in patients with GSD type Ia. Only a few other clinicians (Bartolozzi et al 1975; Gardoni and Giranzani 1978) took up this proposition. All reported an improved glucose, lipid and acid homeostasis and a marked reduction in hepatomegaly in several patients. In most patients, however, diazoxide had to be stopped because of various cutaneous allergic reactions. To our knowledge there are no reports on long-term treatment with diazoxide in GSD patients, and more specifically effects on growth retardation in GSD Ia.

The mode of action of diazoxide seems to be linked to K^+-ATP channel activation. The resulting hyperpolarization of the membranes decreases insulin release (Dunne et al 1987; Edwards and Weston 1990). Diazoxide is usually given in 3–4 doses at meal times. Its half-life in the body after oral administration is 24–36 h;

elimination is through the kidneys. In spite of its rather slow excretion, it appears reasonable to give it at the beginning of meals and eventually before going to bed. The drug is usually well tolerated and allergic reactions to the presently commercially available preparation are rare.

Following diazoxide therapy, lactic acidaemia in both patients improved and in patient 1 triglycerides and HDL-cholesterol levels nearly normalized. Although there were no significant changes of plasma pH and in bicarbonate concentrations, negative values of base excess ameliorated in both patients, suggesting a reduction in acid load. The impressive increase of height velocity SDS came with a delay of several months and without simultaneous advance in bone age. There was no indication that this initial increase was related to a pubertal growth spurt. Pubertal maturation was delayed in both patients as usually seen in GSD Ia, but in the meantime it has started in both girls.

The diminution of the liver size in both patients on diazoxide therapy was impressive. Diazoxide may lessen fatty infiltration of the liver and hyperlipidaemia through indirect inhibition of peripheral lipolysis. Hyperlipidaemia results from hypoglycaemia-induced lipolysis and increased triglyceride synthesis from plasma free fatty acids in the liver.

We conclude from our observations that diazoxide prolonged the postprandial euglycaemia, preventing early fasting hypoglycaemia. It successfully reduced lactic acidosis and thereby induced the impressive catch-up-growth in our patients. Since short stature is a psychological problem during childhood, we consider that diazoxide may be an alternative add-on treatment, to allow a normal growth during this period in patient with GSD type Ia.

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