Hyperinsulinism and overgrowth without obesity

S Srinivasan, M J Waters, J E Rowland, R C Baxter, C F Verge

CASE REPORT

We report a 5 year old girl with postnatal overgrowth (height velocity >97th centile), hyperinsulinemia, and increased insulin-like growth factor 1 for age, without evidence of bioactive or immunoreactive growth hormone excess or pituitary abnormality. Although her overgrowth may be a result of hyperinsulinism, her serum contains a factor (neither insulin nor IGF-1) which is able to stimulate the proliferation of lymphocyte precursors, and this could also account for the overgrowth. Over the course of two years observation she has developed acanthosis nigricans and diabetes mellitus.

A 5 year old Caucasian female was referred to the endocrine clinic for assessment of tall stature. She was born at 39 weeks gestation following conception by ovulation induction with FSH pump for maternal hypogonadotrophic hypogonadism. Her mother was also noted to have polycystic ovaries. The pregnancy was uneventful. Her birth weight was 2580 g (<10th centile), birth length 48 cm (10–50th centile), and head circumference 32.5 cm (10th centile). There were no neonatal problems. She was generally a well child with normal early developmental milestones. There was a family history of mild non-insulin dependent diabetes mellitus affecting her father and maternal grandmother, treated with diet alone.

Until the age of 2 she was growing along the 75th centile for height and weight, in keeping with her genetic potential (mid-parental height 170 cm, 75–90th percentile). However, between the ages of 2 and 3 her height had crossed from the 75th percentile to 12 cm above the 97th percentile.

On initial examination at age 5 years, she was nondysmorphic and proportionate. Her height was 131.2 cm (standard deviation score (SDS) +5.2), weight 35.85 kg (SDS +3.2, National Centre for Health Statistics 2000 data), and head circumference 52.5 cm. She was normotensive (blood pressure 90/60 mm Hg) and full systems examination was normal. She was prepubertal. Visual field testing and fundoscopy were normal.

Initial investigations showed an advanced bone age at 7 years and 6 months (Greulich and Pyle) at a chronological age of 5 years. She had normal androgen and gonadotrophin concentrations (compared with in-house childhood reference ranges): androstenedione 0.47 nmol/l (0–4.6), dehydroepiandrosterone sulphate (DHEAS) <0.8 µmol/l, 170H progesterone 1.1 nmol/l (0.17–4.0), luteimising hormone (LH) <0.2 U/l (0–5), follicle stimulating hormone (FSH) 2.3 U/l (0–5), and oestradiol 50 pmol/l (37–92). However, her growth markers were increased: insulin-like growth factor 1 (IGF-1) 36 nmol/l (reference range for age 4.7–22), IGF-1 binding protein 3 (IGFBP-3) 14 mg/l (1.7–3.5), and acid labile subunit (ALS) 409 nmol/l (60–280). Growth hormone binding protein (GHBP) was normal at 1.5 nmol/l (0.14–3.28). She was subsequently admitted for further investigations.

FURTHER INVESTIGATIONS

Twelve hours of growth hormone sampling every 20 minutes from 0800 to 2000 showed undetectable growth hormone (GH) concentrations, apart from two small pulses to 3.2 mU/l at 1400 and 3.0 mU/l at 1720 (measured by immunometric assay; Immulite, Diagnostic Products Corporation).

During an oral glucose tolerance test (OGTT), growth hormone concentrations were again undetectable (<0.1 mU/l), but insulin concentrations were very high (table 1) and glucose concentrations were consistent with impaired glucose tolerance by WHO criteria. Fasting lipids (cholesterol 3.5 mmol/l, triglycerides 1.1 mmol/l), and HbA1c (5.4%) were normal. IGFBP-1 concentrations on these samples were low (18 ng/ml) and decreased with the oral glucose load (to 4 ng/ml at 150 minutes), consistent with hyperinsulinism.

Other pituitary function tests were normal. Free thyroxine was 16 pmol/l (normal range 9.8–23.8), thyroid stimulating hormone (TSH) 2.1 mU/l (0.1–3.8), triiodothyronine 2.4 nmol/l (0.9–2.7), cortisol 278 nmol/l at 0800 (155–599), adrenocorticotropic hormone (ACTH) 31 pg/ml (<50), and prolactin 4.0 ng/ml (0–536). Magnetic resonance imaging of her brain, including pituitary cuts, was normal.

Oestrogen primed glucagon and clonidine stimulation tests showed normal growth hormone response to pharmacological stimulation. Peak growth hormone concentrations were 27 mU/l to glucagon and 22 mU/l to clonidine. There was also a normal cortisol response to glucagon stimulation with peak of 529 nmol/l.

Clinically our patient continues to grow with an accelerated growth velocity of 8.7 cm/y (>97th centile for bone age; fig 1). Her bone age remains 2 years 6 months advanced. At the age of 6 years 3 months she was noted to have early acanthosis nigricans affecting the axillae, which has progressed. She has no evidence of lipodystrophy. She has notably impaired social interaction skills, despite high average IQ, and a diagnosis of Asperger’s syndrome is being entertained.

On repeat OGTT at the age of 7.2 years our patient has developed type 2 diabetes mellitus by WHO criteria (table 1). Treatment with metformin has been recommended, but the child’s parents have been reluctant. Her growth markers have spontaneously become normal for age: IGF-1 34 nmol/l (12.6–35), IGFBP-3 3.9 mg/l (2–4), and ALS 284 nmol/l (60–280). She has evidence of adrenarche with early pubic hair and DHEAS of 1.2 µmol/l (0.1–1.5).

Her mother has also had fasting studies which show normal insulin of 4 mU/l (1–25), IGF-1 22 nmol/l (12.1–51), HbA1c 5.4% (4.4–6.4), and ALS 267 nmol/l (120–265), but an increased IGFBP-3 of 7.2 mg/l (2.2–4.6). Her father, who has

Abbreviations: ACTH, adrenocorticotropic hormone; ALS, acid labile subunit; DHEAS, dehydroepiandrosterone sulphate; FSH, follicle stimulating hormone; GH, growth hormone; GHBP, growth hormone binding protein; IGF, insulin-like growth factor; IGFBP, IGF binding protein; LH, luteimising hormone; NCHS, National Centre for Health Statistics; OGTT, oral glucose tolerance test; SDS, standard deviation score; TSH, thyroid stimulating hormone.
type 2 diabetes mellitus, has raised fasting insulin (32 mU/l) but normal IGF-1 (18.1 nmol/l).

**IN VITRO STUDIES OF SERUM BIOACTIVITY**

The possibility of a bioactive but non-immunoreactive growth hormone protein was excluded by non-detectable concentrations of bioactive growth hormone (<2 ng/ml) in a bioassay specific for the human GH receptor. This bioassay is based on the proliferation of mouse proB cells expressing the human GH receptor, and specificity for GH is achieved by measuring proliferation in the presence and absence of a specific GH antagonist. Samples from the patient at age 5 years showed an increased level of non-GH receptor mediated proliferation, corresponding to 15 ng/ml GH equivalent activity. This is higher than we have seen in over a hundred clinical samples. Therefore while the GH antagonist displaceable bioactivity was less than 2 ng/ml, the non-GH receptor mediated proliferation was equivalent to 15 ng/ml. Neither our patient’s extremely high insulin concentrations nor her increased IGF-1 for chronological age were sufficient to explain such an increase in assay baseline. In separate experiments, exposing the proB cells to an insulin concentration similar to that in the patient’s serum produced no stimulation. Using an insulin concentration six times that of our patient, the stimulation was only equivalent to 0.3 ng/ml hGH. We tentatively conclude that the patient is producing a growth promoting factor, other than insulin, IGF-1, or prolactin, which could account for her clinical state.

**DISCUSSION**

Our patient presented with clinical features and raised IGF-1 and IGFBP-3, suggesting a diagnosis of pituitary gigantism. However, there was no evidence of growth hormone excess; instead severe insulin resistance in the absence of obesity was revealed by the oral glucose tolerance test. There is a group of rare disorders with generalised or partial absence of subcutaneous fat (lipodystrophy), hyperinsulinaemia with insulin resistance, overgrowth and acromegaloidism, hyperlipidaemia, and non-ketotic diabetes mellitus. However, as loss of subcutaneous fat and hyperlipidaemia are early manifestations, our patient does not fit into this spectrum of disorders.

Our patient may represent a childhood variant of previously reported “insulin mediated pseudoacromegaly”, of which there have been a few reports in the adult endocrine literature. Pseudoacromegaly or acromegaloidism is a rare disorder characterised by overgrowth and acromegalic changes without excessive growth hormone or IGF-1 and without pituitary abnormality. Flier and colleagues reported an adult case similar to ours, except that his patient had normal IGF-1 concentrations (measured at age 19). Over time his patient developed acral enlargement, prognathism, wide spacing of the teeth, severe acanthosis nigricans, and notable enlargement of the tongue and ears—that is, features of acromegaly but without growth hormone excess. Our patient, by age 7 years, has not developed acral changes or coarsening of facial features. This may develop in time, by analogy with the situation in growth hormone excess in which a patient may develop acromegaly or pituitary gigantism depending on the timing of growth hormone hypersecretion in relation to epiphyseal fusion.

Flier and colleagues found a dissociation between the metabolic and mitogenic actions of insulin in pseudoacromegaly. While the insulin receptor sequence and expression are normal, insulin stimulated phosphoinositide 3-kinase activity is notably reduced in some patients with pseudoacromegaly.

| Table 1 Oral glucose tolerance test results, age 5 and age 7 |
|--------------------------|--------------------------|--------------------------|--------------------------|
|                         | Age 5                   |                         | Age 7                   |
|                         | Fasting 120 min         | Fasting 120 min         |
| Glucose (mmol/l)        | 4.2                     | 9.3                     | 4.4                     | 12.4                    |
| Insulin (mU/l)          | 53                      | 1588                    | 65                      | 3834                    |
| GH (mU/l)               | <0.1                    | <0.1                    |                         |                         |
| IGFBP-1 (ng/ml)         | 18                      | 6                       |                         |                         |

Figure 1  Patient’s height (A) and weight (B) data plotted for age (centiles from CDC NCHS data 2000).
There are no previous reports of paediatric “pseudoacromegaly” or “pseudogigantism”. Our patient’s raised growth markers at age 5 could be a feature early in the disorder. Alternatively, while IGF-1 of 36 nmol/l is notably increased for a child age 5 years (reference range 4.7–22), it is only mildly increased for her corresponding bone age of 7.5 years (reference range 12.6–35). Nevertheless the IGFBP-3 and ALS concentrations were initially raised, even when normalised for bone age. These later became normal, which makes autonomous activation of the IGF axis unlikely.

Our patient has postnatal overgrowth associated with severe hyperinsulinism progressing to type 2 diabetes mellitus. She also has increased bioactivity in a cell proliferation assay which is evidently not a result of increased insulin, IGF-1, or prolactin. This suggests the presence of another circulating growth promoting factor. Such a factor has been previously proposed to explain the syndrome of “growth without GH” seen in some children with panhypopituitarism.  

Preventable blindness in Africa

It has been estimated that some 1.4 million children around the world are blind and about three quarters of them live in Asia or Africa. Much of this blindness could be prevented or treated and a report from Nigeria (IR Ezegwui and colleagues. Br J Ophthalmol 2003;87:20–23) well illustrates this point.

In southeastern Nigeria there are three schools for blind pupils. Of 162 pupils, 142 were examined and two were excluded from the study because they were not blind. The rest were either blind (136 pupils) or had severe visual impairment (4). Six functionally blind pupils had significant vision when supplied with appropriate lenses. The most common cause of blindness was cataract (33, 24%). Thirty pupils (21%) had disease of the whole globe, of whom 17 had phthisis bulbii (a soft and shrunken eye usually following infection or trauma). The other 13 had anophthalmos, microphthalmos, or disorganised globe. Corneal scarring was the cause of visual loss in 30 pupils (21%) and was attributed to measles in 26. The contribution of vitamin A deficiency was not assessed. Glaucoma or buphthalmos were the cause in 13 (9%). Ten cases (7%) were thought to have been the result of using traditional eye medicaments. For 54 pupils (39%) their blindness had resulted from factors active in childhood, 21 (15%) were considered hereditary, 11 (8%) from intrauterine causes, and for 54 (39%) the timing of the insult was unknown. In all, 91 pupils (65%) were blind from causes considered preventable (such as measles) or treatable (such as cataract).

Much childhood blindness in developing countries can be avoided. The causes of blindness vary between and within countries and local data are important in determining approaches to prevention and treatment.

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