Clinical and Biochemical Variability of Growth Hormone (GH) Insensitivity Syndrome in a Pakistani Kindred

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Introduction

Availability of recombinant insulin-like growth factor I (rIGF-I) has led to a search for children who would benefit. We present four previously undiagnosed patients with growth hormone insensitivity syndrome (GHIS), whose features contrast with our existing case of Laron Syndrome (1). She is a caucasian gypsy child who has now grown 19 cm in 2 years of therapy with rIGF-I (Pharmacia). Pre-treatment at age 3.9 year, her height SDS was -5.5, fasting GH 48 mU/L rising to 460 mU/L after glucagon, IGF-I less than 2.0 nmol/L before and after GH administration, circulating GH binding protein (GHBP) negative. In none of the new patients is diagnosis so straightforward.

Patients and Results

We have presented four cases of GHIS in two pairs of brothers, cousins from Pakistani families in Birmingham. The mothers are sisters and both marriages are consanguineous. At age 4.4 to 8.5 y the boys range in height SDS from -5.8 to -3.3. Patients 1 and 2 have parents of height SDS -1.9 and -2.8 and one brother of normal height; patients 3 and 4 have parents of height SDS -1.4 and -1.0 and three normal height siblings. The affected boys were of normal birth weight (3.18 to 3.70 kg), 1 and 2 breech presentations delivered by caesarian section 3 and 4 spontaneous vertex deliveries. Patient 2 had coronal hypospadias, 3 an undescended testis. Shallow orbits and a depressed nasal bridge are more apparent in the first pair than the second; none shows marked midface crowding. All failed to thrive from infancy, with marked feeding difficulties and microcytic anemia. Their results are summarised in the table.

Spontaneous GH secretion was measured every 20 min for four hours from before breakfast until lunchtime. In three boys GH levels fell below 4 mU/L at some point, in two boys for half of the morning. On a previous occasion they had produced values of well over 100 mU/L on provocation testing.

Discussion

Within and between the four there is considerable heterogeneity of GH secretion. Only one shows sustained levels above 4 mU/L suggested as a diagnostic criterion of GHIS (2). Three show typically high GH values on one day but not the other. Considered in isolation, the earlier GH provocation tests on brothers 1 and 2 had been accepted as within normal lim-
its. Confirmation of the diagnosis lies in the failure of the low (but not very low in all) IGF-I and BP-3 levels to increase in response to exogenous GH, although the optimum duration of this test has not been determined (2).

Between patients there are some expected associations. The shorter pair has the shorter parents. The tallest for age has the highest IGF-I and BP-3, approaching or exceeding the lower limit of normal. Unexplained is the correlation between height and GHBP concentration. Of the 25% of previously reported cases from Europe who are GHBP-positive, all are girls (1). The results in these 4 boys suggest a different mechanism which produces variably partial GH insensitivity.

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References
