Convergence of two types of familial short stature in a pedigree

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Abstract. This study reports an unusual family with coexistence of isolated growth hormone deficiency transmitted as an autosomal dominant trait (Rimoin Type II) and constitutional short stature.

Pituitary deficiency may result from a heterogeneous group of disorders characterized by genetic or acquired defects in Growth Hormone (GH) secretion or action (Rimoin & Horton 1978). GH deficiency may be monotropic (isolated GH deficiency) or multirropic. Isolated GH deficiency, when hereditary, is a rare condition of which at least two varieties are known. The first, less rare and also called type I, is inherited as autosomal recessive character, while the second (type II) is transmitted as an autosomal dominant trait (Rimoin 1976). Further heterogeneity within the recessive type has been postulated on the basis of the immunological response to GH treatment (Illig et al. 1970). Thus, it is likely that isolated hereditary GH deficiency includes forms other than type I and type II (Rimoin 1976).

This report describes a family in which the wife and one of her five children had type II GH deficiency whereas her husband and four children had constitutional short stature. Since this coexistence of two variants of familial short stature within the same pedigree is very unusual, our report seems worthy of illustration.

Case Report

A. The proband

M.G., a girl of 10, was admitted to the Pediatric Clinic, University of Catania, for evaluation of short stature. Born after 42 weeks of uneventful gestation by a normal delivery, she weighed 2600 g and was 48 cm long. Growth retardation was evident from her first years of life and contrasted with an apparently normal mental development. When she was admitted, her weight was 14 kg and her length 100 cm (normal values for Sicilian girls of the same age: 27 kg and 129 cm, according to Bulgarelli 1974). Apart from growth retardation (below the 3th percentile) physical examination did not demonstrate any abnormalities. The following laboratory investigations gave normal results: urine analysis, blood urea nitrogen, serum Na, Cl, Ca, K, P, blood acid-base balance, alkaline phosphatase, total proteins and fractions, as well as ECG, EEG, EMG and karyotype (46, XX). Serum cholesterol was 6 mmol/l, and the renal clearance of creatinine was 89 ml/min/1.73 m². Ophthalmological examination showed divergent strabismus, astigmatism, and myopia of mild degree. Radiological examination of several skeletal segments, according to the method of Tanner et al. (1975), showed an average bone age of 8.3 years (Table 1). The skull and the sella were normal by conventional views. The fasting blood glucose level ranged from 2.45 to 6.60 mmol/l on several determinations. GH determination was performed by radioimmunoassay (RIA) (Schlich & Parker 1964) after iv infusion of both arginine (0.5 g/kg body weight) and of insulin (0.1 U/kg body weight). In our laboratory normal subjects give values above 5 µg/l in at least one sample in these stimulatory tests. In the proband both arginine and insulin induced marked hypoglycaemia, but the GH level, initially very low, did not reach 3 µg/l.
Table 1.
Family M.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Stature (cm)</th>
<th>Skeletal age (years)*</th>
<th>GH secretion after stimulation**</th>
</tr>
</thead>
<tbody>
<tr>
<td>III.5</td>
<td>70</td>
<td>M</td>
<td>143</td>
<td></td>
<td>normal</td>
</tr>
<tr>
<td>III.6</td>
<td>64</td>
<td>F</td>
<td>143</td>
<td></td>
<td>not studied</td>
</tr>
<tr>
<td>IV.3</td>
<td>36</td>
<td>M</td>
<td>144</td>
<td></td>
<td>normal</td>
</tr>
<tr>
<td>IV.4</td>
<td>29</td>
<td>F</td>
<td>142</td>
<td></td>
<td>absent</td>
</tr>
<tr>
<td>IV.6</td>
<td>25</td>
<td>F</td>
<td>142</td>
<td></td>
<td>not studied</td>
</tr>
<tr>
<td>V.2</td>
<td>12.6</td>
<td>M</td>
<td>131</td>
<td>12.9 14.8 11.5</td>
<td>normal</td>
</tr>
<tr>
<td>V.3</td>
<td>11.6</td>
<td>F</td>
<td>126</td>
<td>11.6 12.8 10.5</td>
<td>not studied</td>
</tr>
<tr>
<td>V.4</td>
<td>9.2</td>
<td>F</td>
<td>100</td>
<td>7.6 6.0 8.5</td>
<td>absent</td>
</tr>
<tr>
<td></td>
<td>10.9</td>
<td></td>
<td>108***</td>
<td>9.9 10.0 9.4</td>
<td></td>
</tr>
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<td>V.5</td>
<td>8</td>
<td>M</td>
<td>106</td>
<td>7.8 8.6 8.0</td>
<td>absent</td>
</tr>
<tr>
<td>V.6</td>
<td>3.4</td>
<td>M</td>
<td>84</td>
<td>3.3 3.4 2.6</td>
<td>normal</td>
</tr>
</tbody>
</table>

* Evaluated according to the method of Tanner et al. (1975) (mean of three different evaluations).


RUS: radius-ulna short finger bones.

** See Table 2.

*** After therapy with Grorm (Serono) 2 x 2 U/week for about 14 months.

Fig. 2). Other findings were: serum T3 (by RIA): 1.58 nmol/l (normal range: 1.23 – 3.08 nmol/l); T4 (by RIA): 90 nmol/l (normal range: 56 – 144 nmol/l); TSH (by RIA): 7 µU/ml (normal range: 1 – 8 µU/ml); urinary I7-KS (by column chromatography, Ketchrome™ method, Bio-Rad Lab.): 22 µmol/day (normal range: 2.5 – 13

![Fig. 1.](image)

GH response to arginine stimulation (0.5 g/kg body weight).

![Fig. 2.](image)
III.5: old.
The appeared was treatment (normal range: 2.2–6.6 μmol/day).

IV.3: sisters were conscripts tall (average value for the age: 140 cm);
V.2: the oldest brother of the proband, 12½-years-old, was 131 cm tall (normal average for the age: 140 cm);
V.3: a 11½-years-old girl, was 126 cm tall (normal average for the age: 134 cm). She refused to submit herself to stimulation tests;
V.5: a 8-years-old brother, had a stature of 106 cm (normal value for the age: 118 cm);
V.6: male, the last born sib, 3-years-old, was 84 cm tall (normal height for his age: 88 cm).

Among his paternal relatives, the following members were of unusually short stature: his maternal grand-mother (1.4), his mother (1.6) and two of her sisters (1.11 and 1.12);
IV.3: father of the proband, is 36-years-old and 144 cm tall;
IV.4: mother of the proband, is 29-years-old and 142 cm tall (average height for Italian women of 19 according to De Toni et al. 1968: 159 cm). Her menarche was at 14 years. She reported that her sister IV.6 and her grandmother II.16 were of very short stature;

B. The family

The pedigree of the family is reported in Fig. 3. The following subjects were directly examined by us:
III.5: paternal grand-father of our proband, 70-years-old. He was 143 cm tall (average height of Italian conscripts 18-years-old according to De Toni et al. 1968: 168.2 cm). Among his maternal relatives, the following members were of unusually short stature: his maternal grand-mother (1.4), his mother (1.6) and two of her sisters (1.11 and 1.12);
IV.3: father of the proband, is 36-years-old and 144 cm tall;
IV.4: mother of the proband, is 29-years-old and 142 cm tall (average height for Italian women of 19 according to De Toni et al. 1968: 159 cm). Her menarche was at 14 years. She reported that her sister IV.6 and her grandmother II.16 were of very short stature;
V.2: the oldest brother of the proband, 12½-years-old, was 131 cm tall (normal average for the age: 140 cm);
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V.5: a 8-years-old brother, had a stature of 106 cm (normal value for the age: 118 cm);
V.6: male, the last born sib, 3-years-old, was 84 cm tall (normal height for his age: 88 cm).

Apart from their short stature, all the subjects were apparently normal and had normal bone age (Table 1) and sellar regions on radiological examination. GH determinations after iv arginine (0.5 g/kg) and insulin (0.1 U/kg) were performed repeatedly (at least twice) in the seven available relatives of the proband (Table 2). Four of them (III.5, IV.3, V.2 and V.6) had normal GH responses to both stimuli. The mother (IV.4) had a significant hypoglycaemic response to both arginine and insulin stimulation tests but GH levels did not increase appreciably (Table 2). The same result occurred in the brother V.5, for whom nevertheless GH deficiency could be excluded on the basis of his normal skeletal age and growth rate at follow-up (more than 4 cm/year).
Table 2.

<table>
<thead>
<tr>
<th>Patients studied</th>
<th>B</th>
<th>0'</th>
<th>30'</th>
<th>60'</th>
<th>90'</th>
<th>120'</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Arginine stimulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III.5</td>
<td>2.2</td>
<td>3</td>
<td>5.8</td>
<td>3</td>
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<td>1.2</td>
</tr>
<tr>
<td>IV.3</td>
<td>0.5</td>
<td>2</td>
<td>11</td>
<td>12.5</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>IV.4</td>
<td>0.5</td>
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<td>0.3</td>
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<td>0.7</td>
<td>1</td>
</tr>
<tr>
<td>V.2</td>
<td>10</td>
<td>9</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>V.5</td>
<td>1.8</td>
<td>3</td>
<td>2.7</td>
<td>1</td>
<td>0.8</td>
<td>1</td>
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<tr>
<td>V.6</td>
<td>3.8</td>
<td>3.8</td>
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<td>4.2</td>
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<td>b. Insulin stimulation</td>
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<tr>
<td>III.5</td>
<td>5.8</td>
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<td>5</td>
<td>1.8</td>
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<td>IV.4</td>
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<td>V.2</td>
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<td>V.5</td>
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<td>1.2</td>
<td>0.7</td>
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</tr>
</tbody>
</table>

GH values (μg/l) after iv arginine (0.5 g/kg) and iv insulin (0.1 U/kg) stimulation.

Discussion

There are few reports in which GH deficiency appears to be transmitted as an autosomal dominant character.

In two of nine families studied by Rimoin et al. (1967), matings between affected individuals produced affected and unaffected children, so that autosomal recessive inheritance could be excluded. Sheikhalislam & Stempfel (1972) reported a family in which the father, whose short stature was probably dependent on a new mutation, had transmitted isolated GH deficiency-trait as a dominant character to four of his seven children. Later, Poskitt & Rayner (1974) described two families where isolated GH deficiency was present in two successive generations, suggesting an autosomal dominant inheritance.

In the family we described, short stature was not associated with other evident abnormalities or other...
endocrinological disturbances. The short individuals fell into one of two types: in the first (isolated GH deficiency) induced hypoglycaemia did not cause an appropriate increase of serum GH whereas in the second (familial short stature), a normal GH response followed the post-arginine and post-insulin hypoglycaemia. The first type of defect lay in the maternal line while the second was in the paternal one. The convergence in this pedigree of two different traits was probably a coincidence due to non random assortive mating. The short stature with normal GH secretion, present in the paternal side, is obviously inherited as autosomal dominant character; in fact, short stature-trait is present in five successive generations of which the last three were studied by us with hormone stimulation tests. The short stature with GH deficiency, present in the maternal side, cannot be explained easily because it was present only in the proband’s mother and in one of her sisters, both daughters of normal stature parents. As far as the five subjects of the proband’s sibship were concerned, V.2 and V.6, who showed a normal response to both stimulation tests, had inherited the short stature from the paternal side. The same possibility could be applied to V.3 and V.5, whose skeletal age was normal (in spite of the inadequate GH response in V.5). As far as the proband (V.4) is concerned, several genetic interpretations are possible; the most simple is that she had inherited the short stature-trait with GH deficiency from the maternal side, but we cannot exclude a contemporaneous presence of the paternal short stature trait which might have exerted an additive effect.

References


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