Growth hormone receptor deficiency (Laron syndrome) in black African siblings

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Non-Caucasians with growth hormone receptor (GHR) deficiency/Laron syndrome among the approximately 180 recognised cases are rare, and include a Japanese and 3 African Americans. Black African siblings, a brother and a sister seen initially at 11 years 9 months and 5 years 6 months of age respectively were –7,4 and –8,0 on the standard deviation score for height. They had characteristic features and biochemical findings including prominent forehead; depressed nasal bridge; central adiposity; high-pitched voices; micropenis; high GH levels and low levels of insulin-like growth factor (IGF)-I, IGF-II, insulin-like growth factor-binding protein 3 (IGFBP-3), and GH-binding protein (the solubilised extracellular domain of the GH cell surface receptor). Molecular genetic studies revealed a dinucleotide deletion in both siblings on exon 7 of the GHR gene, a mutation not found in any other GHR-deficient patient studied, including the North Americans of African origin. Since African Americans have a substantial admixture of Caucasian genes, it is of interest to document the presence of this condition in siblings from Africa.

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The clinical appearance of severe growth hormone (GH) deficiency, including features such as prominent forehead, depressed nasal bridge, central adiposity and extremely short stature, but with elevated serum levels of GH, was first noted in Israel among inbred Jewish populations from Arabic countries. Forty-one patients from Israel with Laron syndrome (LS) were eventually described including 11 Arabs.[1] Sporadic cases, frequently involving siblings, have included approximately 75 additional patients from predominantly Mediterranean countries and the Indian

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subcontinent. Another concentration of over 60 patients has been found in southern Ecuador, also in an inbred population of Spanish origin, and predominantly conversos, i.e. Jews who became Catholic during the Inquisition.[2,3] Non-Caucasian instances have included a Japanese patient,[4] and 3 unrelated African Americans.[5,6] We are unaware of any instances of LS previously reported from Africa.[7]

A defect in the GH receptor (GHR) has been recognised as responsible for this condition since cells obtained from liver biopsies of 2 patients failed to bind radioactive GH.[8] Subsequent demonstration that the circulating high-affinity GH-binding protein reflected the extracellular domain of the GHR made it possible to confirm GHR abnormality without resorting to liver biopsy.[6] Localisation of the GHR gene to chromosome 5 and characterisation of the gene permitted a search for molecular defects in these patients.[9] Considerable genetic heterogeneity has been suggested, even among Israeli patients;[10] 10 mutations have been described in the extracellular domain of the GHR.[7] In the Ecuadorian cohort, however, all but 1 of 46 probands studied had a nucleotide substitution resulting in abnormal splicing of RNA for the GHR in an area that is preserved through all known species.[11]

It was of great interest to discover a brother and sister from Africa with GHR deficiency, since the only other known patients of African origin were from the USA, where Caucasian gene admixture is expected.

Case report

The patients are shown in Fig. 1. They were first seen when the boy was 11 years 9 months and the girl 5 years 6 months of age. The boy had had episodes of extreme floppiness in the morning with non-arousability and occasional convulsions between the ages of 2 and 8 years, and the girl had been experiencing these since the age of 2 years. There was no known parental consanguinity. The patients come from Sekukuniland in the Transvaal. Except for the symptoms noted, they had been in good health. Parents' heights were as follows: father 172 cm, –0,7 standard deviation score (SDS) for North Americans;[12] mother 153 cm (–1,8 SDS). Three unaffected sisters and an unaffected brother were of normal stature for age. The boy had been treated for micropenis with testosterone injections for several months. He was an excellent student and loved school. At age 13 years, he had a height of 95,5 cm (–7,4 SDS, height age 3 years) and 1-year growth velocity of 4,3 cm (–2,4 SDS for bone age 8,5 years at age 12); the girl's height at age 7 years was 77,5 cm (–8,0 SDS, height age 1 year and 3 months) and her 1-year growth rate was 2,9 cm. Weights were 100% and 94% of ideal for height, respectively. The boy's head circumference of 50,1 cm was normal (50th percentile) for height age and the girl's of 48,5 cm large (90th percentile) for her height age. Hand and foot lengths were at the 50th percentile for height. The patients had prominent foreheads, depressed nasal bridges, central adiposity and high-pitched voices.

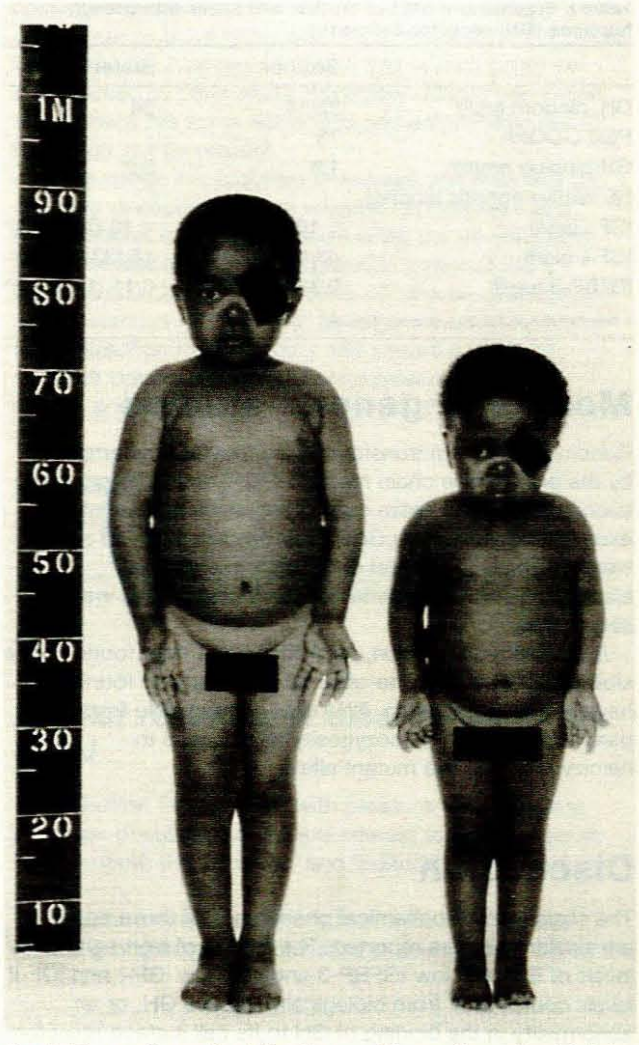

Fig. 1. 11-year 9-month-old brother and 5-year 6-month-old sister with GHR deficiency (note prominent forehead, depressed nasal bridge and central adiposity).

Biochemical studies

Biochemical studies were done at the Endocrine Sciences Laboratories (Tarzana, California). GH levels in serum were determined by radio-immunoassay, as were serum insulin-like growth factor (IGF)-I and IGF-II concentrations, following acid chromatographic separation from their binding proteins. Serum GH-binding protein was determined by gel filtration of serum incubated with ^{125}I-labelled human growth hormone and expressed as relative specific binding (sample specific binding divided by the specific binding of the reference adult male serum pool x 100). IGF binding protein 3 (IGFBP-3), the GH-dependent binding protein accounting for 80% or more of circulating IGF, was measured by a specific radio-immunoassay. Results are shown in Table I. All values were consistent with GH resistance.[2] Random GH levels were elevated and IGF-I unmeasurable; IFG-II levels were very low. GH-binding protein activity was minimal in both patients and the GH-dependent IGFBP-3 was also extremely low.

Table I. Biochemical data of brother and sister with growth hormone (GH)-receptor deficiency

	Brother	Sister
GH, random (µg/l)	23;14	34
Post L-DOPA	75	
GH-binding protein (% relative specific binding)	1.8	5.2
IGF-I (µg/l)	< 10 (180 - 440)*	< 10 (70 - 288)*
IGF-II (µg/l)	43 (334 - 642)*	16 (334 - 642)*
IGFBP-3 (µg/l)	0.32 (2.1 - 6.2)*	0,11 (1.5 - 3.4)*

* Normal range for age in parentheses.

Molecular genetic studies

Genomic DNA from transformed leucocytes was amplified by the polymerase chain reaction (PCR) and PCR products encompassing the entire coding sequence and all intron-exon boundaries of the GHR gene (except those of exon 3) were analysed by parallel denaturing gradient gel electrophoresis. Fragments with abnormal results were sequenced.[7,11]

A dinucleotide deletion, del 230TA or AT, was found in one sibling's GHR gene.[7] The other sibling was later found to have the same mutation. DNA was not available from the parents to confirm homozygosity as opposed to hemizygosity for the mutant allele.

Discussion

The clinical and biochemical phenotypes of these patients are similar to others reported. The finding of high serum levels of GH with low IGFBP-3 and very low IGF-I and IGF-II levels could result from biologically inactive GH, or an abnormality in the binding of GH to its cell surface receptor; it could also result from abnormality in post-receptor action. The virtual absence of GH-binding protein activity in the circulation, however, indicates that the defect is in the GHR, since the GH-binding protein appears to be the solubilised extracellular domain of the GHR.[6] The finding of a dinucleotide deletion in exon 7 of the GHR gene affecting transcription confirms this. The mutation was not found in any other GHR-deficient patient studied, including 2 purportedly unrelated African American individuals who share a single-base substitution which generates a stop codon in exon 7 of the GHR.[7]

African Americans have a substantial admixture of Caucasian genes. It can therefore be postulated that the three occurrences in African Americans are evidence of geographical drift of the same Mediterranean/southern European/Middle Eastern origin of all but a few of the known instances. Such admixture is less likely in the patients we are reporting and the appearance of this rare condition in these patients is therefore of particular interest.

Consanguinity is typical in the affected populations in Israel and Ecuador and frequently noted in sporadic isolated or familial occurrences. Given the rarity of the GHR deficiency and the rarity (1 instance) of compound heterozygosity for mutations in affected subjects,[7,9-11] unrecognised consanguinity appears likely in the few 'unrelated' parents, such as in this family.

Although this article does not deal with therapeutics, exciting developments in recombinant DNA technology have made this condition amenable to therapy. Since this article was originally drafted, these patients were started on IGF-1 (Igef-Kabi Pharmacia) and have responded dramatically to this. Growth velocities have improved to well above the 97th centile for bone age, and there has been a marked improvement in their general well-being and appetite. The hypoglycaemic episodes that the younger of the 2 patients was experiencing up until the start of therapy have ceased.

Clearly, continued trials of this new therapeutic modality will be required to establish its safety and long-term efficacy.

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