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A half-century of studies of growth hormone insensitivity/Laron syndrome: A historical perspective☆

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ABSTRACT

A growth hormone (GH) dependent substance responsible for sulfate uptake by costal cartilage of hypophysectomized rats, labeled sulfation factor, was reported in 1957. In 1962 the radioimmunoassay for GH was described. The clinical picture of severe GH deficiency but with high serum concentrations of GH was reported in 3 siblings in 1966 and followed by a 1968 report of 22 patients belonging to 14 consanguineous oriental Jewish families in Israel. Defective sulfation factor generation was demonstrated in 15 of these individuals and in a 1971 report; FFA response to IV GH and growth response to GH injections suggested competitive saturation of peripheral tissue receptors by an abnormal GH. However, studies published in 1973 demonstrated normal fractionation of their circulating GH, and normal binding of GH from 22 patients to various antisera used for radioimmunoassay. In 1976, the Israeli investigators reported that circulating GH from 7 patients reacted normally in the recently developed radioreceptor assay for GH. In 1984, using hepatic microsome pellets, they demonstrated that the defect was a failure of GH binding to receptors. Characterization of the human GH receptor (GHR) gene, reported in 1989, included the initial description of a genetic defect of the GHR in 2 of 9 Israeli patients. At about the same time began the identification in Ecuador of what was to become the largest population of GH insensitivity in the world, ~100 individuals, and the only substantial population with a common mutation of the GH receptor. Treatment studies with recombinant IGF-I began in 1990. Growth response was modest compared to that of GH treated GH deficient subjects. The spectrum of GH insensitivity has expanded beyond GH receptor deficiency to include postreceptor abnormalities: IGF-I gene mutation (1996); IGF-I receptor mutation (2003); signal transducer and activator of transcription 5b mutation (2003); and mutation of the GH-dependent acid labile subunit (2004).

Conclusion: Rare conditions of GH insensitivity caused by GH receptor and postreceptor abnormalities have provided insights into the processes of growth, body composition, and metabolism.

1. Background

In 1957, Salmon and Daughaday observed that the uptake of ^{35}S-sulfate by the costal cartilage of hypophysectomized rats was stimulated by normal rat serum but not by growth hormone (GH), even at high dosage [1]. Thus, normal rat serum appeared to contain a GH dependent substance that was labeled "sulfation factor", later identified as somatomedin or insulin like growth factor I (IGF-I). These observations gave rise to the somatomedin hypothesis, which states that GH induces growth indirectly via stimulating production of a growth factor. Other investigators had been able to stimulate sulfate and thymidine uptake by prolonged exposure to GH, but to a lesser degree, explained by the expanded somatomedin hypothesis which invokes local effects of GH on the growing tissue, chondrocyte proliferation and the generation of paracrine/autocrine IGF [2]. Thus, normal growth induction by GH requires both hepatic generation of endocrine IGF-I and the local effects of GH.

The extraction of GH from human pituitary glands obtained at autopsy and preserved in acetone or frozen, using hot glacial acetic acid, was reported by Raben in 1957 [3]. The following year he reported the treatment of a "pituitary dwarf" with the GH extract [4]. In 1962, the radioimmunoassay for GH was described [5].

The comprehension of the basis for hormone unresponsiveness in the mid-1960s is reflected in the 1965, 3rd edition, of Lawson Wilkins' classic, The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. In the chapter, Endocrine Relationships and their Influences upon Growth, the section titled Responsiveness of Peripheral Tissues to Hormonal Action reads: "There are a number of disorders in which endocrine symptoms are due to irresponsiveness of the tissues ("end organs") to normal amounts of hormone. Examples are nephrogenic diabetes insipidus, pseudohypoparathyroidism, and the inability of some male pseudohermaphrodites with feminizing testes

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to develop sexual hair even when androgen is administered. These are probably due to genetically determined defects of intracellular enzyme systems."

2. Discovery

It was in the context of this mid-1960s perspective that Laron, Pertzelan, and Mannheimer reported their historic discovery in 1966 [6]. Their proband was a 3-year-old boy with a height SDS −7 who had the appearance of classic GH deficiency.

GENETIC PITUITARY DWARFISM WITH HIGH SERUM CONCENTRATION OF GROWTH HORMONE A NEW INBORN ERROR OF METABOLISM?

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He was one of 3 affected siblings of a Yemenite Jewish family with grandparents who were first cousins. When these patients were given 5 mg human pituitary GH intravenously, fat mobilization was demonstrated by a rise in free fatty acids (FFA) and the authors concluded, "Since exogenous growth hormone was active in these patients, the endogenous secretion of an abnormal growth hormone molecule is postulated."

These observations were expanded in 1968 in a study of 22 patients belonging to 14 consanguineous oriental Jewish families [7]. Reported was elevation in baseline FFA with further increase following intravenous GH in 11 subjects as in the first 3 patients, with nitrogen retention in metabolic balance studies during 4 days of high dose GH (5 mg/day) in 6 subjects; in 3 individuals treated with GH (3 mg thrice weekly) for several months there was decreased frequency of spontaneous hypoglycemia with reduction in skinfold thickness; 2 of them had a growth response. The authors concluded, "These patients showed no evidence of primary end organ unresponsiveness or of growth hormone overactivity; they responded to exogenous growth hormone and had a reduced reserve of pancreatic insulin, a finding characteristic of prolonged HGH deficiency. It is suggested that the syndrome is due to an inborn error of HGH synthesis resulting in an immunologically reactive but biologically inactive molecule."

The first patient reported outside of Israel was also in 1968, a 30-year-old man who had elevated levels of GH which were further increased by hypoglycemia and arginine infusion [8]. He had no nitrogen retention in response to exogenous GH and striking insulinopenia after glucose and arginine and after a glucose load, both before and following 4 days of GH, in contrast to 4 GH deficient subjects whose insulin concentrations increased following the GH injections. The authors considered it possible that a functionally deficient GH molecule could saturate receptor sites and prevent normal exogenous GH from reacting with the end organ or that the normal metabolic actions of GH were blocked by abnormal receptor sites in peripheral tissues. Over the next few years failure of metabolic and growth response to GH was reported in other patients from outside Israel, beginning with a report of Arab siblings in 1971 [9].

3. Identifying the defect

In 1969, defective sulfation factor generation was reported in 6 of the patients from Israel [10] and in 1971, in a total of 15 patients [11]. It was postulated on the basis of the dramatic FFA mobilization response to IV GH, comparable to that in GH deficiency, and growth response during 3 to 7.5 months administration of GH in 5 of the 11 children treated, that lack of sulfation factor activation was not adequate explanation for the syndrome. The authors again concluded that, "These patients showed no evidence of primary end organ unresponsiveness or of growth hormone overactivity;…" and again suggested, "that the syndrome is due to an inborn error of GH synthesis resulting in an immunologically reactive but biologically inactive molecule." The unique observation in the Israeli patients of metabolic effects, and in some individuals growth response, to exogenous pituitary extract human GH in the presumed absence of a functional GH receptor might be attributable to a combination of other pituitary hormones in the extract (e.g. ACTH stimulating cortisol release with metabolic effects) and improved nutrition while under study, which has been shown to independently improve growth (i.e. without IGF-I administration) in GH receptor deficient subjects [12,13].

Studies published in 1973 failed to demonstrate abnormal GH to explain the syndrome. Serum from 2 Canadian patients showed normal fractionation of their GH [14] and the reaction of GH from 22 Israeli patients with various antisera used for radioimmunoassay was shown to be normal by the Israeli investigators [15], who further reported, in 1976, that circulating GH from 7 patients reacted normally in the GH radioreceptor assay [16].

The GH cellular receptor was identified as the site of the defect by the Israeli investigators and reported in 1984 [17]. Liver microsome pellets were prepared from tissue obtained by open biopsy from two patients aged 4 and 26 years. There was no specific binding of radioiodinated GH whereas, in 31 assays of liver microsomes obtained from 6 healthy subjects who were kidney transplantation donors, binding was 8–24% of the radioiodinated ligand.

4. Circulating GH binding protein (BP) and GHR molecular studies

Identicality between mammalian (rabbit) specific GHBP in serum and GHBP in liver cytosol was initially demonstrated in 1985 [18]. The following year, the specific GHBP in human plasma was characterized [19]. Two years later, reports appeared only a month apart of GHBP absence from the sera of patients with GH insensitivity [20,21]. That same year, the purification and protein sequencing of human serum GHBP demonstrated that it was structurally identical to the extracellular hormone binding domain of the membrane-bound GH receptor [22].

The characterization of the human GH receptor (GHR) gene was reported in 1989 and included the first description of a genetic defect of the GHR, deletion of exons 3, 5, and 6, in 2 of 9 Israeli patients with LS [23], demonstrating that even in this ethnically homogeneous population, there was genetic heterogeneity. Recognition that the exon 3 deletion was a common polymorphism that encodes a variant receptor protein without functional significance resolved the dilemma of explaining deletion of nonconsecutive exons [24]. Subsequently, over 50 mutations of the GHR gene have been identified. In addition to the original exon 5, 6 deletion, another deletion of exon 5 has been described, along with numerous nonsense mutations, missense mutations, frameshift mutations, splice mutations, and a unique intronic mutation resulting in insertion of a pseudo-exon [25]. In 1997 a heterozygous dominant negative mutation of the intracellular domain of the GHR, resulting in a milder LS phenotype, was described in a British mother and daughter [26] and in 1998 a similar heterozygous point mutation also resulting in mild growth failure was described in Japanese siblings and their mother [27].

5. Discovery of an Ecuadorian population with GHI

Beginning in 1988, increasing numbers of adult women who appeared to have isolated GH deficiency were being referred from Loja province in Southern Ecuador to the Institute that had been recently established by Dr Jaime Guevara-Aguirre in Quito, who found that they had elevated circulating GH. The initial 22 individuals included only one male, hence the original publication referring to the "Little women of Loja" [28]. Identification of another cohort in the neighboring

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