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Laron Z, Pertzelan A & Mannheimer S. Genetic pituitary dwarfism with high serum concentration of growth hormone: a new inborn error of metabolism? *Isr. J. Med. Sci.* 2:152-5, 1966.
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A new kind of genetic dwarfism was described with high serum levels of human growth hormone. The original paper hypothesized a defective growth hormone molecule, but the problem is a defective growth hormone receptor gene. [The *SCI*® indicates that this paper has been cited in over 160 publications, making it the most-cited paper from this journal.]

Hereditary Dwarfism with High GH Levels

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A snap decision made more than 30 years ago can be said to have changed the course of my entire life. As a young pediatric endocrinologist, I was slated to take up a new position in the north of Israel when a telephone call came through from Beilinson Hospital near Tel Aviv, from my medical school teacher, Professor Andre DeVries, asking me to establish a pediatric endocrine clinic. On the spur of the moment, I accepted the offer, cancelling all my previous plans, and therewith began my lifelong affair with a group of very small people and a quest for the culprit in their peculiar syndrome of dwarfism.

Not far from the hospital, there is what was then a settlement of new Jewish immigrants, the great majority having come from Yemen. Soon after its establishment in 1958, there appeared in the clinic a number of children from this community, belonging to two related families and with the striking feature of extremely high-pitched voices, easily identifiable from afar. They exhibited the typical appearance of human growth hormone (hGH) deficiency and the corresponding metabolic features of hypoglycemia, elevated plasma free fatty acids, and so on. When quantitative methods for circulating hGH became available, we were surprised to find that these patients had very high levels of plasma hGH, and our first thought was that we had discovered a hereditary disease with an abnormal hGH molecule.

In the following years, I and my associates A. Pertzelan and M. Karp identified many more such patients, all belonging to Jewish families of Oriental origin, and described their detailed clinical features. These included generalized obesity, acromicria, including small facial bones, and small gonads and genitalia. Subsequently, we learned that these patients undergo delayed puberty but reach full sexual development; some got married and begot children. We also began a series of studies to start the elucidation of the pathophysiology of this new entity. We observed that these long-term IGF-I deprived patients have hypoglycemia in childhood, but this biochemical abnormality is normalized with age by the development of counterregulatory mechanisms that in few adults overshoot to glucose intolerance.

Collaborative studies with W.H. Daughaday of Washington University, St. Louis, Missouri, revealed very low activity of the serum sulfation factor (later called somatomedin-C or IGF-I) with no rise upon exogenous administration of hGH, demonstrating a state of resistance to GH, and we hypothesized a defect in somatomedin generation.[1] Research in our laboratory by R. Eshet using gel chromatography and comparing immuno- and bioassay activity yielded evidence that the hGH molecule is completely normal and biologically active, giving rise to the suspicion of an hGH receptor or postreceptor defect.

We should like to note that throughout the years of continuing research these patients were exceptionally cooperative in allowing us

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to obtain blood samples as needed and to undergo repeated testing, always of course in the hope that we would make a breakthrough discovery of some means of treatment. In fact, it was thanks to the willingness of two of these patients to go far beyond what would ordinarily be asked of them that we eventually secured proof for a receptor defect. In 1983 we were able to obtain open liver biopsies, following informed agreement by the parents and the patients and approval by the Ethical Committee of the hospital, and these showed conclusively that there was no binding of ^{125}I-hGH by their liver membranes[2] compared to liver membranes from healthy transplant donors.

In the meantime many more patients with this syndrome had been described in various populations not only around the Mediterranean, but also in Argentina, Denmark, Japan, and, recently, Brazil; and in the literature we found that it had been coined "Laron type dwarfism (LTD)" (which in the beginning always felt somewhat embarrassing). The syndrome aroused much interest since it was a model in nature of a feedback mechanism defect for a peptide hormone.

The recent characterization of the hGH receptor gene has opened the way for still further elucidation of the nature of the receptor defect. In collaboration with W.I. Wood and associates from Genentech as well as J.S. Parks of Emory University, Atlanta, Georgia, it was found that LTD patients have deletions of certain exons of the extracytoplasmatic portions of the hGH receptor,[3] confirming that the pathogenesis in this syndrome resides in defects in the structural gene for the GH receptor. Almost simultaneously a French group reached the same conclusions.[4] Another recent finding, that the extracytoplasmatic portion of the hGH receptor is identical with the circulating GH binding proteins (confirmed by the absence of this protein in the serum of LTD patients),[5] has made it possible for us to identify the heterozygote carriers for this disease[6] and thus may be of considerable practical importance in genetic counselling.

It now appears that the only possible hope for therapy for this disease is the missing hormone IGF-I. The recent biosynthesis of IGF-I by recombinant DNA technology made it possible for us to initiate the first clinical therapeutic trials in patients with LTD.[7]

This syndrome, in addition to presenting a new disease entity, serves as a unique human model to learn about the physiology of hGH and IGF-I and their interaction. By monitoring the 24-hour hGH secretion in LTD patients,[8] we found that they secreted values similar to those observed in acromegalics, however, with opposite metabolic effects. This demonstrates that hGH exerts its main actions not directly, but via IGF-I. On the other hand, optimal IGF-I action may depend on hGH: in LTD patients in whom the GH-dependent binding protein (IGF-I BP3) is missing, the biological half-life of injected IGF-I is shorter than in healthy subjects.[9,10]

It took 20 years from the description of the disease to the elucidation of its pathogenesis. It is hoped that it will take much less time to find the correct way to use IGF-I to make possible the achievement of normal growth and height for these unfortunate children.

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