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Fifty seven years of follow-up of the Israeli cohort of Laron Syndrome patients—From discovery to treatment

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ABSTRACT

Clinical and laboratory investigations of dwarfed children newly Jewish immigrants from Yemen and Middle East and who resembled patients with isolated growth hormone deficiency were started by our group in 1958. In 1963 when we found that they have high serum levels of hGH, we knew that we had discovered a new disease of primary GH insensitivity. It was subsequently coined Laron Syndrome (LS, OMIM #262500). The etiopathogenesis was disclosed by 2 liver biopsies demonstrating a defect in the GH receptor. Subsequent investigations demonstrated deletions or mutations in the GHR gene. The defect lead to an inability of IGF-I generation, resulting in severe dwarfism, obesity, and other morphologic and biochemical pathologies due to IGF-I deficiency. With the biosynthesis of IGF-I in 1986, therapeutic trials started. Following closely our cohort of 69 patients with LS enabled us to study its features in untreated and IGF-I treated patients. This syndrome proved to be a unique model to investigate the effects of IGF-I dissociated from GH stimulation. In recent studies we found that homozygous patients for the GHR mutations are protected lifelong from developing malignancies, opening new directions of research.

1. Introduction

In 1958, at a time when no assay for human growth hormone (hGH) was available three children aged a few days, 1.5 and 3.5 years (2 males and 1 female) with marked growth retardation were referred to our clinic [1]. They belonged to a consanguineous Jewish family recently immigrated from Yemen. Older siblings were of normal height. Within one year we were able to collect a total of 22 children with the same features all belonging to consanguineous families coming from the Middle East or Arabian Peninsula [2].

Their characteristics were dwarfism, obesity, small genitalia in the boys and severe hypoglycemia. They had a typical head configuration, a small face, and a protruding forehead resulting in a saddle nose. Their voice was high pitched and they had sparse hair. Phenotypically they resembled what was known as GH deficiency, at the time that they were diagnosed with dwarfism and insulin induced hypoglycemia non-responsiveness due to insulin sensitivity [3].

When radioimmunoassays for hGH became available in 1963 [4], we were surprised to find that these children had markedly elevated serum hGH levels [1,2]. We recognized that we had discovered a new disease. We were confronted with 2 possible explanations:

a) An abnormal structure of the GH
b) Resistance to GH of normal structure.

Technological limitation delayed the final answer for 20 years. Immunological studies comparing the patients' serum hGH by radioimmuno and radio-receptor assays for hGH showed identical behavior with serum from healthy controls indicating a normal structure of the GH in the LS patients [5,6]. This was confirmed subsequently by hGH gene analysis [7]. Proof of insensitivity to GH was shown by the lack of response to exogenous hGH administration and the absence of rise of serum somatomedin (IGF-I) [8]. So the "IGF-I generation test" was born. The name Laron Dwarfism (later changed to Laron Syndrome (LS)) was coined by Elders et al. [9].

Definite evidence for GH resistance was found by liver biopsy in 2 LS patients, showing that I^{125}hGH did not bind to the liver membranes of these patients, in contrast to membranes from controls (taken during renal transplants) [10]. Cloning of the GH receptor in 1987 [11] enabled the identification of partial gene deletion in the GH receptor gene in 2 of our patients [12]. The discovery of the PCR technique enabled the identification of many mutations in the GHR also in our patients [12-14]. With time our cohort of patients increased in size and comprises at present 69 patients, belonging to different ethnic groups.

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Table 1
Laron Syndrome — the Israeli cohort.
Ethnic origin.

	Females	Males	Total
Jews	20	13	33
Oriental (Iran, Iraq, Lebanon, Syria, Morocco, Yemen, Afghanistan)			
Muslims	3	13	16
Druse	1		1
Christians	11	8	19
Total	35	34	69

The total number of LS patients worldwide is not known as many are probably undiagnosed. The number of known and/or published LS patients is around 350.

1.1. Subjects

The number of LS patients in the Israeli cohort and their ethnic origin are shown in Table 1. All families originate from the Middle East or Mediterranean area. Many belong to consanguineous families and in several families more than one child is affected.

Table 2 presents their age at referral. It is seen that 33 were referred below age 4, enabling treatment in those referred after the year 1987. Table 3 shows their present age including the age at death of 5 of our patients.

2. Methods

During the growth periods the patients were followed every 3–4 months, on which occasion they underwent body measurements, complete physical examinations and laboratory investigations. Our close follow-up of all the patients by the same team enabled us to study the clinical characteristics and the physio-pathology of hGH and IGF-I deficiency to late adult age in the untreated LS patients, and to study the pharmacology and effects of IGF-I in the treated children and adults. Our overall findings have been summarized in two major publications [15,16]. Following are the most striking findings in our cohort of LS patients.

2.1. Clinical characteristics of Laron Syndrome

As young children they have a special facial phenotype, a small face, a protruding forehead, sparse hair and a below normal head circumference [17].

Dwarfism is already evident by short birth length which if untreated deviates more and more from the lower centiles reaching sizes of −4 to −8 height SDS [18]. From the typical growth pattern we designed specific growth charts [19], which fit any congenital IGF-I deficiencies [20], except the acid-labile subunit (ALS) syndrome [21].

Puberty and full sexual development are delayed mainly in boys [22].

Table 2
Laron Syndrome — the Israeli cohort.
Age at referral.

Age	Females	Males	Total
4 days–6 m	2	5	7
1 y–3 y 11 m	15	11	26
4 y–9 y 11 m	12	12	24
10 y–16 y 9 m	4	4	8
34 y–51 y	2	2	4
Total	35	34	69

Part of the referrals were before IGF-I was available.

Table 3
Laron Syndrome — the Israeli cohort.
Current age.

Age — years	Females	Males	Total
<10	4	2	6
10–20	6	9	15
20–30	5	7	12
30–40	2	4	6
40–50	5	4	9
50–60	8	5	13
>60	5	3	8
Total	35	34	69

Final heights range from 116–142 cm (males) and 108–136 (females) with an increased upper/lower body ratio, denoting short limbs [18].

One of the major complications is marked obesity, lipidemia and fatty liver [23–25]. The obesity, reaching 60% of body composition in females and 40% in males, is not due to overeating or low energy expenditure [26] but to a metabolic dysfunction, one of its characteristics being high serum adiponectin [27].

LS patients also have pathologies in the carbohydrate metabolism. In infancy they suffer from hypoglycemia (sometimes severe); subsequently during progressing obesity they develop glucose intolerance and even Type 2 diabetes (Table 4). Ten patients developed cardiovascular disease (Table 5). Psychological tests revealed a below normal IQ in part of the patients with improvement of the verbal IQ with time [28]. MRI of the skull showed overt pathological findings in the CNS in some of the patients [29,30]. Noteworthy is the underdevelopment of the sinuses. LS patients have a tendency for auditory defects [31] as do also patients with other disorders causing congenital IGF-I deficiency.

2.2. Treatment

Twenty one children (11 girls, 10 boys) were or are still treated by recombinant IGF-I (Fujisawa (Astellas) or TERCICA–IPSEN); in doses ranging from 150–220 μg/kg once daily [32,33]. Their height, brain and organ growth respond rapidly to the IGF-I administration but to a slightly lesser degree than GH deficient children to hGH. Mean growth velocity in the 1st year of treatment was 8 cm/y. Linear growth catch-up and changes in the U/L ratio showed a change in Ht SDS from -6.1 ± 1.2SDS to -4.6 ± 1.2SDS ($p < 0.001$) without change in the U/L ratio. IGF-I increased the mean ($\pm$SD) head circumference from -3.3 ± 0.9 to $+0/87 \pm 1.8$. Injecting the IGF-I only with the main meal, resulted in less adverse effects than reported with twice daily injections, yielding the same results [34]. After a short decrease in adiposity and lipidemia, both increases again progressively resulting in marked obesity at the end of puberty [35].

Treatment of 5 adult LS patients by IGF-I in doses of 50–150 μg/kg once daily for one year resulted in beneficial metabolic effects [36].

Table 4
Laron Syndrome patients with diabetes mellitus (NIDDM).

Patient	Sex	Age at referral (y/m)	Age range of (abnormal) OGTT only[a]	Age at Dg DM[b]	Age at (April 2015)
1	M	36 y 10 m	39 y 4 m	39 y 4 m	Deceased at 75.8
2	M	1 y	7 y 10 m–28 y 9 m	37 y 3 m	51 y 9 m
3	M	5 m	12 y 2 m–26 y	39 y 8 m	Deceased at 49 y 6 m
4	M	6 m	14 y 2 m–16 y 7 m	37 y	38 y 3 m
5	M	3 y 1 m	16 y–39 y 4 m	60 y	60 y
6	F	3 y 7.5 m	14 y 8 m–36 y 4 m	58 y	59 y 4 m
7	M	7 y 9 m	15 y 6 m–26 y 4 m	58–59 y?	61 y

[a] Fasting glucose levels were normal until DM was diagnosed. There were no symptoms suggestive for DM.
[b] Glucose intolerance and/or hyperinsulinism.