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Case Report

CASE REPORT

Laron syndrome in three female siblings with the development of subclinical hypothyroidism and dyslipidemia in one case: first report of a Syrian family

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Abstract

Laron syndrome (LS) is a rare autosomal recessive disorder characterized by dwarfism and typical facial phenotype. This report is the first to present three cases of Laron syndrome affecting three female siblings from Syria. The index case presented at age of 8.5 years with severe short stature: low level of Insulin-like growth factor 1 (IGF-1), elevated levels of fasting and post-stimulation growth hormone (GH), consistent with the diagnosis of Laron syndrome. At the age of 9.5 years, she developed non-autoimmune subclinical hypothyroidism treated with Levothyroxine, then she developed dyslipidemia at the age of 11.3 years. Later, we identified two female siblings of the patient with Laron syndrome. Laron syndrome is a rare genetic disease, reporting of new cases of this rare syndrome must encourage pediatricians to develop high clinical suspicion if faced with patients with very short stature and typical facial features.

INTRODUCTION

Laron syndrome (LS) is a rare genetic disorder inherited in an autosomal recessive type, first described in 1966 by Laron and colleagues in a Jewish family [1]. Since then, about (300–500) cases have been reported worldwide, most patients are of Mediterranean or Middle Eastern origin or descendants of these populations [1].

LS is caused by genetic mutations of the GH receptor gene. The molecular defects vary from multi-exon deletions to non-sense, missense, and splice-site mutations. Up till now, more than 70 different gene defects have been identified, the majority of defects exist in the extracellular domain exons (3–7) [2].

It is characterized by dwarfism, characteristic faces, and abnormal body composition with obesity [2]. Here, we present the first known cases of LS in three siblings from a Syrian family.

CASE REPORT

The first patient, an 8.5-year-old female, was referred to the endocrinology clinic to be evaluated for short stature. She was born at term from healthy consanguineous parents (first cousin).

On examination, her height was 97 cm (−6.4SD), weight 17.2 kg (−3.4SD) and Tanner stage 1. Her blood pressure was 110/70 mmHg with a heart rate of 85 bpm. She had a prominent forehead, flattened nasal bridge, hypertelorism and short limbs concerning trunk length (Fig. 1). There were no goiter, hepatosplenomegaly or skin manifestations.

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Table 1: Hormonal evaluation for the cases

	TSH (UL/ml)	Cortisol (mcg/dl)	IGF1 (ng/ml)	Fasting GH (ng/ml)	After stimulation (min)	
					30	90
Case 1	3.8	16.9	10.2	31.5	14.5	15
Case 2	1.7	6.3	12.5	8.7	6.8	17.9
Case 3	2.3	8.5	10	5.8	11.8	13.7

Figure 1: Two affected siblings with LS at age 8.5 and 12 years. Note dwarfism, characteristic facial features.

Figure 2: Three affected siblings with clinical features of LS at age 11.3, 15 and 16 years.

Her biochemical workup tests (Table 1) showed normal levels of thyroid-stimulating hormone (TSH) and cortisol, a low level of insulin-like growth factor (IGF1) and a high level of fasting growth hormone (GH). GH stimulating test with insulin (0.1 U/Kg/IV) showed high levels of GH post-stimulation. Her bone age was 5 years, the combination of typical features, low level of IGF1 and elevated levels of fasting and post-stimulating GH to lead to the diagnosis of LS (index case). At the age of 9.5 years, she developed subclinical hypothyroidism (TSH: 8 UL/mL with normal free thyroxine FT4: 8.4 µg/dL and thyroid peroxidase antibodies (TPOAb): 21 IU/mL), treated with levothyroxine (3 mcg/kg/day).

The second patient, a 12-year-old female, was born at full term. She had a very short stature with the same characteristic features as her sibling (Fig. 1).

On examination, her height was 114 cm (−4.5 SD), weight 22 kg (−3 SD) and Tanner stage 2. Her blood pressure was 110/75 mmHg with a heart rate of 80 bpm. Laboratory findings (Table 1) showed a low level of IGF1, elevated levels of fasting and post-stimulation GH, which support the diagnosis of LS.

The third patient was consulted at the age of 16 years. On examination, her height was 125 cm (−6.6 SD), weight 52.5 kg (+0.07 SD) and Tanner stage 5. Her blood pressure was 120/80 mmHg with a heart rate of 70 bpm. She had characteristic features like her siblings (Fig. 2). Laboratory findings (Table 1) showed a low levels of IGF-1, high levels of fasting and post GH stimulation consistent with the diagnosis of LS.

The evaluation for the metabolic status showed a high level of triglyceride and a low level of HDL only in the first patient, Table 2.

DISCUSSION

Reports highlighting the occurrence of LS in both siblings in a family have not been well documented in the medical literature, the first description of LS by Laron (1966) in three siblings who belonged to a Jewish family of Yemenite origin [1]. This is the second report of LS in siblings of the same sex (female) from a Muslim Syrian family after the first description of LS by Chakraborty in a Muslim family of Indian origin [3]. What is distinguished in this case is the presence of 3 females from an Arab family who has the disease diagnosis at relatively old age for treatment.

The current case report is the first report described the association between subclinical hypothyroidism and dyslipidemia in LS case. Hypothyroidism occurred in the index case at the age of 9.5 years. Thyroid hormones are normal in LS, and there were no reports of hypothyroidism in LS except one case of hypothyroidism in a 13-year-old girl with LS, and she was treated with rhIGF-1 for eight years [4]. Dyslipidemia was detected in the index case at the age of 11.3 years. There were no reports of dyslipidemia in LS children patients. However, there was a case of a Mexican female with untreated LS who developed metabolic syndrome at the age of 53 years [5]. It may result from GH/IGF-1 deficiency that causes disorders in adipose tissue metabolism and obesity that progress with age [6].

There was no explanation in the literature review of this association in LS. LS does not associate with any hormonal

Table 2: Biochemical parameters for the cases

Case	Age (years)	Glucose (mg/dl)	Cholesterol (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	Triglyceride (mg/dl)
Case 1	11.3	86	140	33	97	172
Case 2	15	83	145	49	85	95
Case 3	16	76	148	47	81	81

deficiency that the question arises, is this a case of hazard? We cannot find any familial or hormonal cause of dyslipidemia.

Patients usually have normal birth weight and length but present with moderate to severe postnatal growth failure. The final height in untreated adult patients usually ranges between 116 and 142 cm in males and 108 and 136 cm in females. Obesity in LS children starts in utero and increases postnatally in a progressive manner [7].

LS should be suspected in patients with severe growth failure and a low level of IGF1. The diagnosis can be made based on the typical phenotype and biochemical testing. The genetic test should be performed to make an etiological diagnosis [7]. We always focus on the role of GH after requesting IGF1 because of the technical difficulties and side effects of insulin as an inducer with different results, but a high value on an empty stomach in time zero is the most important sign. We could not perform the genetic analysis in our setting and the diagnosis was made by typical phenotype and biochemical testing.

Early diagnosis is essential to initiate treatment with recombinant IGF-1 (rIGF-1) to improve the final height. The recommended dose is 80 to 120 mcg/kg twice daily, continued until height velocity has decreased to less than 2 cm per year [6]. rIGF-1 was indicated, but in the presence of the current war crisis, the drug was neither available nor affordable. Patients with LS are protected from developing cancer, even when treated with rIGF1 [6]. LS children should be monitored due to metabolic disorders for many reasons as obesity.

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CONFLICT OF INTEREST STATEMENT

None declared.

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ETHICAL APPROVAL

No ethical approval required.

INFORMED CONSENT

The patients' parents have given written consent for publication of this case report.

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