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Case Report

Laron syndrome. First report from Greece

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ABSTRACT

Laron-type dwarfism is an autosomal recessive disorder caused by deletions or mutations of the growth hormone receptor gene. It is characterized by high circulating levels of growth hormone (GH) and low levels of insulin-like growth factor I (IGF-I). Patients are refractory to both endogenous and exogenous GH, and present severe growth retardation and obesity. Therapy with recombinant human insulin-like growth factor-I (rhIGF-I) accelerates linear growth. We describe a 2-year old girl with Laron syndrome, who presented with postnatal growth failure and hypoglycaemic seizures. Her evaluation disclosed high GH values during a glucagon test (peak GH value 170 ng/ml) and very low IGF I value (0.1 ng/ml) with no rise following GH administration. The growth velocity improved considerably with the administration of IGF I. Molecular analysis showed a heterozygous mutation on exon 4 of the GH receptor gene, inherited from the mother, a rather puzzling finding considering the clinical findings in mother and infant. This case constitutes the first report of Laron syndrome from Greece.

Key words: growth failure, growth hormone insensitivity, Laron syndrome

INTRODUCTION

A genetic form of dwarfism, having clinical and biochemical features of growth hormone deficiency (GHD) but abnormally high concentrations of immunoreactive serum growth hormone, was first reported in 3 Yemenite Jewish siblings in 1966[1]. Within 2 years, 19 additional Israeli patients of Mid-Eastern Jewish ancestry were identified[2] and several patients have been reported worldwide since then[3,4]. The majority of patients are traced to Semitic or Mediterranean origin. Further studies showed that the GH molecule was normal[5] and that the GH receptor gene was defective[6,7]. This explained the unresponsiveness to endogenous and exogenous GH and the inability to generate IGF-I[8]. Initially named Laron-type dwarfism, this condition is currently known as Laron syndrome (LS), primary GH insensitivity (GHI), or primary GH resistance syndrome[9]. With the introduction of the PCR method, it was found that the molecular defects in patients with LS vary from exon deletions[7] to mutations in the extracellular[10], transmembrane[11,12] or intracellular domain[13] of the GH receptor as well as by post-receptor defects[14]. We here report the first patient with LS of Hellenic origin.

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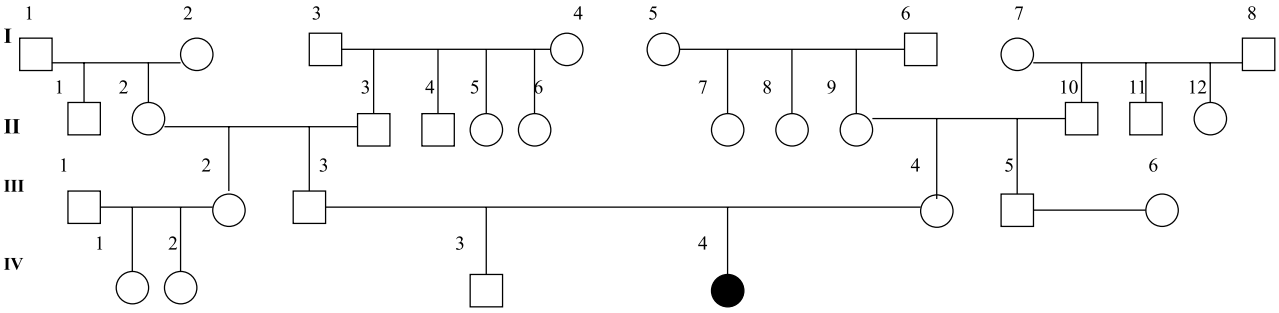
PATIENT REPORT

A 19-month old girl was admitted to the fourth Pediatric Dept of Aristotle University because of failure to thrive. According to the parents, both weight and length had remained unchanged since the age of 6 months. She was the product of a full-term, uneventful gestation and delivery. Her birth weight, birth length and head circumference were normal, 3340 g, 50 cm and 33.5 cm, respectively. She was breast fed for one month. She had neonatal jaundice, urinary tract infection at 2 ½ months and bronchiolitis at 4 months, as well as one episode of gastroenteritis at the age of 6 months. At the ages of 12 and 15 months, the infant experienced two episodes of seizures, attributed to hypoglycaemia. She has a 4-year old brother who is growing along the 50th percentile. Her parents are unrelated and of Hellenic origin. Her mother originates from Asia Minor and the father from Halkidiki, a region in Northern Greece (Figure 1). Maternal and paternal heights were 163 cm and 171.5 cm, respectively. Diabetes or other chronic illnesses were not reported in the family.

Physical examination revealed an extremely short infant with a body length of 66 cm, who weighed 7800g (well below the third percentile for both length and weight). By contrast, the head circumference was 50cm (97th percentile). An open fontanel, frontal bossing, blue sclerae, hypoplastic nasal bridge (Figure 2), small hands and feet (acromicria) and delayed dental development were noted. She could not walk and all other gross motor milestones were delayed. Furthermore, she had a high-pitched voice. Lungs, heart and abdomen (liver, spleen) examination revealed no pathologic findings. A wide spectrum of diseases related to growth failure and seizures were excluded, as demonstrated by the detailed laboratory findings listed in Table 1. Karyotype analysis showed a normal female, (46,XX). Serum GH values prior to and following a glucagon provocation test (1 mg IM) were high, namely 20, 120, 150, 170, 165 ng/ml at 0, 30, 60, 90 and 120 minutes, respectively. An IGF-I generation test following rhGH administration (0.1 U/kg/24hrs for four consecutive days) showed no change in the serum IGF-I values, which were 0.10 ng/ml on the first and fifth day of the test. Serum IGF-BP3 was also low for her age: 344.2 ng/ml (normal >1200 ng/ml). Bone age at the chronological age of 19 months corresponded to 6 months. Retinal vascularization was less than expected at fundoscopy[15].

An MRI scan of the brain showed mild scapho-



Generation		**Height**					
I	**4:** 165cm	**5 :** 145cm	**7:**158cm	**8:**168cm			
II	**1:** 158cm	**2:** 145cm	**3:**171cm	**7,8,9:** 153cm	**10:**168cm	**11:**168cm	**12:**165cm
III	**2:**163cm	**3:**171.5cm	**4:**163cm	**5:**160cm			
IV	**3:**108cm	**4:**66cm					

	Origin
I	5, 6, 7, 8: Greek, born in Asia Minor
II	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12: Halkidiki, Northern Greece

Figure 1. Pedigree of the patient's family.

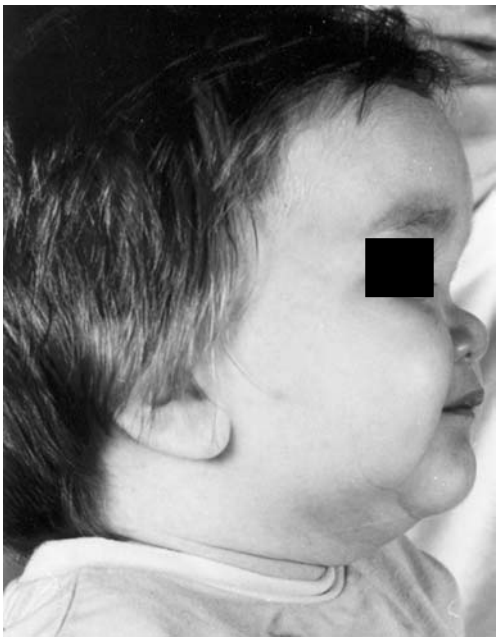


Figure 2. Typical Laron syndrome appearance of the patient, at the age of 19 months.

cephaly, hypoplastic corpus callosum and lateral ventricular focal leucoencephalopathy, particularly in the frontal horns[16]. The hypothalamus and the pituitary gland were normal.

Molecular investigation of the GH receptor gene

DNA was isolated from peripheral blood leukocytes, both from the patient and her parents. All exons were amplified by PCR with specific intronic primers. Analysis of single strand conformation polymorphism (SSCP) was performed to detect aberrant bands. Direct sequencing of all exons disclosed that the patient carried a heterozygous mutation in exon 4 (R43X) and a heterozygous polymorphism in exon 6 (G168). The mutant allele was inherited from her heterozygous mother, who was homozygous for the polymorphism. The father was found to be heterozygous for the same polymorphism[17].

Response to treatment

The patient was started on recombinant human insulin like growth factor I (rhIGF-I) at the dose of 100 ng/kg/day once a day subcutaneously. Frequent blood glucose measurements were performed on a portable glucometer, and a reduction in hypoglycemic episodes was registered. She started walking 2 months following the institution of therapy and her speech and dentition improved. In nine months she grew 8.4 cm and gained 12.5 kg in weight.

Table 1. Pertinent Laboratory findings at age 1 7/12 years

Hb	11.7 g/dl	Fe	61 γ
Hct	35.8 %	Ferritin	248 μg/L
WBC	8300	Glucose	70 mg/dl
Granulocytes	37.6 %	BUN	40 mg/dl
Lymphocytes	56.1 %	Creatinine	0.80 mg/dl
Monocytes	6.3 %	ALP	277 IU/L
RBC	4180000	Cholesterol	218 mg/dl
PLT	337000	Triglycerides	214 mg/dl
IgA	0.396 g/L	AST (GOT)	78.2 UI/L
IgM	0.533 g/L	ALT (GPT)	45.6 UI/L
IgE	17.5 UI/L	γGT	2.33 UI/L
IgG	3.876 g/L	Albumin	4.18 g/dl
Rast:			
Alpha-lactalbumin Beta-lactoglobulin Gluten	Neg.	Total proteins	6.25 g/dl
AGA	Neg.	PT	10.6/10.1
EMA	Neg.	PTT	30/29.9
ARA	Neg.	Fibrinogen	280/264
CIC	Neg.	Calcium	10.5 mg/dl
Serum Aminoacids	Normal	Phosphorus	4.42 mg/dl
Urine Aminoacids	Neg.	Potassium	4.9 mEq/L
Lactate	Normal	Sodium	140 mEq/L
Ammonia	Normal	pH	7.38
Karyotype	46,XX	HCO_3	21 mEq/L

AGA: (Antigliadin abs), EMA: (Endomysium abs), ARA: (Antireticulin abs), CIC: (circulating immune complexes)

Table 2. Hormonal Evaluation

Glucagon test					
Time in min	0	30	60	90	120
GH μg /L	20	120	150	170	165

IGF-I generation test	**IGF-I μg/L**
Base line	0.1
5th day of hGH Rx	0.1
Serum Total T4 μg/dl 8.6	(NV 5-12.5)
Serum Total T3 ng/dl 124	(NV 80-200)
TSH μu/ml 2.5	(NV <5)
IGF-BP 3 μg/L 344	(NV >1200)

DISCUSSION

The diagnosis of Laron syndrome (LS) in this patient was based on the characteristic clinical features, the high serum values of growth hormone and the low IGF-I serum levels before and after GH administration (IGF-I generation test)[1-3,8]. The patient was found to have a heterozygous mutation on Exon 4 (R43X) and a heterozygous polymorphism on exon 6 (Gly168Gly). The mutation R43X was inherited from her mother, who is also heterozygous for this mutation. The mother is, in addition, homozygous for the polymorphism G168. The father was found to be heterozygous for the same polymorphism[17]. There is no explanation for the observation that the patient presents the complete typical phenotype of LS, whereas the mother, having the same defect, has normal height and normal features. From previous studies we know that heterozygous family members, carriers of molecular defects of the GH-R gene, are of normal height, with the exception of a few mothers[18,19]. The father, who is heterozygous for the polymorphism, is not expected to have a pathologic phenotype.

The origin of most patients with LS reported previously is in the Mediterranean region, the Middle East and the Indian subcontinent[3,20,21]. Consanguinity was common in most of the above populations. This is the first patient of LS of Hellenic origin. The patient, however, traces her origin to Asia Minor (great-grandparents). There is no consanguinity between her parents and none reported to have accrued in previous generations. The mutation of GHR on Exon 4 detected in this patient is one of 41 reported to date and has been found in patients originating from the Mediterranean region[19].

The brain abnormalities obtained by MRI were attributed to the lack of IGF-I, which is known to play a significant role in the development of the brain and bony structures of the cranium[16].

Treatment with rhIGF-I improved height velocity, body weight and serum IGF-I levels in this patient. The rhIGF-1 therapy is being well tolerated except for some hypoglycemic episodes due to irregular feeding habits. The parents were instructed to recognize the signs and symptoms of hypoglycemia, and to monitor blood glucose at home. Her psychomotor development, extremely delayed at diagnosis, improved significantly following the introduction of therapy. Her final intellectual development cannot be predicted. Large variability, ranging from normal intelligence to severe mental retardation has been reported[22]. Despite the difficulties in the current availability of the drug, it is hoped that it will be possible to treat the patient continuously to prevent the late consequences of lack of therapy[23].

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