A RARE PRESENTATION OF CLINICAL SHORT STATURE DUE TO INSENSITIVITY OF GROWTH HORMONE (LORAN SYNDROME)

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ABSTRACT: Laron type dwarfism is an autosomal recessive disorder caused by deletions or mutations of growth hormone receptor gene. It is clinically characterized by postnatal growth failure and very low serum levels of insulin like growth factor 1 (IGF-I) despite increased secretion of growth hormone (GH). Fifty one different mutations in the GH receptor (GHR) gene have been discovered, whereas only three deletions causing the disorder have been reported so far. Patients are refractory to both endogenous and exogenous growth hormone and present with severe growth retardation and obesity. Therapy with recombinant human insulin like growth factor I (rhIGF-I) accelerates linear growth. We report a case of a 12 year old boy who presented with complaints of absent growth since six years. His evaluation revealed disclosed high levels of growth hormone. Very few cases of Laron syndrome have been reported till date from all around the world.

KEYWORDS: Loran syndrome, Short stature, Insensitivity to growth hormone.

INTRODUCTION: Growth is an inherent property of life and is mainly the result of the action of growth hormone (GH). GH is secreted from the anterior pituitary gland in the form of pulses throughout the day and night. These bursts of secretion increase the total daily GH secretion during the periods of maximal growth in adolescence. A substantial part (20-40%) of total 24h secretion of GH occurs during the first 90 minutes of nocturnal sleep¹. A genetic form of dwarfism having clinical and biochemical features of growth hormone deficiency (GHD) but abnormally high concentrations of immune reactive serum growth hormone, was first reported in 3 Yemenite siblings in 1966². It has been reported from the Mediterranean, mid-eastern region and in Indian subcontinent³.

CASE REPORT: A 12 year old male child was admitted to our hospital because of failure to thrive. According to his parents, both weight and length had remained unchanged since the age of 6 years. There is no history suggestive of any radiation exposure during the antenatal period. He was a product of full term, uneventful gestation and delivery. His birth weight, length and head circumference were normal. He was breast feed for a period of six months. He has elder brother and sister of 15 and 13 years of age respectively. Both of them show a growth along the 50th percentile. His parents are unrelated and are of Indian origin. Diabetes or other chronic illnesses were not reported in the family. He is a vegetarian with normal appetite. His bowel, bladder and sleeping habits are normal. He had complete routine immunization schedule in time. There is no history suggestive of any drug intake, known drug allergies, surgeries or any head injury.

Physical examination revealed an extremely short stature (104 cm) boy for his age. The normal expected height for his age is 154cm. He weighs about 13.5kg with normal intellectual function. The boy’s parents are about 5’4” and 5’1” tall. Frontal bossing, hypoplastic nasal bridge were noted. He had a high pitched voice. Lungs, heart and abdomen (liver, spleen) examination...
revealed no pathological findings. A wide spectrum of diseases related to growth failure and seizures were excluded. Serum Growth hormone levels of about 105.29 ngm/ml (Normal range – 0-7ngm/ml) were noted. Growth hormone dynamic test (exercise) revealed fasting levels of 105.29, at 15 min – 139.64 and at 30 min – 140.25. Growth hormone dynamic test (clonidine) fasting – 102.61, at 30 min – 132.69, at 60 min – 142.05, at 90 min – 149.27 and at 120 min – 129.81.

Supplementation of insulin like growth factor was the treatment option planned for the patient. Studies reveal the outcome of such treatment option is minimal.

**DISCUSSION:** Children with Laron syndrome clinically resemble isolated growth hormone deficiency Type 1A. Growth hormone receptor is encoded by a single gene located on the short arm of chromosome 5(5p 13-p12). Laron syndrome is due to a variety of homozygous point mutations in the growth hormone receptor gene4. The growth hormone receptor has an extracellular growth hormone binding domain, a transmembrane domain and an intracellular signaling domain. Mutations in the extracellular domain interfere with binding of growth hormone resulting in Laron syndrome5.

Clinically, patients with GHIS present in a manner virtually indistinguishable from those with severe GH deficiency. Birth weight and length are likely to be within the reference ranges, but postnatal linear growth is strikingly abnormal with a rapid decline in growth velocity soon after birth. In this condition IGF-1 and IGF-BP3 are markedly reduced despite normal or elevated serum levels of growth hormone and there is unresponsiveness to endogenous and exogenous GH. The natural history, without proper treatment, results in an extremely short adult stature ranging between 4 and 10 SDs below the median for normal height6.

To date, nearly 300 patients have been identified worldwide, mostly from the Mediterranean, mid-eastern region and from Ecuador. Further, GHIS in these subjects is caused by a great variety of homozygous point mutations and about 30 different mutations (missense, nonsense or abnormal splicing) have been subsequently described (14–20). In contrast to this high number of patients suffering from GHIS caused by a wide variety of GHR gene mutations, there are only a few reports on patients with GHR gene deletions.

Relative obesity is present at birth and increases with age, with a relative excess of adipose tissue in the context of thin bones and diminished muscular mass. The upper-to-lower segment ratio is increased with regard to sex and chronologic age, denoting short limbs for trunk size. Congenital malformations, craniofacial abnormalities, and other physical features may be noted at birth. Facial bone growth is particularly retarded, and fontanel closure is delayed, leading to a disproportionate cephalofacial relationship because of the decreased vertical dimension of the face, with frontal bossing, a saddle nose, shallow orbits, and the setting sun sign of the eyes. Blue sclera may be noted, particularly in patients of Mediterranean or Middle Eastern origin. Hair growth is quite sparse in infancy and through early childhood. It is silky and forms temporal and frontal receditions. Tooth development is delayed, and the teeth may often be defective. The larynx is narrow, resulting in very high-pitched voice. The genitalia and gonads are small from birth.

Pubertal development is delayed, and the pubertal growth spurt is absent, but adult sexual maturation is eventually achieved. Walking and other gross motor developmental milestones are delayed because of the underdeveloped musculature. The hands and feet are small (acromicria). Hip dysplasia, notably avascular necrosis of the femoral head, has been reported in up to 25% of
patients. The skin is thin and has a fine texture with wrinkles as in premature aging. Psychological evaluations suggest a great variability in intellectual development, ranging from normal intelligence to severe mental retardation.

The cardinal biochemical features of GHIS are low levels of all GH-dependent proteins, including very low or even undetectable serum IGF-1 levels, IGF binding protein 3, and acid labile subunit in association with normal or increased GH levels. The regulation of GH secretion and feedback mechanisms is normal. The most important functional test for the diagnosis is the IGF-1 generation test because serum IGF-1 levels are low and do not increase with the administration of exogenous rGH for days or weeks, demonstrating the state of GH resistance in these patients. Metabolic abnormalities include fasting hypoglycemia and hypercholesterolemia.

The underlying metabolic defect lies in the lack of responsiveness of the target organs to endogenous GH. In 1984, it was proven by liver biopsy that GH does not bind to its receptors and therefore is unable to generate IGF-1 [8]. This explains why patients with primary GHIS typically have low to undetectable serum levels of IGF-1, even though serum GH levels are normal or high. In addition, exogenous rGH fails to accelerate growth or to stimulate serum IGF-1 levels or IGF binding protein 3. The only effective treatment is the daily administration of rIGF-1 starting from early childhood and probably throughout life. The rIGF-1 treatment accelerates linear growth velocity, and appropriate dose titrating results in tripling of the baseline growth rate during the first year of treatment. Even if these patients may never experience sufficient catch-up growth to bring their height within the normal range, they do achieve an adult height significantly greater than expected in the absence of therapy. The main reasons could be, on the one hand, the inability to replicate physiological IGF-1 distribution and action and, on the other hand, the inability to restore GH defects, because animal studies indicate that GH has growth-promoting effects apart from the IGFs. Evidence exists that rIGF-1 therapy also reduces body fat, stimulates kidney function, and maintains left ventricle dimension and function within the normal range of age-matched control subjects.

**CONCLUSION:** Primary GH resistance or GHIS, also known as Laron syndrome, is a hereditary disease caused by deletions or mutations in the GHR gene or the post-receptor mechanisms. These polymorphic defects lead to the inability to generate IGF-1, which is the anabolic effector of GH. The early and continuous IGF-1 deficiency causes dwarfism as well as skeletal and muscular underdevelopment. Daily administration of rIGF-1 is effective in promoting catch-up growth and is safe. However, no data are available concerning treatment throughout life. An early correct diagnosis of this syndrome is crucial for appropriate preventive care and therapy.

**REFERENCE:**

CASE REPORT


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