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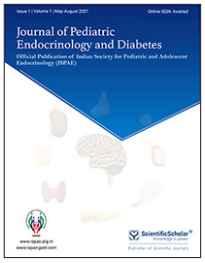

Editorial Commentary

Laron syndrome – A perspective on diagnosis and management in India

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The biological ineffectiveness of endogenous or exogenous growth hormone (GH) (i.e., a state of resistance) has been reported in several clinical conditions. Laron syndrome (LS), or primary GH insensitivity (GHI), is the most common genetically mediated cause. Inherited as an autosomal recessive disorder of the GH receptor (GHR) gene, it is clinically indistinguishable from isolated GH deficiency (GHD).

Ever since its first description by Laron *et al.* in 1966 in three siblings from a Jewish family in Yemen,[1] population estimates from the USA suggest fewer than 5000 people to be affected by this disorder and the published world literature describes <500 proven cases.[2,3] The spectrum of GHI has expanded beyond GHR deficiency to include post-receptor abnormalities like insulin-like growth factor-1 (IGF-1) gene mutation (1996); IGF-1 receptor mutation (2003); signal transducer and activator of transcription 5b mutation (2003); and mutation of the GH-dependent acid labile subunit (2004).

Indian literature on LS is largely limited to clinical profiles and diagnosis.[4-8] The series of six cases presented by Rajalakshmi *et al.* in this issue adds to the data on diagnosis from South India.[9] In a study by Desai *et al.* in 1991, of the 430 children referred for short stature, 100 (23%) had GHD/GHI of which 89 were confirmed to have GHD on two stimulation tests. Primary GHI was seen in 11 cases.[10] As with all rare endocrine diseases in India, the case detection may be higher than that is reported in Indian literature.

LS, caused by homozygous or compound heterozygous mutation in *GHR* gene located on chromosome 5 (5p13.1-p12), is a fully penetrant gene with more than 70 mutations identified so far, most of which affect the extracellular domain of the GH receptor.[11] For these reasons, often patients with LS show low or undetectable GH binding protein (GHBP) levels, as GHBP is created by proteolytic cleavage of the extracellular GH-binding domain of the GHR. However, mutation elsewhere in the *GHR* gene may result in normal or elevated GHBP levels. Thus, normal GHBP levels are insufficient to exclude the diagnosis of LS. Post-GH-receptor defect due to mutations in the *STAT5B* gene has LS phenotype with associated immunodeficiency. Some *GHR* gene mutations may also present with partial GHI and were previously labeled as idiopathic short stature.

The cardinal feature of LS is severe postnatal growth failure, which is also seen in the case series described by Rajalakshmi *et al.*, with a marked reduction in final height. Children present with a height standard deviation score (SDS) between –3 and –12 and untreated individuals reach a final adult height of 119 cm in females and 124 in males.[12] The clinical phenotype is not

very different from the cases of isolated GHD. Typically, it includes a history of decreased fetal movements in the antenatal period. Although the birth weight and length are usually normal, some may have decreased birth length and features of intrauterine growth restriction. Respiratory distress, hypoglycemia, and indirect hyperbilirubinemia may be seen in the newborn period. Rarely strabismus, cataract, aortic stenosis, micropenis, undescended testis, and developmentally dysplastic hip may be seen. The child may also have sparse hair, frontal bossing, hypoplastic nose, shallow orbit, blue sclera, high-pitched voice, preserved truncal pad of fat, and limited joint mobility. Maturational delay in the form of delayed dentition, delayed bone age, and pubertal delay are often present. Despite a delay in the onset of puberty by 3–7 years, sexual functions, and fertility are preserved. Intellectual disability may be seen but severe disability is rare. Osteopenia, obesity, dyslipidemia, dysglycemia, and hip degeneration are seen in adolescents and adults. The presence of immunodeficiency points to *STAT5B* mutation.

Hormonal investigations show high circulating basal GH levels with low IGF-1 and/or IGF-1 binding protein-3. Exogenous GH does not cause IGF-1 to increase or restore normal growth, which forms the basis of IGF-1 generation test. This consists of a brief trial of GH administration for approximately 1 week. In patients with GHI, the low baseline IGF-1 will not rise after exogenous administration of GH for 4–9 days. The poor IGF-1 response was seen in all cases in this series by Rajalakshmi *et al*. However, the protocols for performing this test have not been standardized and the levels of IGF-1 achieved are quite variable. A scoring system to identify patients with GHI has been suggested. This scoring system includes basal GH, IGF-1, IGF-1 generation, height SDS, and GHBP. The maximum possible score is 7 points. Patients with a score of 5 or more are considered to have significant GHI.[13]

The only treatment available for LS since 1986 is recombinant IGF-1.[14] Laron *et al*. describe in their study where 23 children received treatment for many years and four adults for 1 year. A single daily dose of 150–220 μg/kg of recombinant IGF-1 was given with the largest meal, resulting in a fast catch-up growth in the head circumference from a mean of –3.3 ± 0.9 to +0.87 ± 1.8 SD and a slower catch-up in the linear growth as compared to that observed in GH-treated GH deficient children. The growth velocity of IGF-1 treated LS children in the first year of treatment was 8 cm/year as compared to 10–12 cm/year in GH deficient children. Only one of these children reached close to normal height.[15]

Treatment of LS with twice daily subcutaneous injection of recombinant human IGF-1 (rhIGF-1, Mecasermin, Increlex®; Ipsen Pharma, Boulogne-Billancourt, France) costs more than 15 lakh Indian rupees/year of treatment for a child weighing 20 kg. The drug is also not readily available in our country. However, the response to recombinant IGF-1 therapy is variable. In one study, the height velocity increased from 2.8 cm/year at baseline to a mean of 8 cm/year during the first year of treatment and the height velocity remained above baseline for up to 8 years following initiation of IGF-1 therapy.[16]

There are few reports of the use of rhIGF-1 in Indian literature. Boro *et al*. described their experience in the use of rhIGF-1 in two cases after obtaining special permission from the Drug Controller General of India (DCGI) to import rhIGF-1 (Inj. Increlex; Mecasermin [rDNA origin], Ipsen Pharma, France).[5]

Case 1 was started on rhIGF-1 at a dose of 40 μg/kg twice a day for 1 week followed by 80 μg/kg twice a day. After the first year of treatment, her height increased to 106.5 cm (growth velocity of 6.5 cm/year). She gained another 5.5 cm during the second year of treatment but her response during the third year was unsatisfactory (growth velocity of 3.5 cm/year) which was attributed by the authors to the fact that her dose could not be adjusted due to resource constraints. She developed lipohypertrophy over her injection sites, but there was no episode of hypoglycemia or any other adverse effects.

Case 2 was started on rhIGF-1 at a dose of 80 μg/kg body weight/day. After 6 months of treatment, her height was 101.5 cm that corresponded to a height velocity of 4 cm/year and after 2.5 years of treatment, her height was 110.3 cm which corresponded to a height velocity of 3.5 cm/year and −7.9 SDS. The authors mention that due to financial constraints and procurement difficulties, her treatment was not very regular and she missed doses in between. Similar to Case 1, this child also developed lipohypertrophy over injection sites, but without any episode of hypoglycemia or any other adverse effect.

In view of the costs of diagnosis and treatment besides variable outcome to therapy, one might argue that in a country like India, it might be challenging to diagnose, treat, and study the outcome in the children with LS. More such case series and studies on LS from Indian literature should emerge to improve our understanding of the disease.

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