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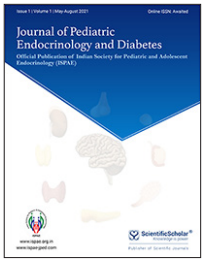

Editorial Commentary

Laron syndrome, the prototypic primary growth hormone insensitivity syndrome

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Received : 16 March 2023
Accepted : 16 March 2023
Published : 11 April 2023

DOI
10.25259/JPED_11_2023

Quick Response Code:

Growth hormone (GH) insensitivity syndrome (GHIS) can be primary or secondary. Primary GHIS is due to genetic causes such as mutations in the GH receptor (*GHR*) gene (termed Laron syndrome, LS) or post-receptor defects including mutations in signal transducers and activators of transcription 5B, insulin-like growth factor 1, (IGF-1), IGF-1 receptor, insulin-like growth factor binding protein, acid labile subunit (ALS), or human pregnancy-associated plasma protease A2 gene. Secondary GHI is due to GH-inhibiting antibodies, malnutrition, poorly controlled diabetes mellitus, chronic inflammatory states, renal, or hepatic diseases.

Among the primary GHIS, LS (OMIM: 262500) is the most common and well-studied entity. The disease was originally identified in the late 1950s in Jewish patients of Yemenite origin. LS or "classical" GHI is due to *GHR* gene mutations characterized clinically by marked postnatal growth failure secondary to severe GH resistance.[1] LS is associated with severe deficiencies of serum IGF-1, insulin-like growth factor binding protein-3 (IGFBP-3), and ALS. *GHR* mutations can be classified according to the location of the mutation in the extracellular, transmembrane, or intracellular domains of the *GHR* gene.[1] There is significant phenotypic and biochemical variability in LS. Autosomal recessive is the most common mode of inheritance in LS.[2] The most common genetic defect in LS is defects in the extracellular domain of the *GHR* and these generally present with severe phenotypes. The milder forms of LS are caused either by heterozygous *GHR* mutations in the intracellular and transmembrane domains (dominant-negative effect) or by the homozygous intronic *GHR* pseudoexon (6Ψ) mutation.[3] In the literature, more than 90 homozygous, compound heterozygous, missense, nonsense, and splice site mutations of the *GHR* gene have been reported.

The diagnosis of LS can be suspected because of clinical (consanguinity, postnatal growth failure, frontal bossing, midfacial hypoplasia, and normal intelligence) and biochemical features. Due to a state of GH resistance, children with LS have high circulating levels of basal and stimulated GH. Serum IGF-1 concentrations are very low, often undetectable, and do not rise on the administration of exogenous human GH (IGF-1 generation test). The circulating level of GH-binding protein (GHBP), which in humans is formed by shedding of the extracellular portion of GHR by a metalloprotease (tumor necrosis factor-α-converting enzyme [TACE or ADAM-17]), is low in LS. However, a normal level of GHBP does not necessarily exclude a diagnosis of LS due to mutations in the transmembrane or intracellular domains or missense mutations that do not result in loss of GHR protein but still impact GHR function. The definite diagnosis of LS rests on the demonstration of mutation(s) in the *GHR* gene.

Recombinant human IGF-1 (rhIGF-1, Mecasermin®) was approved by the US Food and Drug Administration in 2005 for the treatment of LS.[4] rhIGF-1 is effective in promoting growth in

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children with LS. However, the growth response is less than that observed in severely GH-deficient children given GH replacement and these children with LS are unlikely to reach adult heights in the normal range.[5] This divergence in the growth response is believed to be due to the lack of restoration of direct (non-IGF-1 mediated) effects of GH on growth, the failure to replicate paracrine/autocrine effects of IGF-1 on growth, and because rhIGF-1 administration does not correct low concentrations of IGFBP-3 and ALS in LS. Mecasermin® is administered as a twice-daily subcutaneous injection with an initial dose of 0.04–0.08 mg/kg/dose. If tolerated the dose can be increased every 7 days or so in 0.04 mg/kg/dose increments to a maximum dose of 0.12 mg/kg/dose twice daily. The drug must be administered within 15–20 min of a meal or snack to decrease the risk of hypoglycemia. In addition to hypersensitivity reactions, the main side effect is hypoglycemia. This side effect is more pronounced in small children with inconsistent oral intake. Lymphoid hypertrophy has been reported and may lead to complications such as snoring, sleep apnea, and chronic middle ear effusions. Lipohypertrophy at sites of injections and raised intracranial hypertension are other reported side effects. Recently, a proof-of-concept study in a mouse model of LS, using a hepatocyte-specific adeno-associated adenovirus virus expressing the mouse *GHR* gene, was shown to yield encouraging results raising the possibility that eventually, this type of gene therapy approach may be useful for the treatment of LS in humans.[6]

The manuscript by Rajalakshmi *et al*. in the current issue of the Journal presents detailed clinical and biochemical features of five children with GHIS from South India.[7] In two children, the diagnosis of LS was confirmed by genetic testing that revealed a homozygous variant in the *GHR* gene. Since GHIS presents as overlapping features with a wide spectrum of disorders including LS, in the absence of genetic analysis, the diagnosis of LS in the other three children remains presumptive. The availability of rhIGF-1 remains a major barrier to the management of these children in India. The establishment of a national registry of patients with primary GHI would be a significant step in elucidating the possible unique clinical, biochemical, and genetic characteristics of these patients from India.

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How to cite this article: Menon RK. Laron syndrome, the prototypic primary growth hormone insensitivity syndrome. J Pediatr Endocrinol Diabetes 2022;2:102-3.