

## Case Reports

# Laron syndrome: A case report

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## Introduction

Laron syndrome is due to growth hormone insensitivity and is clinically characterized by postnatal growth failure and very low serum levels of insulin like growth factor 1 (IGF-1) despite increased secretion of growth hormone (GH). This mainly autosomal recessive syndrome is clinically indistinguishable from isolated GH deficiency (IGHD). It was first reported by Laron and colleagues in 1966 in 3 Israeli Jewish siblings with hypoglycaemia and clinical phenotype of GHD. It has been reported from the Mediterranean, mid-eastern region and Indian subcontinent<sup>1,2</sup> and has been described in a Sri Lankan child who lived in Switzerland<sup>3</sup>. We report a three year old girl with Laron syndrome diagnosed in Sri Lanka.

## Case report

A three year and four month old girl, the only child of first cousin parents with average height, was referred for evaluation of short stature. She was born following an elective caesarean section and weighed 3.35kg at birth. Her length at birth had not been recorded. She was exclusively breastfed for 6 months and was growing along the birth centile. Thereafter, weight faltering was noted which was attributed to inadequate weaning. Her mother had also noted that her linear growth was inadequate from approximately nine months of age. Apart from a mild delay in her gross motor milestones, her development was normal and the first tooth had erupted at seven months of age.

Examination revealed a cheerful child with midfacial hypoplasia and subtle dysmorphism with frontal prominence, saddle nose, flat nasal bridge and a high pitched voice. She weighed 6.8kg and her length was 72cm, both of which were well below the third centile. Her occipito-frontal circumference (OFC) was 43cm which was just

below the third centile. Her length was also well below the mid parental height range. Her upper segment: lower segment ratio was 1.03:1 and body mass index was 13.6kg/m<sup>2</sup>. There was no Turner phenotype and her physical examination was unremarkable.

Her basic haematological, renal and liver function tests were normal as were her thyroid function tests and 0800h serum cortisol level and serum calcium level. Skeletal survey excluded a skeletal dysplasia. Her bone age was 24 months at a chronological age of 3 years and 2 months. Pituitary gland was normal on neuro-imaging. Buccal smear was positive for Barr bodies. She demonstrated fasting hypoglycaemia and severe symptomatic hypoglycaemia at 120min and 150min during the glucagon stimulation test. All growth hormone levels were >40ng/ml and the basal cortisol was 646nmol/l. We did an IGF-1 level which was very low at <25ng/ml (49-289). Thus a diagnosis of growth hormone resistance was made but insulin-like growth factor binding protein-3 (IGF-BP3) or genetic studies could not be done.

## 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 gene<sup>4</sup>. The growth hormone receptor has an extracellular growth hormone binding domain, a transmembrane domain and an intracellular signalling domain. Mutations in the extracellular domain interfere with binding of growth hormone resulting in Laron syndrome<sup>5</sup>. In this condition IGF-1 and IGF-BP3 are markedly reduced despite normal or elevated serum levels of growth hormone<sup>1</sup> and there is unresponsiveness to endogenous and exogenous GH.

Clinical presentation is with extreme short stature with length more than 4SD below the mean by 1 year of age<sup>5</sup>. Pregnancy is uncomplicated and birth weight and length are usually within the reference range. After infancy the length/height deficit ranges between 4 and 10 height SDS below the median for

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normal length/height<sup>6</sup>. Skeletal maturation is retarded starting in utero and continues throughout life.

Protruding forehead, saddle nose, sunset appearance of eyes and a high pitched voice, small hands and feet (acromicria) and short limbs with upper segment: lower segment ratio more than 1, which are typical features of Laron syndrome<sup>6</sup> were seen in our patient. Motor development in infancy is delayed as was seen in our patient. In Laron syndrome puberty is delayed without the typical growth spurt but both sexes reach full sexual development with normal fertility<sup>7</sup>.

Treatment with recombinant IGF-I improves growth rate (8cm in the first year and 4–5 cm in the following years) and normalizes the biochemical abnormalities<sup>8</sup>. The best response is seen in very young patients and treatment should therefore be started as early as possible<sup>3,9</sup>. Intermittent therapy is shown to be equally cost effective as daily treatment<sup>3</sup>. There is an inverse relationship between age at start of rhIGF-I treatment and total height gain in patients treated for more than 4 years<sup>9</sup>.

IGF-1 is not licensed to be used in Sri Lanka, but it is possible to give it on a case by case basis. Our patient was diagnosed at 3 years and 4 months of age and would have shown a good response to treatment. However, the parents could not afford the extremely high cost of therapy. Without treatment her adult height would be approximately 108-136cm<sup>8</sup>. She will need close monitoring for hypoglycaemia, obstructive sleep apnoea, obesity, hypercholesterolemia and diabetes mellitus<sup>1</sup> and long term psychological support.

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