

## An update on Laron syndrome

Laron syndrome<sup>1,2</sup> is a unique model of a peptide hormone receptor defect that has enabled the study of the physiology of insulin-like growth factor-I (IGF-I) deprivation and recently, with the initiation of its use in clinical treatment, the physiology of IGF-I activity.<sup>3</sup> The recent advances in the study and treatment of this disease will be reviewed.

### Definition and epidemiology

Laron syndrome is a hereditary disease where there is a primary resistance to growth hormone because of a polymorphic molecular defect in the growth hormone receptor. It is clinically and in many biochemical aspects undistinguishable from isolated growth hormone deficiency (IGHD), and is characterised by high circulating growth hormone concentrations and low serum IGF-I values, which do not rise upon exogenous growth hormone administration. This disease, also called Laron type dwarfism, was first described in Israel in 1966<sup>1,2</sup> in a group of oriental Jewish children, and has since been described in an increasing number of subjects of Mediterranean or Middle Eastern origin and descendants of these populations.<sup>4</sup> The largest cohorts described so far are from Israel, 41 oriental Jewish and Arab patients, and 56 patients in Ecuador of Spanish and possibly Jewish descent.<sup>5</sup> Isolated patients have also been reported in European countries, among black Americans, and in Japan, etc. It is assumed that the pygmies have a molecular defect of the growth hormone receptor similar to that found in Laron syndrome.<sup>6</sup> Analysis of the Israeli pedigrees led to the conclusion that Laron syndrome is caused by an autosomal fully penetrant recessive gene.<sup>7</sup>

The main clinical features identical to untreated IGHD are dwarfism, obesity, prominent forehead, acromicria including a small face, saddle nose, small hands and feet, and small gonads and genitalia. Puberty is delayed mainly in males, but full sexual development and reproductive capacity are attained.

### Laron syndrome – a primary growth hormone resistance disease

One of the characteristic laboratory findings is the high circulating plasma concentrations of growth hormone.<sup>1,2,8</sup> Concomitantly there are low or undetectable serum concentrations of IGF-I.<sup>9</sup> Proof for a growth hormone receptor defect was obtained in 1984 when it was shown that <sup>125</sup>I-labelled growth hormone did not bind to microsomal pellets of liver tissue obtained by biopsy from two patients with Laron syndrome.<sup>10</sup>

### The molecular defect of the growth hormone receptor

The cloning of the growth hormone receptor enabled the investigation of the receptors in patients with Laron syndrome. Several types of receptor defects have been described so far. Godowski *et al* found in two of seven Israeli patients of Iranian origin a non-contiguous loss of exons 3, 5, and 6 and retention of exon 4.<sup>11</sup> Further studies on a large cohort of the Israeli patients with Laron syndrome defined the borders of the gene deletion towards exon 4.<sup>12</sup> Amselem *et al* reported a 'serine' substitution to phenylalanine at position 96 in the extracellular domain in one out of eight patients with Laron syndrome of Mediterranean origin studied.<sup>13</sup> Studies of the patients from Ecuador revealed a 'guanidine' for 'adenine'

substitution in the third position of codon 180 of exon 6 in 45 of 52 affected individuals.<sup>14</sup>

The growth hormone receptor defects described so far, whether large gene deletions or point mutations, are in the extracellular domain of the receptor, as confirmed by the absence of the identically structured growth hormone binding protein (GHBP) in the serum of patients with Laron syndrome.<sup>15</sup> However, families with Laron syndrome and normal circulating GHBP have recently been reported, indicating a defect in the transmembrane or intracellular domain of the receptor.<sup>16</sup> Irrespective of the defect, location or size, the growth hormone receptor becomes inactive leading to a full phenotypic expression of the disease.

### Pathophysiology

The inability to bind to its receptor makes the pituitary growth hormone an ineffective hormone, resulting in low circulating serum IGF-I,<sup>9</sup> which in turn by a negative feedback mechanism leads to an abnormally increased growth hormone releasing hormone and growth hormone synthesis.<sup>8</sup> Serum GHBP is also low in most instances. The growth hormone dependent insulin-like growth factor binding protein (IGFBP)-3 is also reduced<sup>17</sup> whereas the non-growth hormone dependent IGFBP-1 and 2 are abundant.<sup>18</sup> The number of IGF-I receptors in target tissue is also increased (Eshet *et al*, in press, *J Mol Endocrinol*). The main typical biochemical changes are hypoglycaemia, mainly in childhood, and a tendency for increased blood lipids.

### Treatment

The biosynthesis of IGF-I by recombinant DNA technology a few years ago enabled the initiation of clinical trials. The induction of hypoglycaemia, suppression of insulin, growth hormone, growth hormone releasing hormone, and thyroid stimulating hormone by an intravenous injection of 75 µg/kg IGF-I (FK-780 Fujisawa Pharmaceutical Co Ltd) in 10 patients with Laron syndrome revealed the responsiveness of these patients to the exogenous hormone they cannot generate, and raised the hope that long term treatment will also affect linear growth.<sup>19,20</sup>

Despite the fact that the biological half life of exogenous IGF-I in patients with Laron syndrome was found to be half of that found in healthy subjects,<sup>21</sup> explained by low values of IGFBP-3,<sup>17</sup> daily injections of IGF-I for one week induced a rise in procollagen III.<sup>22</sup> Continuous infusions of IGF-I (16 µg/kg/hour, Genentech) for 11 days induced urea nitrogen and phosphorus retention<sup>23</sup> proving the anabolic effects of IGF-I.

Long term treatment of five prepubertal children with Laron syndrome with daily subcutaneous injections of IGF-I (150 µg/kg FK 780 Fujisawa Pharmaceutical Co Ltd) resulted in a rise of growth velocity from 2.8–5.8 cm/year to 8.8–13.6 cm/year.<sup>24</sup> The linear growth occurred both in the limbs as well as in the body segment and there was a marked catch up in head circumference presumed to denote brain growth. There was also a significant decrease in subcutaneous skinfold thickness that proves there is a reduction in body fat. No undesirable effects of the drug were observed for a period of over a year and there were no incidents of symptomatic hypoglycaemia. The above findings show that Laron syndrome is not an untreatable disease any more and it

is foreseen that more and more patients will be diagnosed and treated, enabling younger children to attain a normal height.

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