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EXTENSIVE PERSONAL EXPERIENCE

Laron Syndrome (Primary Growth Hormone Resistance or Insensitivity): The Personal Experience 1958–2003

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Clinical and laboratory investigations starting in 1958 of a group of dwarfed children resembling isolated GH deficiency but who had very high serum levels of GH led to the description of the syndrome of primary GH resistance or insensitivity (Laron syndrome) and subsequently to the discovery of its molecular defects residing in the GH receptor and leading to an inability of IGF-I generation. With the biosynthesis of IGF-I in 1986, therapeutic trials started. Continuously more and more patients are being diagnosed in many parts of the world with a variety of molecular defects. This syndrome proved to be a unique model that enables the study of the consequences of GH receptor defects, the physiopathology of GH-IGF-I disruption, and comparison of the GH-independent IGF-I effects. This review presents the personal experience gained from the study follow-up and treatment of the 60 patients followed up for many years in the Israeli cohort. (*J Clin Endocrinol Metab* 89: 1031–1044, 2004)

A SNAP DECISION made more than 40 yr ago can be said to have changed the course of my entire life. Just returned from postgraduate training in pediatric endocrinology at the Department of Pediatrics at Massachusetts General Hospital in Boston and the Children's Hospital in Pittsburgh, I was slated as a young pediatric endocrinologist to take up a new position in the north of Israel when a telephone call came through from the Beilinson Hospital Tel-Aviv, from my medical school teacher, Professor Andre DeVries, asking me to establish a pediatric endocrine clinic. On the spur of the moment, I accepted the offer, canceling all my previous plans, and therewith began my lifelong affair with a group of very small people and a quest for the culprit of their peculiar syndrome of dwarfism (1).

The Early Years

In 1958–1959, at a time when no assay for human GH (hGH) was as yet available, we started to study three siblings because of marked short stature. Their ages were 3.5 yr, 1.5 yr, and a newborn baby. Two were males, one a female (2) (Fig. 1). They belonged to a consanguineous Jewish family of Yemenite origin (the parents' grandparents were first cousins) (Fig. 2). They had five older siblings of normal stature. According to their appearance, they resembled children with hypopituitarism (3), such as dwarfism, obesity, and severe hypoglycemia. It was only a few years later when purification of hGH permitted the development of specific RIAs for hGH (4, 5) that we found out to our surprise that the patients had very high serum hGH levels in the acromegalic range (Fig. 3). We concluded that we had discovered a familial, most probably hereditary, new syndrome involving hGH (6). We envisaged two possibilities: an abnormal molecule of hGH or lack of responsiveness of the target organs (7). It took 20 yr to prove scientifically which of the two was the right answer. Within 2 yr after the first observation, we were able to collect and start the study of an additional 20 Jewish Oriental patients (7) to be followed up over the years by the study of patients of Israeli and Palestinian Arab origin and a few patients from other Mediterranean countries (8). At present, the Israeli cohort consists of 60 patients (9). Following our description, patients were diagnosed in many parts of the world, many of them of Mediterranean or Mideastern origin or in their descendants (9), most belonging to consanguineous families as listed in review articles (10–13). In fact, continuously more and more patients are diagnosed.

The early stages of research concentrated on the clarification of the *in vitro* and *in vivo* properties of the circulating GH in these patients. We found that the circulating GH behaves normally by immunologic (14) and radioreceptor tests using either rabbit (15) or human GH receptors (GH-Rs) obtained from human livers (16). Obtaining permission to biopsy the liver of two patients, we showed in 1984 (17) that ^{125}I hGH does not bind to GH-Rs prepared from their liver membranes. We interpreted these findings as evidence that these patients have a defect in the GH-R (17), which explained the findings that these patients cannot generate sulfation factor (somatomedin, IGF-I) (18, 19).

Cloning of the GH-R gene by Leung et al. in 1987 (20) and its characterization in 1989 (21) as well because new laboratory technologies such as PCR enabled the study of the

Abbreviations: CT, Computed tomography; DEXA, dual-energy x-ray absorptiometry; GHBP, GH binding protein; GH-R, GH receptor; hGH, human GH; IGFBP, IGF binding protein; LS, Laron syndrome; MRI, magnetic resonance imaging.

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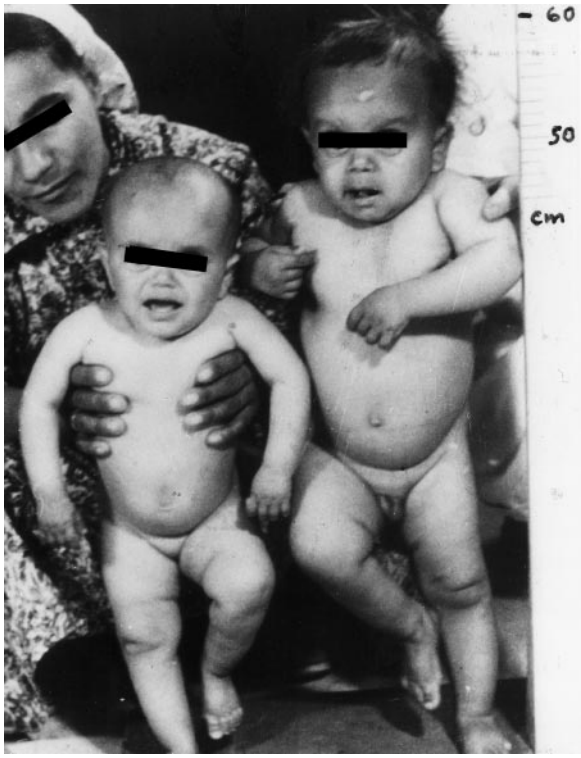

FIG. 1. The first two patients with LS referred in 1958. The boy is 3.5, the girl 1.5 yr old. The photo is published with the written permission of the parents. Reproduced with permission from Laron (2).

molecular defects of the GH-R in this disease (21, 22) (see details below).

Nomenclature

The early descriptive name of genetic pituitary dwarfism with high-serum GH (6) was changed to Laron dwarfism (23); Laron type dwarfism (8); and subsequently Laron syndrome (LS) (11), GH insensitivity, or GH-R deficiency (12). Because GH resistance can be primary or secondary, a consensus classification and nomenclature of GH insensitivity syndromes were published in 1993 (24). An updated version is shown in Table 1.

Genetic Aspects

Almost all of our patients belong to consanguineous families and inbred clans (Fig. 2) with different molecular defects, depending on the ethnic and geographical origin (see below). Analysis of our cohort led to the conclusion that LS is caused by a fully penetrant autosomal recessive mechanism (25). In the literature there are, to the best of our knowledge, two reports on dominant-negative defects of the intracellular domain of the GH-R (26, 27).

Clinical Aspects

The following descriptions are based mainly on the 60 patients of our Israeli cohort, many of whom have been followed up closely from infancy into adult age; when appropriate, comparison is made with reports from other investigators.

Gestation and delivery

According to the mothers' accounts, available hospital records, and our own witnessing, the pregnancies with LS patients and deliveries were uneventful (28). Some mentioned weaker movements of the fetus, compared with normal siblings. Birth length (not available in all patients) revealed that the majority were short, measuring 42–46 cm; this was also found in patients from other countries and in newborns with hGH gene deletion (29) or IGF-I gene defects (30). Birth weight was more than 2500 g in most newborns with LS, but some babies weighed less than 2100 g. The adipose tissue was well developed in all.

Congenital malformations

One male infant with LS is known to have had congenital dislocation of one hip joint; another had mild aortic stenosis or undescended testicles. Two female patients had congenital cataracts or convergent strabismus, respectively.

Early childhood

Young children resemble those with hereditary or congenital isolated GH deficiencies (Fig. 1). They are short and obese, and the boys have hypogenitalism and hypogonadism (31). The head showing the typical appearance of a protruding forehead, saddle nose, and sunset look (Fig. 4, *upper left*) seems large for the body, but in effect the head circumference is below the normal size or in the low normal ranges (32–35) (Fig. 4, *upper right*). There is underdevelopment of the facial bones (32, 33) (Fig. 4, *lower left*). The hair is sparse, thin, silky (34), and easy to pluck and forms temporal and frontal recessions. The hair and nails grow slower than in healthy, same-aged children and need rarer trimming. If of Mediterranean or Mid-Eastern origin, the patients have blue sclerae. Onset of teething is delayed, and in most patients the teeth become defective at an early age (28, 31) (Fig. 4, *lower right*). Subsequently they become crowded due to the small mandible.

The infants are obese, not by weight, but as evidenced by skinfold measurements or soft tissue x-ray because the bones are thin and the muscles underdeveloped. The motor development is slow. The children and even some adult females have a very high-pitched voice (31) due to a narrow oropharynx (35). Newborns and infants sweat profusely due to marked hypoglycemia. The typical story of the mother is that they cry at night until they receive a sweetened drink and that the pillow is soaked in sweat.

Body proportions and growth

Special growth charts of this syndrome have been derived from the longitudinal follow-up of untreated patients of the Israeli LS cohort (36). They fit also congenital GH deficiency (29) or IGF-I gene deletion (30). If untreated, as most patients with LS are, they slow their growth velocity. From infancy on, the height deficit ranges between 4 and 10 height SDS below the median for normal height. The upper/lower segment ratio is above the norm for sex and age, denoting short limbs for the trunk size (37). The hands and feet are small (acromicria). During infancy they wear doll shoes because

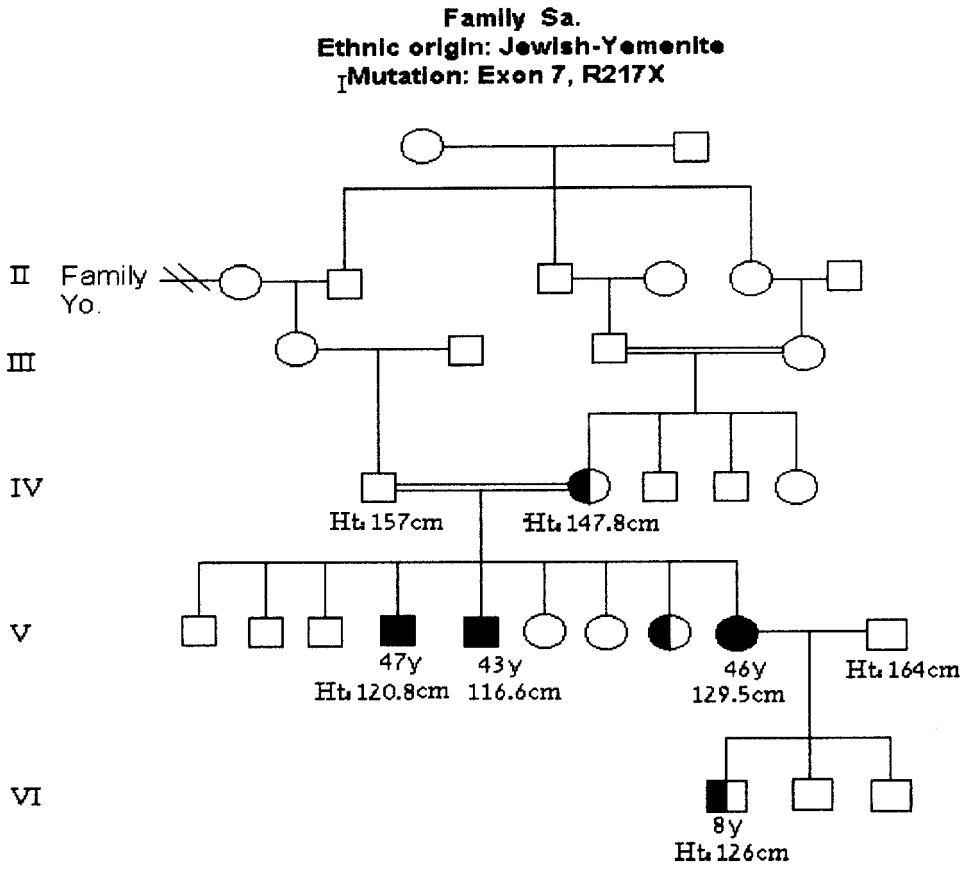

FIG. 2. Pedigree of the first family with LS studied. Note consanguinity of parents and relation to another affected family.

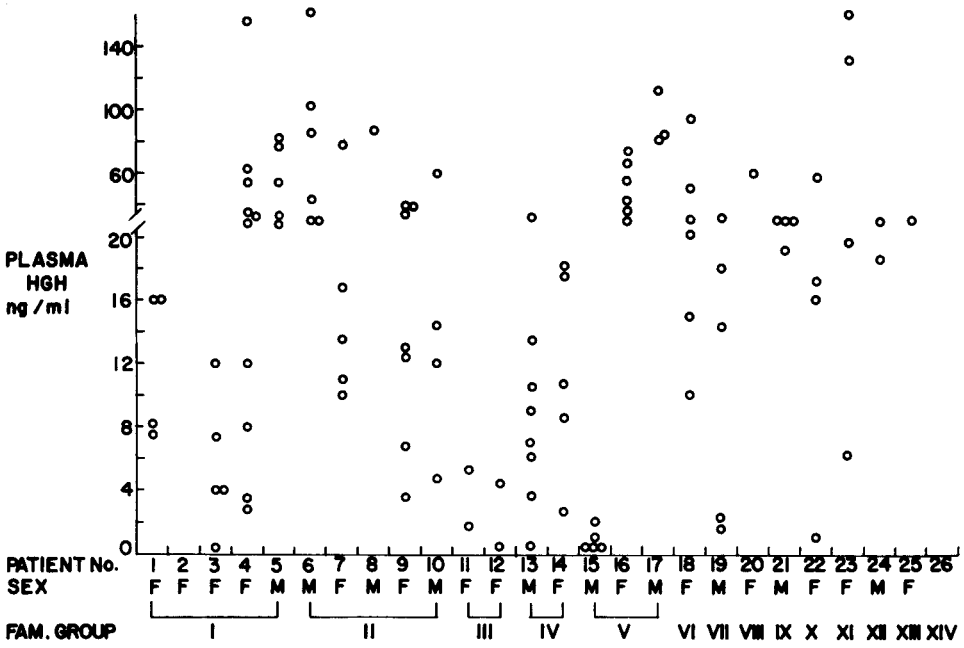

FIG. 3. Repeated overnight fasting serum GH levels in the first 25 patients with LS. Conversion factors: ng/ml = μg/liter; 1 mU = 3 μg.

shoe shops do not carry their size, and most of their life they have difficulties in finding appropriate clothing (38).

Their final height ranges between 116 and 142 cm in males and 108 and 136 cm in females (39). The adult stature in the larger Ecuadorian cohort has been reported to be 95–124 cm for females and 106–141 cm in males (40).

Analysis of the height of parents and adult siblings revealed that male heterozygotes are of normal height but below the 50th centile, but some of the mothers and sisters are below the third percentile (41). The same was described in the Ecuadorian cohort of LS patients (40). Whether this is due to their being heterozygous for the disease or belonging

TABLE 1. Classification of hGH resistance (insensitivity)

1. Primary GH resistance (insensitivity) syndrome = classical Laron syndrome (hereditary conditions)
a. GH receptor defects (quantitative and qualitative)
b. Abnormalities of hGH signal transduction (postreceptor defects)
c. Primary defects of synthesis and action of IGF-I
2. Secondary GH resistance (insensitivity) diseases (acquired conditions; sometimes transitory)
a. Circulating antibodies to hGH that inhibit GH action (hGH gene deletion patients treated with hGH)
b. Antibodies to the hGH receptor
c. hGH insensitivity caused by malnutrition
d. hGH insensitivity caused by liver disease
e. GH insensitivity caused by uncontrolled diabetes mellitus
f. Other conditions

Modified from Laron *et al*. (24).

to Oriental ethnic groups with lower height standards is as yet unsettled.

Sexual maturation, puberty, sexual relations, reproduction

The genitalia and gonads are small since birth (31), which is easily evident in the males presenting a small penis and testes (42). In the girls the genitalia are also small (8) and small-size ovaries are evident by ultrasonography. Puberty is delayed, more so in boys than in girls (43), and patients with LS do not show the typical pubertal growth spurt. The sequence of pubertal signs in boys is as follows: testicular enlargement was found to begin between 13 and 16 yr and axillary hair after age 16. The first conscious ejaculation, an important milestone in boys (44), which normally occurs at a mean age of 13.5 yr was found to take place between 17 and 21 yr (43). In girls, puberty is less retarded and menarche occurred between 13 and 15 yr in most patients. Both sexes reach full sexual development. The final length of the penis in males is between 8 and 10 cm and the testicular volume 5–9 ml (31, 43). The breasts of the females reach normal size and in some patients are large, compared with body size (39). In early adulthood there are no difficulties with reproduction. Five of our female patients married non-LS husbands and have one to three normal-sized children; so does one male patient. Another male, married to a heterozygote female for this disease, has two children with LS. Another four couples have no children. Several of our unmarried patients have sexual relations; others never had due to psychological inhibitions or lack of opportunities.

Nutritional state

Since birth, children with LS are obese, despite eating very little. Their obesity is progressive during childhood and adulthood, when it becomes excessive (45) (Figs. 4, upper left, and 5).

Orthopedic problems

With progressively increasing weight, reduced muscle strength, and weakening of the connective tissue, adult patients, especially the females, complain of pains and swelling of the knee joints.

Sleep disorders

Sleep disorders are a common feature of adult patients with LS (my unpublished observations). The narrow oropharynx (35), leading to constriction of the upper airways, and marked obesity predispose to sleep apnea. One adult patient with severe breathing difficulties due to obstructive sleep apnea syndrome requires the use of continuous positive airway pressure (46).

Aging, longevity, and mortality

Despite the appearance of early aging signs (39), such as thin and wrinkled skin (10), patients with LS have a long life, over the 70s, both in our (47) and the Ecuadorian cohorts (48). We registered one death, the sister of one of our patients. She died at age 3 yr of meningoencephalitis with convulsions (may be hypoglycemia?), in 1950 before we recognized the disease. In the Ecuadorian cohort, a series of deaths before age 7 yr have been attributed to infections and heart disease in adults (48). Table 2 summarizes the main clinical characteristics of untreated LS patients.

Investigations

Imaging by x-rays, computed tomography (CT), and magnetic resonance imaging (MRI): skeletal system

Radiographic studies of patients with LS are scant. Skeletal maturation is retarded starting *in utero* and slow in progressing. Closure of the epiphyseal cartilage of the long bones occurs between ages 16 and 18 yr in girls and 20 and 22 yr in boys (10). The diploë of the skull is very thin and the sinuses are underdeveloped (Fig. 6). The fontanels and sutures of the skull close much later; some are open even in adult age (49). The facial bones, especially sphenoid and mandible, are underdeveloped (32, 33) (Fig. 4, *lower left*). The diameter of the oropharynx is significantly smaller in the LS patients than in the same-aged controls (35). Of note is the normal size of the sella turcica (50). The long bones are thin, and already in young adult age, abnormalities of the spine including degenerative changes of the atlantoodontoid joint and spinal stenosis are found (35).

Dual-energy x-ray absorptiometry (DEXA)

Examination of bone mineral density in young adults with LS by DEXA revealed osteoporosis (51); however, when bone mineral apparent density is calculated for the size of the patients, values become normal (52, 53).

Histological examination of the skin

Microscopic examination of skin biopsies of prepubertal patients with LS revealed moderately thickened elastin fibers with a tendency to cluster; in pubertal patients there was a reduction in the number of elastin fibers in the papillary layer and clustering of collagen fibrils in the reticular area (54). The skin in young adults is very thin and appears to have lost even more elastic fibers. This seems evidence of the role of IGF-I deficiency on connective tissue and cause the early aging changes.

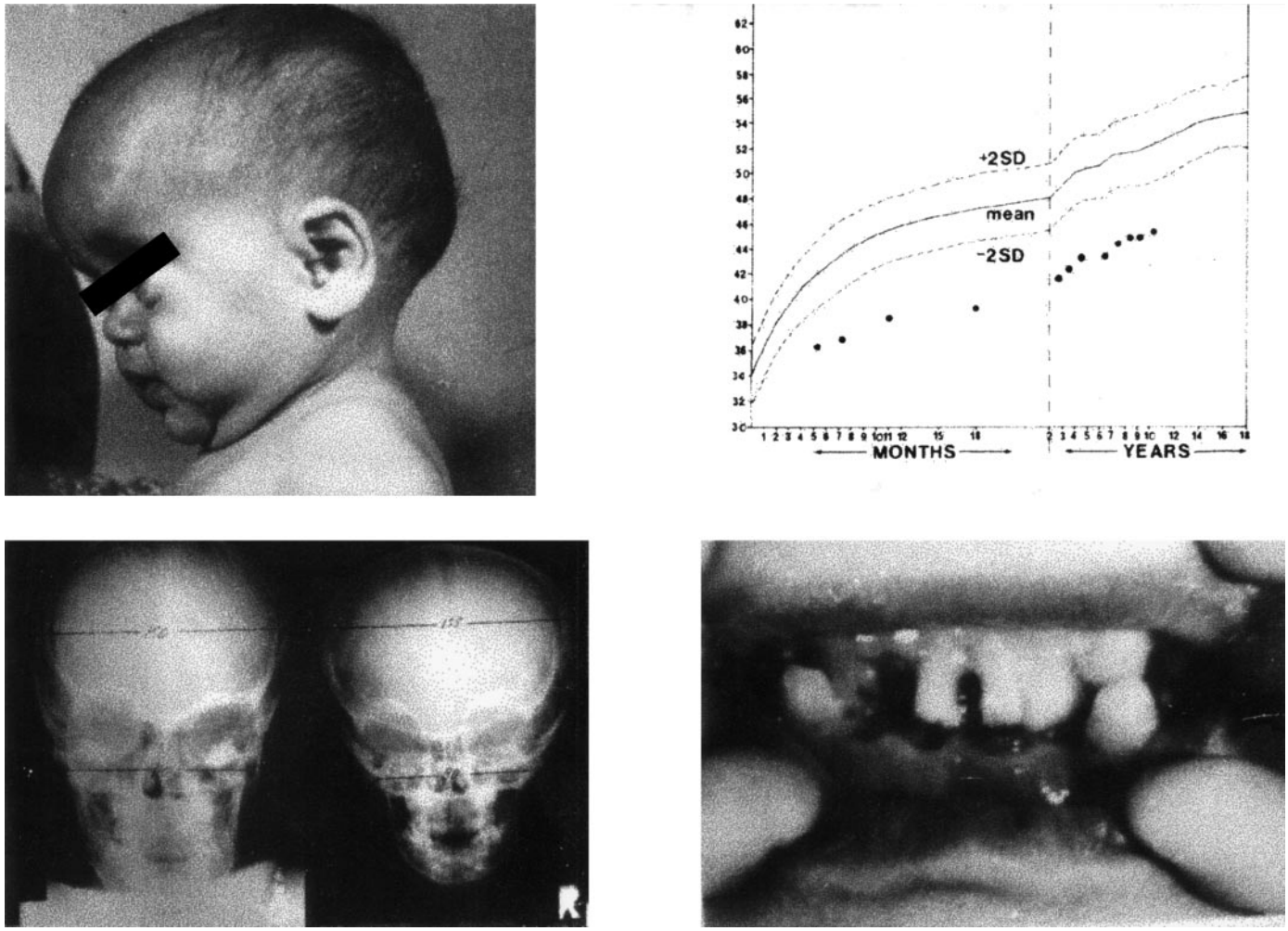

FIG. 4. *Upper left*, Lateral face of a 4½-yr-old girl with LS. Note protruding forehead, saddle nose, sunset look, small chin (double chin), and sparse hair (same girl as in Fig. 1). *Upper right*, Head circumference growth in an untreated girl with LS. Note subnormal size. *Lower left*, Anterior skull x-ray of a normal child (*left*), compared with a boy with LS (*right*). Note small bicondylar diameter in boy with LS and smaller facial bones. *Lower right*, Delayed teething and defective and broken, crowded teeth in 9-yr-old boy with LS.

Eyes

Evaluation of retinal vessel morphology by digital analysis of ocular fundus photographs in eight patients with LS of our cohort and patients with other defects of the GH/IGF-I axis revealed a significantly lower number of vascular branching points, compared with a reference group (55). Two of our adult patients who have diabetes developed diabetic retinopathy (Laron Z. and D. Weinberger, in preparation). Most young adults become short-sighted and need spectacles.

Hair

In the young age, hair growth is sparse (34); it is silky and forms temporal and frontal recessions, more prominent in boys (Fig. 4, *upper left*). Adult males develop alopecia.

Light and electromicroscopic studies of the hair of untreated children and adults with LS revealed four main structural defects in the hair shaft: pilli torti, grooving, pseudomonilethrix, and trichorrhexis nodosa (56). Whereas pili torti is a congenital abnormality, the other changes are usually acquired and likely to occur in genetically fragile hair.

Teeth

Already in infancy, teeth are defective, with many caries and breaking early (Fig. 4, *lower right*). Histological examination of primary and permanent teeth of patients with LS showed increased enamel thickness, compared with controls, and showed more pronounced striae of Retzins (Horsey, G. D., J. T. Wright, and Z. Laron, in preparation). Around age 40 yr, many of the patients lose their teeth and need a prosthesis.

Muscular system

Untreated patients with LS, both children and adults, have reduced muscle development and reduced muscle strength and endurance (57).

Cardiopulmonary system

Cardiological investigation using chest x-rays and stress echocardiography of untreated adult LS patients revealed cardiomicria, reduced width of the cardiac muscle, and a

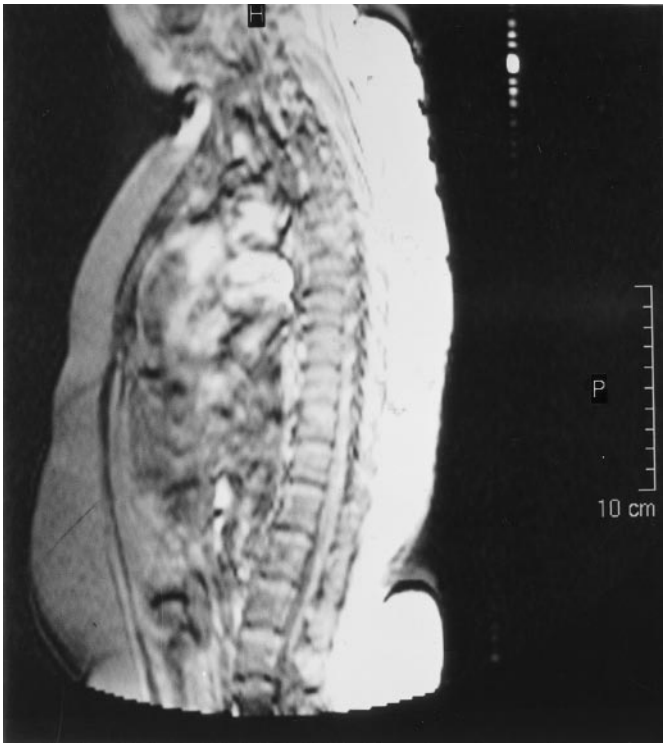

FIG. 5. Lateral body MRI of a 41-yr-old male with LS. Note excessive sc and visceral fat, including pericardial fat.

TABLE 2. Signs and symptoms of primary IGF-I deprivation (LS) during puberty and adulthood

- Dwarfism (height = <4–10 SD score
- Marked obesity
- Delayed puberty
- Late closure of bony epiphyses
- Thin bones
- Small gonads but full sexual development and reproductive potential
- Thin skin; early wrinkling
- High-pitched voice
- Reduced lean body mass
- Reduced muscular strength
- Reduced bone density (osteopenia—DEXA)
- Variable psychological performance (from normal to marked retardation)

reduced left ventricular output (58). Pulmonary function studies showed a reduced maximal aerobic capacity (59). Resting blood pressure is within normal limits.

Neuropsychological development

Brain growth as evidenced by head circumference (Fig. 4, *upper right*) is below normal starting *in utero* (31, 41), and motor development in infancy is slow and delayed (6, 7). Electroencephalograms performed during childhood in 14 patients showed a normal pattern in 12, an epileptic pattern in one, and a paroxysmal pattern in another (7).

Pneumoencephalography (before the time of CT) in six children revealed normal-sized ventricles (7). Skull CT performed in two patients was normal, but MRI imaging of nine untreated adult patients and three untreated children with LS revealed diffuse parenchymal loss of various degrees in one child (60) and in the adult patients (49) (Fig. 6). Three patients had localized atrophy in the occipital lobe, and one had a lacunar infarct in the caudate nucleus. One patient had leucomalacia, and a young untreated girl had a hypoplastic corpus callosum and lateral ventricular focal leucoencephalopathy (60).

Brain MRI in one 11-yr-old girl treated by IGF-I for 8 yr was normal (49). The patients with LS in our cohort vary greatly in their mental development; from normal intelligence (one PhD, two MAs) to severe mental retardation. The patient with the most severe retardation had on MRI areas of periventricular leucomalacia (49).

Repeated psychological evaluations of untreated patients at various ages revealed an overall lower distribution pattern in intelligence tests than the same-aged general population. Of note is that greater deficits were recorded in the performance IQ than the verbal IQ, the latter showing some improvement with age (61). The investigators of the cohort in Ecuador came to different conclusions (62). The importance of the effects of IGF-I and pathology of GH/IGF-I deficiency on the brain have been reviewed recently (63). Because these patients suffer from hypoglycemia in infancy, metabolic disturbance could thus also have influenced impaired intelligence in some of the patients.

Chromosomal analysis

Karyotype examination with banding performed in more than 20 patients of both sexes were normal.

Blood chemistry

Neonates and babies with LS suffer from severe hypoglycemia (7, 31). Low blood glucose levels continue throughout childhood and young adulthood, the patients having symptomatic or asymptomatic hypoglycemia (7, 8, 31), probably related to the state of fasting or feeding. Before age 6 yr, children with LS have insulin nonresponsiveness (28). The response to hypoglycemia challenge becomes normal during puberty (8, 28) by the development of counterregulatory mechanisms. In later life, some develop glucose intolerance and even diabetes mellitus (64).

Serum alkaline phosphatase, inorganic phosphorus, and creatinine (the latter as an index of glomerular filtration) are low (65), as are serum procollagens (66). Serum total and low-density lipoprotein cholesterol are low or normal during early childhood but increase progressively with age and degree of obesity to supranormal levels (45). Fasting free fatty acids are high during severe hypoglycemia (8).

Hormones

Overnight fasting serum GH levels are high (6, 7, 28) (Fig. 3), and nocturnal pulses may reach peak levels of 200–300 ng/ml (μg/liter) (67). The regulation of GH secretion and feedback mechanisms are normal as evidenced by the normal number of 24-h GH pulses, the response to stimulatory agents (insulin hypoglycemia, arginine, *etc.*) (7, 8), and suppression by glucose administration, drugs such as corticosteroids (8) or somatostatin (68), or exogenous IGF-I administration (69). After somatostatin suppression there is

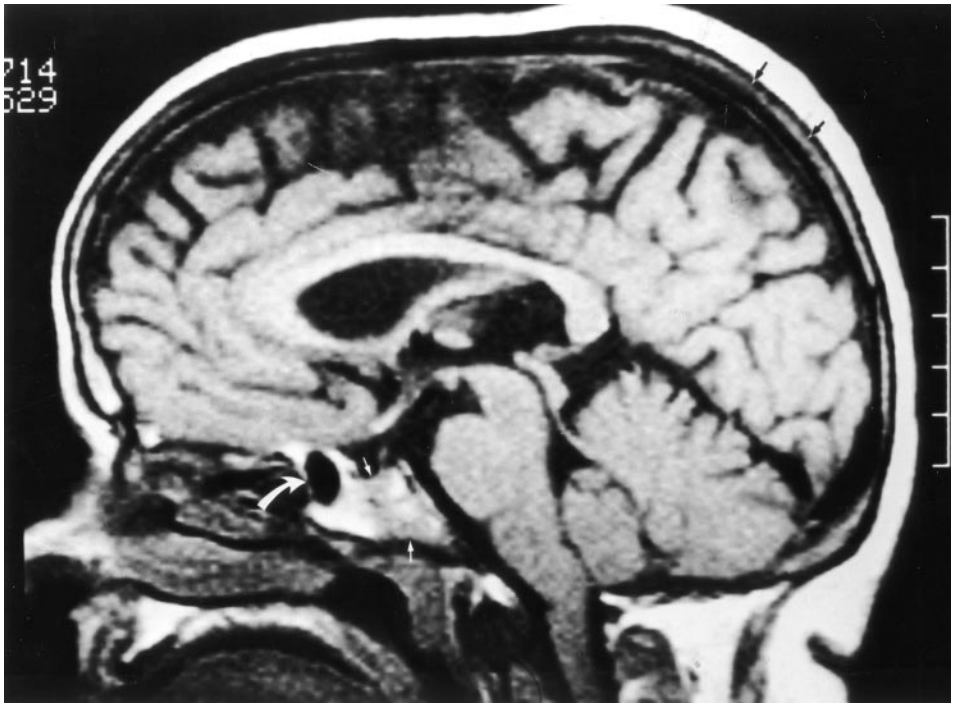

FIG. 6. Lateral view of an MRI cut of the skull of a 68-yr-old patient with LS. Note absence of frontal sinus, small sphenoid sinus (*curved arrow*), thin diploë (*double arrows*), a normal sized pituitary, and atrophy of the cerebellum. Reproduced with permission from Laron (49).

overshooting of the hGH levels to very high peaks (68). Despite the lifelong oversecretion of pituitary GH (67), the pituitary gland in patients with LS is not enlarged (50) (Fig. 6). One possible explanation is that, similar to other organs, the growth of the pituitary gland is IGF-I dependent. No antibodies against hGH were ever detected.

Serum IGF-I levels are very low, even undetectable, and do not rise on the administration of exogenous hGH (18, 19, 28) for days or weeks, evidence for the state of GH resistance in these patients. The number of unoccupied IGF-I binding sites (*i.e.* receptors) in the tissues is increased (70), being modulated by the circulating IGF-I levels (71). Serum IGF binding protein (IGFBP)-3 is low (72), but IGFBP-I is elevated (73). The levels of IGFBP-II are normal or high (12).

Thyroid function is normal (74), as is the secretion of adrenal hormones. Prolactin levels were occasionally elevated and rose to high levels when stimulated (75). We interpret this finding as due to a drift phenomenon to the high GH secretion by the somatomammotrophic cells and may be the cause of the large breasts in many adult female patients.

Despite the low glucose levels, serum insulin is relatively high, denoting a state of insulin resistance (64). This state, present already in infancy, increases with advancing age and the progressive obesity. In few patients, glucose intolerance and hyperinsulinism was registered during an oral glucose tolerance test. The insulin resistance can lead in adult age to insulin exhaustion and diabetes.

Hematopoietic system

Untreated children and adolescents with LS present with subnormal values for the erythropoietic indices (red blood cell count, hemoglobin, hematocrit, and mean corpuscular volume) (76). During adult age the values become normal. These findings show that during the active growth periods, IGF-I is an essential component of the erythroid line formation. Untreated LS patients have an elevated monocyte count in the presence of a normal total neutrophil count and a tendency for a low lymphocyte count (76).

The molecular pathology of the GH-R

Shortly after proving that the syndrome was due to defects in the GH-R (17), the cloning of the GH-R gene (20) enabled specific examination of the receptor in these patients. In collaboration with Godowski et al. (21), we reported exon deletions in the extracellular domain of the GH-R, and Amselem *et al.* (22), using the newly introduced PCR method, described a series of mutations in patients from North Africa. In the following years, patients from many parts of the world were investigated, describing defects of the GH-R such as exon deletions to nonsense, frameshift, and splice and missense mutations of exons and introns (10, 21, 22, 26, 27). The majority are in the extracellular domain of the receptor: exons 2–7 and introns resulting in the absence of circulating GH binding protein (GHBP) (77, 78) (see below). Four reports describe mutations affecting the transmembrane domain (exon 8) (26, 79–81), and another two report mutations in the cytoplasmatic domain (exons 9 and 10) (26, 27). It is of note that despite the great variability in the molecular defects of the gene, all result in lack of GH signal transmission. Indeed, a single amino acid substitution in the extracellular domain of the hGH receptor prevents ligand binding to the GH-R (82) as does defective membrane expression (83). In 1993 we described the first patients with a postreceptor defect (84), resulting in the generation of IGFBP-3 but not IGF-I, denoting separate signaling pathways for the transcription of the two genes. Because of lack of cooperation of the patients, we have failed so far to identify a specific molecular defect in these patients. Recently a girl from Argentina with LS was found

to have a postreceptor defect due to a missense mutation in the signal transducer and activator of transcription signal transducer and activator of transcription 5b (85).

It is of note that in 37 patients investigated from the large Ecuadorian cohort the same mutation in exon 6 of the GH-R (E180 splice, A to G at 594) was found (86), whereas in the smaller Israeli multiethnic cohort, a series of molecular defects was registered (21, 79, 84, 87) (Table 3).

GHBP

GHBP independently described by Herington *et al.* (88) and Baumann *et al.* (89) is identical in structure with the extracellular domain of the GH-R (20). Quantitative measurements revealed that its serum concentrations vary with age, being low in neonates and reaching maximal values in young adulthood (90). Determination of serum GHBP can be used as a simple quantitative estimation of the extracellular domain of the GH-R (91), its absence denoting a defect in this domain of the receptor. Normal or elevated serum GHBP in classical LS patients denotes a defect in the transmembrane, intracellular or post-GH-R areas (26, 79, 80). A low-serum GHBP concentration in relatives of patients with LS helps identify heterozygous carriers in patients with defects in the extracellular domain of the GH-R (91).

Definition of LS

The typical features of classical LS are short stature of −4 to −10 SDS below the median normal height, typical face, obesity, acromicria, high basal serum GH, and low-serum IGF-I unresponsive to the administration of exogenous GH. The molecular diagnosis reveals defects in the GH-R gene. Whether the patients with a postreceptor defect or IGF-I gene defects should be called Laron type II is debated (OMIM 24550).

Treatment

The only effective treatment for LS is replacement therapy with recombinant biosynthetic IGF-I available since 1986 (91). Unfortunately, the restricted amounts of drug for clinical use permitted treatment of only a small number of patients.

An iv bolus injection of IGF-I (75 mg/kg) in the fasting state induced marked hypoglycemia in both children and adult patients with LS as well as in healthy controls. The concomitant decrease of serum insulin proved that the hypoglycemia was IGF-I induced. The injected IGF-I was more rapidly eliminated in untreated patients with LS than in control subjects ($t_{1/2}$ = 2.57 ± 0.67 *vs.* 4.43 ± 0.52 min) (92) due to the low concentration of serum IGFBP-3 in LS (72). Intravenous IGF-I administration suppressed circulating GHRH, GH, TSH (93), and glucagon. This is explained by the stimulation of somatostatin secretion by IGF-I (94). One week IGF-I administration reduced the number of specific binding sites of red blood cells to normal values (71).

Each group using biosynthetic IGF-I from different sources, (exception Israel and Japan, who used the same preparation) were of identical structure. The only difference is that whereas our group uses one sc injection per day administered before breakfast to avoid hypoglycemia, the other groups administered two injections of IGF-I a day (95).

Short-term and transitory effects are water and electrolyte retention and calciuria (51, 65). Administration of IGF-I for months or years persistently suppressed GH and serum insulin, preventing hypoglycemia and stabilizing blood glucose levels, provided that meals were regular (96). This was also confirmed by Walker *et al.* (97). Sensitive markers of IGF-I activity during treatment are a rise in serum alkaline phosphatase, procollagen-I, amino-terminal propeptide of type III procollagen (66), serum phosphate, and glomerular filtration rate (65). IGF-I administration also raised sex hormone binding protein (98) and decreased serum lipoprotein(a) (99), and to a lesser degree, cholesterol (51).

IGF-I administration also affects its specific binding proteins participating in its own regulation of available free hormone. During the first weeks of administration, IGF-I suppresses the IGFBPs (73) including IGFBP-3 (72), but longer administration leads to the generation of this largest

TABLE 3. Molecular defects of the GH-R gene in the multiethnic Israeli cohort of patients with LS

Ethnic origin	No. of patients	Mutation	Location
Jewish-Iranian	2	230delT	Exon 7
Jewish-Iraqi	3	R211H	Exon 7
	3	W-15X[a]	Signal peptide
	6	exon deletion	3,5,6
Jewish-Moroccan	1	E180 splice	Intron 6
Jewish-Yemenite	3	R217X	Exon 7
Palestinian Arab	4		
Druse	1	785-1 G to T	Intron 7
Peruvian	1		
Malthusian	1	R43X	Exon 4
Greek-Anatolian	1	R43X/G168 polymorphism[b]	Exon 4/Exon 6
Italian	1	L141X[a]	Exon 6
Iranian	1	Y86D[a]	Exon 5
Maronite	1	A to G, R161C, G223[c]	Intron 2, Exons 6 and 7
Palestinian Arab	3	?	Post receptor defect

[a] New mutations described by our group.
[b] Double heterozygote.
[c] In collaboration with Dr. S. Wakim.

of the IGFBP-3 (100) and its acid labile fraction (101) as well as the other binding proteins. This finding has practical importance because it prolongs the biological half-life of the administered IGF-I during long-term treatment (102) and requires in most patients a progressive reduction of the IGF-I dose to prevent overdosage and adverse effects.

One of the major effects of IGF-I is acceleration of linear growth. Due to limitations in the availability of the drug, there are only few reports on long-term treatment of children with LS. There are four reports on 2- or 3-yr treatment (96, 103–105), one on 4 yr (106), one on 5 yr (104), and one on 7 yr (107). In the first year of treatment, the growth velocity was higher than in subsequent years. It seems that once-daily IGF-I administration (96) is as effective in promoting growth as is twice-daily IGF-I administration (102–108) (Fig. 7). On the other hand, twice-daily injections or not decreasing the IGF-I dose with time (109) caused more adverse effects (95, 109, 110). With continuous treatment there was also a progressive growth of the extremities (hands, feet, chin, and nose). Despite the effective stimulation of linear growth, the growth velocity is not as intense as that of GH in GH deficiency (108, 111). During IGF-I treatment we also registered a fast catch-up of the head circumference even at ages 10–14 yr (112), denoting brain growth, and some reduction in adipose tissue as measured by skinfold thickness. The latter was more accentuated in a group of adult patients with LS treated for 9 months (51) and lasted for only 1 yr at the most. Recently we found the IGF-I treatment of patients with LS to have a significant stimulatory effect on erythroporesis (76). Whether this effect is mediated by erythropoietin is under investigation. IGF-I treatment also normalized the high blood monocyte counts and reduced, within normal limits, the number

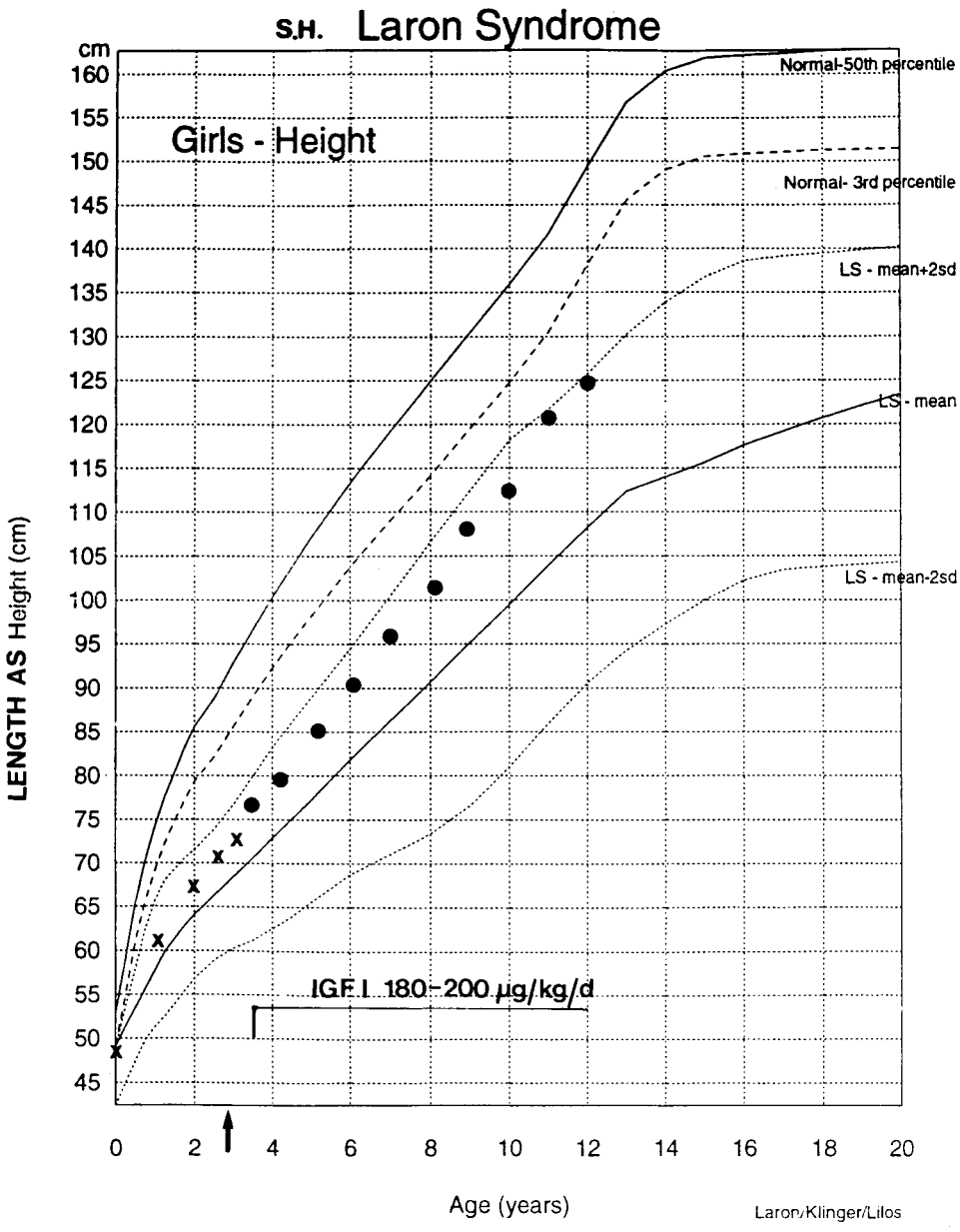

FIG. 7. Growth response of a girl with LS treated with IGF-I for 8 yr by once-daily sc injection administered with breakfast.

TABLE 4. GH-R deletions and mutations reported in patients with LS

Mutations	Molecular defect	Nucleotide change	Exon involved	Domain[a]	Ref.	No.
Deletion	Exons 3-5-6		3-5-6	EC	Godowski *et al.*, 1989	21
Nonsense	W-15X	G→A at 83	2	EC	Shevah *et al.*, 2003	87
	C38X	C→A at 168	4	EC	Amselem *et al.*, 1991	116
	R43X	C→T at 181	4	EC	Amselem *et al.*, 1991	116
	Q65X	C→T at 197	4	EC	Sobrier *et al.*, 1997	117
	W80X	G→A at 293	5	EC	Sobrier *et al.*, 1997	117
	L141X	T→A at 476	6	EC	Shevah *et al.*, 2003	87
	W157X	G→A at 525	6	EC	Sobrier *et al.*, 1997	117
	E183X	G→T at 601	6	EC	Berg *et al.*, 1994	118
	R217X	C→T at 703	7	EC	Amselem *et al.*, 1993	119
	Z224X	G→T at 724	7	EC	Kaji *et al.*, 1997	120
Frameshift	21delTT	del TT at 118	4	EC	Counts and Cutler, 1995	121
	36delC	del C at 162	4	EC	Sobrier *et al.*, 1997	117
	46delTT	del TT at 192-193	4	EC	Berg *et al.*, 1993	122
	230delT	del T at 744	7	EC	Sobrier *et al.*, 1997	117
	230delAT	delAT at 743-744	7	EC	Berg *et al.*, 1993	122
	309del C	del C at 981	10	IC	Kaji *et al.*, 1997	120
Splice	Intron 2	G→A at 70+1		EC	Sobrier *et al.*, 1997	117
	Intron 4	G→A at 266+1		EC	Amselem *et al.*, 1993	119
	Intron 5	G→A at 71+1		EC	Berg *et al.*, 1993	122
	Intron 5	G→C at 130-1		EC	Berg *et al.*, 1994	118
	Intron 5	G→C at 440-1		EC	Amselem *et al.*, 1993	119
	Intron 6	G→T at 189-1		EC	Berg *et al.*, 1993	122
	Intron 6	G→T at 619-1		EC	Berg *et al.*, 1993	122
	Intron 7	G→T at 785-1	7/8	EC/TM	Silbergeld *et al.*, 1997	79
	E180splice	A→G at 594	6	EC	Berg *et al.*, 1992	86
	G223G	C→T at 723	7	EC	Sobrier *et al.*, 1997	117
	G236splice	C→T at 766	7	EC	Baumbach *et al.*, 1997	123
	R274T	G→C at 874	8	TM	Woods *et al.*, 1996	80
	GHR(1-277)[b]	G→A at 876	9	TM/IC	Iida *et al.*, 1998	27
	GHR(1-277)[b]	G→C at 876	9	TM/IC	Ayling *et al.*, 1997	26
Missense	M-18L	A→T at 73	2	EC	Quinteiro *et al.*, 2002	124
	C38S	T→A at 166	4	EC	Sobrier *et al.*, 1997	117
	S40L	C→T at 173	4	EC	Sobrier *et al.*, 1997	117
	E42K	G→A at 178	4	EC	Chen *et al.*, 2003	125
	W50R	T→C at 202	4	EC	Sobrier *et al.*, 1997	122
	R71K	G→A at 266	4	EC	Amselem *et al.*, 1993	119
	F96S	T→C at 341	5	EC	Amselem *et al.*, 1989	22
	V125A	T→C at 428	5	EC	Amselem *et al.*, 1993	119
	P131Q	C→A at 446	6	EC	Walker *et al.*, 1998	126
	V144D	T→A at 485	6	EC	Amselem *et al.*, 1993	119
	D152H	G→C at 508	6	EC	Duquesnoy *et al.*, 1994	82
	D152G	G→A at 509	6	EC	Yang *et al.*[c]	
	I153T	T→C at 512	6	EC	Wojcik *et al.*, 1998	127
	Q154P	A→C at 515	6	EC	Wojcik *et al.*, 1998	127
	V155G	T→G at 518	6	EC	Wojcik *et al.*, 1998	127
	R161C	C→T at 535	6	EC	Amselem *et al.*, 1993	119
	Y178S	A→C at 587	6	EC	Oh *et al.*, 1999	128
	Y208C	A→G at 677	7	EC	Enberg *et al.*, 2000	106
	R211G	C→G at 685	7	EC	Amselem *et al.*[d], 1993	119
	S226I	G→T at 731	7	EC	Jorge *et al.*[d]	
	D244N	G→A at 784	7	EC	Enberg *et al.*, 2000	106

[a] EC, Extracellular; TM, transmembrane; IC, intracellular.
[b] These two mutations were identified on the same GHR allele.
[c] Yang, C., *et al.* (Taiwan), personal communication; [d] Jorge, A., I. Arnhold *et al.* (Argentina), personal communication.

of platelets (76). We also found that IGF-I treatment raises serum androgens in males and in adults also the gonadotropins.

Because these patients suffer from thin bones and weak muscles (57), it is not certain that LS patients are good candidates for limb lengthening unless they are treated by IGF-I several years before and during the operation. The dwarfism of untreated patients with LS, the underdevelopment of the skeletal and muscular system, the progressive obesity, limitations in mobility, and the variable deficits in the neuropsychomotor systems limit their occupational opportunities and make relationships with the other sex difficult. These facts are a source of emotional suffering, even depression, necessitating continuous psychosocial counseling (41).

It is expected that most of the above consequences could be avoided if IGF-I treatment would be initiated at birth or in infancy. It is to be regretted, to say the least, that in our advanced society, a treatable disease remains untreated with the exception of a small number of children on time-limited clinical trials (95). Prenatal diagnosis is also now possible in pregnancies at risk.

Conclusions

Looking back, there is no doubt that this defect in nature has enabled us and other investigators to unravel the physiology and pharmacology of IGF-I; and many aspects of the interrelationship between GH and IGF-I and the follow-up of many of the patients from infancy to adult age proved that IGF-I deficiency is an important hormone, its deficiency is very detrimental, and an early diagnosis and replacement treatment are indicated.

Looking forward, so many mysteries are still unsolved and need a response. What makes these patients grow *in utero* and postnatally to reach a short stature? Do they have autonomous paracrine IGF-I, or are other factors involved? If so, which? What mechanisms cause the progressive obesity and changes in lipid and carbohydrate metabolism? Can early start and continuous postnatal replacement treatment prevent the progressive pathological changes? Are some forms of idiopathic short stature due to defects of the GH-R (113)?

The mouse model with the disrupted GH-R/binding protein gene (114) has helped to verify a series of clinical observations (115) and could be very useful in the study of tissues not accessible in humans. However, in certain respects, the mice model differs from man. The mice are not obese as the patients and thus resemble in this respect patients with a postreceptor defect. Further interesting questions to be resolved are the seemingly normal phenotype in family members heterozygote for this disease on the one hand and the pathology of double heterozygosity and the occasional typical phenotype of LS associated with heterozygosity and polymorphism on the other hand. Table 4 lists all the molecular defects of the GH-R reported so far.

Finding the answers to the above questions will help us to be not only more knowledgeable scientists but also better doctors.

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