Oral and Dental Findings in a Child With Growth Hormone Insensitivity Syndrome

Jenny Abanto, DDS *Paula Celiberti, DDS, MSc*
Fabiana Bucholdz Teixeira Alves, DDS, MSc
Viviane Rossier, DDS *Stella Alves Campos Vieira, DDS, MSc*
Ana Lidia Ciamponi, MSc, PhD *Daniela Prócida Raggio, MSc, PhD*

ABSTRACT

Growth hormone insensitivity syndrome, also known as Laron syndrome, is an autosomal recessive disorder caused by defects the of growth hormone receptor gene and may lead to increased growth hormone levels. This syndrome's main clinical features are: dwarfism; acromicria; organomicria; cervical spinal stenosis; early osteoarthritic changes of the atlantoaxial joint; small oropharynx; decreased growth velocity; insulin resistance; hypoglycemia; delayed skeletal maturation and osteoporosis; and muscular and central nervous tissue underdevelopment. The facial bones, especially sphenoid and mandibular, are also underdeveloped. No reports of the incidence of growth hormone insensitivity syndrome in the population are available in the literature. The purpose this case report was to describe oral findings and particularities of dental treatment in a child with growth hormone insensitivity syndrome.
(J Dent Child 2010;77:54-8)

Received December 4, 2008; Last Revision February 19, 2009; Revision Accepted February 19, 2009.

KEYWORDS: CHILDREN WITH SPECIAL HEALTH CARE NEEDS, GROWTH AND DEVELOPMENT, ORAL MEDICINE

Growth hormone insensitivity syndrome (**GHIS**) (OMIN 262500)[1] is an autosomal recessive disorder caused by defects of the growth hormone receptor gene, which may lead to increased growth hormone (**GH**) levels. Initially named Laron-type dwarfism, this condition is usually known as Laron syndrome, GH insensitivity, or GH deficiency.[2] Because GH resistance can be primary or secondary, a consensus classification and nomenclature of GH insensitivity syndromes were published in 1993.[3]

A functionally abnormal but immunoreactive GH molecule was first postulated to be the cause of GHIS. The demonstration of deficient sulfation factor (somatomedin or IGF1; IGF2) generation suggested that the mutation could involve that substance.[4] Through the analysis of a gene mutation, a recent study revealed the presence of the same homozygous mutation of S65H (TCA-->CCA) in exon 4 of 2 GHIS patients. This novel gene mutation might be a new cause of GHIS.[5]

Autosomal recessive and autosomal dominant modes of inheritance have been reported in different families. The study of the pedigrees, as well as the GH receptor gene analysis indicated that GHIS is a recessively inherited disease.[6] With the introduction of the PCR method, it was found that the molecular defects in GHIS patients vary from exon deletions[7] to mutations in the

Dr. Abanto is a specialist in pediatric dentistry and MSc student, and Drs. Celiberti and Alves are specialists in pediatric dentistry and PhD students, all in the Department of Pediatric Dentistry; Dr. Rossier is volunteer dentist and Dr. Vieira is assistant professor, both at the Center for Patient With Special Needs, and Drs. Ciamponi and Raggio are assistant professors of the Pediatric Dentistry and Orthodontics Departments, all at the Dental School, University of São Paulo-USP, São Paulo, Brazil.
Correspond with Dr. Abanto at jennyaa@usp.br

extracellular,[3] transmembrane,[8,9] or intracellular domain[10] of the GH receptor and also vary by post-receptor defects.[11]

Despite one study, from a province in Ecuador,[12] which assessed the incidence of GHIS no further reports considering the incidence of this syndrome in populations worldwide can be found. Guevara-Aguirre et al.12 observed a distorted gender ratio (19 females and 2 males) among affected cases. Regarding the origin, most patients were shown to be predominantly from the Mediterranean region, Middle East, and the Indian subcontinent.[13,14,15,16]

A definite diagnosis of GHIS can be made based on characteristic clinical features and serum levels of GH, insulin-like growth factor I (**IGF-I**), insulin-like growth factor binding protein-3 (**IGFBP-3**) and GHBP.[5,16] Therefore, GHIS is characterized by: clinical signs of GH deficiency (despite normal or increased plasma GH levels) such as short stature, decreased growth velocity, delayed bone age, and occasionally blue sclerae and hip degeneration; low IGF-I and IGFBP-3 levels that are unresponsive to exogenous GH; and low GHBP levels.

Individuals also show: dwarfism; acromicria (abnormally small head and extremities); organomicria (abnormally small viscera); small oropharynx; cervical spinal stenosis; early osteoarthritic changes of the atlanto-axial joint; marked obesity; chronic diseases (malnutrition and starvation); subnormal values for the erythropoietic indices; insulin resistance; hypoglycemia; retardation of skeletal maturation and osteoporosis; muscular and central nervous tissue underdevelopment; and a series of biochemical changes, including hypercholesterolemia.[2,15,17,18]

Although Guevara-Aguirre et al.[12] described normal or superior intelligence in Ecuadorian GHIS patients, some studies related a large variability of mental conditions, ranging from normal intelligence to severe mental retardation.[2,19] Because these patients may suffer from hypoglycemia in infancy, metabolic disturbance may also have an influence on the impaired intelligence of some patients.

Studies using magnetic resonance imaging scans of the brain typically showing mild scaphocephaly, hypoplastic corpus callosum, and lateral ventricular focal leucoencephalopathy, particularly in the frontal horns.[16,17] Brain abnormalities are attributed to the lack or low levels of IGF-I, which is known to play a significant role in the development of the brain and bony structures of the skull.[17] The facial bones, specially the sphenoid bone and the mandible, are usually underdeveloped.[20,21] Protruding forehead, saddle nose, large eyes, sparse and thin silky hair, and high-pitched voice have also been described by some authors.[5,12]

In a 45-year follow-up study, Laron[2] described that the teeth of GHIS infant patients may be defective and present many carious lesions. Due to the small mandible, the teeth may also be crowded. Histological examination of primary and permanent teeth of GHIS patients showed increased enamel thickness and more pronounced striae of Retzius when compared with nonaffected patients. In this follow-up study, it was also shown that near 4-years-old, many of the patients lost their teeth and needed prosthesis.

CLINICAL MANAGEMENT

The only effective treatment for GHIS, which has been available since 1986,[11] is replacement therapy with recombinant biosynthetic IGF-I, administered subcutaneously once a day. Unfortunately, the restricted amounts of drug for clinical use permitted the treatment of only a small number of patients.[2] The treatment showed a striking increase in head circumference and higher growth rates, body weight, and serum IGF-I levels in those patients.[2,16,22] The multiple pathologies and the dwarfism of untreated patients may impair their quality of life, resulting in emotional suffering and even depression, making these patients in need of continuous psychosocial counseling.[15] It is expected that most of the described consequences could be avoided if IGF-I treatment begins at birth or in infancy and continues throughout life.[2] In spite of many clinical features, GHIS patients have a long life, with the ability to live for more than 70 years.[2,14]

CASE REPORT

An 11-year-old Caucasian boy was brought by his mother to the Pediatric Dentistry Clinic, School of Dentistry, University of São Paulo, Brazil, in 2006 and has been under treatment since then. His chief complaint was prolonged retention of primary incisors, delayed eruption of his permanent teeth, and pain originating from mucosa ulcerations around the area of tooth # 30. Consent forms for examination and authorization of images disclosures for scientific publication were properly signed by the child's legal guardian, according to protocols of the 1996 resolution of Brazil's National Health Council of the Ministry of Health. A copy of the medical report was presented along with the medical exams and clinical diagnosis of GHIS.

Laboratory tests showed markedly elevated GH serum concentrations, low serum IGF-1 with no effective response after exogenous GH, and low serum GHBP. The report suggested that the patient's condition was probably due by recessively inherited disease. Medical reports also related other systemic diseases like hypothyroidism and spastic tetra paretic cerebral palsy with neuropsychomotor delayed development and muscular tissue underdevelopment. The pregnancy was uneventful. The patient was born at 28 weeks gestation by normal vaginal birth. Apgar scores of 5 and 6 were recorded at 1 and 5 minutes, respectively. He did not cry and showed cyanosis, which was treated using mechanical

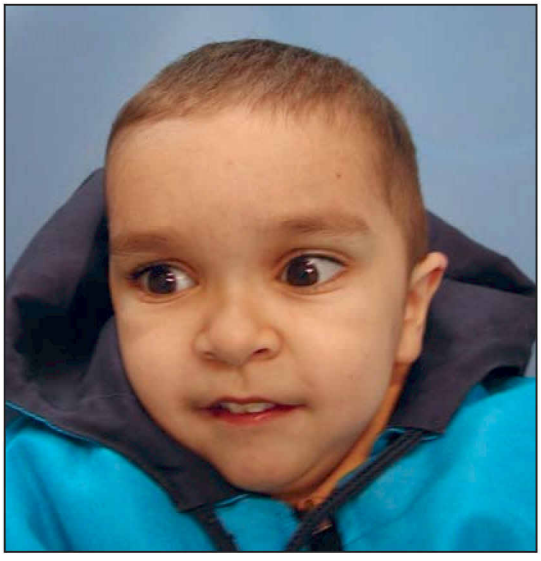

Figure 1. Clinical features of growth hormone insensitivity syndrome.

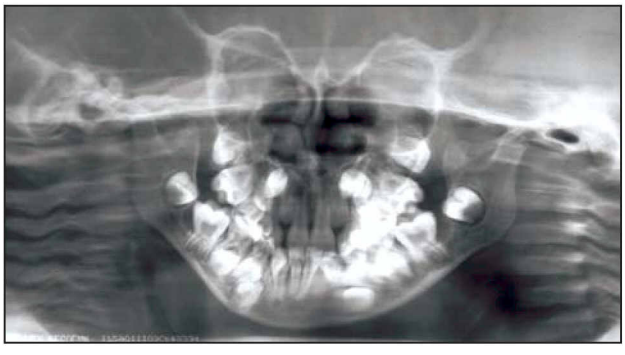

Figure 2. Panoramic radiograph showing lack of space for eruption of permanent teeth on both arches.

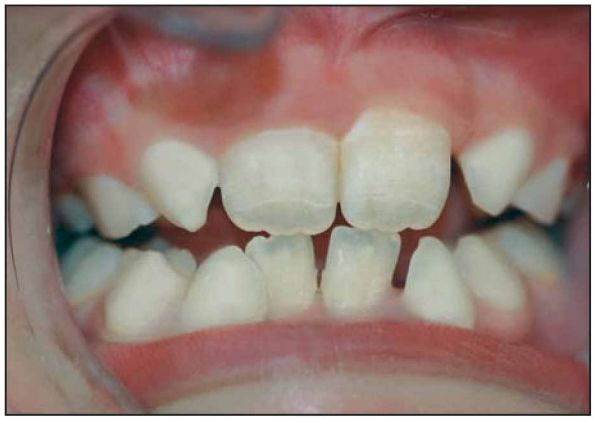

Figure 3. The enamel of a permanent maxillary central incisor shows pronounced striae of Retzius in its incisal portion.

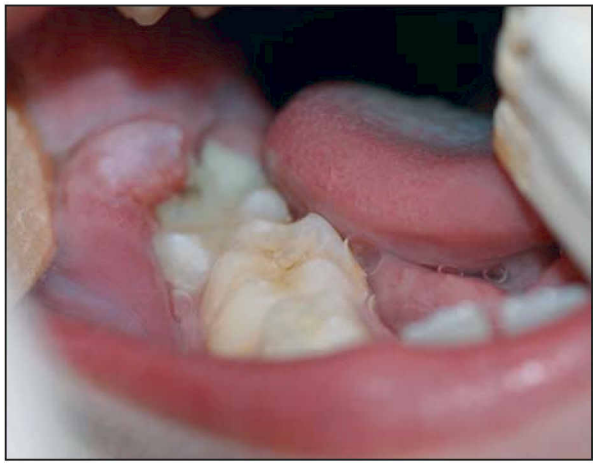

Figure 4. Recurrent ulceration on masticatory mucosa of the permanent mandibular first molar was present due to the lack of space in the posterior area.

ventilation support. At birth, the infant weighted 4.4 pounds and measured 16.53 inches.

The patient's first tooth erupted at 12 months of age. He first lifted his head when he was 4-years-old and was able to sit down without support at 10-years-old. He presented a history of anemia, dehydration, convulsions, and hypoglycemia, which are currently controlled. The patient presented strabismus since early childhood, and was admitted to surgery during the dental treatment, to correct this vision disorder. He has received medical supervision since he was 4-years-old and has not responded to IGF-1 replacement therapy with IGF-I.

Currently, the 13-year-old patient weighs approximately 29 lbs and is 34.64 inches tall. He is totally dependent on others for locomotion, with his mother usually carrying him in her arms (Figure 1). Recent radiographs of the hand and wrist bones were taken to assess his bone age, which was 54 months, despite his chronological age of 158 months.

NONDENTAL FINDINGS

The patient had clinical signs of: dwarfism; delayed bone age; degeneration of the knees; retardation of skeletal maturation; acromicria; latent bilateral nystagmus; spastic tetra paretic cerebral palsy with neuropsychomotor delayed development; muscular and central nervous tissue underdevelopment; hypothyroidism; hypoglycemia; and moderate mental retardation. Cranio-orofacial features showed braquicephaly, increased head circumference, mild strabism even after surgery, both ears slightly folded, mild saddle nose, large eyes, sparse and thin hair, and moderate micrognathia.

DENTAL FINDINGS

The patient's oral and dental features at his first appointment included:

1. ogival palate, probably due to the persistent habit of pacifier-sucking, and mouth-breathing, due to adenoid vegetations;

2. bucally inclined primary maxillary left lateral incisor due to dental trauma and primary mandibular incisors slightly crowded due to a small mandible;
3. prolonged retention of primary teeth and delayed eruption of permanent teeth. This was apparent at 11-years-old, when his 8 primary mandibular and maxillary incisors were still present and 7 of his permanent incisors were unerupted.

DENTAL TREATMENT AND FOLLOW-UP

Considering his behavior, the patient was quiet, but with peaks of anxiety and irritation in the clinical dental setting. He was able to hear and comprehend almost everything that was communicated to him verbally and through body language, but he was not always cooperative. He cooperated well during radiographic examination, but less so during clinical examination and photographic documentation. A variety of behavior management techniques such as tell-show-do, modeling, nonverbal communication, voice control, and positive reinforcement were used to establish a positive relationship with the patient. Neither nitrous oxide nor any type of restraining device was used to facilitate the treatment. When needed, however, the mother was asked to lie across the child's legs to restrain his legs and arms.

Orientations and instructions for diet and oral hygiene were given to the mother, considering the difficulty she had with brushing her child's teeth. This patient needs regular professional dental prophylaxis sessions and fluoride varnish application to counterbalance his deficient oral hygiene and promote inactivation of white spot lesions.

To solve prolonged retention of the primary teeth, delayed eruption of the permanent teeth, and lack of space on both arches, a program of serial extractions was established. As the permanent successors were nearly fully formed, dental extractions of his 8 primary incisors were performed at 2 different appointments. At 13-years-old, the patient presented: lack of space for eruption of permanent lateral incisors on both arches (Figure 2); pronounced striae of Retzius on the incisal portion of permanent maxillary central incisors (Figure 3); and recurrent ulcerations on masticatory mucosa in the area of permanent mandibular first molars, due to the lack of space in the posterior area (Figure 4).

Currently, the patient remains in a program of serial extraction of primary canines for subsequent tentative eruption of permanent lateral incisors and canines. He is likely to ultimately have 20 teeth: 2 incisors; 1 canine; 1 permanent premolar; and 1 molar in each hemi-arch.

DISCUSSION

The patient is currently receiving dental care at the School of Dentistry, University of São Paulo, which will continue in the coming years. The patient's behavior has improved at each consultation. Despite cerebral palsy and moderate mental retardation, the child has been able to collaborate during surgical interventions. Oral hygiene education must continue to be intensive, constant, and given to the mother or caregiver, as the child has neuropsychomotor delayed development and muscular tissue underdevelopment, hindering his motor coordination to perform proper tooth-brushing.

The early introduction of educational, preventive, and orthodontic/orthopedic measures are considered key factors to maintain good oral health throughout a patient's life. Due to systemic characteristics presented, dentists must keep themselves informed about diseases related to this syndrome and be aware if they are properly controlled by the medical specialist before beginning any dental treatment. Therefore, a transdisciplinary treatment must be maintained for these patients.

Since this is the first known case report describing oral findings in a GHIS patient, further study is needed to allow standardized oral characteristics of GHIS, and adequate dental intervention.

CONCLUSIONS

When treating growth hormone insensitivity syndrome patients, dentists have to provide high-quality dental care using behavioral management techniques that enrich the relationship with the patient, maintain constant oral hygiene with parents and caregivers' help, and provide an early orthodontic evaluation. These are the key elements to maintaining good oral health.

REFERENCES

1. OMIM: Online Mendelian inheritance in man. Available at: "www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=262500". Accessed September 18, 2008.
2. Laron Z. Laron syndrome (primary growth hormone resistance or insensitivity): The personal experience 1958-2003. J Clin Endocr Metab 2004; 89:1031-44.
3. Laron Z, Blum W, Chatelain P, et al. Classification of growth hormone insensitivity syndrome. J Pediatr 1993;122:241.
4. Daughaday WH, Laron Z, Pertzelan A, Heins JN. Defective sulfation factor generation: A possible etiological link in dwarfism. Trans Assoc Am Physicians 1969;82:129-40.
5. Ying YQ, Wei H, Cao LZ, Lu JJ, Luo XP. Clinical features and growth hormone receptor gene mutations of patients with Laron syndrome from a Chinese family. Zhongguo Dang Dai Er Ke Za Zhi 2007;9:335-8.

6. Shevah O, Laron Z. Genetic analysis of the pedigrees and molecular defects of the GH-receptor gene in the Israeli cohort of patients with Laron syndrome. Pediatr Endocrinol Rev 2007;5:470.
7. Godowski PJ, Leung DW, Meacham LR, et al. Characterization of the human growth hormone receptor gene and demonstration of a partial gene deletion in two patients with Laron-type dwarfism. Proc Natl Acad Sci U S A 1989;86:8083-7.
8. Silbergeld A, Dastot F, Klinger B, et al. Intronic mutation in the growth hormone (GH) receptor gene from a girl with Laron syndrome and extremely high serum GH binding protein: Extended phenotypic study in a very large pedigree. J Pediatr Endocrinol Metab 1997;10:265-74.
9. Ayling RM, Ross R, Towner P, et al. A dominant-negative mutation of the growth hormone receptor causes familial short stature. Nat Genet 1997;16:13-4.
10. Woods KA, Fraser NC, Postel-Vinay MC, Savage MO, Clark AJL. A homozygous splice site mutation affecting the intracellular domain of the growth hormone (GH) receptor resulting in Laron syndrome with elevated GH-binding protein. J Clin Endocr Metab 1996;81:1686-90.
11. Laron Z, Klinger B, Eshet R, Kanety H, Karasik A, Silbergeld A. Laron syndrome due to a post-receptor defect: Response to IGF-I treatment. Isr J Med Sci 1993;29:757-63.
12. Guevara-Aguirre J, Rosenbloom AL, Vaccarello MA, et al. Growth hormone receptor deficiency (Laron syndrome): Clinical and genetic characteristics. Acta Paediatr Scand 1991;377(suppl):96-103.
13. Laron Z. Natural history of the classical form of primary growth hormone (GH) resistance (Laron syndrome). J Pediatr Endocrinol Metab 2001;14:568.
14. Rosenbloom AL, Guevara-Aguirre J, Rosenfeld RG, Francke U. Growth hormone receptor deficiency in Ecuador. J Clin Endocrinol Metab 1999;84:4436-43.
15. Laron Z. Final height and psychosocial outcome of patients with Laron syndrome (primary GH resistance): A model of genetic IGF-I deficiency. In: Gilli G, Schell L, Benso L, eds. Human Growth from Conception to Maturity. London, UK: Smith-Gordon Publishers; 2002:215–25.
16. Galli-Tsinopoulou A, Nousia-Arvanitakis S, Tsinopoulos I, Bechlivanides C, Shevah O, Laron Z. Laron syndrome: First report from Greece. Hormones (Athens) 2003;2:120-4.
17. Kornreich L, Horev G, Schwarz M, Karmazyn B, Laron Z. Laron syndrome abnormalities: Spinal stenosis, os odontoideum, degenerative changes of the atlanto-odontoid joint, and small oropharynx. AJNR Am J Neuroradiol 2002;23:625-31.
18. Sivan B, Lilos P, Laron Z. Effects of insulin-like growth factor-I deficiency and replacement therapy on the hematopoietic system in patients with Laron syndrome (primary growth hormone insensitivity). J Pediatr Endocrinol Metab 2003;16:509-20.
19. Galatzer A, Aran O, Nagelberg N, Rubitzek J, Laron Z. Cognitive and psychosocial functioning of young adults with Laron syndrome. In: Laron Z, Parks JS, eds. Lessons from Laron Syndrome (LS) 1966-1992. Basel, Switzerland: Karger; 1993:53-60.
20. Scharf A, Laron Z. Skull changes in pituitary dwarfism and the syndrome of familial dwarfism with high plasma immunoreactive growth hormone: A roentgenologic study. Horm Metab Res 1972;4:93-7.
21. Konfino R, Pertzelan A, Laron Z. Cephalometric measurements of familial dwarfism and high plasma immunoreactive growth hormone. Am J Orthod 1975;68:196-201.
22. Backeljauw PF, Underwood LE. The GHIS Collaborative Group—Therapy for 6.5-7.5 years with recombinant insulin-like growth factor I in children with growth hormone insensitivity syndrome: A clinical research center study. J Clin Endocr Metab 2001;86:1504-10.