Growth Hormone Insensitivity Syndrome: Unusual Oral Manifestations

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ABSTRACT

Children with significant growth retardation and normal levels of growth hormone are diagnosed with growth hormone insensitivity. The main oral findings observed in patients with growth hormone insensitivity syndrome (GHIS) are underdeveloped jaws, crowded teeth and delayed eruption of permanent teeth. This manuscript describes a 9-year-old child diagnosed with GHIS, who had delayed eruption of permanent teeth and 14 unerupted supernumerary teeth. All supernumerary teeth were extracted except for two maxillary and one mandibular teeth which were difficult to identify and access. Multiple supernumerary teeth have never been reported before in patients with GHIS. (J Dent Child 2013;80(3):150-3)

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Growth hormone insensitivity syndrome (**GHIS**), or Laron Syndrome, is an autosomal recessive disease caused by genetic alterations in growth hormone (**GH**) receptors, which can cause body resistance to and high levels of GH.[1] It is classified into primary form, with genetic origin and mutations involving the molecular structure or hormonal function, or secondary form, such as in malnutrition, inflammatory conditions, sepsis, and trauma.[2]

This disorder was first described by Laron, who observed children presenting with a genetic form of dwarfism and similar characteristics to the GH deficiency syndrome but with elevated serum levels of this hormone.[1] The molecular defects in patients with GHIS may be caused by post-receptor defects or may be exon deletions or mutations in the extracellular, transmembrane, or intracellular domain of the GH receptor.[2-6] Affected patients have low serum levels of insulin-like growth factor I (**IGF-I**), insulin-like growth factor binding protein-3 (**IGFBP-3**), and growth hormone binding protein, but may present with increased GH levels.[7] In addition to that, patients may fail to respond to exogenous GH administration.[1,4,7,8] Daily subcutaneous administration of biosynthetic recombinant protein IGF-1 is the treatment of choice for GHIS.[1,7]

The diagnosis of GHIS is based on its characteristic clinical features, high GH serum values, and low IGF-I serum levels before and after GH administration (IGF-I generation test).[8,9] These patients may also exhibit an impaired sense of psychological well-being, depressed mood, social anxiety, and fatigue.[10,11] Increased LDL cholesterol concentration and reduced bone mineral density are additional common features.[11]

Short stature, trunk obesity, small feet and hands, saddle nose, frontal bossing, underdevelopment of facial

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bones, hypogonadism, hypogenitalism, larynx closure, high-pitched voice, and delayed dentition are possible clinical features.[1,12] Oval palate, small jaws, and delayed eruption of permanent teeth are other common findings in these patients.[7,13-15] Additionally, the patients may present thicker enamel and dental crowding as a result of mandibular underdevelopment.[16,17]

In GHIS patients, it is important to perform imaging exams to detect jaw abnormalities.[18,19] For this purpose, cone beam computed tomography (**CBCT**) has been widely used, since it provides dentists with the most accurate, three-dimensional anatomical information of the maxilla, mandible, teeth, and supporting structures as well as the best possible cost-benefit relationship between dosage and information.[18,20]

The purpose of this paper is to report a case of a young patient with GHIS who presented 14 supernumerary teeth.

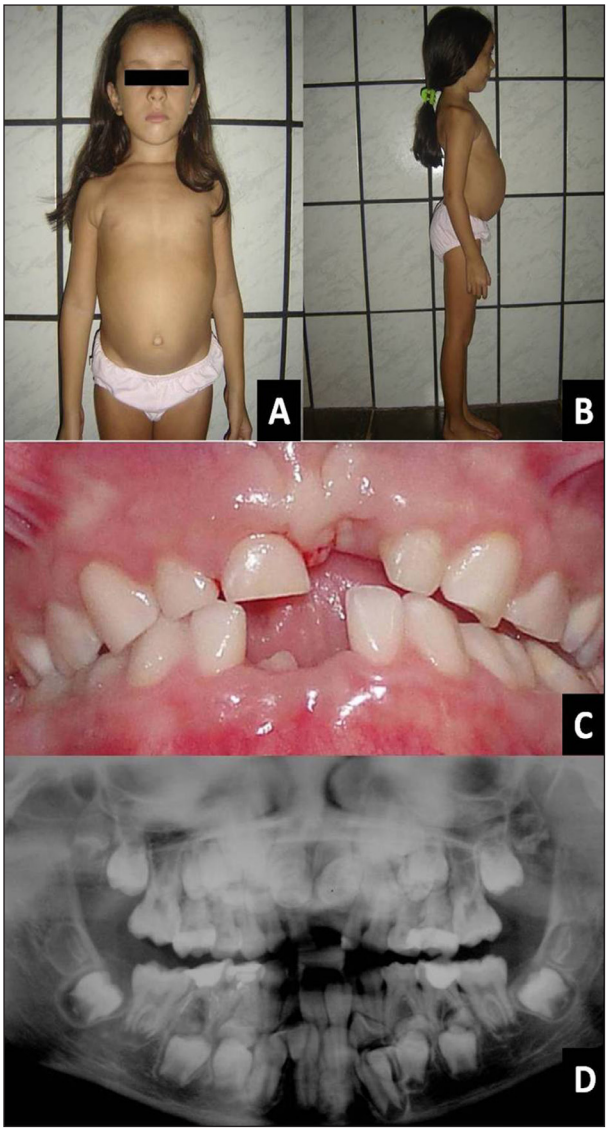

Figure 1. 9-year-old female with GHIS with immature development in addition to short stature, large belly (A), and exaggerated lumbar curvature (B). Intraoral photo showing mixed dentition stage (C). Panoramic radiograph showing multiple supernumerary teeth (d).

CASE DESCRIPTION

A 9-year-old Caucasian girl sought dental care in the Department of Restorative Dentistry, at the School of Dentistry, University of Cuiaba, Brazil, with the chief complaint of delayed eruption of permanent teeth. She had been diagnosed with GHIS by an endocrinologist at 2 years of age. The diagnosis was made based on a clinical observation of short stature (75 cm at that age), positive GH response to clonidine stimulation, and low titers of IGF-I (0.06 ng/mL; normal level: 64-358 ng/mL) and IGFBP-3 (1.76 ng/ml; normal levels: 1.8-7.1 mcg/mL).

On physical examination, the patient was 121.5 cm tall, weighed 19.8 kg, and presented with a large belly and exaggerated lumbar curvature (Figures 1A-B). The intraoral examination revealed healthy soft tissues, underdeveloped jaws, and delayed eruption of permanent teeth (Figure 1C). The panoramic radiograph showed 7 supernumerary teeth in the maxilla and 7 in the mandible (Figure 1D). A CBCT confirmed the presence and position of the supernumerary teeth and their interference with the eruption path of the permanent teeth (Figures 2A-F).

The removal of supernumerary teeth was done under general anesthesia. Lidocaine 2 percent with epinephrine 1:200,000 was administered, and palatal and lingual approaches with intrasulcular incision and raising of maxillary and mandibular full mucoperiosteal flaps were made. Eleven supernumerary teeth were removed after osteotomy with a carbide tungsten bur and copious saline irrigation. An osteoplasty was performed and the soft tissues were sutured. Two maxillary and 1 mandibular supernumerary teeth could not be removed at that time due to difficulty with identification and access (Figures 3A-B).

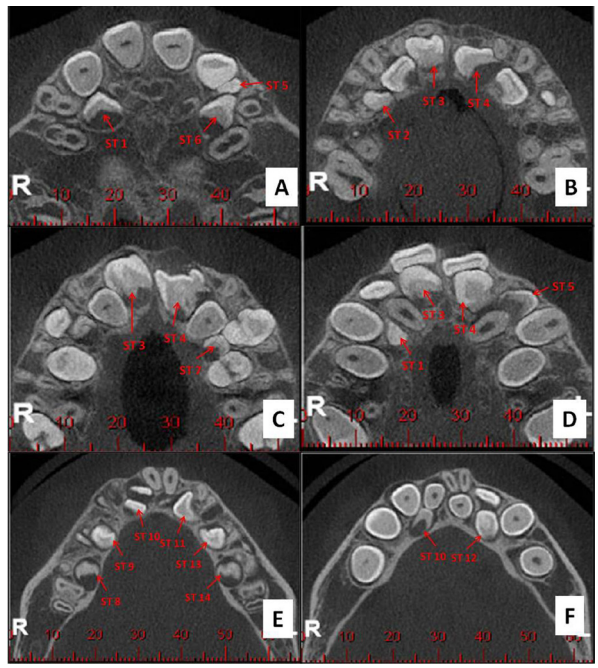

Figure 2. CBCT image showing 7 supernumerary teeth in the maxilla (A–D) and 7 in the mandible (E–F).

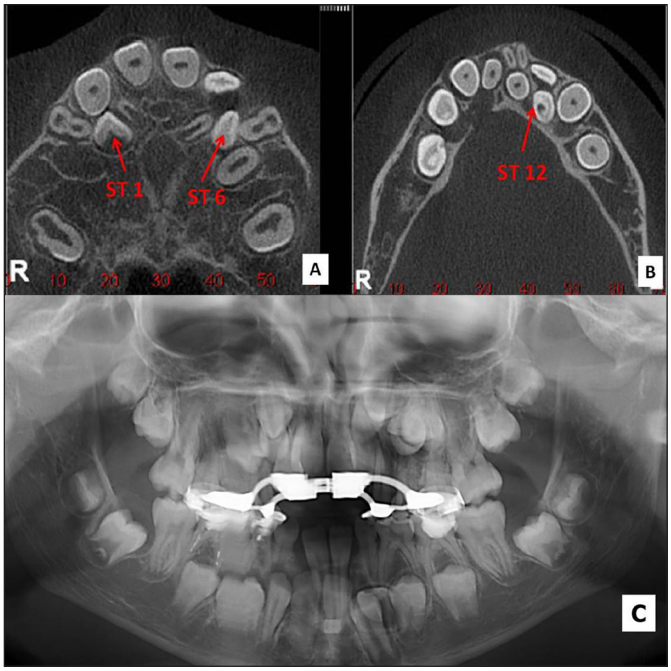

Figure 3. Postsurgical CBCT showing the remaining 2 supernumerary teeth in the maxilla (A) and 1 in the mandible (B). Panoramic radiograph view taken 2 years later (C).

After 2 years, the patient showed exfoliation of the primary teeth, eruption of the permanent teeth, and evidence of bone formation in the surgical sites (Figure 3C). The patient will undergo surgery to remove the remaining supernumerary teeth under local anesthesia in the near future. Follow-up appointments will be scheduled to monitor the patient's oral health status.

DISCUSSION

Most patients with GHIS belong to consanguineous families, suggesting the penetrating and recessive character of the syndrome.[21] However, in this case there was neither kinship between the patient's parents nor other cases of the syndrome in the family.

One of the chief characteristics of GHIS is the patient's nonresponse to exogenous GH administration,[1,7] as the development failure is provoked by alterations in the GH receptor[1] rather than the GH secretion, as in other syndromes.[22] Prolonged retention of primary teeth, delayed eruption of permanent teeth, crowding, and small jaws are the most common oral manifestations found in patients with GHIS.[1,7] Furthermore, tooth development may be accelerated in patients with early replacement of IGF-I.[7]

The presence of multiple impacted permanent teeth, supernumerary teeth, and root anomalies was already described in cases of Gardner syndrome associated with GH deficiency.[23] However, to our knowledge, this is the first case report of multiple supernumerary teeth in GHIS. The large number of supernumerary teeth (7 in the maxilla and 7 in the mandible) seen in this patient is rather uncommon, even in syndromic patients. Their presence, together with the underdevelopment of the dental arches and the characteristic eruption delay seen in patients diagnosed with GHIS, may have interfered in the exfoliation of primary teeth and in the eruption of permanent teeth.

The tooth development process depends on epithelial-mesenchymal interactions, whereby communication by secreted paracrine signals is established to direct dental morphogenesis and the polarization and differentiation of the cells producing hard dental tissue. It was demonstrated that the overexpression of specific signaling protein markers could induce an increase in cellular activity that may possibly help to explain some dental defects such as hyperdontia.[24] GH elevated serum levels in early moments of odontogenesis could have played a role in the development of the supernumerary teeth seen in this case. Hyperdontia, however, has not been previously described in GHIS.[1,7]

There is no consensus on the best diagnostic tool for the accurate identification of supernumerary teeth, whether it be clinical examination alone, image exams, or another means.[19,25,26] Imaging exams are always required to evaluate the development of the dentition and assess possible alterations in the maxillary bones.[18] In our case, the visualization of the supernumerary teeth in the panoramic radiographic exam was hampered due to its two-dimensional characteristic. Thus, the radiograph showed the images of superimposed tooth germs due to the large amount of supernumerary teeth. Moreover, the onset of mineralization depends on the tooth type; hence, tooth buds with a late onset of mineralization could give a false-negative diagnosis of supernumerary teeth on radiographs, making them an inappropriate diagnostic tool.[19] CBCT is capable of producing images of the oral and maxillofacial region with higher quality and sharpness, largely replacing conventional tomography.[20] This feature was crucial in this case, as it allowed the accurate localization of the permanent and supernumerary tooth germs.

Despite the quality of the images and the surgeon's dexterity, 2 maxillary supernumerary teeth around the canine region were not extracted, since excessive bone removal was needed to guarantee appropriate access. Moreover, a mandibular supernumerary tooth was not removed during a second surgery due to the difficulty in its identification during the procedure.

CONCLUSION

Delayed tooth eruption in patients diagnosed with GHIS may be due to the presence of supernumerary teeth.

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