CASE REPORT

Hutchinson-Gilford Progeria Syndrome (HGPS): relevant aspects of a rare syndrome diagnosed in a Brazilian child

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Abstract:

Hutchinson-Gilford Progeria Syndrome (HGPS) is an extremely rare genetic condition characterized by premature aging and it's about one case for every four to eight million people. Children affected usually have premature death due to cardiovascular problems. The gene that causes progeria was recently discovered and it has attracted the interest of the scientific community worldwide not only by the possibility of cure of this genetic pathology but also because of the possibility to retard or to minimize the effects of premature aging caused by the disease in human beings. Among the oral and facial findings is remarkable the delay in tooth eruption, the micrognathia and the disproportion between the skull and face. Dental treatment is directed to preventive aspects and strict supervision of oral conditions in order to minimize the need for more invasive treatments. The authors highlight the most relevant aspects related to that syndrome, emphasizing the important aspects to all the oral and maxillofacial surgeons, reporting a case of progeria in a five-year old Brazilian child.

Keywords: cell aging; oral manifestations; progeria.

INTRODUCTION

Hutchinson-Gilford Progeria Syndrome (HGPS) is an autossomal dominant genetic condition extremely rare and fatal, affecting one person in every four to eight million person, affecting both sexes. The term progeria is originated from Greek and means "prematurely old". Hutchinson[1] and Gilford[2] were who first described the disease, respectively in 1886 and 1904 in England. Since then, fewer than 100 cases have been reported and currently around 40 cases diagnosed[3]. In 2006, Hennekam[4] reviewed the phenotypic expression of 132 patients with HGPS from published reports, and other 10 of his case series in one of the most complete paper found in the literature.

The origin of HGPS is linked to a genetic alteration in the LMNA gene producer of the lamin A protein, responsible for maintaining the architecture of the cell nucleus. It is suggested that the absence of that protein provides instability of the cells and its consequent aging period before the physiologically expected[3-6]. The most common mutation in patients with HGPS is located at codon 608 (G608G)[3]. Recently, several studies have been conducted using inhibitors of the genetic alteration for the purpose of establishing a cure and providing better quality of life for affected patients[7-11].

The appearance and growth of the child are usually normal during the first year of life and the clinical picture is typical when installed, rarely requiring differential diagnosis with other diseases. Alopecia, exophthalmos, pinched nose, thin lips, craniofacial disproportion, micrognathia, scleroderma-like skin, hypotrichosis, eyebrows and eyelashes often absent, nail dystrophy, delayed and abnormal dentition are common findings, mental development is preserved[12]. Hennekan[4] showed the main features of HGPS after analyze 132 patients with the pathology arising from the scientific literature and he added 10 patients (Table 1).

There are many oral manifestations of HGPS, and Dentistry professionals can accomplish an important role in the study of patients with the syndrome, requiring the collection of information about those events involving the mouth, head and neck that can be clinically evident and radiographic analysed[13]. Oral, facial and bone manifestations of patients affected by HGPS have been comprehensively presented in the Table 2.

This paper aims to highlight relevant aspects related to HGPS, emphasizing oral and maxillofacial findings through the report of a case involving a Brazilian child of five year and ten months old.

Table 1. Findings in patients with Progeria (Hennekam, 2006).

Feature	Frequency
Prenatal growth delay	+
Postnatal growth delay	++++
Normal skull growth	+++
Cognitive development	++++
Hair sparse/alopecia	++++
Increased visibility vessels	
Cranium	++++
Nasal bridge	++++
Prominent forehead	++
Absent eyebrows/eyelashes	+++
Small face	++++
Thin nasal skin	++++
Convex nasal profile	++
Crowded teeth	+++
Increased dental decay	+++
Absent ear lobule	++
High voice	++++
Lipodystrophy	++++
Narrow upper torax	++++
Prominent abdomen	++++
Broadened finger tips	+++
Nail dystrophy	+++
Horse riding stance	+++
Decreased mobility	
Elbows	++++
Wrists	++
Fingers	++++
Hips	++++
Knees	++++
Ankles	++
Stroke	
Angina pectoris	

+: 0-25%; ++: 25-50%; +++: 50-75%; ++++: 75-100%.

CASE REPORT

A female, 5 year-old and 10 months, born in the city of Sobral, Ceará State, Brazil, was referenced to a basic health unit to carry out dental treatment in the outpatient clinic for patients with special needs of the Specialty Dental Center of Sobral. The patient already had a diagnosis of HGPS and was met regularly for about a year and a half by a medical team at Albert Sabin Children's Hospital, located in the city of Fortaleza, capital of Ceará State, 220 km away from Sobral.

Her medical history included low immunity, frequent respiratory crises and recurrent episodes of high fever that required hospitalization, but no fever screening about six months.

Her latest available complete blood count (CBC) was with normocytic and normochromic red blood cells, neutrophils

Table 2. Oral, facial and bone manifestations of patients affected by Progeria (Maloney, 2009).

Dental manifestations of HGPS	Head and facial manifestations of HGPS	Jaw manifestations of HGPS
Secondary incisors located lingually and palatally	Sparse to absent eyebrows and eyelashes	Micrognathia
Delayed tooth eruption of primary and secondary dentition	Sparse to absent scalp hair	Hypoplastic mandibule
Abnormal tooth formation	Craniofacial disproportion	Atrophy of alveolar process
Anodontia	Sculpted beaked nose	Retarded anterior and vertical growth
Hypodontia	Peri-oral cyanosis	Obtuse mandibular angle
Discoloration	Large cranium	Craniofacial disproportion
High caries incidence	Prominent forehead and frontal bossing	Short mandibular ramus
Poor oral hygiene	Prominent scalp veins	Small maxillary arch
Narrow pulp chambers	Prominent eyes	Narrow and high palatal vault
Irregularity in sizes and shapes of the odontoblasts	Small mouth	Comparative paucity of vertical growth of the condyle
Delay in calcification of the crowns of the permanent teeth	Relatively large tongue	
Reticular atrophy of pulp	No subcutaneous fat	
Calcification along the nerve fibers and the vascular walls	Delayed closure of fontanelles and sutures	
Incomplete formation of roots of primary molars		

without signs of degeneration and lymphocytes without any atypia, platelets in normal number and shape, and mild eosinophilia. Rates of LDH (lactate dehydrogenase), CPK (creatine), GOT (aspartate aminotransferase) and GPT (alanine aminotransferase) normal, and c-reactive protein negative. Vital signs were preserved.

Physical and extra-oral atypical features for her age were observed, including: alopecia, aged appearance of skin with numerous spots, increased skull ratio in relation to the face with a clear view of cranial veins, pinched nose, the absence of lashes and eyebrows, upper and lower limbs with clear visualization of the bone contours, suggesting the absence of subcutaneous fat, dystrophic nails of fingers and toes, evident knees, prominent eyes, hypertelorism, low weight and height for children from same age (Figure 1A, 1B and 1C). Relatives said the child was born with weight, height and aspects of normality and the first signs of changes were observed at 4 years of age, with marked alopecia. Parents are not consanguineous and the other children in family are normal. The cognitive and affective functions of the child are completely preserved including the following school activities. She shows communicative, expansive and receptive approach to dental treatment, establishing emotional bonds with all professionals.

Intraoral physical examination was hampered by the limitation of mouth opening, around 25 mm (Figure 2A), but it was possible to observe the tongue without papillae (Figure 2B), poor oral hygiene, with the presence of calculus, gingival inflammation, tooth mobility and numerous cases of caries in deciduous teeth (Figure 2C). The teeth appeared

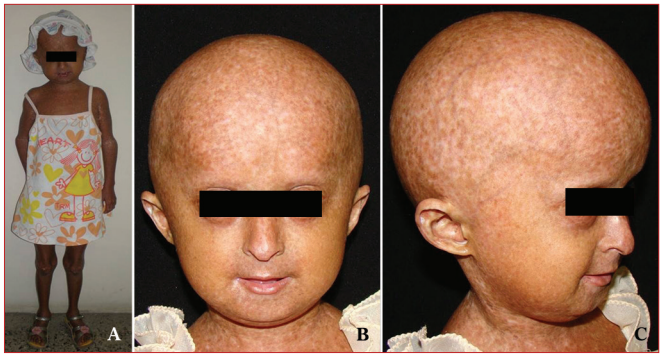

Figure 1. Clinical aspects. A: Aged appearance of skin, upper and lower limbs with clear visualization of the bone contours and evident knees. B: Alopecia, proeminent eyes and absence of lashes and eyebrows. C: Increased skull ration in relation to the face, clear view of cranial veins and pinched nose.

extremely fragile and palate showed up in an ogival shape. The panoramic radiography was requested, dated of August of 2006, where were observed agenesis of tooth germ of inferior left pre molar, multiple cavities in the upper lateral incisors, canines, upper and lower molars and upper and lower tooth left inferior deciduous canine, and the absence of the central deciduous. The mandible presented in small sizes. Periapical bone rarefaction could be observed in tooth left inferior deciduous molar. The germs of all permanent teeth were noted, except for germ of mandibular pre molar (Figure 3). Were faced limitations for a better interpretation of this test, because the movement of the patient during its acquisition.

Dental treatment consisted of oral health status improvement procedures, prophylaxis, and application topical fluoride,

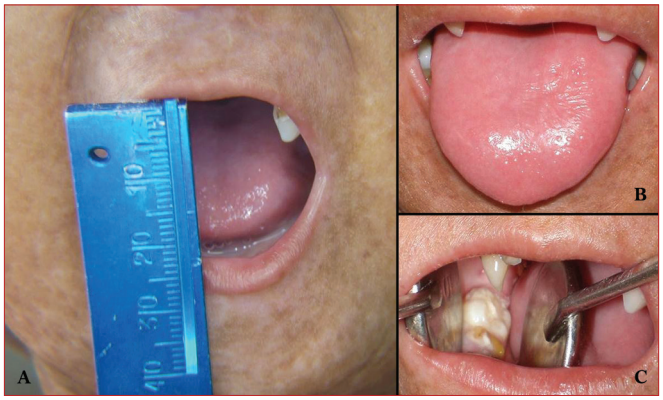

Figure 2. A: Limitation of mouth opening; B: Tongue without papillae; C: Caries in deciduous teeth.

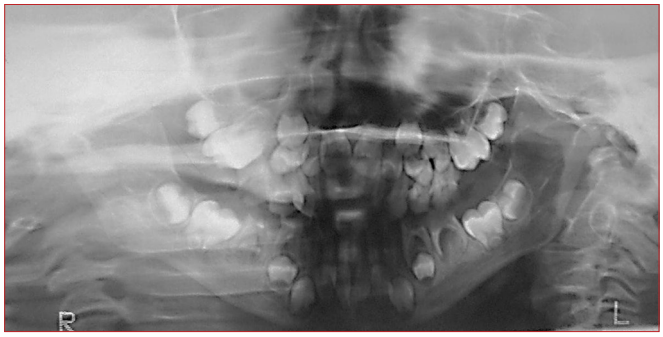

Figure 3. Initial panoramic radiography.

removal of teeth sunk, restoration, removal of dental calculus (Figure 4). The family and the patient were thoroughly informed about the importance of oral health and oral hygiene guidelines were systematically passed. Considering the difficulties of transport and movement of the patient, the family was advised of the need to return the patient weekly for the first two months and monthly after that period with the purpose of reviewing and implementation of procedures if necessary. New panoramic radiograph was obtained on February of 2009 (Figure 5). Only the upper deciduous canines were present and restored, while the 52 and 64 teeth were decayed. The teeth 32, 31, 41 and first permanent molars, with normal dimensions, had erupted normally in the oral cavity and the upper incisors presented clear delay in the process of eruption, considering the patient was 8 years and 4 months old. On June of 2009 a radiograph was obtained for evaluation of carpal bone age, estimated at 3 year-old and 7 months, despite the patient meet with 8 year-old and 8 months (Figure 6). All dimensions obtained were lower than normal (length of the metacarpals, hamate, capitate and proximal phalanges, and reduced width of the capitate and distal epiphysis). Lateral radiographical analysis showed bimaxillary micrognathia, considerable craniofacial disproportion and measurement of the gonial angle above normal proportions (Figure 7).

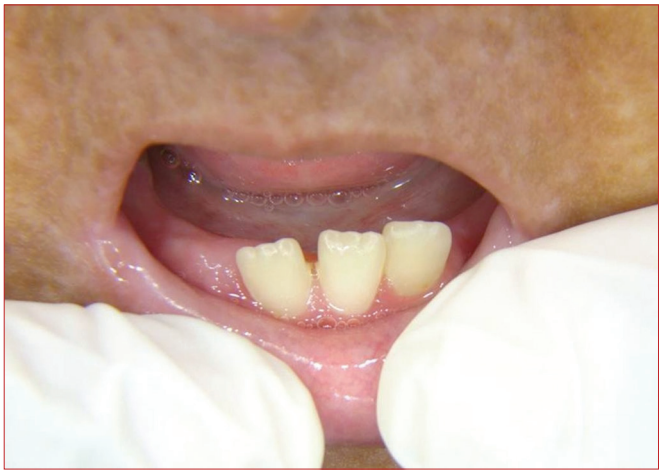

Figure 4. Prevention and conservative dental treatment.

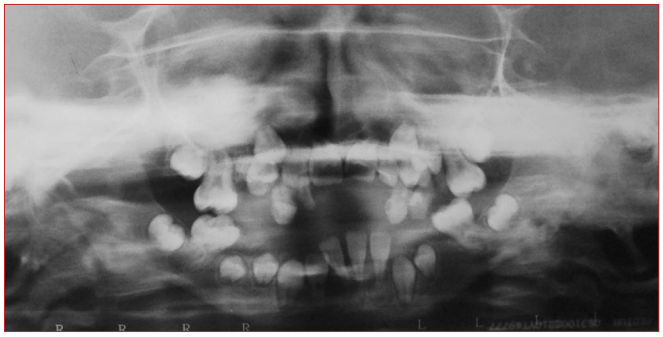

Figure 5. New panoramic radiography obtained after 2 years and 6 months.

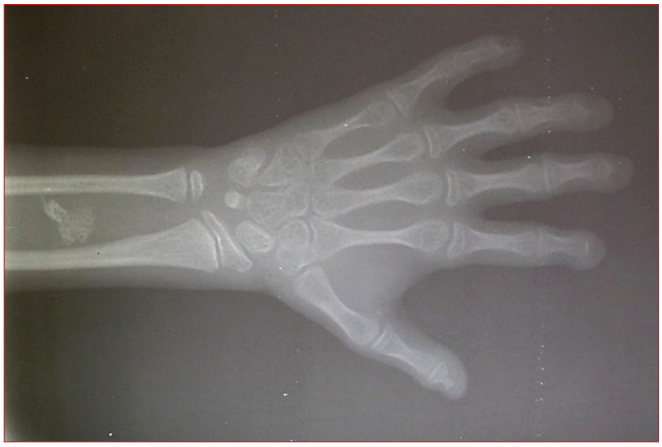

Figure 6. Evaluation of carpal bone age, estimated at 3 year-old and 7 months, despite the patient meet with 8 year-old and 8 months.

The patient is in medical (undergone cardiac evaluation, since the cardiovascular disease, which is a relevant issue of this syndrome, and it can modify the treatment plan) and dental follow-up. From the dental point of view there is not any modification for the treatment compared with patients not affected by HGPS only care about the weight of the patient,

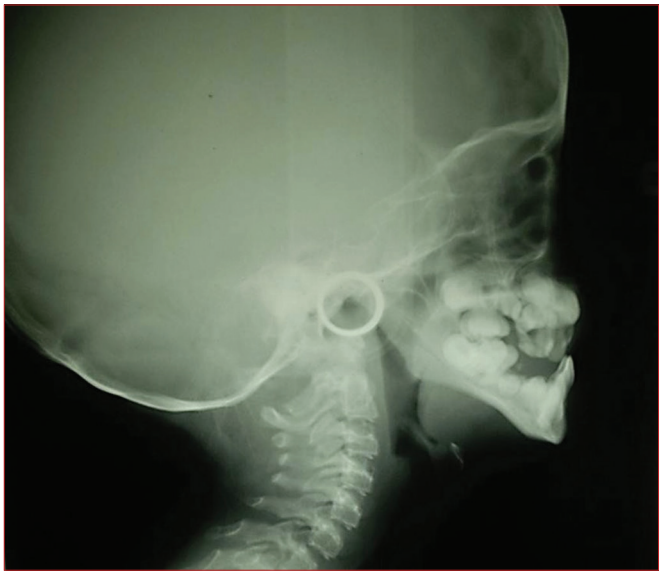

Figure 7. Lateral radiographical showed bimaxillary micrognathia, craniofacial disproportion and measurement of the gonial angle above normal proportions.

to avoid an excessive dose of local anesthesia when necessary use and being very important for other drugs prescription as antibiotic and analgesic that currently used in dental practice. The limited mouth opening makes it difficult to dental care indicates the great need for preventive measures, minimizing the need to perform more invasive procedures (dental extractions of permanent teeth for example).

DISCUSSION

The HGPS is a genetic dramatic condition since the literature shows an average life expectancy of 13 years in affected patients, having as a life limitation the cardiovascular disease and typical progressive atherosclerosis of individuals with advanced ages[3,14,15]. A fatal case of lung hypertension was reported in a male child younger than 12 year-old[16] and another report was the association between osteosarcoma and HGPS[17]. The fact that life expectancy is reduced arguably puts the health professionals at a serious dilemma because they cannot omit any information or even the real diseases course. The patient reported here already had a diagnosis of HGPS, making it less uncomfortable for the dental team to address the aspects of the syndrome with relatives. The patient was under medical supervision without major diseases associated with support and supplementary regular laboratory tests. Despite the recent discovery of the gene that causes HGPS[3,5,6], there is still no cure of HGPS, although recent studies go on and move forward toward finding drugs that inhibit or prevent that premature aging of patients protecting their lives. Inhibitors of the enzyme called farnesyl-transferase (FTIs) prevent the Lamin A protein of adding the farnesyl group in its structure, thereby preventing the mutation[7-11]. The biggest obstacle to the establishment of cure is the small number of cases, beyond that not all patients have the typical phenotype[3].

Regarding the differential diagnosis the Werner's syndrome has many similarities in regard with HGPS, being a key distinction between the two pathologies besides the involvement of the WRN gene instead of LMNA, the age at diagnosis, which occurs in adulthood in the first and in childhood in the second[18].

It deserves a remarkable citation the work of the Progeria Research Foundation (http://www.progeriaresearch.org/index.html), an organization whose mission is the discovery of a cure and effective treatment of this condition and its changes related to aging. All available information about HGPS, including scientific literature, the case record, contact and assistance to affected patients and their families, recent advances and scientific meetings are available on the web page. Several workshops were organized by the Foundation in 2001, 2003, 2004, 2005 and 2007 with representatives of the largest clinical scholars and researchers on the subject areas of molecular biology, immunology, geriatrics, endocrinology and genetics, among others[19,20].

Viégas et al.[21] reported cases of twin Brazilian males, affected by HGPS. Both patients presented alopecia, craniofacial disproportion, absent eyebrows, short and sparse eyelashes. Had the appearance of aging skin, especially hands and feet, and nail dystrophy. According to the authors, the twins had complete dentition and malocclusion, high palatal vault and micrognathia. Had normal IQ, although severely depressed and have difficulties in adapting to the hospital. Except for the complete dentition, the other characteristics are similar to the case reported in this study differed also with regard to behavioral aspects.

In 1981, Lembke et al.[12] also in Brazil addressed the biopsychosocial aspects related to a 17-year-old, female, carrier of HGPS. The patient had all the typical features of HGPS and the emphasis of this work was the story of the family situation, living and food conditions, understanding by the family and the psychological aspects. Unfortunately the story is very similar to the case described here, as the humble origin of the patient and poor housing conditions and food provided by family, often the result of the absence of public politics for social inclusion of people through access to education and health services. It reflects a sad reality in countries where social gains are still far from ideal. Fortunately, medical and dental treatment has been available to patients by the Health Unique System (HUS) - the medical and dental public service from Brazil - as well as guarantees of transportation to all the outpatient services, a situation not so common to most of the poor people in Brazil.

Yu et al.[22] reported the first case of a Chinese child with HGPS, a boy of 11 year-old with no family history of consanguinity. Common features of HGPS were observed in the patient.

The oral and maxillofacial region had craniofacial disproportion, hydrocephalic aspect, pinched nose and beak-shaped, "face like a bird", mandibular micrognathia, very few hair and eyebrows, microphthalmia, microcornea suffering from cataracts and glaucoma. The oral examination revealed a small mouth opening and pale mucous membranes. The tooth 21 was the only of the permanent dentition; the deciduous teeth were all present except for 62 and a mandibular central incisor. The teeth were relatively small, brownish yellow, lusterless, and as a result of maxillary hypoplasia, were found crowded teeth in buccal and lingual views. The palate was high and narrow and level of the tongue were high due to the narrowing of the mandible. There was no alteration of TMJs and radiographically was observed short and obtuse mandibular ramus, and marked hypodontia, present only the germs of the four first permanent molars and tooth 21. Except for the absence of most permanent teeth and involvement, the other characteristics are consistent with this reported case.

Batstone and Macleod[14] reported a case in a male child of 12 year-old and 6 months. The patient was referred for extraction of second molars, frequently affected by pericoronitis despite good hygiene of the patient. In a follow-up period of three years, no progression in the eruption of these teeth, and prevent the eruption of first molars. The patient had the typical features of HGPS. Mouth opening corresponded to a 2-year-old, around 30 mm. The teeth appeared normal color, shape and size. At 12 years of age the patient had dental eruption compatible with the age of 9 years and root development was compatible with the age of 11 years. The authors presented radiographic follow-up for a period of five years. He was suspended the use of aspirin a week before the day of tooth extraction, which occurred under general anesthesia through the use of fiber-optic intubation. The authors mention the inelasticity of the skin, a factor that impeded access, causing lesions in the labial commissure. Extractions were performed by surgical approach and by tooth section. The patient's compromised systemic conditions, including ischemic cardiovascular disease, probably determined the choice by the use of general anesthesia, notwithstanding the difficulties of access and possible trauma to the patient if local anesthesia was used, unlike this present study where the dental procedures were possible under local anesthesia despite the difficulty of access due to the extreme limitation of mouth opening. This report also warns about the need for preventive dental actions in relation to patients with HGPS to minimize the need for more invasive procedures.

Rodrigues et al.[23] reported a case involving a Brazilian child, female, eight years old. The patient originated from an uncomplicated pregnancy of consanguineous parents, born with normal weight and height. The mother reported has not observed any abnormality until 3 years old and since then noticed hair loss and growth retardation, no deficit of intelligence to eight years old, normal neurological development and school and psychosocial skills unchanged. There were all the typical features of HGPS, with no similar reports in the family, including four brothers without amendments. She possessed approximate size of a three year-old child. Its feature include alopecia, hypertelorism, absence of eyebrows and eyelashes, small and pinched nose, craniofacial disproportion, the cranial veins prominent, low-set ear and micrognathia. In relation to the dentition she had frail teeth, delayed eruption and poor oral health condition. Generalized osteoporotic changes were seen radiographically, including osteolysis of distal phalanges in both hands. The authors cite the creation of proper medical monitoring of children and symptomatic treatment as necessary. In general, the features described are consistent with those reported in this clinical case, both in relation to oral and maxillofacial findings and in relation to the general findings.

Gordon et al.[24] studied retrospectively and prospectively information on 41 children from the Progeria Research Foundation and the Research Database Brown University Center for Gerontology suffering from HGPS arising from 14 different countries. For oral and maxillofacial findings in all seven children who had magnetic resonance between the ages of 8 and 11.3 years, showed the permanent incisors located in the lingual and palatine mandible and maxilla respectively, in relation to deciduous teeth. All children were crowd and delay of eruption of deciduous and permanent teeth of maxilla and mandible. Progressive acroosteolises in some or all fingers of the hand with increasing age was a common finding, as well as abnormalities in the development of the mandible. Overall was observed progressive bone dysplasia in patients with HGPS, which varies in relation to classic aging. The study showed focal demineralization and non-classic bone structures, higher when compared to the general demineralization seen in osteoporosis of normal aging, but no increased risk of fracture, and one sign of vascular insufficiency. There was no rheumatoid arthritis or osteoarthritis. The involvement of patients in relation to weight gain was an important finding of the study (0.44 kg/year). Considering the clinical case described in this paper, some points of comparison are not possible because if the limitation of our dental center of obtaining imaging examinations of other non facial anatomical structures. In relation to oral and maxillofacial region, delay in dentition is consistent with the results of the study, but the crowding was not observed because of the deciduous incisors were extracted earlier. The hypo mandibular development and changes of the phalanges were also observed in the patient in this study.

In 2008, Merideth et al.[15] prospectively characterized clinical fifteen white patients suffering from HGPS between one and 17 years of age, 7 men and 8 women. The clinical diagnosis was performed on average at 19 months of life of patients, ranging from 3 ½ months to 4 years, based on the failure of children's development and changes in the skin, seen in all of them. Alopecia was observed in 13 patients, sleep with eyes open in 11; circum oral cyanosis in 09; scalp veins prominent in 08, and decreased joint movements in 07. All had proven mutation of the LMNA gene. Two patients died from acute myocardial infarction at 13 years and 5 months of age and 17 years and 11 months of age respectively. All patients had aged appearance, prominent eyes, micrognathia, little subcutaneous fat, dimpled and mottled skin, prominent dermal blood vessels, changes in the fingers and joints. The majority had changes in skin color and pigmentation. All had normal average weight at birth. Oral abnormalities of these patients were subsequently evaluated by Domingo et al.[6]. Hypodontia occurred in seven patients, five dysmorphic teeth, mandibular angle acute in eleven, and basilar bone thinning in eleven. Deep palate was seen in eight patients, median cleft palate in seven, and seven had ankyloglossia. The average dental age (9 months to 11 years and 2 months of age) was lower than chronological age (1 year and 6 months of age to 17 years and 8 months of age) patients. In cephalometrical evaluation, the gonial angle was enlarged in all patients. Regarding the case reported in this study, there were no cleft palate and shortened frenulum, while the tongue without papillae found in our patient was not mentioned by Domingo et al.[25].

The implications of oral and maxillofacial presented by Maloney[13] show the amount of possible changes to be observed in patients with HGPS. We reaffirm the reasoning of the author about the importance of dentists regarding the knowledge of that syndrome, as well as records and disclosure. Not all characteristics mentioned in the article are present in the patient reported herein, such as the condition often quoted, the crowding and dental bad position, in this case by the very lack of eruption of teeth. We understand that many of the oral manifestations are from each other, thus micrognathia represents less space for the tongue and the normal eruption of teeth, probably due to delayed eruption and crowding. Similarly, the limitation of mouth opening provides greater difficulty of cleaning the mouth, resulting in a higher chance of developing caries and periodontal diseases. About the size, shape and color of teeth literature is not unanimous on the findings, it is not an atypical fact that the patient has normal range of these parameters, despite the appearance weakened by decay and involvement of many of his teeth. The tongue without any papillae found in our patient, was not mentioned by the author. Based on the findings of Eriksson et al.[6] on the etiology of HGPS structurally related to the gene LMNA new horizons were opened to the scientific community. In addition to the healing of HGPS, who knows the ramifications arising from its research and analysis, especially in genetics, providing greater knowledge about the aging process and age-related diseases such as atherosclerosis and thus are discovered the source youth or the elixir of life, as cited Pollex and Hegele[3].

The Progeria Research Foundation was recently contacted to notify the case of HGPS described in this work. In the literature was observed only four reports of patients with HGPS at Brasil[12,21,23], including the case of twins, in a country of continental size and population currently estimated at 192 million[2]. Publications in journals focused on dentistry, emphasizing oral and maxillofacial aspects of HGPS, we found only four[13,14,22,25].

CONCLUSION

This case report aims to contribute to a better knowledge of this rare condition among the scientific community dentistry.

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