Treatment Considerations in Hutchinson-Gilford Progeria Syndrome: A Case Report

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Hutchinson-Guilford progeria syndrome is an extremely rare condition classified as one of the premature ageing syndromes. This case presents a 16-year-old Israeli female patient, suffering from a variant of Hutchinson-Guilford progeria with a history of treatment with oral biphosphnates. The patient presented with typical cranial and facial features of the syndrome including delayed teeth eruption and root development probably due to insufficient jaw growth and severs retrognatic position of the maxilla and mandible. Orthodontic treatment considerations are described along with those required in light of the previous treatment by oral biphosphonates.

All primary teeth were extracted in three appointments while creating as minimal trauma as possible to the surrounding tissue and alveolar bone. For now, the patient refuses to begin the orthodontic treatment course. There are no limitations to conduct any dental procedures in progeria patients, however, extreme caution must be exercised during oral surgery due to the inelasticity of tissues and dermal atrophy. Orthodontic procedure commencement should be early enough to manage the delayed development and eruption of teeth. Patients taking oral biphosphonates should be advised of this potential complication. If orthodontic treatment is considered appropriate, plans should be assessed and modified to include compromises.

Key words: *Hutchinson-Guilford progeria, Orthodontics, Biphosphonates*

INTRODUCTION

Among the different premature ageing syndromes, Hutchinson-Guilford progeria syndrome (HGPS) is an extremely rare condition functioning as a model of accelerated senescence [1].

Its incidence is reported between 1 in 8 million to 1 in 4 million births, as males are affected 1.5 times more than females and 97 % of cases are of Caucasian origin [2-3]. Although affected children typically appear normal at birth, within the first year of life they begin to demonstrate features of accelerated aging [4]. Median age of death is 13, usually related to the early onset of severe atherosclerosis that occurs as part of the syndrome [2].

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The inheritance of HGPS is autosomal dominant with the HGPS gene, LMNA, appears on chromosome 1q [5]. In most cases the cause for HGPS is a de novo single-nucleotide substitution leading to the mutated product lamin A protein (called progerin). Progrin is a structural component of the nuclear membrane [6-7], partly responsible of the integrity of nuclear structure and mechanisms of chromatin regulations [8]. Normally, progerin is expressed at very low levels, however, in HGPS, its expression is increased to a much greater levels causing damage to the nuclear membrane and nucleus that resolve in premature cell death[4].

Clinical features are presented in Table 1. The facial features, in particular, exhibit prominent eyes and a beaked nose resulting in a typical 'plucked-bird' appearance, which is related to disproportionate craniofacial growth and often missing skin appendages such as eye lashes, eyebrows, and earlobes or general alopecia with easy mapping of the scalp veins [4]. The neurocranium is relatively normal-sized but the facial structures growth is greatly reduced. Anteroposterior and vertical growth deficiencies of the maxilla and mandible are apparent in cephalometric analysis , as the mandible is more severely affected, thus leading to a retrognathic appearance and class II malocclusion [2].

Dental manifestations include delayed development and eruption of teeth, discoloration, crowding, rotation and displacement of anterior teeth and localized areas of enamel hypoplasia [9-12].

Case report

We report the case of a 16-year-old Israeli female patient, suffering from Hutchinson-Guilford progeria, who was referred to Orthodontic and Craniofacial Center, Graduate School of Dentistry at the Rambam Health Care Campus, Haifa, Israel for an orthodontic examination. The patient's complaints included functional and aesthetic impairment due to delayed mixed dentition period and malalignment.

Four months prior to her visit, she received an experimental treatment with I.V. biphosphonate (a single dose of zoledronic acid (0.0125mg/kg)). The bisphosphonates were discontinued as the patient developed hypocalcemic tetany.

History revealed that at the age of nine years old, she was diagnosed as having osteosarcoma of the right tibia and treated by excision surgery and chemotherapy to full recovery. At the age of eleven, the patient was clinically examined by a pediatric doctor due to a complaint of growth retardation and loss of scalp hair. The phenotype arise doctor suspicious to HGPS. Therefore she was further referred to a clinical geneticist who conducted a genetic testing of the DNA and discovered heterozygous point mutation in axon 11 (c.1868C>G) of LMNA gene. The predicted effect of the translated protein sequence was amino acid change of Thereonin to Serin at position 623 (p.T623S). All the other members of the patient's family were clinically normal.

General clinical examination revealed classical stigmata of progeria (Fig 1A and B) as the patient looked older than her age. She was short statured with an abnormal gait and weighed 35 kg. She exhibited a relatively large cranium, sunken eyes, thin, beaked nose, malformed tragus and earlobes. Facial height was reduced and maxillary and mandibular retrognathia (with mandibular retrognathia being more prominent), creating a convex profile. No tempromandibular joint (TMJ) disorders or tenderness were recorded. Blood vessels were generally prominent, in particular on lower limbs and scalp. Dermal sclerosis, lack of subcutaneous fat, atrophy and inelasticity of facial soft tissues were apparent, along with relative microstomia. Her voice was unusually high pitched and creaky.

Radiographs of the thorax indicated mild distal osteolysis of the clavicles and small thorax aperture.

Intraoral examination revealed normal size mouth opening with slightly constricted maxilla. The mixed dentition including all primary canines, maxillary left and right and mandibular right deciduous molars were all moderately mobile (Fig 2A-C). The erupted teeth were of normal size, shape and color. Moderate to severe crowding was noticed on both dental arches, primarily in the anterior and canine region. The intercuspal occlusion (IC) presented with a bilateral cross bite of the posterior segments (Fig 2D and E).

A panoramic radiograph (Fig 3) showed that tooth eruption was consistent with that of an 11-year-old child. Root development was consistent with that of a 14-year-old child. All permanent teeth were in normal size and shape and the upper permanent canines seemed to be palatally impacted (Fig 4). The lower right third molar was missing. The vertically positioned mandibular canal along the mandibular ramus reflects a shorter ramus, larger mandibular angle and posterior rotation of the mandible [13].

A lateral cephalogram in the rest position (Fig 5 and Table 2) revealed a class II skeletal relationships with a retruded mandible and a slightly retruded maxilla resulted in ANB angle of 6°. An effective small sagittal dimension was recorded for both the

Table 1: Clinical features of Hutchinson-Guilford progeria syndrome

• Severe growth retardation
• Loss of subcutaneous tissues
• Baldness
• Diffuse osteoporosis
• Early onset arthritic changes
• Respiratory and cardiovascular capacities of senior citizens
• Distinctive bone changes:
1. Resorption of the clavicles and replacement by fibrous tissue
2. Osteolysis of the distal phalanges
3. Joint dislocations

Figure 1: Extraoral photographs of the patient exhibiting classical stigmata of progeria: a relatively large cranium, sunken eyes, thin, beaked nose, malformed tragus and earlobes. A. Frontal repose. B. Profile appearance (right).

Figure 2: Intraoral photographs presenting moderate to severe crowding in both dental arches, primarily in the anterior and canine region and a bilateral cross bite of the posterior segments. A. Maxillary occlusal view. B. mandibular occlusal view. C. Frontal view (at rest position). D. left buccal view (at rest position). E. Right buccal view (at rest position).

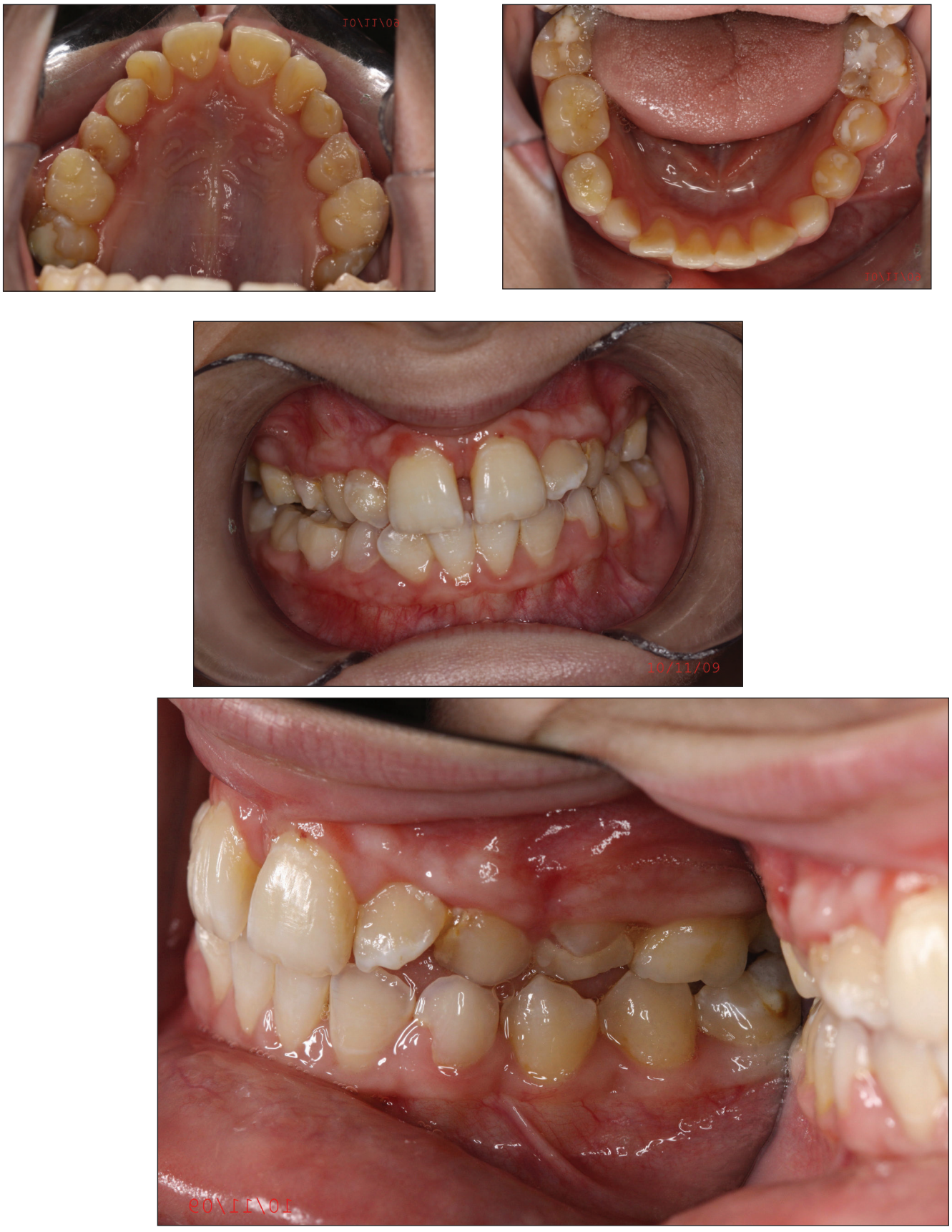


Figure 3: Panoramic X ray revealing a delay in tooth eruption and root development.

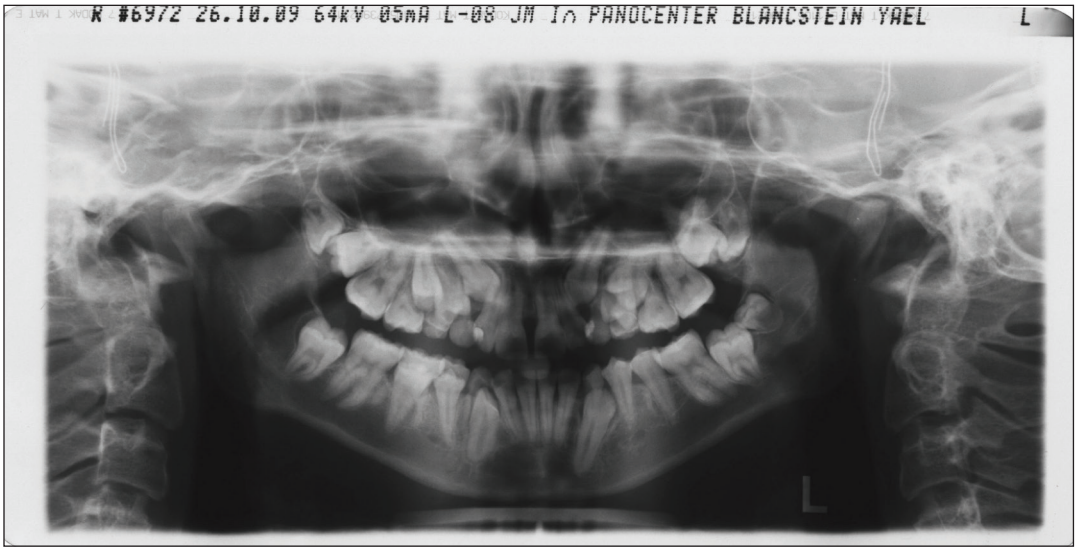
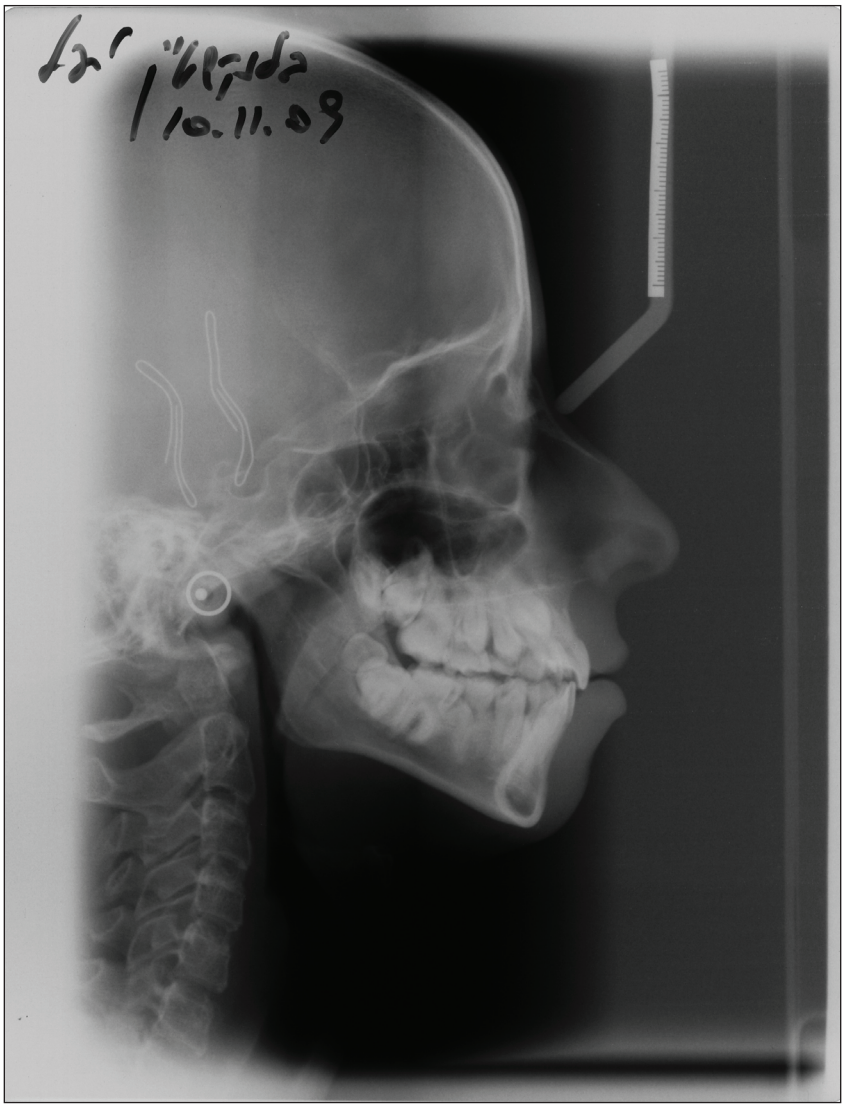


Figure 4: Periapical X rays demonstrating impacted maxillary canines.



maxilla and the mandible with the mandible was more severely affected leading to McNamara's Maxillomandibular differential of only 10 mm [14]. Maxillary incisors were retroclined and mandibular incisors were proclined. Vertical growth pattern measured according to FH plan revealed a more horizontal skeletal growth pattern with a short face tendency, whereas according to SN a slightly vertical growth pattern was recorded. Soft tissue analysis found to be within normal range.

The patient did not display any cognitive disorders, and considered a brilliant student with high academic achievements. Her personality was cheerful and sociable.

Treatment plan

The treatment objectives included extraction of all primary teeth preventing eruption of their successors, thus creating space for spontaneous eruption and commencement of a full orthodontic treatment. Special consideration was required as the patient was treated by oral biphosphonate at the age of 15 years.

Treatment course

All primary teeth were extracted in three appointments while creating as minimal trauma as possible to the surrounding tissue and alveolar bone. A few weeks after the extractions, the upper premolars and the lower canines spontaneously erupted into the dental arch. The maxillary canines have also erupted however in a palatal inclination. Moderate to severe crowded dentition was evidenced in both dental arches with a diastema of 1 mm between the maxillary central incisors. For now, the patient refuses to begin the orthodontic treatment course which included rapid maxillary expansion and distalization in both dental arches to create interdental spaces for crowding alleviation.

Table 2: Cephalometric analysis of the presented Hutchinson-Guilford progeria syndrome case

SNA	80°
SNB	74°
ANB	6°
Co-A	68 mm
Co-Gn	79 mm
difference	11 mm
Convexity at A Pt.	7°
FMA	24°
Y Axis - FH	54°
SNA	38°
Y Axis - SN	68°
S-Go:N-Me	57%
Face Height Ratio U/T %	45%
Ar-Go-Me	120°
Upper 1 to SN	96°
Upper 1 to A-Pog	4°
Lower 1 to Mand. Pl	102°
Upper 1 to lower 1	122°
Nasolabial Angle	104°
Upper Lip to E-line	-3 mm
Lower Lip to E-line	0 mm

DISCUSSION

This case report describes a patient with a mild variant of HGPS, expressed by typical cranial and facial features (without the baldness), sever growth retardation, loss of subcutaneous tissues and the distinctive clavicular changes. Tooth size, shape and color are normal in this case but the eruption and root development are significantly delayed by 5 and 2-year period respectively (compared to the chronological age) probably due to insufficient jaw growth and sever retrognatic position of the maxilla and mandible which are typical to HGPS patients. This delayed eruption is a consistent finding in patients with progeria [2-4,10] as well as crowding of the lower anterior dentition. These factors are probably accounted for the etiology for the common palatally impacted canine manifested in HGPS patients [15].

The genetic testing discovered a point mutation on the LMNA gene (p.T623S). Due to the clinically normal phenotype of the other members of the patient's family we can assume that this mutation is new. Fukuchi et al [16] already described in 2004, a Japanese subject with a late onset HGPS who died of myocardial infarction at 45 years of age. Transcripts issued from the mutated allele were of two kinds; one carries the mutation, causing the missense amino acid substitution at position 623 (p.Thr623Ser) in Lamin A isoforms, as presented in our case. The other carries a 105 base pair in-frame deletion from nucleotide 1864 to nucleotide 1968 (r.1864_1968del), causing the appearance of a truncated Prelamin A product missing amino acids 622 to 656 (p.Val622_Gln656del), following the creation of a cryptic splicing site inside exon 11. The accumulation of Prelamin A in the cell is toxic to the cell and is the origin of the premature aging phenotypes observed in patients [16-18].

Compared to classical cases of HGPS, the onset of the disease in the patient that Fukuchi et al.[16] reported about was late and it took a longer time to develop full-blown HGPS. This description may fit our reported patient, since she carries the same mutation and for now the syndrome has only a mild expression, which might be the prodrome of an advanced disease.

Prior to any orthodontic treatment planning, careful assessment of the eruption potential is mandatory. Clinical examination should be done methodically and must begin with the overall physical evaluation of the patient. Intraoral examination should include inspection, palpation, percussion, and radiographic examination. The clinician should inspect for gross soft tissue pathology, scars, swellings, and fibrous or dense frenai attachments. If a tooth is lagging in its eruption status, as presented in our case, active treatment is recommended when more than 2/3 of the root has developed [15]. Occasionally, a deciduous tooth may prevent the eruption of the succedaneous tooth [15,19-20]. In most cases, its removal will enable a spontaneous eruption of the successor [15], as we suggested in the treatment plan. There are no limitations to conduct any dental procedures in progeria patients, however, extreme caution must be exercised during oral surgery due to the inelasticity of tissues and dermal atrophy.

In the presented case we faced an additional dilemma due to the fact that the patient underwent a course of experimental treatment for progeria four months prior to her first orthodontic visit which included oral biphosphonates. This raised the concern of osteonecrosis as was reported in adult cases [21-26]. However, according to the literature no clear association was reported between early treatment of biphosphonate and osteonecrosis in a pediatric patient following extraction of primary teeth [27-29] and the most recent guidelines indicate that the risk in adult patients is low as well [30-31]. However, case reports have recounted inhibited tooth movement in patients receiving bisphosphonates [32-33] due to osteoclast destruction and reduced bone vasculature. Therefore, patients should be advised of this potential complication and the orthodontist should obtain detailed information about the duration of treatment, the dosage, and the frequency of use [34-35]. If orthodontic treatment is considered appropriate, plans should be assessed and modified to include compromises such as avoiding or minimizing elective surgery and extractions, favoring interproximation over extractions, minimizing tooth movement, minimizing pressures on tissues during treatment and retention, and limiting treatment to facilitate the possible need for early discontinuation of treatment.

Even though that the patient in the presented case received bisphosphonate treatment 4 months prior to her visit it would probably not significantly reduce the probability of potential complications because of the extremely long duration of storage in bone [34]. Since alveolar bone turnover is stimulated during orthodontic treatment, thus which is causing more bisphosphonates uptake and release, the possibility of localized jaw osteonecrosis is increased and therefore she should be monitored carefully.

After the extractions, full orthodontic treatment was planned to resolve to the skeletal class II malocclusion and moderate to severe crowding in both dental arches. In addition, radiographic examination showed an ectopic position of the developing canines. Some of these self-corrected deviations [36], might be spontaneously resolved over time. A severe ectopic canine position may successfully treated by exposure accompanied by orthodontic traction [15]. In light of the nature of HGPS, several considerations should be taken before the initiation of orthodontic treatment.

CONCLUSION

In Hutchinson-Guilford progeria syndrome, Orthodontic procedure commencement should be early enough to manage the delayed development and eruption of teeth i.e. not a passive “wait and see” follow-up of teeth eruption. Furthermore, early orthodontic intervention is recommended, as treatment period is limited due to the ongoing deterioration in the medical condition. Changes of dermal elasticity and potential anesthetic difficulties minimize the elective surgery and extractions during the orthodontic course of treatment.

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