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RESEARCH ARTICLE

FOCUS ON ODONTOHYPOPHOSPHATASIA

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ABSTRACT

Introduction: Hypophosphatasia (HPP) is a disease that was first described by the canadian pediatrician John Campbell Rathbun in 1948. **The objective** of this work is to define hypophosphatasia and its various clinical forms, to define the repercussions of the HPP on the oral cavity, to establish the means of diagnosis and to describe the management of this pathology. **Materials and methods:** To achieve these objectives, we adopted two documentary research strategies: computer research and manual research. Then we chose some recent and relevant articles that we read correctly. **Results:** Hypophosphatasia is a rare metabolic disease characterized by a deficient enzymatic activity of the tissue-nonspecific alkaline phosphatase (TNAP) that generates a defective mineralization of bone and/or teeth. Six forms of HPP are distinguished, odontohypophosphatasia is the most benign form of the disease and it's characterized by premature exfoliation of primary and/or permanent teeth without skeletal manifestations. The early loss of teeth is explained by an anomaly in the formation of the cementum, which ensures the attachment of the tooth to the alveolar bone via the alveolar-dental ligament. In addition to the early loss of teeth, these patients may have defective mineralization of dentin and / or enamel hypoplasia and thus increased susceptibility to caries. A reduced enzymatic activity of Alkaline phosphtase (ALP) measured on a blood sample is the key marker of the disease, and the genetic test confirms this diagnosis. No established therapy has been available until the recent success of enzyme replacement therapy (ERT) using Asfotase Alfa. This therapy was able to prevent the early loss of teeth in infants. **Conclusion:** The dentist plays a very important role in screening for HPP, when the patient present an early loss of the primary teeth and / or permanent without traumatic history, the dentist should suspect hypophosphatasia.

INTRODUCTION

Hypophosphatasia is a disease that was first reported by Canadian pediatrician John Campbell Rathbun in 1948 (1). It is a rare metabolic disorder characterized by a deficiency of the activity of the non-specific iso-enzyme of the PAL (Alkaline Phosphatase) tissue and caused by mutations of the ALPL gene (alkaline phosphatase, liver / bone / kidney) who codes it. This condition causes a bone mineralization disorder that may or may not be associated with dental problems (2,3). Hypophosphatasia is a rare condition that can affect all races, one per 100,000 births (4). The symptoms are variable in their clinical manifestations and range from stillbirth without bone mineralization to only dental problems without bone phenotype. For the most severe forms, the diagnosis can be made in-utero or at birth, but less symptomatic forms such as odontohypophosphatasia and the shape of the adult can be under diagnosed.

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It should be noted that one of the telltale signs of possible hypophosphatasia is the inexplicable early loss of lacteal and / or permanent teeth, so in the face of any patient with a history of premature loss of teeth without a history of trauma, the attending physician should suspect hypophosphatasia. The thorough understanding of this disease is very important for the dentist, he must be able to formulate an early and accurate diagnosis of hypophosphatasia.

The dentist plays an important role in:

- The orientation of the patient and his family to specialized consultations.
- The realization of a broader genetic diagnosis and appropriate management.
- The possibility for the patient and his family to benefit from genetic counseling.
- The establishment of an oral prevention program adapted to the patient and his pathology.
- The programming of treatment sessions that help to perpetuate the existing dental potential, improve

aesthetics and function and preserve bone and dental capital until adulthood.

The number of cases varies from country to country. The prevalence is higher among Mennonites in Canada (1 per 2500 births) (5.6). In Japan, the number of cases affected by lethal perinatal hypophosphatasia is increased compared to other countries (7). There is no current data on the prevalence of this disease in Morocco, rare diseases need to be now recognized in Morocco as a public health priority.

The objective of this work is:

- Define hypophosphatasia and its different clinical forms.
- Define the impact of hypophosphatasia (HPP) on the oral cavity.
- Establish the means of diagnosis.
- Describe the management of this pathology.

Hypophosphtasia

Definition: Hypophosphatasia is a rare hereditary disease characterized by a disorder of mineralization of hard tissues such as bone and tooth, due to a deficiency of serum alkaline phosphatase activity. Its development results from the set of mutations of the ALPL gene Alkaline Phosphatase, Liver / bone / kidney) which codes for the non-specific alkaline phosphatase of the tissue (TNAP) (8).

Epidemiology: Hypophosphatasia is a disease that can affect all races, but with a very variable prevalence. This disease is particularly prevalent in Canada, the prevalence of PPH has been estimated at 1 in 100,000 births in the Toronto area of Canada (9), the prevalence is higher in the Canadian Mennonite population (up to 1/2500 case), where 1/25 individuals can be carriers (5,6). In European populations, the prevalence of severe PPH has been estimated at 1/300000 (10). In Japan, the perinatal lethal form has an estimated prevalence of 1: 900,000, with an estimated carrier frequency of 1/480 (7). In African-Americans, hypohphosphatasia appears to be extremely rare (11). The frequency of moderate forms is more difficult to assess because of the variety of symptoms and the frequency of undiagnosed cases. Mornet et al (10) estimated the prevalence of moderate PPH using the proportion of dominant mutations among the severe alleles and by estimating the penetrance of the disease in heterozygotes for dominant mutations, according to a genetic model with four resulting alleles. in 10 distinct genotypes, the prevalence of moderate dominant PPH in European populations was estimated at 1/6370 (10). The prevalence of PPH has never been estimated in the Moroccan population.

The different clinical forms of hypophosphatis: Hypophosphatasia is a disease that has a very variable spectrum, ranging from lethal form to birth characterized by the virtual absence of bone mineralization, to the odontological form characterized by the premature fall of teeth without bone involvement. Depending on the age of diagnosis, six clinical forms are defined:

- The lethal perinatal form.
- The perinatal form is benign.
- The shape of the infant.
- The shape of the child.
- The shape of the adult.
- L'odontohypophosphatasie.

Odontohypophosphatasia

Definition: Odontohypophosphatasia is the most benign form of hypophosphatasia. It is characterized by only dental manifestations without skeletal lesions and can occur at any age (12). In this form, the primary exfoliation of the lacteal and / or permanent teeth is preceded by increased mobility without a history of trauma, which is generally the reason for consulting these patients. Severe dental caries can also be seen, and anterior teeth are usually the most affected. The X-ray shows a reduced level of alveolar bone, a pulp chamber and wide channels. The diagnosis is confirmed by the PAL assay showing an abnormally low level (13) and obviously a genetic test revealing a mutation on the ALPL gene.

Description of odontohypophosphatasia

Odontohypophosphatasia is characterized by a moderate reduction in serum ALP (Tab 1). Teeth are mineralized organs, composed of three unique hard tissues, enamel, dentin and cementum and supported by the surrounding alveolar bone. Although odontogenesis differs from osteogenesis in many ways, tooth mineralization is sensitive to developmental failures similar to bone. Dental development and especially cementogenesis is the most sensitive process to TNAP function, implying changes in Pi / PPi ratio (14, 15). The early loss of temporary and / or permanent teeth is linked to an anomaly in the formation of the attachment of the tooth by its cementum to the alveolar bone via the alveolar-dental ligament. Temporary teeth are lost before age 3 with an intact root (Figure 1). Formation and mineralization anomalies affect all the hard tissues of the tooth, namely: enamel (presence of striations, hypoplasias), dentin (at the coronal and radicular level) cementum and alveolar bone. (Foster, Nociti et al, 2013) (16)

Effects of hypophosphatasia on dental development

- Phypophosphatasia has several effects on dental development. The typical and striking oral manifestation of PPH is the early loss of lacteal and / or permanent teeth. The deficiency of TNAP activity characterizes hypophosphatasia.
- The premature exfoliation of the teeth results from aplasia or hypoplasia of the cementum and therefore poor fixation of the periodontal ligament. PPi is an essential regulator of root cell acellular cementation development and mineralization and is a key determinant of the hard-soft interface between cementum and the periodontal ligament (17).

The means of diagnosis

Early loss of teeth may be an isolated clinical sign, without additional abnormalities of the skeletal system or may be accompanied by other clinical signs of hypophosphatasia. The diagnosis of odontohypophosphatasia is based on the identification of characteristic signs and symptoms, through a detailed interview of the patient, a thorough clinical examination and a set of additional tests to confirm the diagnosis, including a radiological examination. , a biological examination and a genetic examination (20).

Table 1. Serum level of PAL in the different clinical forms of PPH (18)

Clinical forms	Serum concentration of PAL
In utero (lethal perinatal form or begnin)	Low rate in amniotic fluid
Infant Form	Low Serum PAL +2-15 UI/L (Whyte et coll, 1996) +0-150 UI/L (Taketani et coll, 2014)
The shape of the child	Low serum level +15-90 UI/L (Whyte et coll, 1996) +75-250 UI/L (Taketani et coll, 2014) +Filles : 53.6UI/L +Garçons : 37.5UI/L (Whyte et coll, 2015)
The shape of the adult Odontohypophosphatasia	Low serum level +4-25 UI/L (Whyte et coll, 1996) +15-98 UI/L (Berkseth et coll, 2013) +150-325 UI/L (Taketani et coll, 2014)

Proper examination of odontohypophosphatasia is easy for doctors who are familiar with this kind of disorder. However, most dentists have little or no knowledge of PPH, and as a result, affected patients and families may experience a delay in diagnosis and thus delay in management. In front of any patient with early loss of teeth, the doctor must suspect PPH and follow a diagnostic procedure (20).

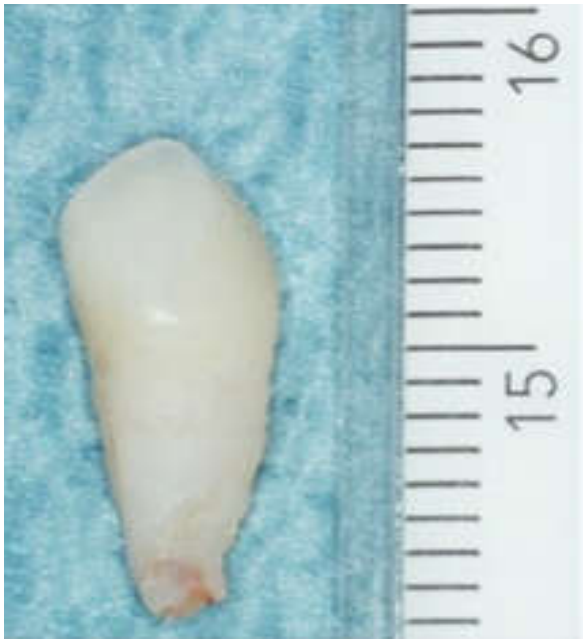

Figure 1. Whole right maxillary canine with its root lost before age 3 in a patient with PPH (19)

The interrogation

The dentist must conduct a thorough examination, which investigates:

Age: the age of the patient must be known in order to evaluate the loss of the tooth in relation to the age of the patient.

The history of the disease: it is necessary to note since when there is a dental mobility, and if this mobility was accompanied with a context infectious or inflammatory for example a spontaneous bleeding.

Family history: Ask if a family member has a history of early loss of teeth without a history of trauma.

Other signs: the doctor should ask if other clinical signs accompany the early loss of teeth, such as: muscle weakness, chronic pain, neurological disorders (seizures, delayed motor development).

The clinical diagnosis

The clinical examination must evaluate the periodontal status of the patient. The dentist must examine the patient's oral cavity in order to evaluate oral hygiene, gum condition and look for signs of periodontitis that may be the cause of dental mobility, and thus make a differential diagnosis between HPP and periodontitis. Early loss of teeth in PPH is generally not associated with an inflammatory and infectious context (Figure 2) so if infection and inflammation are present, other general diseases should be considered (19,21). If the lost teeth are preserved, they must be examined to determine if the roots are intact. The early loss of teeth usually concerns the incisivo-canine group and especially the maxillary and mandibular central incisors. The first sign of odontohypophosphatasia is often tooth mobility, which is the reason for consulting the patient's family. Other oral manifestations characterize the hypophosphatasia, we will see these dental anomalies according to the number, the shape, the size, the structure and the eruption of the teeth.

Anomaly of number: Teeth missing because of their early losses, supernumerary teeth or agenesis do not characterize PPH.

Anomaly of form

- Anomalies of crown shape: small, bulbous crowns with cervical constriction.
- Anomalies in the shape of the root and the pulp (we will see them in more detail in the radiological diagnosis).

Anomaly of size: microdontics or macrodontia do not characterize PPH.

Anomaly of structure: Enamel hypoplasia (Figure 2,3).

- Tye dye defects usually due to mineralization defects of the dentine, we can also observe severe caries.

Eruption anomaly: Eruption delay (Figure 2) (19).

These abnormalities are not always present, they depend on the severity of the disease.

The radiological diagnosis

Radiological examination is essential in a patient with early loss of teeth. Dental X-rays; generally panoramic and retro-alveolar radioraphy show several characteristic symptoms of odontohypophosphatasia such as: (19,20,22,23)

- A reduced level of alveolar bone, reflecting alveolar bone loss due to poor periodontal fixation (Figure 4).
- Coronal (Figure 5) and Root Anomalies
- Taurodontism of molars (Figure 6) (20)
- Short roots (Figure 7)
- Wide pulp chambers.

Other radiographs may be requested in doubtful cases to make the differential diagnosis between odontohypophosphatasia and other forms (of the child, of the adult), to see if there is a skeletal disorder.

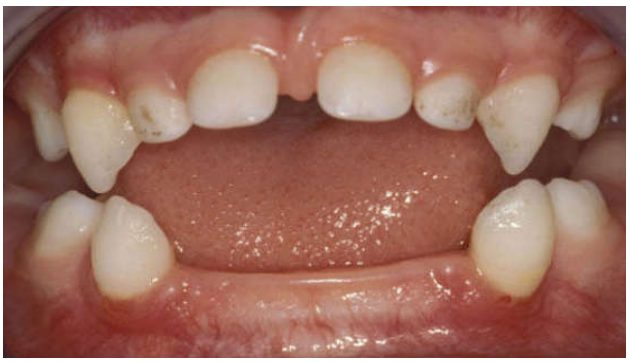

Figure 2. Photograph of the arches of a patient with PPH, note the absence of the lower incisors with no sign of inflammation of the gingiva (19)

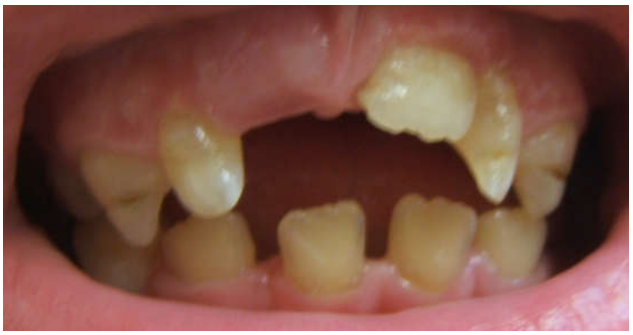

Figure 3. Photograph of the oral cavity of a 7.5-year-old patient with PPH (19)

This photograph reveals linear amelaria hypoplasia of the maxillary canines (53 and 63) and a delayed eruption of the 11 while the 21 has already erupted at 6.5 years. The color of the permanent teeth is dark yellow.

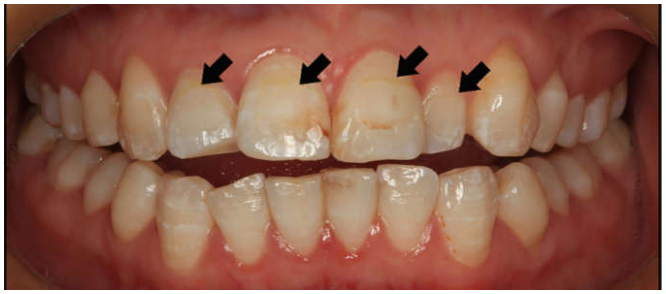

Figure 4. Intraoral frontal view showing crown level tasks due to enamel hypoplasia (22)

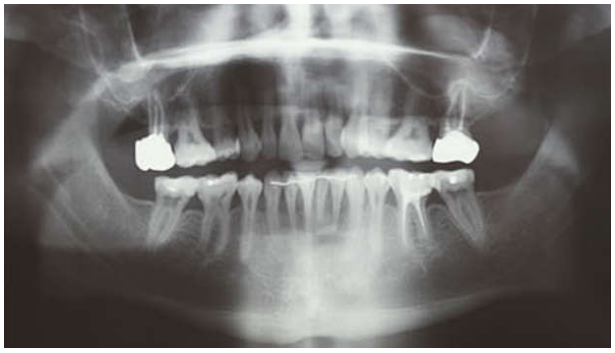

Figure 5. A panoramic X-ray showing a reduced level of alveolar bone, particularly in the anterior region in a patient with PPH (23)

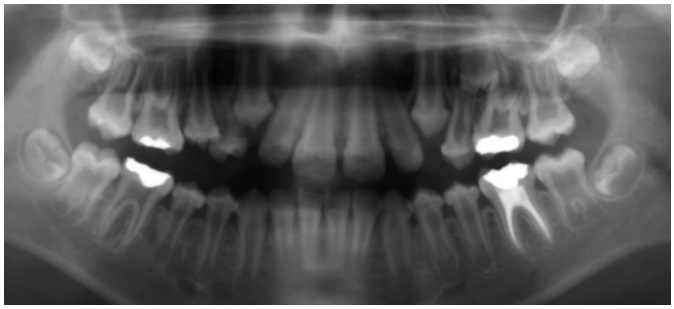

Figure 6. A panoramic X-ray of a 12-year-old child with HPP (19). This X-ray shows large pulpal chambers, abnormalities of crown shape. The second molars show taurodontism more severe than the first molars

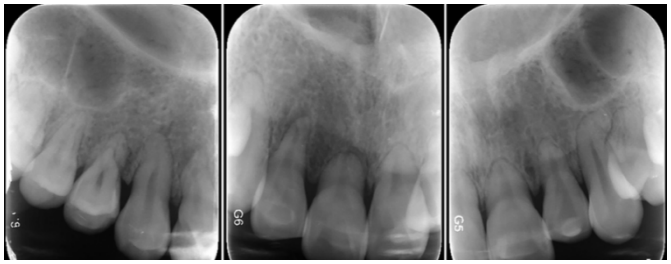

Figure 7. Retro-alveolar patients with PPH, showing short roots (22)

Biological diagnosis

Once the HPP is suspected, it is necessary to request tests to measure the serum level of PAL. A low PAL level is characteristic of PPH, but it is not sufficient to confirm the diagnosis, because many conditions may result in a low level of ALP, such as: pregnancy, some medications such as birth control pills younger women and estrogen replacement therapy in older women (24), hypothyroidism, anemia and celiac anemia (20). Serum PAL is a biochemical marker of the disease phenotype and corresponds to the severity of the disease. The lower the serum level of ALP, the more severe the disease (25). In the case of odontohypophosphatasia for example, the level of PAL may be close to the lower limit of normal. PAL activity is dependent on age, gender, and laboratory procedures (Figure 18). Infants, children, and adolescents in good general health have significantly elevated PAL levels higher compared to adults; in children, hepatic (25%) and bone isoforms (67%) predominate. In addition to the PAL activity test, other urine phosphoethanolamine (PEA) tests, pyridoxal-5-phosphate (PLP), inorganic pyrophosphate (IPP), may be requested. These are the natural substrates of TNAP. For children, these tests can be supplemented by the analysis of: calcium, phosphate, parathyroid hormone and vitamin D, in order to make the differential diagnosis and eliminate the causes of rickets.

Total serum activity of the PAL: weak

It is weak in all clinical forms of hypophosphatasia. Laboratories use different methods and have very different reference ranges. The sex and age specific reference range determined by each laboratory should be used.

Urinary concentration of PEA: elevated

A high urinary PEA concentration supports the diagnosis of PPH, it adds specificity to the interpretation of the test results,

but it is not characteristic of PPH, patients with PPH may have a normal PEA.

Serum concentration of PLP: elevated

PLP is a biologically active metabolite of vitamin B6 and is the most sensitive indicator of PPH (20).

The urine PPi: high

It is a sensitive marker in patients with PPH and even asymptomatic carriers.

- Serum concentration of calcium and inorganic phosphate: normal
- A normal level of these parameters distinguishes HPP from other forms of rickets.
- Serum concentration of vitamin D and parathyroid hormone: normal

A normal level of serum vitamin D concentration makes it possible to make a differential diagnosis between PPH and hypocalcemia, which may also be responsible for irritability, depression, neurosis and muscle pain (20).

Genetic diagnosis: Except for the perinatal form where genetic diagnosis is essential, PPH can be diagnosed by routine clinical, biochemical and radiological diagnostic means. However, sometimes clinical and biochemical data are not clear enough or do not distinguish HPP from other diseases, in which case a genetic diagnosis is required. This genetic diagnosis is essential to confirm the diagnosis on the one hand and on the other hand for genetic counseling in affected families and especially for severe forms (27). Genetic counseling is the process of providing individuals and families with information about the nature, inheritance and consequences of genetic disorders to help them make informed medical and personal decisions. In patients with severe PPH, two ALPL pathogenic variants are identified in approximately 95% of individuals of European descent. In the milder forms such as odontohypophosphatasia a pathogenic variant allele is considered sufficient to cause the disease (28).

Differential diagnosis: Dental abnormalities represent an aspect of rare diseases or syndromes. Hypophosphatasia is mainly characterized by early loss of teeth preceded by tooth mobility and a reduced level of alveolar bone, these signs are also seen in periodontal disease. HPP is characterized by ameloid hypoplasia and dentinal hypomineralization, and these manifestations are also observed in amelogenesis imperfecta and dentinogenesis imperfecta.

Periodontal disease: Periodontal diseases are defined as multifactorial infectious diseases. They are characterized by symptoms and clinical signs that may include visible or invisible inflammation, spontaneous or variable gingival bleeding, pocket formation related to attachment loss and alveolar lysis, tooth mobility and can lead to early loss of teeth. The classification of the American Academy of Periodontology (APA) (ARMITAGE, 1999) distinguishes three types of periodontitis: (29)

- The aggressive periodontitis.
- Chronic periodontitis.
- Periodontitis as manifestations of systemic diseases.

The aggressive periodontitis: It corresponds to inflammation of the gingiva with a scanty plaque, and vertical bone lysis radiologically visible. This causes mobility of the incisors and first molars (30).

Chronic periodontitis: It mostly affects adults, but can rarely reach younger individuals (31). This type is characterized by a marked gingival inflammation and a bleeding tendency to sounding.

Periodontitis as manifestations of systemic diseases: This type of periodontitis can reach temporary and permanent dentition. This periodontitis is rare, it is characterized by gingival inflammation and alveolar lysis which later gives mobility and early loss of teeth. General diseases can be:

- Papillon Lefèvre syndrome: an autosomal recessive rare disorder characterized by premature loss of temporary and permanent dentition.
- Chediak Higashi syndrome.
- Leucémies.
- Juvenile diabetes.
- SIDA (30,32).

Amelogenesis imperfecta (AI): Amelogenesis imperfecta (AI) is a group of developmental abnormalities affecting the structure and clinical appearance of enamel of all or nearly all teeth, both temporary and / or permanent. The diagnosis is based on family history, the study of the family tree and a meticulous clinical and radiographic examination. To date, genetic diagnosis is only available as part of a research protocol (33).

Dentinogenesis imperfecta (DI): DI and dentinal dysplasia are diseases that are characterized by abnormal dentin structure, usually affecting both temporary and permanent teeth. All these conditions are easily distinguished from odontohypophosphatasia by biochemical results (13).

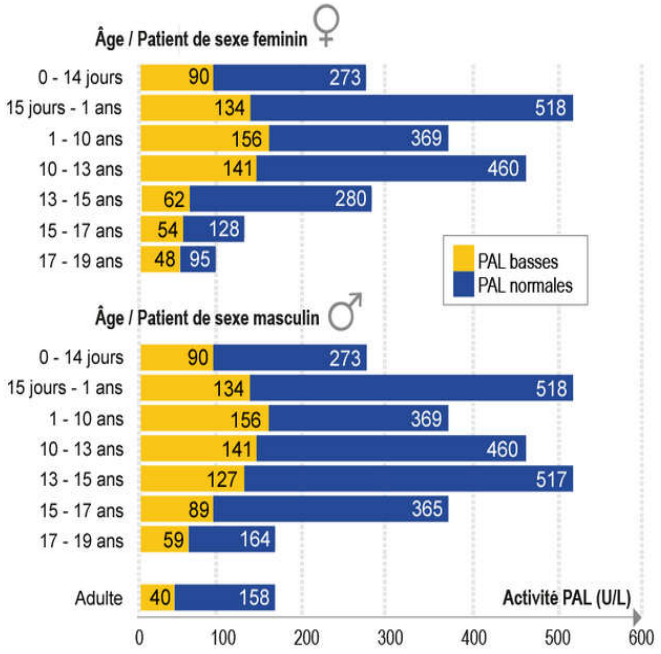

Figure 8. Figure showing normal and low PAL values by age and sex (26)

Results of clinical cases

Table 2. Presentation of clinical cases 1 and 2

	Case 1 (34)	Case 2 (34)
Age and sex	A boy aged one year and 7 months	A girl 3 years and 3 months
Medical History	- At the age of one year and 2 months: loss of 71 and 81 (with intact root) (Figure 22a) -At the age of one year and 6 months: loss of the 72 (without history of trauma)	-At the age of 3 years: loss of the 71 (with intact root) (figure 23 a)
Family history	Nothing to report (RAS) RA	RAS
Clinical signs	-Absence of the 3 mandibular incisors (Figure 22b) -Mobility of anterior teeth -Stature short	-Absence of the 71 (figure 23 b) -Mobility of other incisors
Radiological Signs	-Panoramic Radar: Reduced Level of Alveolar Bone (Figure 22c) -Extra-oral radio (hand and lower limbs): RAS	Panoramic radio and RA: Moderate absorption of the alveolar bone (Figure 23 c) -Extra-oral radio (hand and lower limbs): RAS
Biological tests	-PAL: 192 IU / L (low rate) -PEA: 898.8 nmol / mg Cr (high rate)	-PAL: 254 UI/L
Genetic Testing	TNPAL Gene Sequencing Demonstrated Heterozygous Mutation	-Absence of Data
Diagnosis	Odontohypophosphatasia	Odontohypophosphatasia

PAL: Alkaline phosphatase,
PEA: Phosphoethanolamine,
IU: International unit,
nmol: nanomole, L: liter.

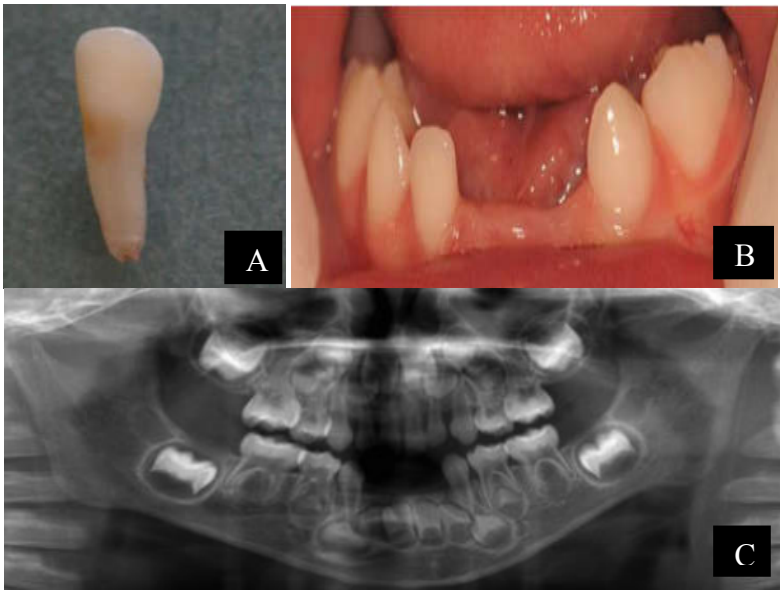

Figure 9. Photograph and X-ray of case 1: this is a boy aged 1 year and 7 months with PPH. (34) A: Photograph of the exfoliated tooth with an intact root. B: Photograph of the mandibular arch showing the absence of the 3 mandibular incisors. C: Panoramic X-ray showing a reduced level of the alveolar bone

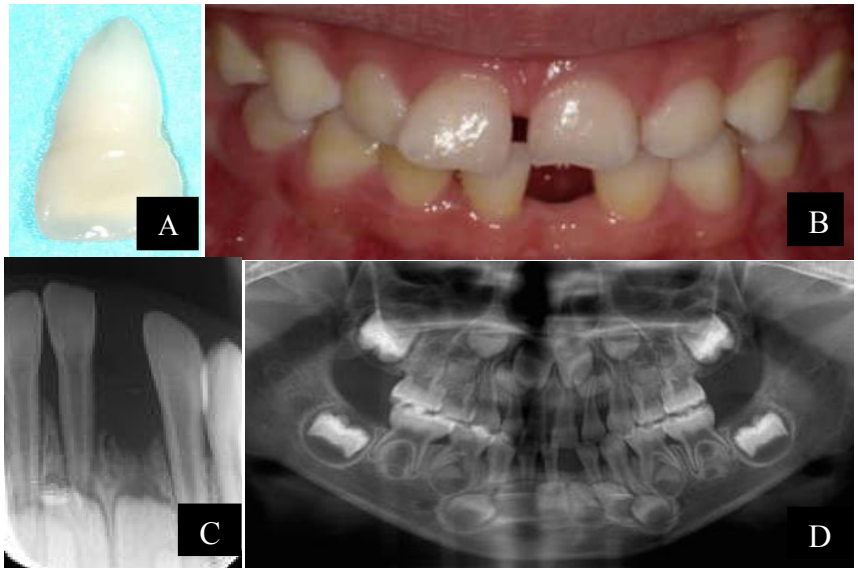

Figure 10: Photograph and X-ray of Case 2: This is a girl aged 3 years and 3 months who has HPP (34). A: Photograph of the exfoliated tooth showing an intact root. B: Photograph of the oral cavity of the child who has lost 71. C: Panoramic X-ray showing a reduced level of the alveolar bone. D: A retro-alveolar of the mandibular incisors showing a reduced bone level

Table 3. Presentation of clinical cases 3 and 4

	Case 3 (25)	Case 4 (25)
Age and sex	A girl aged 3 years (Figure 24 A)	A girl aged 4 years and 8 months
Medical history	Early loss of upper and lower incisors at 2 years and a half	Early loss of incisors and canines a few months after their eruptions
Family history	RAS	RAS
Clinical signs	Absence of incisors (Figure 24 B) No bone deformity was detected.	Absence of central incisors, lateral incisors and canines
X-ray Signs	Panoramic Radio: Reduced Bone Level (Figure 24C)	-Radio Panoramic: Reduced Level of Alveolar Bone Wide pulp chambers (Figure 25 A) -Oradio radiography: wrist x-ray revealed slight metaphyseal irregularities and bone age of 3 years and X-rays of the lower extremities showed almost normal growth plates without any evidence of deformities and fractures, but a bone defect focal at the distal metaphysis of the femur (Figure 25B)
Biological tests	PAL: 67 IU / L (low rate)	-PAL: 27 IU / ml (low rate) -PEA: / Cr of 84 µmol / mmol (high rate) -PLP: 393 µg / L (High rate) -Ca: 9.7 mg / dl (normal) -P: 5.1 mg / dl (normal)
Genetic test	Confirms the presumptive diagnosis	Shows a mutation and confirms the diagnosis
Diagnosis	Odontohypophosphatasia	Child form

PAL: Alkaline phosphatase,
PEA: Phosphoethanolamine,
PLP: Pyridoxal-5-phosphate,
Ca: Calcium, P: Phosphate.

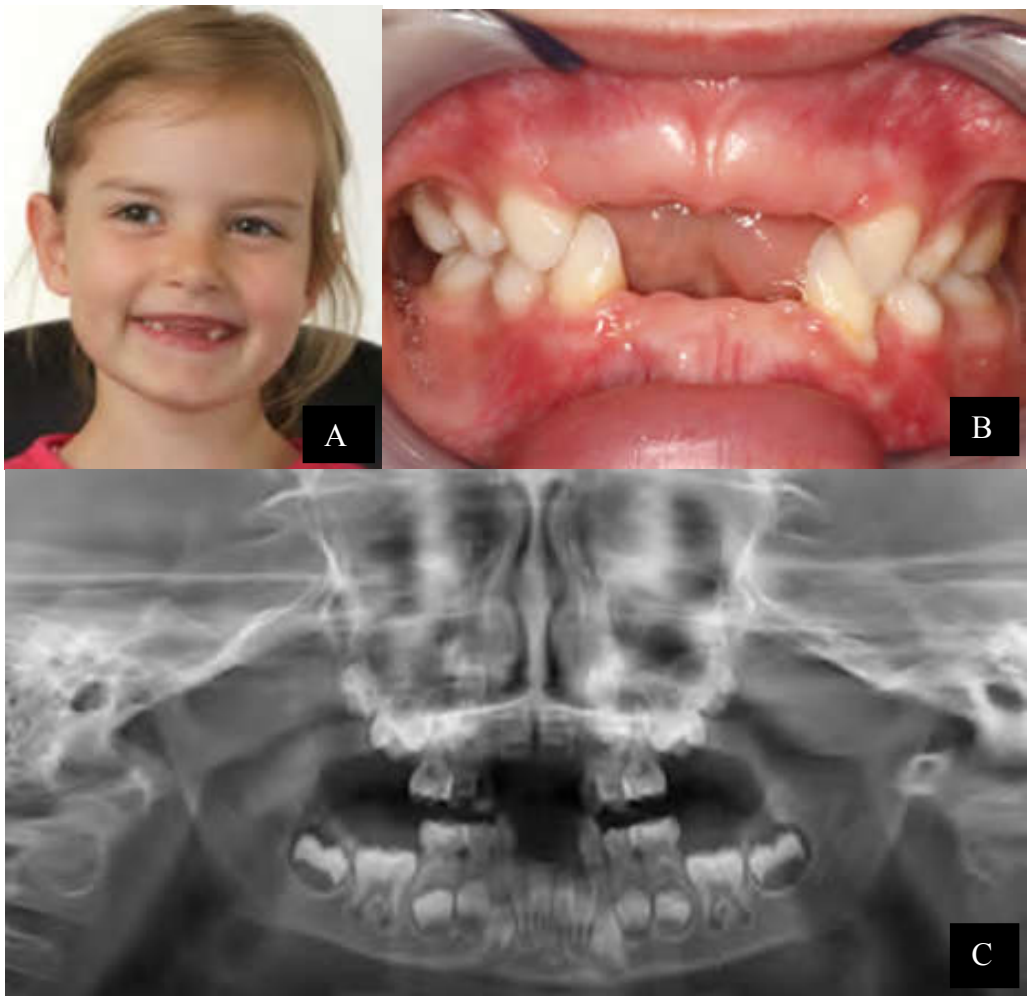

Figure 11. Photograph and X-ray of Case # 3: This is a girl aged 3 years with PPH (35)
A: Photograph of the girl with odontohypophosphatasia showing absence of maxillary incisors.
B: Photograph of the oral cavity of this patient showing the absence of maxillary and mandibular incisors.
C: Panoramic X-ray showing a reduced level of the alveolar bone

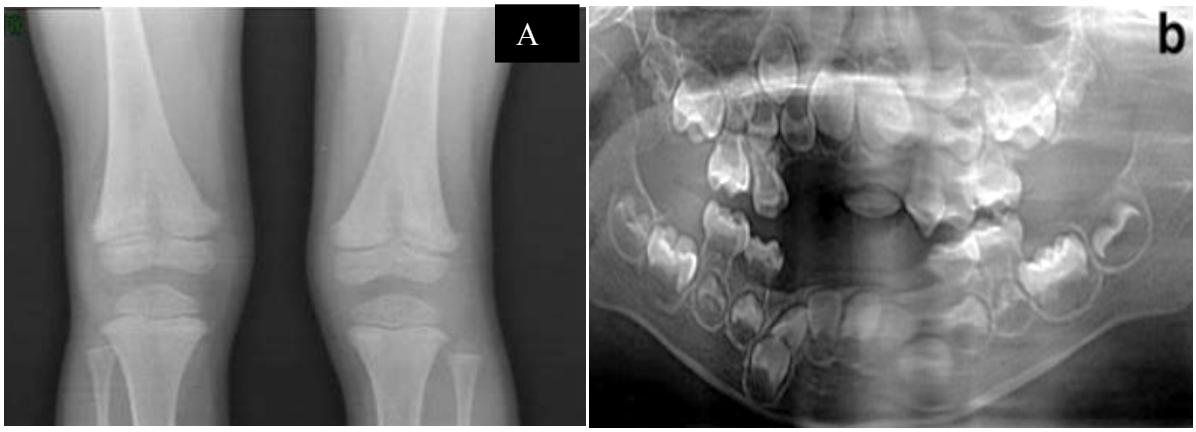

Figure 12: Photograph and X-ray of case 4: this is a girl aged 4 years and 8 months with PPH (25). A: Panoramic X-ray showing the absence of several temporary teeth in addition to wide pulpal chambers at the level of the molars. B: An X-ray of the lower extremities showing almost normal growth plates without any deformation or fracture, and a focal bone defect at the distal metaphysis of the femur

Table 4. Presentation of clinical cases 5 and 6

	Case 5 (36)	Case 6 (37)
Age and sex	A boy of 9 years	A girl of 15 years old
Medical History	-Diagnosed a year and a half ago from HPP -Mobility of anterior teeth -At the age of 11 months, the suspected cause: Traumatism. Subsequently exfoliation of the 71 and 81, the mobility of the 63, 51, 52, 61.62 -At the age of 3, deflection of 63, 61, 73 -Treatment and restraint and prosthesis (Figure 26 A	). -Exfoliation of teeth after eruption -Cariogenesis, mobility of the lacteal and permanent teeth after eruption ⟍ gradual loss of teeth -No history of trauma -Vomiting, chronic diarrhea, fatigue (between 2 and a half years and 3 years ⟍ blood transfusion 2 to 3 times + additional calcium prescription
Family history	- Low serum PAL activity in parents, without clinical or radiological signs.	-RAS
Clinical signs	- At 3 years old: deep periodontal pockets, root caries, gingival recession -At 9 years of age: delayed eruption of permanent teeth, absence of tooth mobility, 50% plaque control, absence of inflammation or infection (Figure 26 B). -	-Exobuccal examination: RAS - Endobuccal examination: Dental signs: In the maxillary: presence of root condition on 16 and 23, presence of 17 caries 11, 26, 27 (Figure 27 A). At the mandible: presence of 42 in the root state, presence of 37, 47 caries, 36 and 46 (Figure 27 B). Periodontal signs: poor oral hygiene, reddish gingiva, soft and oedematous, reduced height of the marginal and attached gingiva, gingival recession class II and mobility class II at 26 and 36.
Radiological signs	- At the age of 3 years: Wide pulpal chambers, reduction of the alveolar bone around the lacteal teeth, short roots (Figure 26 C). At the age of 9 years: Increased level of the alveolar bone in the permanent teeth (Figure 26 D).	- Panoramic radio revealed the following teeth: 17, 11, 27, 37 and 47 with: wide pulp chambers and reduced bone height, the 45 and 35 are included (Figure 27 C).
Biological tests	PAL: 266UI / L (low rate) PEA: 840 µmol / g Cr (high rate).	PAL: Normal limit
Genetic testing	A mutation that confirms the diagnosis of HPP	No data
Diagnosis	Odontohypophosphatasia	Odontohypophosphatasia

PAL: Alkaline phosphatase,
PEA: Phosphoethanolamine.

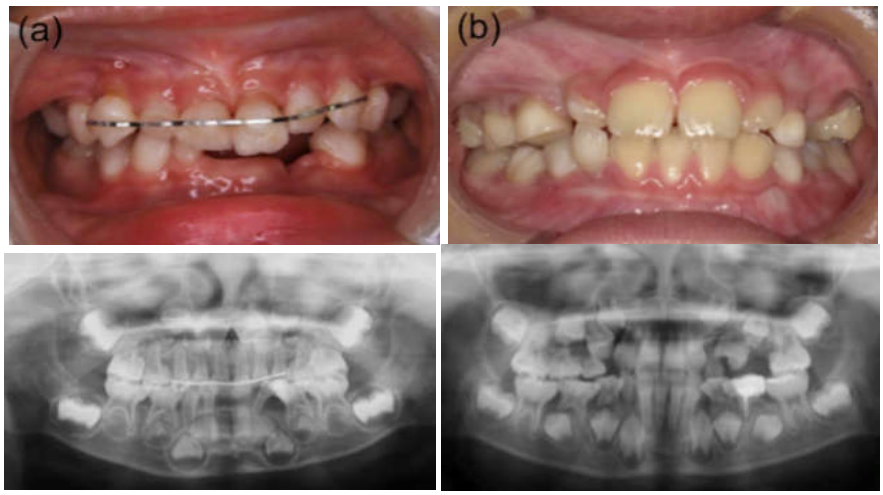

Figure 13. Photograph and X-ray of Case # 5: This is a 9 year old boy with HPP (36). A: Oral photograph taken at the age of 3 years and 11 months showing the absence of mandibular incisors and compression for the maxillary incisors. B: Oral photograph taken at the age of 9 years and 5 months showing the normal eruption of the 8 incisors without signs of inflammation. C: Panoramic X-ray taken at the age of 3 years and 11 months showing a reduced bone level around the lacteal teeth. D: Panoramic X-ray taken at the age of 9 years and 5 months showing the increase of the bone level around the permanent teeth.

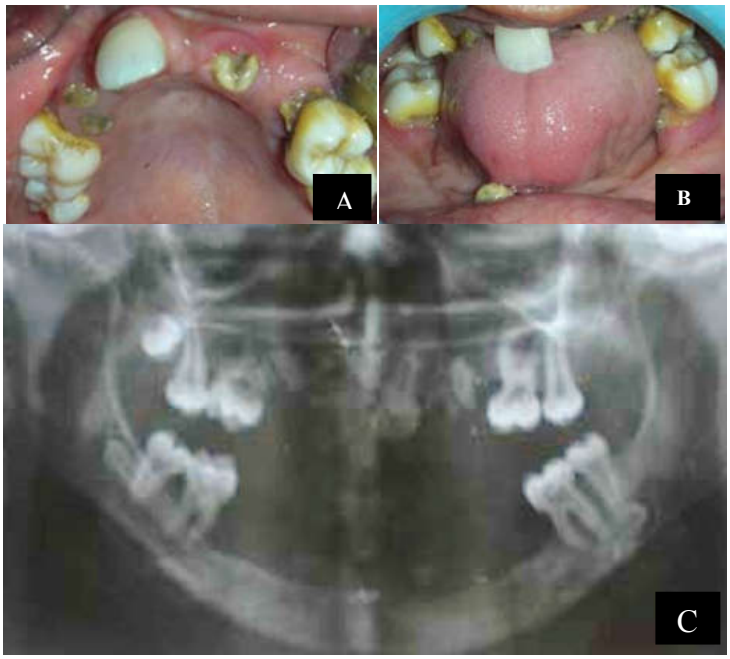

Figure 14. Photograph and X-ray of Case 6: A 15-year-old girl with PPH (37). A: Photograph of the maxillary arch. B: Photograph of the mandibular arch. C: Panoramic X-ray showing the absence of several teeth and the presence of large pulpal chambers at the level of the molars in addition to a reduced bone level

Table 5. Presentation of clinical cases n ° 7 and n ° 8.

	Case 7 (22)	Case 8 (22)
Age and sex	Female aged 27	Female aged 24
Medical History	- Early Childhood Death During Childhood -Mobility and pain in the maxillary incisors -Contention of maxillary teeth 5 months ago.	-Episode of swelling and pain in the chin for 2 years -History of early loss of baby teeth before 6 years Accidental fracture of the leg at the age of 10.
Family history	RAS.	Her mother lost several teeth at the age of 40.
Clinical signs	-Anxiety, tremors, palpitations, muscle pains -Goitre, exophthalmia Enamel hypoplasia (Figure 28 A) -Absence of dental mobility after removal of the restraint.	-. Enamel hypoplasia (Figure 29 A) -Absence of the 14 and 31.
X-ray Signs	- Panoramic and Retro-alveolar Radar: Short Roots of All Teeth (Figure 28B) - Chest radio and radio of the upper and lower limbs.	Panoramic radio: Short roots of all teeth, reduced level of alveolar bone and root cysts (Figure 29 B) -Radio of the skeleton: RAS
Biological tests	-PAL : 59.0 UI/L (normal rate) -TSH : <0.011 UI/L	PAL : 35.0 UI/L (Low rate)
Genetic test	Absence of data	Absence of data
Diagnosis	Odontohypophosphatasia associated with hyperthyroidism (this hyperthyroidism explains compensation for the reduction of PAL level caused by HPP	Odontohypophosphatasia

PAL: Alkaline phosphatase, TSH: thyroid stimulating hormone.

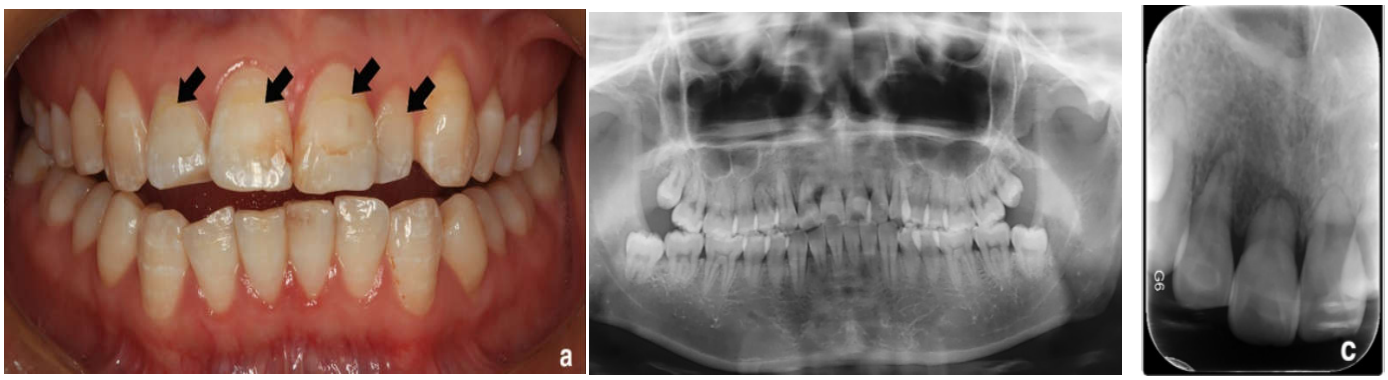

Figure 15. Photograph and X-ray of Case # 7: This is a 27-year-old woman with PPH (22). A: Photograph of the oral cavity showing enamel hypoplasia in the maxillary incisors B: Panoramic X-ray showing the presence of all teeth, with short roots. C: A retro-alveolar of the maxillary incisors showing short roots

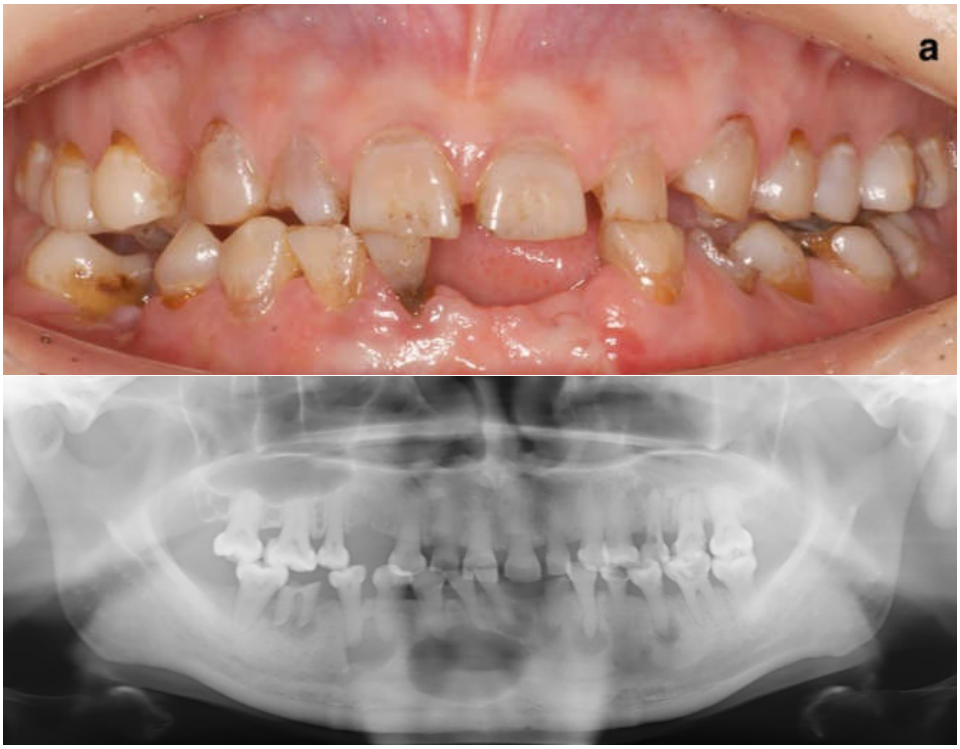

Figure 16. Photograph and X-ray of Case 8: This is a 24-year-old woman with HPP (22)
A: Photograph of the oral cavity showing the absence of the 31 and 14.
B: Panoramic X-ray showing short roots in all teeth, reduced level of alveolar bone and root cysts

Conclusion

Hypophosphatasia should be suspected in individuals with any of the following signs: -A lack of bone and / or dental mineralization -An early loss of lacteal and / or permanent teeth unexplained -A reduced serum level of PAL It should be noted that the sign common to the various forms of HPP is the premature loss of teeth, so the dentist plays a very important role in the detection of this disease, in front of any patient with early loss of lactating teeth and / or permanent without history of trauma, the dentist must:

- Season hypophosphatasia.
- Search for other clinical signs.
- Request a dosage of the PAL.
- Order the patient to specialist doctors, because the management of PPH is often multidisciplinary.

Odontohypophosphatasia is the mildest form of PPH and is difficult to diagnose due to a lack of systemic symptoms. However a correct and well conducted diagnostic procedure makes it possible to make the positive diagnosis and to initiate an appropriate treatment. This diagnostic procedure is traditional with an interrogation specifying the medical and family history, a clinical examination, radiological, biological and sometimes a sequencing of the defective gene to confirm the diagnosis. To conclude, we note that our work, whose content is interesting and enriching based on clinical cases of the literature, can be an important tool to enrich the knowledge of students and dentists about this disease and it can be considered as a a basic source to sharpen students' attention to HPP-related thesis topics to better understand this disease and keep up to date with newly-discovered scientific data.

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