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Local and systemic permanent second molar eruption pathology: diagnostic and therapeutic decision trees

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ABSTRACT

Permanent second molar eruption anomalies, although rare, seem to have become increasingly frequent over the past decades. The present article first inventories and, when necessary, defines the many local and systemic etiologies. Then two decision trees are described, to help clinicians in case of non-eruption of second molars at the normal age; the first seeks to specify diagnosis, and the second to guide treatment planning.

KEY WORDS

Second molar, mechanical failure of eruption, primary failure of eruption

INTRODUCTION

Second molar retention is generally discovered serendipitously, being asymptomatic in 68.5% of cases[3]. It is thus very rarely a presenting symptom in orthodontics. Precise diagnosis is very difficult to establish, as the numerous etiologies are still not clearly defined. One or several factors may be involved[2]: germ and alveolar bone, via the dental follicle; gum mucosa, which plays an important role in the last stages of eruption and may induce fibromucosal inclusion; and/or insufficient facial and maxillo-mandibular growth, inducing dento-maxillary dysharmony.

Eruption delay may concern a single tooth, with local etiology; this is the most frequent case[25]. However, a group of teeth or all the teeth may be involved, in which case etiology is more often systemic or genetic[16].

The present article will list the various etiologies, with precise definitions as needed.

The most useful diagnostic data come from meticulous history-taking and radiology, with possible follicular biopsy. This information, included in a decision tree that will be presented below, guides treatment strategy.

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LOCAL SECOND MOLAR ERUPTION PATHOLOGY

A reminder of some definitions will help understanding.

- Impaction: a tooth is said to be impacted when eruption is arrested by a clinically or radiologically detectable obstacle (mechanical failure of eruption: MFE) or by an eruption pathway abnormality (ectopia)[21]. Mesial angulation is often found (fig. 1).
- MFE due to an obstacle in the eruption path, visible on radiography or not[24], is the main cause of impaction.

Germ abnormalities

Germ abnormalities impair the communications triggering eruption. They may be hereditary (impaired amelogenesis and dentinogenesis, enamel nodule, etc.) or acquired (trauma).

Dental obstacles

Loss of space due to unduly early avulsion, absence of guidance by the distal root of the first molar if the latter has been extracted ("guidance" theory[10]), dentomaxillary dysharmony due to relative macrodontia, short arcade and skeletal growth pattern[9], as well as supernumerary teeth and/or odontomas may hinder harmonious second molar positioning. Retarded second molar progression may also be due to third molar agenesis (fig. 2).

According to Andreasen, lack of space leads to follicular collision between germs[17].

Gum obstacles

Localized gingival hyperplasia.

Tumoral obstacles

Odontogenic tumor, ameloblastoma, regional odontodysplasia, cyst and myxoma.

Pericoronary hamartoma: certain authors[5] described a tumor-like tissue deformity composed of an abnormal combination of elements normally

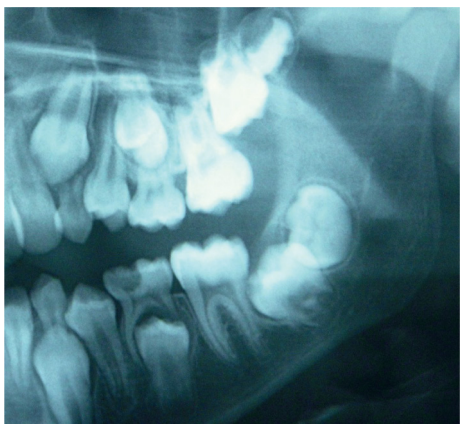

Figure 1
MFE, with impaction of 37 and angulation >30°.

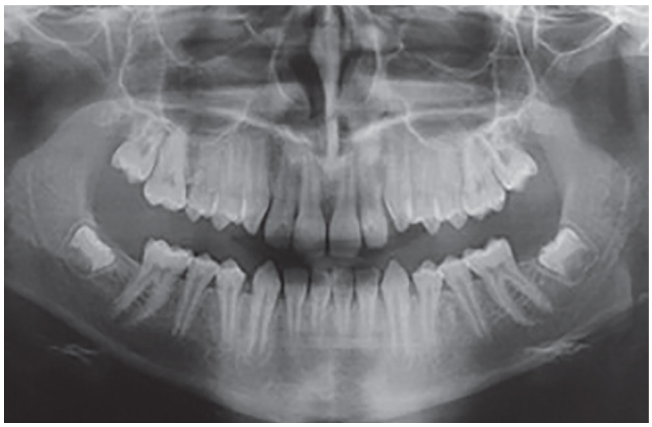

Figure 2
Patient aged 13 years 7 months. Retarded second molar progression with wisdom tooth agenesis.

found in the organ: osteodentine, cementum, pulp-analog components, multinuclear mesenchymal giant cells, dysplastic dental matrix. The deformity is of embryonic origin, and is also known as dysembryoplasia.

Radiologically, it is characterized by radiolucency surrounding a non-evolved tooth. The constituent elements induce active tissue remodeling, causing gingival fibrosis. Location is most often posterior mandibular, and there is systematically association with a non-erupted tooth. There may or may not be associated syndromes.

This lesion requires particular attention, as the radiologic aspect greatly resembles that of primary failure of eruption (PFE). Differential diagnosis looks for small radioopaque structures within an enlarged image of the follicle. Follicle biopsy analysis confirms diagnosis. In hamartoma, eruption follows its normal course after resection of the fibrous tissue.

Bone obstacles

Increased local density, or defect in case of cleft[23].

Mucosal obstacles

Interference of cheeks, fingers, parafunctions.

Ectopic eruption pathway

The eruption pathway may be abnormal, usually with medial angulation, causing impaction.

Non-hereditary PFE

Prevalence ranges from 45% to 85%[1].

PFE (in French, "arrêt idiopathique de l'éruption"[6]) represents a dissociation between resorption forming the eruption pathway and the various motors of eruption (Proffit and Vig 1981[20]). PFE associates most of these characteristics[20], but with many phenotypic variants.

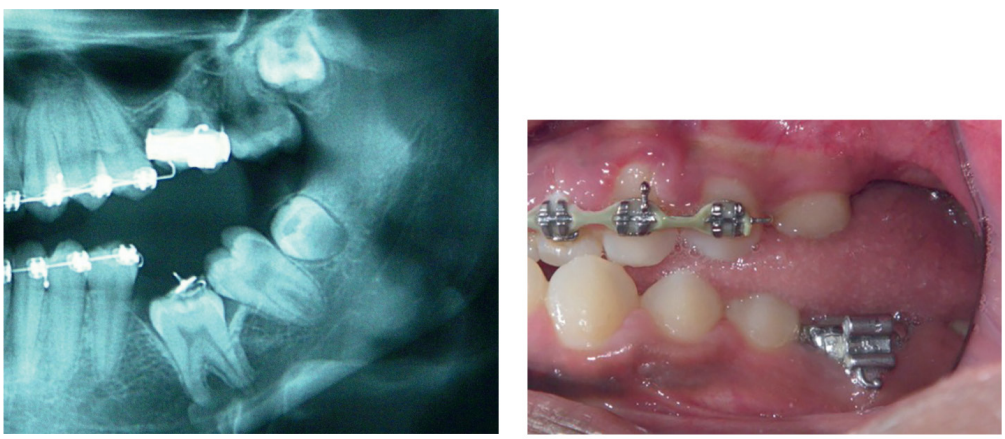

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Figure 3
a) PFE involving 6, 7 and 8 of quadrants 2 and 3. b) Oral view: posterior infra-occlusion due to PFE.

Posterior teeth are more involved than anterior teeth. PFE generally begins with the first permanent molar, by ankylosis of the deciduous second molar (fig. 3a). More rarely, premolars and canines may be involved, but never the incisors. Teeth distal to the first affected tooth are all involved to a greater or lesser degree (types I and II).

Affected teeth may have begun eruption but ceased at a certain point: primary and secondary retention. PFE covers a wide phenotypic spectrum, with severity ranging from simple retarded eruption to complete inclusion. Different mutations may be implicated.

Deciduous and permanent teeth may be involved.

The phenomenon may be uni- or bilateral, but is most often asymmetric and unilateral.

The alveolar bone above the crown is resorbed, creating a radiologically visible eruption pathway..

Affected permanent teeth generally show no ankylosis. However, applying orthodontic force to reposition the teeth in the arcade is generally unsuccessful and leads to ankylosis. The affected teeth do not show normal orthodontic response; they may sometimes slowly be pulled for 1 or 2 mm, but then egression stops. Isolated cases (idiopathic, sporadic mutation) have been reported.

The phenomenon induces a posterior gap, the size of which depends on the severity of the pathology (fig. 3b).

When involvement begins only with the second molar, diagnosis cannot be made before 14 years of age; this is known as moderate PFE. Certain wisdom teeth in retention may be concerned by PFE: it is not lack of space that prevents eruption.

Proffit and Vig hypothesized an anteroposterior eruption gradient along the dental lamina, which might explain the greater frequency found in the more posterior teeth (M3++).

There may be a genetic link between local molar ankylosis and PFE, as the two may be found in different quadrants in the same subject.

According to Frazier-Bowers[12], etiology may be distinct between ankylosis, primary retention, secondary retention and PFE.

Idiopathic eruption failure is probably genetic, but etiology may also be multifactorial. Secondary retention, the causes of which remain unelucidated, may associate physiological, mechanical and/or genetic factors[12]. Most cases are related either to ankylosis or, more often, to PFE.

The morphologic characteristics are the same as in hereditary PFE.

SYSTEMIC SECOND MOLAR ERUPTION PATHOLOGIES

Retention in these cases is usually due to generalized gingival fibrosis, supernumerary teeth or growth defect, rather than PFE as such. Well-conducted medical history taking regarding patient and forebears guides diagnosis.

Endocrine etiologies

Endocrine disorders may affect both craniofacial development and alveolo-dental growth; eruption may be affected to a greater or lesser degree according to the hormone in question and age at onset. Genetic and acquired endocrine disorders may be distinguished. Bone base and alveolar process growth may be involved, greatly delaying eruption by slowing alveolar bone formation or causing MFE by dentomaxillary dysharmony.

Hypothalamic and pituitary functions, and especially the GHRH-GH-IGF-1 axis, are determining in regulating growth[4]. Acting via IGF-1, growth hormone (GH) or somatotropin is the main growth determinant (hypopituitarism), and is synthesized and released by the anterior pituitary. Thyroid hormones also play an essential role in statural growth, and especially in the skeletal maturation of the growth plate (hypothyroidism, hypoparathyroidism). Thyroxin stimulates the growth cartilage, and thyrocalcitonin inhibits bone catabolism and promotes osteogenesis. The effects are both direct and indirect, via activation of GH gene transcription. PTH (parathyroid hormone) has hypercalcemic and hypophosphatemic action, stimulating both bone formation and resorption, thus renewing the bone while maintaining skeletal integrity. PTHrP (parathyroid-related protein) is required for dental eruption (Philbrick, cited by Frazier-Bowers, Puranik, Mahaney[12]). The gonadic steroids LH (luteinizing hormone) and FSH (follicle-stimulating hormone) are mainly involved in the acceleration of growth observed at puberty (hypogonadism).

Moreover, developmental and hormonal genes interact: gene promoter sequences show hormonal response.

Local paracrine regulation and circulating hormones control bone tissue development and remodeling throughout life.

Deficiencies

- Vitamin D deficiency (rickets): One of the three main actions of vitamin D is on bone tissue, itself involved in craniofacial edification. Vitamin D is a steroid that can be seen both as a hormone and as a vitamin. It is a major element in phosphocalcium metabolism. 1,25 (OH)2 D shows hypercalcemic and hyperphosphatemic action on both bone and teeth[4].
- Vitamin A or C deficiency induces gingival hyperplasia[24], and may also delay eruption.
- Likewise, retarded eruption is found in severe prematurity[16].

Drug-related etiologies

Many medical treatments may slow eruption: long-course chemotherapy (fig. 4), or prostaglandin pathway blockers that reduce periodontal osteoclastic activity: aspirin, acetaminophen, ibuprofen, indomethacin, clodronate[26], dihydantoin (used to treat epilepsy), or phenytoin (causing gingival hyperplasia)[24]. Chemically modified tetracyclines inhibit matrix metalloproteinase. Bisphosphonates (pamidronate and alendronate), prescribed to children for primary and secondary osteoporosis, including impaired osteogenesis, delay or inhibit dental eruption by impairing activity[14].

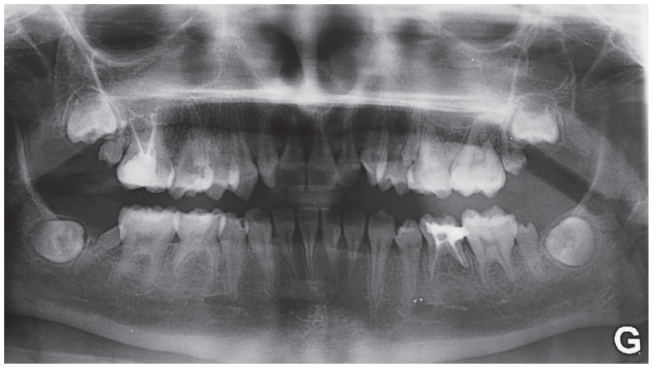

Figure 4
Second molar abnormality and retarded eruption secondary to chemotherapy during infancy.

Genetic etiologies

Genetic etiologies associated with syndromes

Many syndromes are associated with retarded eruption of the permanent teeth (fig. 5).

In 2002, Wise listed 25, half of which involved genetic mutation[27]. Such syndromes are not systematically familial, and may implicate sporadic mutation. Except for Levy-Hollister syndrome and progeria, which affect only permanent teeth, all other syndromes affect both dentitions, usually inducing severe delay rather than primary failure of eruption. eruption may be impacted at different stages, with correspondingly different severity.

The only syndromes presently known to be associated with true PFE are:

– Albers-Schönberg osteopetrosis;
– GAPO syndrome (Anderson and Pindborg: OMIM #230740);
– and Fairbanks syndrome (osteoglophonic dysplasia).

Early diagnosis of dental abnormalities[19] is useful, and indispensable to broader genetic diagnosis and appropriate treatment, with possibility of genetic counseling for patient and family. Drawing up an individualized orodental prevention program, and treatment sequence planning to conserve existing dental potential, improve esthetics and function and conserve dental stock until adulthood (fig; 6).

Non-syndromic hereditary PFE
In 15-45% of cases1, PFE may be familial.

The exact etiology of PFE remains undetermined, but reports of hereditary cases[8,13,21,28] tend to show a link with a genetic mutation of incomplete penetrance and variable expression. Dominant transmission linked to the X chromosome cannot be ruled out. Frazier-Bowers' team situates the main origin of PFE in the alveolar bone[12]. Candidate genes are thus those involved in bone remodeling. It may be wondered whether PFE and ankylosis belong to the same spectrum of mutations …

In humans, PFE has been associated with mutations in Runx2 (*RUN-related transcription factor 2*), TRAF 6 (*TNF Receptor Associated Factor 6*), and FGFR1-3 (Fibroblast Growth Factor Receptor).

Recently, PTH1R mutations were identified in cases of non-syndromic familial PFE with autosomal dominant high-penetrance transmission and variable expression[8,13]. Haploinsufficiency in the common PTH1R receptor of PTH and PTHrP is probably implicated in PFE.

Non-syndromic PFE is now the 5th most frequent pathology linked to PTH1R mutation, after Blomstrand's syndrome (chondrodysplasia), Ollier's disease (enchondromatosis), Eiken's

Figure 5
Table of syndromes associated with retarded and/or arrested eruption, according to Wise[27], completed by Molla[15], Suri[24] and Orphanet[18].

Syndrome	Eruption phenotype	Genetic defect	Transmission	Ref. OMIM
Cleidocranial dysostosis: Pierre Marie and Sainton	Generalized retardation by lack of cellular cementum	6 mutations ≠ of PEBP2αA/CBFA1	Autosomal dominant	# 119600
Albers-Schoenberg osteopetrosis	Idiopathic arrest	TRAF6	Autosomal dominant or recessive	#259700, #259710, #259730
GAPO (Anderson and Pindborg)	Idiopathic arrest, retarded growth		Autosomal recessive	#230740
Osteopathia striata with cranial sclerosis	Idiopathic arrest	Xq11,2	Autosomal dominant	# 300373
Fairbanks' osteoglophonic dysplasia	Idiopathic arrest of permanent teeth	8p11,23; p11,22	Autosomal dominant	# 166250
Singleton-Merten	Dental dysplasia, permanent tooth retardation		Autosomal dominant?	# 182250
Aarskog	Retardation	FGDY1 coding growth reg. fact.	Linked to X, recessive	#100050
Acrodysostosis	23% retardation		Autosomal dominant	#248400 ?
Albright hereditary osteodystrophy: pseudohypoparathyroidism	Retardation	mutations ≠ GNAS1 (protein G) 20q13,32	Autosomal dominant	#174800
Cherubism	Retardation by bone obstacle, tumor, MFE	Mutation SH3BP2 gene (4p16.3.)	AD	#118400
Noonan	Cherubism, MFE	PTPN11(chr 12) KRAS,SOS1, and RAF1 genes	AD	#163950
Ramon	Cherubism, MFE + gingival fibromatosis	?	AR	#266270
Recklinghausen's disease: Neurofibromatosis 1	Cherubism, MFE	NF1 gene (17q11.2)	AD	#162200
Apert acrocephalosyndactily	Generalized retardation ectopia, hypodontia	Mutation FGFR2 gene 10q26,13	Autosomal dominant	#101200 IV #201020
Carpenter acrocephalosyndactily	⏱ bone density hindering resorption	MEGF8, RAB23 6p11,2/19q13,2	AR	#201000 #614976

Syndrome	Eruption phenotype	Genetic defect	Transmission	Ref. OMIM
Ellis van Crevelt Chondroectodermal dysplasia	Retardation, oligo-dontia	4p16 (EVC1) 4p16 (EVC2)	Autosomal recessive limbine	XLHED #305100
Cockayne	Retardation	CSB gene (ERCC6)	Autosomal recessive	
De Lange	Retardation	SHOT ???	Autosomal dominant???	
Dubowitz	Retardation, hypo-dontia, short stature	?	Autosomal recessive??	#223370
Gorlin Cohen, Chaudry-Moss Frontometaphyseal dysplasia	Retardation, decidu-ous ankylosis	?	Autosomal domi-nant??? Linked to X ???	
Goltz Focal dermal hypo-plasia	Retardation, hypodontia, dental hypoplasia	Xp11,23	Linked to X, dominant, fatal in hemizygotic boys	#305600
Hunter Mucopoly-saccharoidosis II	Retardation	Mutations ≠ IDS gene Xq28	Linked to X	#309900
Bloch-Sulzberger Incontinentia pig-menta	Retardation, hypo-dontia in 80% of cases	Xp11.2, rarely IKK gene Xq28	Linked to X, domi-nant, fatal in boys	#308300
Killian/Teschler-Nico-la Pallister Killian	Retardation	Tetrasomia 12p in mosaic	Chromosomal abnormality	PKS #601803
Levy- Hollister	Deciduous retarda-tion	?	Autosomal dominant	
Maroteaux-Lamy Mucopolysaccharoi-dosis type VI	Retardation, micro-dontia	Mutations ≠ ASB gene 5q14,1	Autosomal recessive	MPS6#253200
Hurler's disease Mucopolysaccharoi-dosis type I	Retardation	IDUA - Iduronidase, alpha-L 4p16,3 ?	AR	#607014
Trichorhinophalan-geal syndrome type 1 or 3	Retardation	Mutations TPRS1 gene local-ized in 8q23,3	AD	#190350
Rothmund-Thomson Congenital poikilo-derma	Retardation, agen-esis,. supernum., hypgonadism	8q24,3		#268400
Papillon-Léage Orodigitofacial syn-drome I	Retardation	Mutation OFD1 gene		#311200
Mohr Orodigitofacial syndrome II	Retardation			#252100
Hyperimmuno globulinemia E	Retardation despite resorption		Autosomal dominant	

Syndrome	Eruption phenotype	Genetic defect	Transmission	Ref. OMIM
Osteogenesis imperfecta Type I	Retardation, dental dysplasia	COL1A1 and COL1A2	Autosomal dominant, variable expression	#259410 ?
Hutchinson- Gilford progeria	Retardation of both dentitions, rare hypodontia permanent anodontia	ADN helicase, telomerase	Autosomal recessive	#176670
Pyknodysostosis	Retardation, ↑ bone density hindering resorption, sometimes anodontia	Cathepsin K gene	Autosomal recessive	
Rothmund-Thomson	Retardation, microdontia, supernumerary or missing teeth.	8q24.3 RECQLA, WRN, BLM	Autosomal recessive	#268400
Rubinstein-Taybi	Retardation, hypodontia	16p13 CREBBP, 22q13.2 EP300	Autosomal dominant	RSTS1#180849 RSTS2#613684
Oculofaciocardiodental syndrome	Retardation	Xp11.4 (BCOR°) BL6 corepressor	Linked to X, dominant, fatal in boys	BCOR #300485 MCOPS2#300166
Cerebro-oculo-dento-auriculo-skeletal syndrome	Retardation, cuspid form anomalies	Collagen gene defect?	Autosomal recessive	#600373
Down's	Retardation	21q22,13	Chromosomal abnormality	DSCR3#605298 DSCR4#604829 DSCR6#609892
Turner MRXST	Retardation	Xp11,22		#300706
Gardner Familial adenomatous polyposis (FAP)1	Generalized retardation, ankylosis by cell proliferation, tumors	APC gene 5q22,2	?	#175100
Gorlin NBC BCNS	MFE, odontogenic keratocysts	Mutation PTCH1 gene	AD	#109400
(Axenfeld)Rieger 1, 2, 3	Retardation?, oligodontia ↑ size	PITX2 (4q25) and FOXC1 genes (6p25)	Autosomal dominant, strong penetrance	#601542 RIEG1 #180500 RIEG2#601499 RIEG3#602482
Parry Romberg Progressive hemifacial atrophy	Retardation by bone obstacle	?	AD	#141300
Lowry-MacLean	Retarded growth	?	AD	#600252
Murray-Puretic-Drescher Juvenile hyaline fibromatosis	Gingival fibromatosis	4q21 CMG2 (capillary morphogenesis protein 2)	AR	#228600
Rutherfurd Oculodental syndrome	Gingival fibromatosis	?	AD	#180900

Syndrome	Eruption phenotype	Genetic defect	Transmission	Ref. OMIM
Cross	Gingival fibromatosis	?	?	
Zimmermann Laband	Gingival fibromatosis	critical region in 3p14.3?	AD?	#135500
Aspartylglycosaminuria (AGU)	???	14q32-q33 Finland mutations AGUfin 4q34,3	AR	#208400
Hereditary amelogenesis imperfecta	Retardation, morphologic anomalies	Mutations ≠ gene	≠ transmission modes	14 formes
PFE	Complete or partial idiopathic arrest	3 mutations PTHR1 (13) 3p24.3-p14.3 ; 3p21,31	AD, non-syndromic	#125350

syndrome and Murk-Jansen metaphyseal chondrodysplasia. In general, however, PFE patients do not have associated skeletal abnormalities. However, Frazier-Bowers' team recently reported 2 families with associated osteoarthritis[11]. It thus seems unlikely that PTH1R haplo-insufficiency prevents systemic osteoclast formation and functioning. Non-syndromic PFE is probably caused by defective interaction in epithelial-mesenchymal cells immediately adjacent to the eruption path, altering the delicate balance between bone resorption and formation[8]. In PFE, osteoclasts seem not to express functional PTH1R receptors on their surface. Instead, the dental follicle may contain a paracrine or juxtacrine signaling pathway comprising PTH1R positive cells on the surface. Moreover, the fact that only posterior regions are involved remains unexplained. PTH1R gene products may have specific temporal and spatial action[13].

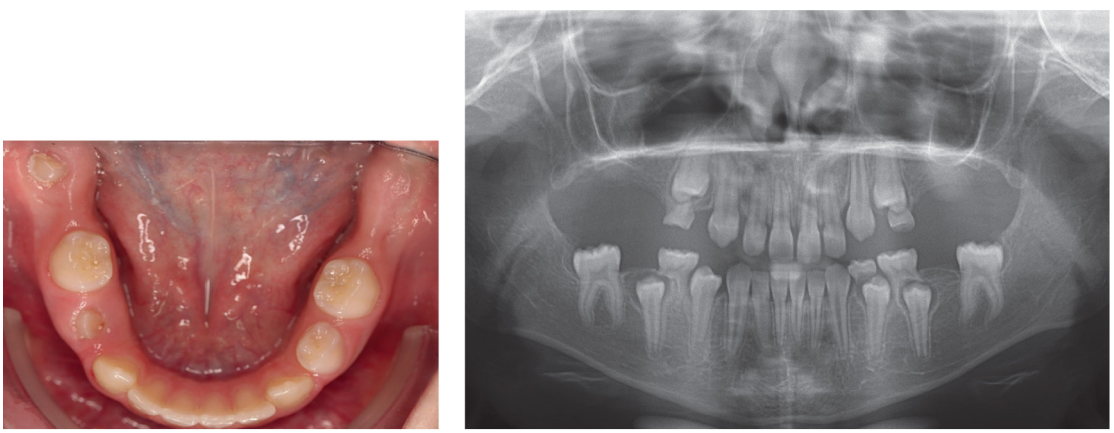

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Figure 6
a) Agenesis and retarded eruption; 2 other siblings, father and grandfather affected; syndrome non-identified. b) Panoramic view, 13 years.

Although PTH1R gene mutations seem clearly implicated in PFE, other genes may also well be involved. PTH1R mutation affects a whole local paracrine regulation system in PFE, although this remains to be identified.

In 2011, Yamagushi's team[28] identified 3 other PTH1R gene mutations that may underlie PFE (*6 mutations in all so far?*), as well as mutations of the TGFBR2 and PROKR2 genes involved in bone metabolism.

Other systemic etiologies[5]

Ionizing radiation

Accidental uranium irradiation or head and neck tumor radiotherapy may cause ankylosis, periodontal ligament lesions and maxillary growth defect.

Systemic diseases

HIV? Anemia, kidney failure…

Drugs

Nicotine, other drugs…

Administrative information:

Family name:

Given name:

Date and place of birth:

Address/country:

Reason for consultation :

General health status :

Was your child full-term?

Were there complications during pregnancy? Were medical treatments prescribed? If so, which? For how long?

Did your child have vitamin deficiencies? Feeding problems? Does he/she take vitamin D supplements every winter?

Does your child take medicines? If so, which? For how long?

Is your child's growth retarded? Late puberty? Does he/she take treatment for that? If so, which? For how long?

Does your child have epilepsy? Hearing problems?

Has your child had radiation therapy for head and neck tumor?

Has your child lived close by a nuclear accident?

Family and medical history:

Have you consulted a geneticist?

Do you have family members with bone disease? Cartilage disease?

Do you have family members with dental abnormalities: eruption problems? Agenesis? Abnormal tooth shape?

Dental history:

Has your child recently had molar region pain?

How long did it last?

Were there associated swellings or discharge?

When did your child produce the first milk tooth?

When did your child lose the first milk tooth? (mandibular incisor)

Did all the milk teeth fall out naturally, without needing extraction?

Has your child had dental treatment?

If so, what? (Prevention/restoration/extraction?)

Has your child sustained facial trauma? Mandibular fracture? Maxillary fracture?

Has your child had orthodontic treatment?

If so, what type? Please send initial documents if possible.

Figure 7
Questionnaire for history-taking[18].

QUESTIONNAIRE

Based on the Orphanet questionnaire (fig. 7), a certain number of points were raised to guide history-taking toward the various above etiologies. The questionnaire should remain open-ended, with new observations being added from new cases.

DIAGNOSTIC AND THERAPEUTIC DECISION-TREES

Depending on the answers to the history-taking questionnaire, clinical observation and radiographic examinations, various authors[7,22,24] have published therapeutic decision-trees. These have been recast in the light of recent discoveries (figs 8 and 9).

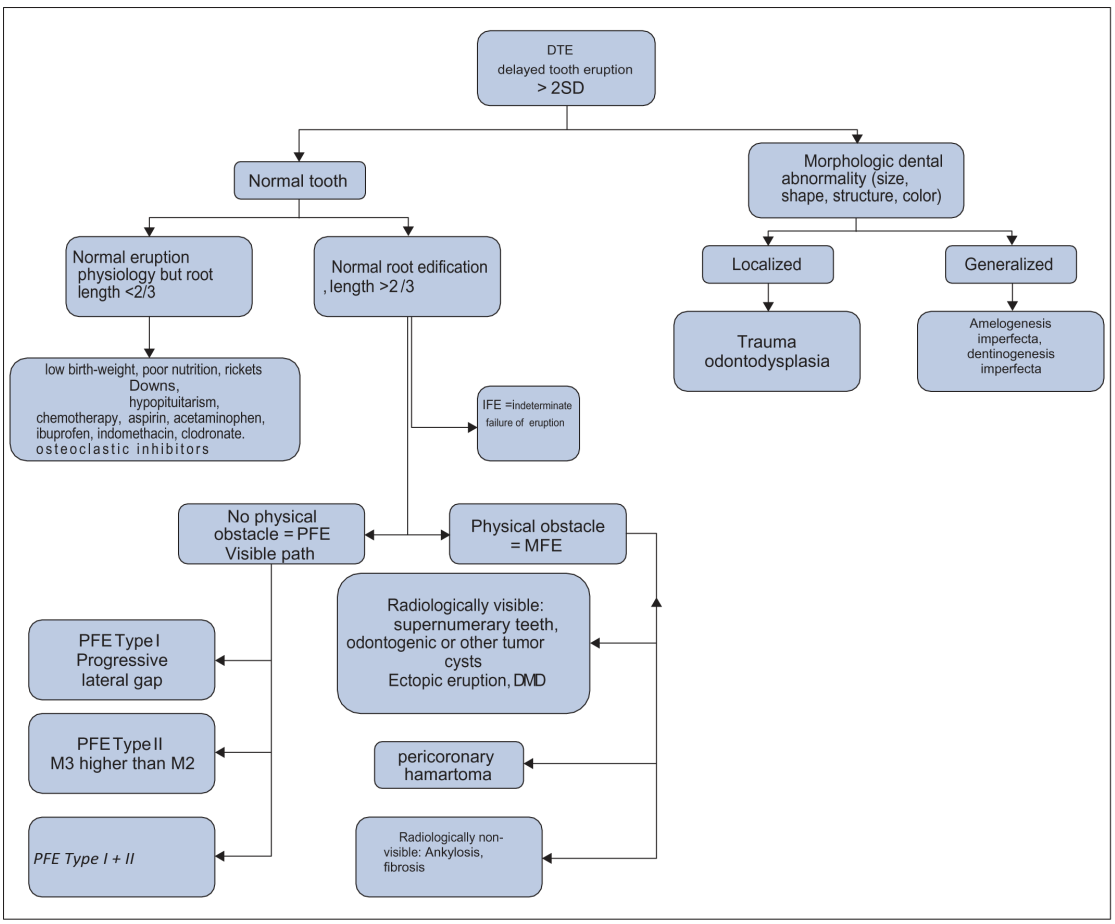

Figure 8
Differential diagnosis and therapeutic decision tree[22], Suri[24].

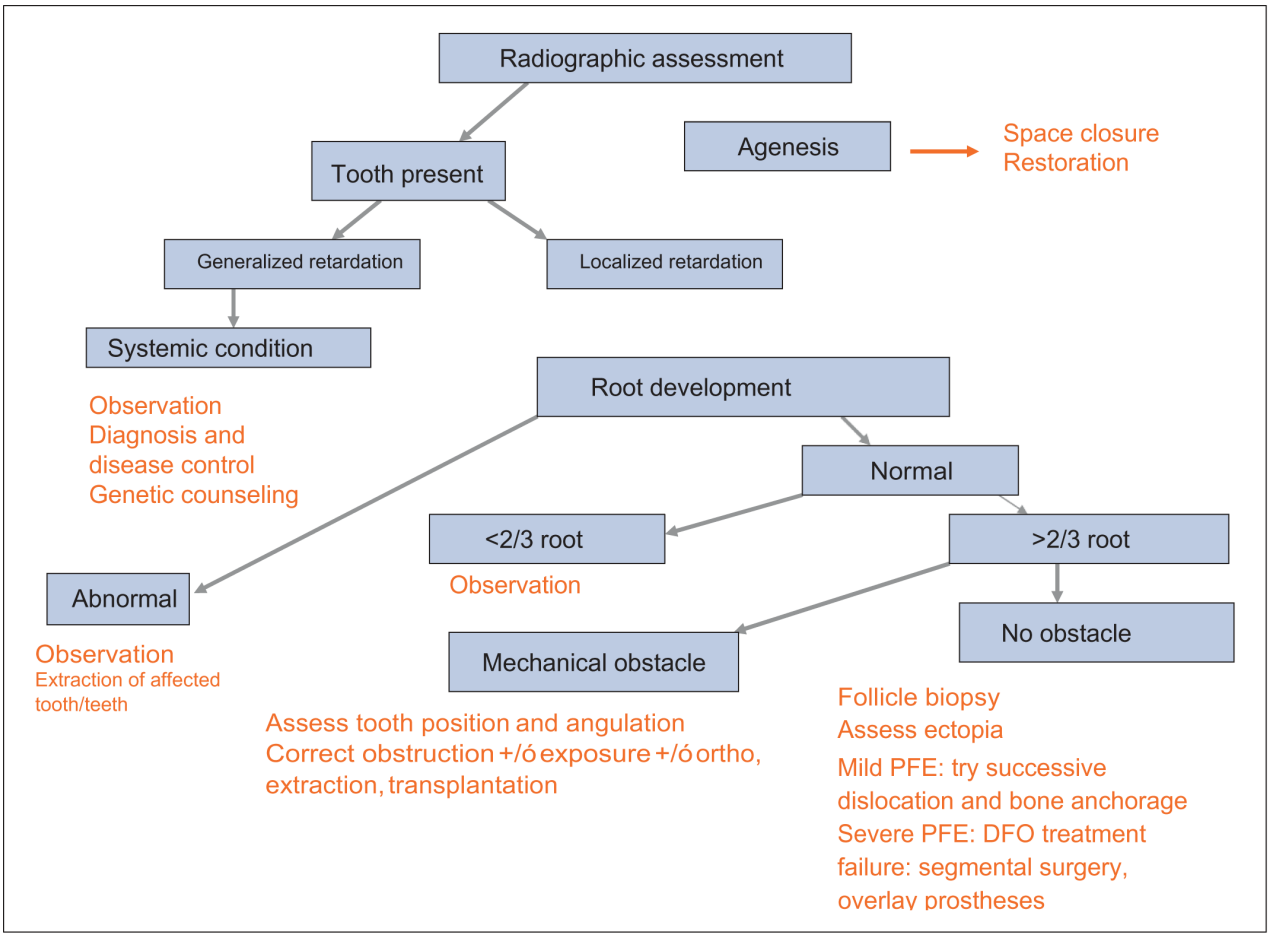

Figure 9
Therapeutic decision tree, Castaneda[7].

CONCLUSION

This long list of possible local or systemic etiologies in case of retarded second molar development allows optimization of treatment.

The mechanism of PFE and the role of osteoclasts remain unknown: elucidation would allow prevention and early treatment. Too often, it is the tooth's response to orthodontic efforts that points to retrospective diagnosis. A tooth that fails to get positioned despite adapted treatment is very likely affected by PFE. It is preferable to have established diagnosis ahead of any mechanical intervention, so as to be able to warn the patient of the uncertainty of outcome and to plan bone anchorages. Diagnosis should be precise, informative and evidence-based. It requires

knowledge of orthodontics, developmental biology and genetics. It may come serendipitously during routine consultation with the dental surgeon, or in the light of a syndromic presentation. The dental surgeon should be able to make such a diagnosis or refer patient and family to a specialist consultation. The diagnostic procedure places the patient in the center of the project, and governs both clinical management and the development of research programs[19].

Conflict of interest

The author declares no conflicts of interest.

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