Review Article

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Developmental Anomalies of Teeth: Pathogenesis and Molecular Enigma

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ABSTRACT

Background: Teeth are influenced by a lot of factors ranging from environmental influences to hereditary variations during their formation. These all conditions in certain circumstances create defects in the dentition. Changes include variations in number, size, defects in dental hard tissues per se. A clear understanding is necessary about the pathogenesis of these anomalies which can help in either preventive or treatment measures. Many of them are related to as early as start of tooth development defects or to a trauma in later stages of life. Genes which are involved in tooth genesis are commonly affected in these defects leading to varied degree of expressivity of them.

Keywords: Developmental, syndromic, genetic.

INTRODUCTION

Developmental anomalies of the teeth include deviations in tooth number (agenesis or supernumerary teeth), abnormalities of size and form, failure of eruption or precocious or delayed eruption, malpositions, as well as defects of dental hard tissues.[1] Qualititative variation is observed e.g. in the tooth size, the root length and the timing of tooth development, shedding and eruption (Table 1). Quantitative deviations are observed in tooth number, either as agenesis of one or more teeth or as development of extra (supernumerary) teeth, in cusp and root number [1]

Table 1: The developmental anomalies of teeth.

NUMERICAL ABNORMALITIES	Anodontia, Hypodontia, Supplemental Tooth, Mesiodens, Distomolar, Paramolar, Supernumerary Teeth.
MORPHOLOGICAL ABNORMALITIES	Microdontia, Macrodontia, Dilaceration, Taurodontism, Gemination, Fusion, Concrescence,Talon's Cusp,Dens In Dente And Dens Evaginatus
STRUCTURAL ABNORMALITIES	Amelogenesis Imperfect, Dentinogenesis Imperfecta And Dentin Dysplasia
FUNCTIONAL ABNORMALITIES	Hypercementosis

Tooth agenesis (anodontia)

- In the literature, the term anodontia (Greek word "ano" for "none") has sometimes been

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used to describe tooth agenesis in general even though it should be restricted to the very rare cases of agenesis of whole dentition. The term oligodontia (Greek word "oligo" for "few") has been used for describing more severe forms of agenesis, usually of at least six teeth excluding third molars. Anodontia is rare, and most cases occur in the presence of hereditary hypohidrotic ectodermal dysplasia.[1]

- Hypodontia- Developmental absent teeth are one of the most common dental developmental abnormalities with a reported prevalence of 3.5% to 8.0% (excluding third molars). A female predominance of approximately 1.5: 1 is reported. [2]

Supernumerary teeth

Development of supernumerary teeth is observed in some syndromes, but they also occur in the permanent dentition of about 2-3.5% of otherwise healthy individuals. Most commonly the supernumerary teeth develop in the incisor region, and a typical supernumerary tooth is a mesiodens. Basically four main morphological types of supernumerary teeth are present- conical as in mesiodens (*Figure 1a*), supplemental as in permanent maxillary lateral incisor in which there can be duplication of teeth in normal series tuberculate & odontome.[2] The aetiology of the supernumerary teeth however remains unclear. Several theories, such as the 'phylogenetic theory', the 'dichotomy theory, a hyperactive dental lamina and a combination of genetic with environmental factors-unified etiologic explanation, have been suggested. Murashima-Suginami et al. studied the growth of molars and incisor supernumerary teeth and fusion between molars and supernumerary teeth in mice with USAG-1 gene deficiency. Supernumerary teeth are frequent in RUNX2 haplo-insufficient humans, and there is a role of RUNX2 in preventing excessive bud assessment in both humans and mice. [3]

Microdontia: The term microdontia has been used for occurrence of teeth with reduced tooth size, but some authors have reserved this term to extreme size reduction and have gene defects in MSX1 and PAX 9. Microdontia involve a single tooth also, most commonly maxillary lateral incisor & third molar.[3]

Diffuse true microdontia is uncommon but may occur as an isolated finding in Down syndrome, pituitary dwarfism and in association with a small number of rare hereditary disorders that exhibit multiple abnormalities of the dentition.[3]

Macrodontia: Refers to teeth which are larger in size than the normal. It can be generalized as in pituitary gigantism but is rare entity. It can be relative in which larger teeth are present in relatively smaller jaws. [1] Diffuse macrodontia has been noted in association with pituitary gigantism and pineal hyperplasia with hyperinsulinism.[3]

Abnormalities in shape of teeth

Abnormalities in shape of teeth are mainly categorized into gemination, fusion, concrescence, talon's cusp, dens in dente, dens evaginatus, taurodauntism & dilaceration.

CROWN ABNORMALITIES

Gemination: Gemination is defined as an attempt of a single tooth bud to divide, with the resultant formation of a tooth with a bifid crown (*Figure 1b*) and, usually, a common root and root canal and tooth count is normal. Clinically these teeth not esthetically amicable along with there is an increased chances of carious lesion. MSX-2 and PAX-9 overexpression especially at the secondary enamel knot region leads to the initiation of division of tooth buds which remains incomplete and therefore have a hereditary tendency.[3]

Fusion- It is a developmental anomaly affecting the shape of teeth characterized by the union of two adjacent teeth (*Figure 1c*). Prevalence of fusion ranges from 0.5% - 2.5 %. Fusion results when development of two tooth germs takes place so closer and they come into contact and fuse before calcification usually a physical force or a pressure from neighboring structures. The clinical problems associated with fused teeth are esthetics, arch symmetry, spacing, malocclusion.

Concrescence - is two fully formed teeth, joined along the root surfaces by cementum (*Figure 1d*). The process is noted more frequently in the posterior maxillary regions. It arises as a result of traumatic injury or crowding of teeth with resorption of interdental bone so that the two roots are in approximation and fused later by cementum.

Extraction of these teeth is a difficult process as while extracting one teeth, the other one is also extracted. [3]

Dens invaginatus / dens in dente- (*Figure 1e*) is a malformation of teeth probably resulting from an infolding of dental papilla during tooth development. Several theories have been proposed for pathogenesis like

- Growth pressure of the dental arch results in buckling of the enamel organ.
- Invagination results from a focal failure of growth of the inner enamel epithelium.(table II)
- Invagination is a result of rapid and aggressive proliferation of a part of the internal enamel epithelium invading the dental papilla. [4]

Table 2: Oehlers [3] classified dens invaginatus based on radiographic interpretation of degree of invagination.

Type I	invagination that is restricted within the crown of the tooth and does not cross beyond the cementoenamel junction.
Type II	inavagination extends below cementoenamel junction and ends in a blind sac that may or may not communicate with adjacent dental pulp.
Type III	extends through the root perforates in apical or lateral radicular area without any immediate communication with the pulp

Dens evaginatus- (central tubercle) is a cusplike elevation of enamel located in the central groove or lingual ridge of the buccal cusp of permanent premolar or molar teeth(*Figure 1f*). It is usually bilateral and demonstrates a marked mandibular predominance. Radiographically, the occlusal surface exhibits a tuberculated appearance and often a pulpal extension is seen in the cusp. [3]

Talon's cusp-In 1970, Mellor and Ripa named the accessory cusps as talon cusp because of its resemblance in shape to an eagle's talon(*Figure 1g*). Talon's cusp occurs early in odontogenesis during the morphodifferentiation stage. Another possible cause of the condition is hyperproductivity of the anterior segment of the dental lamina. Bilateral distribution of talon's cusp, in some genetic syndromes support genetic etiology of the condition like Rubstein- Taybi syndrome.[5] MSX-2 mutation aberrant expression as well as PAX-9 underexpression has been noted in 21 cases of talon's cusp studied by Smith et al.[3]

Taurodontism- a morpho-anatomical change in the shape of the tooth in which the body of the tooth is enlarged and the roots are reduced in size. (*Figure 1h*) The origin of this term is from Greek "tauros" which means "Bull" and "odontos" which means "Tooth". It is caused by the failure of Hertwig's epithelial sheath diaphragm to invaginate at the proper horizontal level. An enlarged pulp chamber, apical displacement of the pulpal floor, and no constriction at the level of the cementoenamel junction are the characteristic features.[6]

Etiology- It has been suggested that the anomaly represents a primitive pattern, a mutation, a specialized or retrograde character, an atavistic feature, an X-linked trait, familial or an autosomal dominant trait. It has also been associated with several developmental syndromes and anomalies including amelogenesis imperfecta, Down's syndrome, ectodermal dysplasia, Klinefelter syndrome, tricho-dento-osseous syndrome, Mohr syndrome, Wolf-Hirschhorn syndrome and Lowe syndrome.[6]

Rhizomegaly and Rhizomicry- teeth with elongation of root sparing the crown is known as rhizomegaly common in maxillary as well as mandibular canines whereas rhizomicry is the occurrence of short roots as compared to the normal root length which is commonly seen in maxillary lateral incisors. In pituitary gland anomalies these can be predominant root defects in few cases but predominantly occur due to local causes.[3]

Root abnormalities

Root abnormalities have been attributed to an epithelial defect and more specifically to a defect of the function of the Hertwig's epithelial root sheath.[1]

Dilaceration-(*Figure 1i*) It is an abnormal angulation or bend in the root or, less frequently, the crown of a tooth. Although a corroborating history may be absent, the majority appear to arise after an injury that displaces the calcified portion of the tooth germ, and the remainder of the tooth is formed at an abnormal angle. [3]

Enamel defects

Failure of tooth development and enamel defects has been linked e.g. by mutants of MSX2 and PAX9 and disruption of the epithelial SHH signaling affect both tooth formation and ameloblast differentiation. Dominant defects in MSX1, PAX9 and AXIN 2 have been described in families with isolated severe tooth agenesis and enamel defects.[1]

Amelogenesis imperfecta

Amelogenesis imperfecta can be inherited as an autosomal dominant trait, or in autosomal recessive or X-linked forms[7] In X-linked amelogenesis imperfecta (XAI) males are fully affected whereas females are often good examples of lyonization, a phenomenon caused by the inactivation of one X chromosome in each somatic cell during development [8] Clearly, then, the amelogenin gene is a candidate gene for XAI so that mutations in this gene might cause XAI.[9] The gene is located in the same region as that involved in dentinogenesis imperfecta as well as genes thought to be involved in enamel development. These genes are the albumin gene and the ameloblastin gene. It is not yet clear whether mutations in these genes are responsible for the ADAI in these families. [9]

Three general categories of AI are recognized: (Table III)

1. Hypoplastic type: Inadequate formation of enamel matrix, both pitting and smooth

types exist. Enamel may be reduced in quantity but is of normal hardness.

2. Hypomaturation type: A defect in the crystal structure of enamel leads to a mottled

enamel with white to brown to yellow colors. (*Figure 1j*)

3. Hypocalcified type: A defect not in the quantity but in the quality of enamel. It is poorly mineralized, soft and chips and wears easily.

Table 3: Modified witkop classification (Four major categories based primarily on phenotype & subdivided into 15 subtypes by phenotype and secondarily by mode of inheritance. Witkop 1988)

Type IA	Hypoplastic, pitted autosomal dominant
Type IB	Hypoplastic, local autosomal dominant
Type IC.	Hypoplastic, local autosomal recessive
Type ID	Hypoplastic, smooth autosomal dominant
Type IE	Hypoplastic, smooth X-linked dominant
Type IF	Hypoplastic, rough autosomal dominant
Type IG	Enamel agenesis, autosomal recessive
Type IIA	Hypomaturation, pigmented autosomal recessive
Type IIB	Hypomaturation, X-linked recessive
Type IIC	Hypomaturation, snow-capped teeth, X-linked
Type IID	Hypomaturation, snow-capped teeth, autosomal dominant
Type IIIA	Autosomal dominant
Type IIIB	Autosomal recessive
Type IVA	Hypomaturation-hypoplastic with taurodontism, autosomal dominant
Type IVB	Hypoplastic-hypomaturation with taurodontism, autosomal dominant

Genes associated with AI are AMELX (amelogenin), ENAM (enamelin),MMP-20 (coding for protein enamelysin),KLK-4 (kallikrein-4), DLX-3 gene,

AMBN gene (ameloblastin). Mutations of ENAM gene is associated with autosomal dominant and recessive patterns of hypoplastic AI whereas mutations with MMP-20 gene is associated with autosomal recessive variety of AI with pigmented hypomaturative variety of AI.

Dentinogenesis imperfecta (DI)

Dentinogenesis imperfecta was first identified as a disorder distinct from amelogenesis imperfecta by Finn.[10] Shields et al classified DI into type I (with osteogenesis imperfecta), type II (without osteogenesis imperfecta) and type III (the Brandywine type). (*Figure 1k*) Witkop classification has 2 categories- type I which is dentinogenesis imperfecta and type II which is brandywine type.

Dentition have blue to brown discoloration and when dentin is exposed it undergoes accelerated attrition. Radiographically also, the teeth have bulbous crowns, cervical constriction , thin roots and early obliteration of root canals and pulp chambers.

The observation that dentine phosphoprotein (DPP) levels were increased in DI led MacDougall et al to investigate the possibility that DPP might be a candidate gene for DI. Using a degenerative oligonucleotype probe and a somatic cell hybrid panel they found no evidence that the gene was associated with DI. [11] The dentine matrix protein 1 (DNP1) gene is expressed in odontoblasts but not in pulp cells or preodontoblasts.[12]

Dentinal dysplasia It is another autosomal dominant form of inherited defects of dentine. Two major varieties are DD1 and DD2. In DD1, i.e. radicular dentin dysplasia dentinal disorganization occurs which leads to teeth mobility, delayed eruption. Radiographically also little or no detectable pulp is evident. In DD2, i.e. coronal dentin dysplasia teeth will have blue to amber coloured transluscency. Radiographically they have bulbous crowns and cervical constriction and early obliteration of pulp. Families with nonsyndromic dentinogenesis imperfecta (DGI) and the milder, dentin dysplasia (DD), have mutations in one allele of the dentin sialophosphoprotein (DSPP) gene (Table IV).[11]DPP is a very repetitive protein that is highly phosphorylated and thought to be involved in the nucleation of hydroxyapatite crystallites and the control of their growth[12].

Overall, the mutations in DSPP that have been described to date consist of a combination of mis-sense and nonsense changes, splicing mutations and deletions which have been hypothesised to lead to intracellular retention of DSPP as a consequence of errors in signal peptide or subsequent processing events.[11]

Table IV: mutations associated with DSPP causing DGI and DD.

Table 1: Mutations of *DSPP* causing DGI and DD.

	Predicted Protein	*cDNA*	*Diagnosis*
Exon 2	p.Y6D	c.16T>G	DD-II
	p.A15V	c.44C>T	DGI-II
	p.P17T	c.49C>A	DGI-II
	p.P17S	c.49C>T	DGI-II
Intron 2	p.V18_Q45del	c.52-3C>G	DGI-II
		c.52-3C>A	DGI-II
Exon 3	p.V18F	c.52G>T	DGI-II/III
	p.Q45X	c.133C>T	DGI-II
Intron 3	p.V18_Q45del	c.135+1G>A	DGI-II
		c.135+1G>T	DGI-II/III
Exon 5	p.S624TfsX687	c.1870-1873del TCAG	DD-II
	p.S640TfsX671	c.1918-1921del TCAG	DD-II
	p.S680fsX1313	c.2040delC	DD-II
	p.S758AfsX554	c.2272del A	DGI-II/III
	p.S842TfsX471	c.2525del G	DGI-II/III
	p.S865fsX1313	c.2593delA	DGI-II
	p.S895fsX1313	c.2684delG	DGI-II
	p.D1146fsX1313	c.3438delC	DGI-II
	p.D1182fsX1312	c.3546-3550delTAGCAinsG	DGI-II

Fig 1: Showing various developmental anomalies of dentition. (Courtesy few images- Neville BW, Damm DD, Allen CM, Bouquot JE. Oral and Maxillofacial Pathology. 3rd ed.Elsevier Publication 2009:77-99.

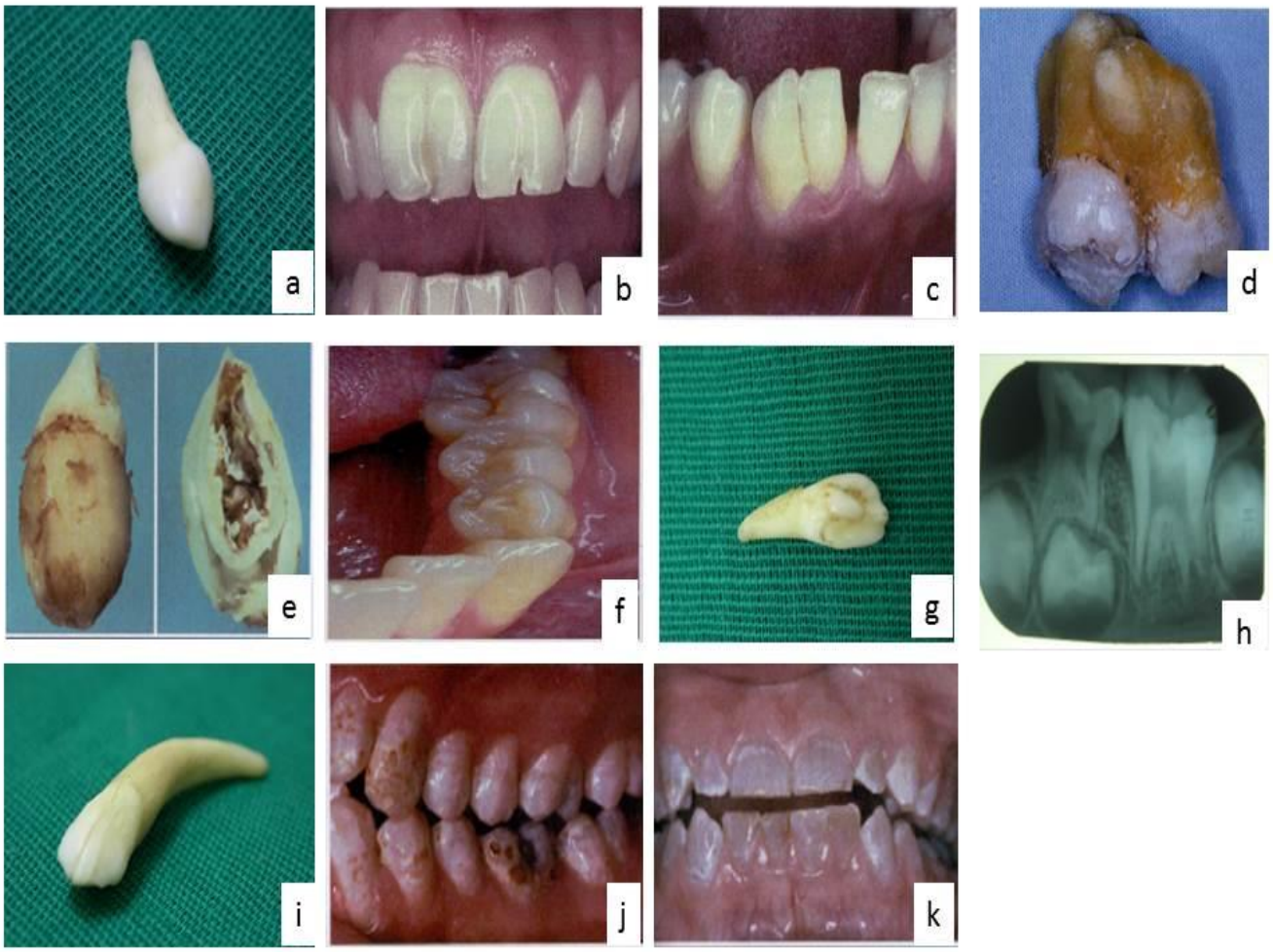

*Fig (a)-Conical teeth representing mesiodens, **Fig (b)**- Gemination which is present in both the central incisors, **Fig (c)**- Fusion-Double tooth in the place of the mandibular right lateral incisor and cuspid, **Fig (d)**- Concrescence showing union of molar teeth by cementum, **Fig (e)**-Coronal dens invaginatus, **Fig (f)**- Dens evaginatus- Cusplike elevation located in the central groove of mandibular first bicuspid., **Fig (g)**-Talon's cusp on the lingual aspect of lateral incisor, **Fig (h)**- Showing enlarged pulp chambers in a deciduous molar tooth depicting taurodontism, **Fig (i)**-Dilaceration of the canine root, **Fig(j)**- Hypomaturative variety of Amelogenesis Imperfecta, **Fig(k)**-Dentinogenesis imperfecta*

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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