Orofacial Manifestations of Congenital Fibrillin Deficiency: Pathogenesis and Clinical Diagnostics

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Abstract

Mutations in the genes encoding *fibrillin*, an extracellular matrix protein involved in providing elastic properties to the connective tissues, may result in specific craniofacial and oral anomalies. A number of craniofacial (retrognathia, dolichocephaly, high palate) and dental (root deformity, pulp calcification) manifestations are considered pathognomic for the Marfan syndrome (MFS), a condition caused by congenital *fibrillin-1* deficiency. Reports on similar features in congenital contractural arachnodactyly (CCA), caused by *fibrillin-2* deficiency, support the hypothesis that fibrillin deficiency might result in a number of morphological anomalies by influencing tissue interaction during growth and development. Hence, clinical manifestations can be related to specific aspects of fibrillin deficiency pathogenesis, and may be adopted as diagnostic tools in the outlook for affected individuals. (*Pediatr Dent.* 2004;26:535-537)

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Congenital Contractaral Arachnodactyly (CCA) (OMIM Entry 121050)[1,2] is a very rare inherited disorder of connective tissue, caused by mutation in *FBN2*, the gene encoding the extracellular matrix protein fibrillin-2. CCA is phenotypically related to Marfan syndrome (MFS) (OMIM Entry 134797), a multisystem disorder that is caused by mutation in *FBN1*, the gene coding for fibrillin-1. MFS is believed to occur in about 1:3,000-5,000.[3] In contrast, CCA is a rare condition which has been documented in less than 50 families (OMIM Entry 121050). To date, only 2 case reports on oral manifestations in CCA have been published.[2,4] Unfortunately, identification of mutations in *FBN2* gene, required for final proof, failed in these reports. The oral findings in CCA are consistent with previous reports on orofacial manifestations in MFS,[5] and in this way support the hypothesis of craniofacial/oral features being the result of both intrinsic and environmental factors in fibrillinopathies.[6,7] In the present paper, the hypothesis that fibrillin deficiency might result in a number of morphological anomalies by influencing tissue interaction during growth and development, is applied to the specific oral features in both MFS and CCA.

Fibrillin is a cysteine-rich glycoprotein that exists in 3 homologous forms,[8] of which fibrillin-1 and fibrillin-2, respectively encoded by the *FBN1* gene on 15q21 and the *FBN2* gene on 5q23[9] are the best characterized.. Fibrillin-1 provides the major structural (ie, load bearing and limitating expansive tissue growth) function of microfibrils [3,10,] whereas expression of fibrillin-2 directs the assembly of elastic fibers during early embryogenesis.[11] Mutations in *FBN1* and *FBN2* cause deficient processing of respectively fibrillin-1 and fibrillin-2, affecting tissues displaying elastic properties. Clinical manifestations are widespread and may involve the skeletal, ocular, cardiovascular and pulmonary systems, muscle, skin and integumentum (Table 1).

The diagnosis of MFS is largely clinical and relies on a set of diagnostic criteria known as the Ghent Nosology.[12] These criteria require the presence of a combination of clinical manifestations in different organ systems (skeletal, ocular, cardiovascular, pulmonary, skin and integumentum, and dura), which are assigned major or minor diagnostic specificity.[12] The presence of an *FBN1* mutation may be established in the majority of affected individuals. Various craniofacial and oral abnormalities have been described in patients with MFS (Table 2). A number of oral manifestations, such as a high incidence of caries, tooth root deformity, abnormal pulp chambers with obliteration, and a high

Table 1. Clinical Manifestations of Congenital Fibrillin Deficiency (Marfan Syndrome and Related Disorders)

System	Manifestations*
Skeletal system	Overgrowth, long limbs, scoliosis, arachnodactyly, narrow face, highly arched palate
Eyes	Eye lens luxation (ectopia lentis), severe myopia
Cartilagenous tissue (ears)	Deformity (crumbled ears)
Cardiovascular system	Mitral valve prolapse, aortic root dilatation and/or dissection
Lungs	Spontaneous pneumothorax
Muscle	Hypotonia
Joints	Hypermobility, recurrent dislocations

* Occurrence and/or expression may vary along with affected type of fibrillin and/or mutation type.

susceptibility to periodontal pathologies, have been reported to be closely related to MFS.[5] Craniofacial abnormalities include dolichocephaly (long face), a highly arched palate, maxillary and mandibular retrognathia, prognathia, and macrocephaly, which have been reported with variable frequencies.[13-15] A recent cephalometric analysis of a population with MFS demonstrated a significant association between MFS and maxillary/mandibular retrognathia, long face, and a highly arched palate.[6] Similar manifestations have been reported in CCA, but, as to date only 2 cases have been documented, the diagnostic validity of these manifestations is low. Sanger et al[4] described a 7-year-old boy with typical skull, mandibular retrognathia, widely spaced teeth in the anterior maxillary area, and a high arched palate. The clinical images presented in Sanger's article, however, are not convincing evidence for any diagnostic specificity of these orofacial features. In fact, the 'typical features' (mandibular retrognathia and spaced teeth) are very common in healthy youngsters of that age. Ayers and Drummond[2] presented a 14-year-old girl with spaced teeth, long tapered roots and abnormal pulps with obliteration and pulp stones. These anomalies are consistent with those reported in a population with MFS,[5] and hence support the hypothesis of fibrillin defciency causing abnormal tissue interaction during tooth morphogenesis.[6]

During recent years an increasing number of genes have been identified that are involved in the regulation of tooth morphogenesis. So far, all genes that have been linked with early tooth morphogenesis have developmental regulatory functions in other organs. The majority of these genes are associated with the signaling pathways transmitting interactions between cells and tissues. Mutations in several different genes lead to an arrest in tooth development in both mutant mice and humans, in the presence of eg, craniosynostosis, ectodermal dysplasia etc.[16] Neither *FBN1* nor *FBN2* have been situated in the complex signaling pathways and networks that modulate tooth morphogenesis. With regard to root deformity, no signaling molecules, receptor or target genes have been related to the specific long, tapered roots as found in MFS and CCA. From a histomorphogenic point of view, fibrillin has no function in the regulation of tooth morphogenesis. In accordance with the specific morphogenesis of craniofacial bones in MFS,[6] fibrillin deficiency may account for an improper tissue response (altered 'supporting' properties) of the stroma surrounding the tooth germ, leading to abnormal tooth crown or root dimensions. 'Compensatory' tissue responses of this nature have been suggested in growth and development of joints and long bones.[17] Since the pulp-dentin complex almost exclusively consists of collagen, any direct relationship between fibrillin deficiency and altered dentin formation (hence abnormal crown and root dimensions) is non-existent. As previously suggested, degenerative changes at the vessel walls in the tooth pulp,[18] caused by minor rupture of the vascular endothelium as a result of altered structural properties, may account for the induction of pulp stone formation in fibrillinopathies.[7]

Table 2. Orofacial Manifestations of Marfan Syndrome (Fibrillin-1 Deficiency)*

Dolichocephaly (long, narrow face)
Deep-set eyes with slight ptosis, small nose
Mandibular and maxillary retrognathia
Highly arched palate, maxillary constriction
Hypermobility of temporomandibular joints with recurrent dislocations
Crowding of teeth
Root deformity
Abnormal pulp chambers with obliteration
High susceptibility to periodontal diseases

* De Coster et al,[5-7] De Paepe et al,[12] Westling et al,[14] and Cistulli et al[15]

There is also no association between enamel formation and connective tissue. Enamel is an ectodermal tissue, whereas connective tissue is descendent from the embryonic mesoderm. Hence, there is no genetic interrelation between structural defects of the enamel and connective tissue. Genetic enamel defects are caused by mutation in *AMBN* (OMIM Entry 601259), *TUFT1* (OMIM Entry 600087), *AMELX* (OMIM Entry 300391), or *ENAM* (OMIM Entry 606585), which are enamel-specific genes encoding a limited number of regulatory proteins. To date, there is no evidence of crossover between human genetic conditions involving genes coding for collagens, fibrillins and/or enamel proteins. The majority of generalized developmental defects of enamel share a metabolic (non-genetical) etiology, especially when presenting in a banded pattern as reported in Ayers' and Drummonds' CCA case.[2] A high prevalence of structural enamel defects (hypoplastic spots in premolars) was previously reported in MFS, which could be related to decay in the preceding deciduous molars.[5] These spots were classified as

enamel defects of local infectious etiology. Hence, this finding may not be used to substantiate the hypothesis that enamel hypoplasia is a feature of CCA.[1]

Finally, restraint is called in assigning dysmorphic oral features, such as cleft palate, to a syndrome. An enlargement of the palatal shelves (byzantine arch palate), as featuring in a number of marfanoid syndromes such as Shprintzen-Goldberg syndrome and Idaho syndrome type II,[19] may easily be confused with a central palatal cleft. Assignment of sporadic symptoms to the diagnostic spectrum of a syndrome may easily mislead the reader, especially when this spectrum is used for determining orofacial signs in order to match an undiagnosed syndrome. It is advisable to mention the diagnostic validity of the given symptoms in case reports (ie, the degree to which these symptoms can be assigned a high or low diagnostic specificity according to the number of reports in literature and an established relationship with known molecular defects).

Conclusions

Assessment of oral features such as root deformity, abnormal pulp chambers with obliteration and pulp stones, a high arched palate and a long face, may help in diagnosing congenital fibrillin deficiency in young patients. However, the practioner should be attentive in assigning diagnostic weigth to dysmorphic features in the oral cavity. A thorough appreciation of both the morphogenic and genetic aspects of tooth development may be helpful in correlating dental anomalies with a syndrome, especially in cases where a complex (multisystem) phenotype is present.

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