Case report

MULTIPLE FRENULA- A MARKER OF UNDERLYING GENETIC ANOMALY: REPORT OF A CASE OF ELLIS-VAN CREVELD SYNDROME.

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Abstract:

Most often during oral examinations, dentists encounter with abnormal attachments of the frenum. These frenal attachments often go unexamined by the dentists during oral examination. Frenal attachments are thin folds of mucous membrane that attach the lips to the alveolar mucosa and underlying periosteum. However, the presence of multiple frenula can be a feature of several inherited syndromes. Ellis-van Creveld (EvC) syndrome, also termed as chondroectodermal dysplasia or mesoectodermal dysplasia is a rare inherited genetic disorder mainly affecting the ectodermal components. The characteristic features of this syndrome include multiple frenula, hypodontia, polydactyly, short stature, cardiac and skeletal anomalies. This paper describes one such syndrome that was suspected based on the multiple frenula noted on oral examination in a teenage girl and confirmed after noting the presence of other co-existing abnormalities.

Keywords: frenum; multiple frenula; Ellis-van Creveld syndrome; genetic syndrome

Introduction:

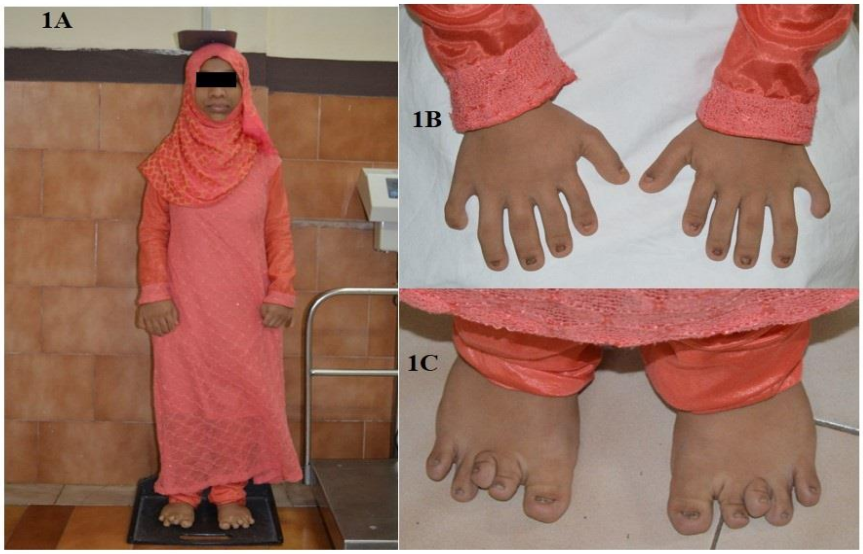
Ellis-van Creveld (EvC) syndrome, also termed as chondroectodermal dysplasia is a rare inherited genetic disorder mainly affecting the ectodermal components.[1,2] The characteristic features of this syndrome include multiple frenula, hypodontia, polydactyly, short stature, cardiac and skeletal anomalies.[1-3] Multi-modality treatment is necessary to provide care to such patients but no permanent cure has been made possible yet. This paper describes one such case of an EvC syndrome that was suspected based on the multiple frenula noted on oral examination in a teenage girl and confirmed after noting the presence of other co-existing oral and systemic abnormalities.

Case presentation:

A 12-year girl reported to our outpatient services with complaints of missing teeth. Antenatal history was non-significant with regular antenatal checkups and she was delivered through a Cesarean section at 38 weeks gestation. Past medical history revealed frequent episodes of respiratory tract infections and cyanosis noted in the infancy period, surgery for atrial septal defect and mitral valve regurgitation at 2 years of age, and multiple corrective surgeries for bilateral genu valgum at 7 years of age. Past dental history revealed removal of natal teeth at 1 month of age due to feeding problems and history of delayed eruption of teeth.

On clinical examination, patient had a short stature (136 cm) polydactyly with bilateral 6 digit hands (hexadactyly), maldeveloped nails and clinodactyly, absent distal crease of thumb, partial cutaneous syndactyly of 2nd and 3rd toes, and overriding of the 3rd and 4th toes (Figures 1A-1C).

Figure 1: Photograph showing disproportionate dwarfism (1A), polydactyly with bilateral 6 digit



hands (hexadactyly) and dysmorphic nails (1B), partial cutaneous syndactyly of 2nd and 3rd toes, and overriding of the 3rd and 4th toes (1C).

Hypertelorism, flat nasal bridge, convex profile and posterior divergence were noted on extra-oral examination. Intra oral examination showed multiple labial frenula, generalized microdontia, transposition of 12, congenitally missing 31and 41 and retained maxillary deciduous second molars. Orthopantomogram and lateral cephalogram confirmed the dental anomalies (Figures 2 and 3). With these morphological anomalies, a diagnosis of Ellis-van Creveld (EvC) syndrome was made.

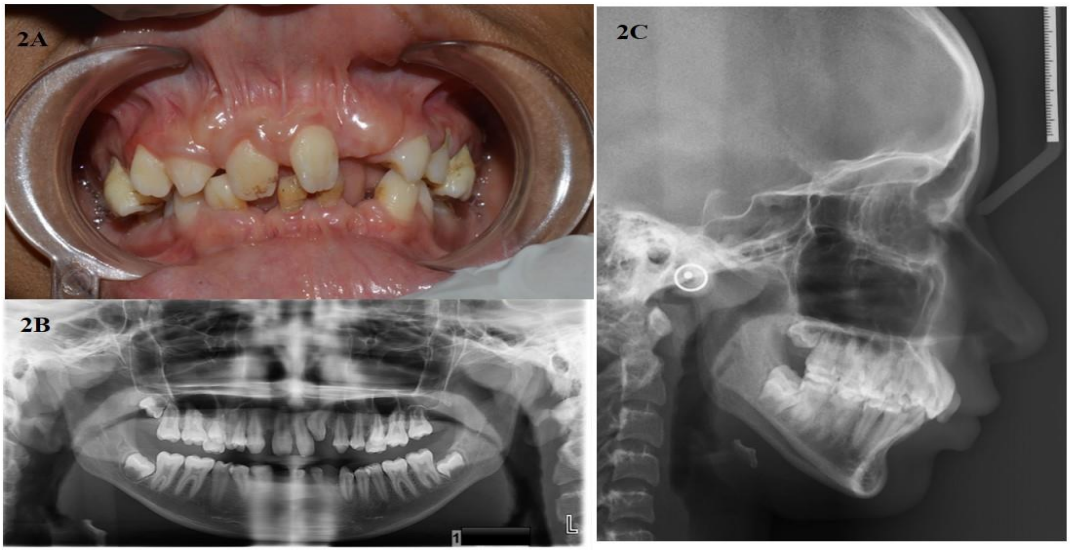


Figure 2: Intra-oral photograph showing multiple labial frenula and hypodontia (2A). Orthopantomogram and lateral cephalogram confirming the dental anomalies listed (2B,2C).

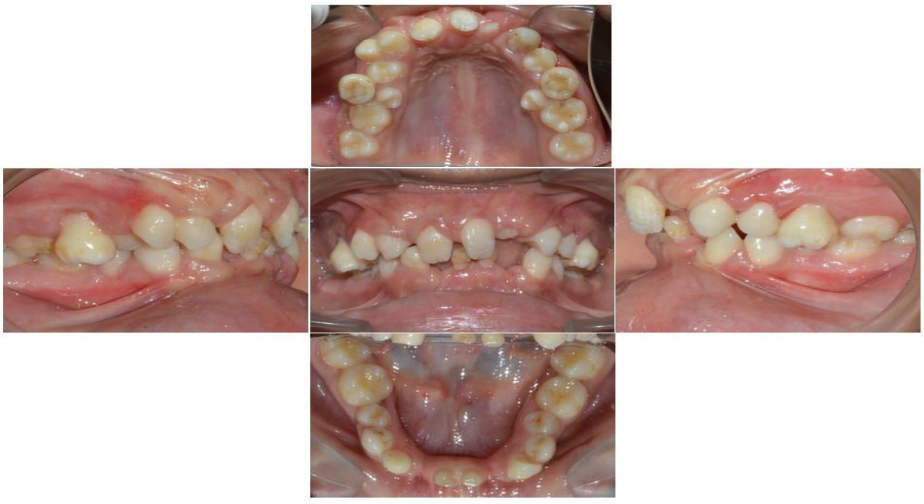


Figure 3: Intra-oral photographs showing generalized microdontia, transposition of 12, congenitally missing 31and 41 and retained maxillary deciduous second molars.

Discussion:

Ellis-van Creveld (EvC) syndrome, also termed as chondroectodermal dysplasia or mesoectodermal dysplasia, is a rare autosomal recessive disorder mainly affecting the ectodermal components such as enamel, nail and hair. EvC is caused by biallelic mutations in EVC or EVC2 genes.[4] The gene for EvC syndrome is located on chromosome 4p16.[1,2] EvC or EvC2 genes encode transmembrane proteins present in the basal body of the primary cilium that promote the hedgehog (Hh) signal transduction.[5] Any impaired Hh signaling in cardiac, skeletal and orofacial tissues during embryonic development causes EvC.[4] Recent findings have also shown that these primary cilia play a critical role during odontogenesis. EvC being one of the rarest ciliopathy, any disruption in the cilia signaling also has an impact on tooth development in ciliopathies.[6] Hence these patients typically present with congenitally missing teeth, abnormal attachments of the frenum, microdontia and hexadactyly. According to a few authors, one of the most important diagnostic characteristic of EvC syndrome is frenum hyperplasia.[3]

Oral manifestations of this syndrome are characteristic. The most constant finding is fusion of the anterior portion of the upper lip to the maxillary gingival margin, as a result of which no mucobuccal fold exists, causing the upper lip to present a slight V-shaped notch in the middle. Other findings include lip-tie, an often-serrated lower alveolar ridge, premature eruption of teeth (natal teeth), delayed eruption of teeth, enamel hypoplasia and multiple small alveolar notches with dystrophic philtrum.[1,2] Systemic manifestations include disproportionate dwarfism, post-axial polydactyly, hidrotic ectodermal dysplasia, congenital cardiac anomalies, musculoskeletal anomalies (genu valgum, narrow thorax, sausage shaped fingers) and occasionally genitourinary anomalies.[7,8]

A multi-modality team including dentists, pulmonologists, pediatricians, cardiologists, orthopedicians and physiotherapists is necessary to provide care to such patients. However, it has to be noted that no definite cure is available for this disease.

The differential diagnoses of EvC syndrome include those syndromes wherein multiple labial frenula are found such as oro-facial-digital syndrome, Pallister-Hall syndrome and Opitz C syndrome.[9-13] The main differentiating features of each of these syndromes are as follows:

a) Oral-facial-digital syndrome: X-linked dominant ciliopathy caused by mutations in the OFD1 gene.[9] Oral manifestations include lobulated tongue, abnormal supernumerary frenula, cleft often in the soft palate, malpositioned teeth and may have enamel hypoplasia.[10]
b) Pallister- Hall syndrome: Autosomal dominant inheritance. Findings include hypothalamic hamarblastoma, craniofacial anomalies, postaxial polydactyly, endocrine dysfunction, short mid-face, flat nasal bridge and anteverted nostrils. Oral

manifestations include micrognathia, microglossia, bifid epiglottis and abnormal supernumerary frenula extending from the buccal mucosa to the alveolar ridge. [11,12]

c) Opitz C syndrome exhibits frenum abnormalities similar to Pallister-Hall syndrome. Oral manifestations include multiple attached buccal frenula along with unusual facial appearance and wide alveolar ridges.[13]

Conclusions:

Frenum may not be closely inspected on routine dental examinations. However, the detection of frenum abnormalities in the form of multiple frenula/hyperplastic frenula along with other oral manifestations may help in the early diagnosis of such syndromic conditions.

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Conflicts of interest: None

References:

1. Atasu M, Biren S. Ellis-van Creveld syndrome: Dental, clinical, genetics, and dermatoglyphic finding of a case. J Clin Paediatr Dent 2000;24:141–5.
2. Tuna EB, Koruyucu M, Kürklü E, Çifter M, Gençay K, Seymen F, et al. Oral and craniofacial manifestations of Ellis-van Creveld syndrome: Case series. J Craniomaxillofac Surg 2016;44:919-24.
3. Mintz SM, Siegel MA, Seider PJ. An overview of oral frena and their association with multiple syndromes and nonsyndromic conditions. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;99:321–4.
4. Niceta M, Margiotti K, Digilio MC, Guida V, Bruselles A, Pizzi S, Ferraris A, Memo L, Laforgia N, Dentici ML, Consoli F, Torrente I, Ruiz-Perez VL, Dallapiccola B, Marino B, De Luca A, Tartaglia M. Biallelic mutations in DYNC2LI1 are a rare cause of Ellis-van Creveld syndrome. Clin Genet. 2017 Aug 30.
5. Al-Fardan A, Al-Qattan MM. Wide-spread cone-shaped epiphyses in two Saudi siblings with Ellis-van Creveld syndrome. Int J Surg Case Rep. 2017;39:212-217.
6. Hampl M, Cela P, Szabo-Rogers HL, Bosakova MK, Dosedelova H, Krejci P, Buchtova M. Role of Primary Cilia in Odontogenesis. J Dent Res. 2017 ;96(9):965-974.
7. Baujat G, Le Merrer M. Ellis-Van Creveld syndrome. Orphanet J Rare Dis 2007;2:27.
8. Gopal G., Belavadi G.B. Case report of a child with Ellis-Van creveld syndrome. Int J Pharm Biomed Res 2014;5:14–7.
9. Bouman A, Alders M, Oostra RJ, van Leeuwen E, Thuijs N, van der Kevie-Kersemaekers AM, van Maarle M. Oral-facial-digital syndrome type 1 in males: Congenital heart defects are included in its phenotypic spectrum. Am J Med Genet A 2017;173(5):1383-1389.
10. Dodge JA, Kernohan DC. Oral facial digital syndrome. Arch Dis Child 1967;42:214–9.
11. Hall JG, Pallister PD, Clarren SK, Beckwith JB, Wiglesworth FW, Fraser FC, et al. Congenital hypothalamic hamartoblastoma, hypopititarism, imperforate anus, and post-axial

polydactyly--a new syndrome? Part I: clinical, causal and pathogenetic considerations. Am J Med Genet 1980;7:47-74.

12. Kraus M, Diu M. Bifid epiglottis in a patient with Pallister-Hall syndrome. Can J Anaesth 2016 ;63(10):1197-8.

13. Flatz SD, Schinzel A, Doehring E, Kamran D, Eilers E. Opitz trigonocephaly syndrome: report of two cases. Eur J Pediatr 1984;141:183-5.

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