Rare disease

Ellis van Creveld syndrome—a report of two siblings

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Chondro-ectodermal dysplasia is a rare autosomal recessive disorder which affects the ectodermal, mesodermal and endodermal derivatives. There are numerous conditions reported under this title which include Ellis van Creveld syndrome. The oral findings include multiple gingivolabial frena, dental abnormality, malocclusion and hypodontia. The diagnosis of Ellis van Creveld syndrome is based on the presence of oral mucosal changes like notching of the lower alveolus, fusion of the upper lip and gingival mucosa; dental changes like oligodontia, conical shape of anterior teeth and occasional presence of neonatal teeth. The authors report a rare case of Ellis van Creveld syndrome occurring among two siblings with oral mucosal, dental and skeletal abnormalities.

BACKGROUND

In 1940, a syndrome comprising a certain type of chondrodysplasia, bilateral postaxial polydactyly of the hands, small and dysplastic units and congenital heart defects was defined by Ellis and van Creveld. They coined the

term chondro-ectodermal dysplasia, now known as Ellis van Creveld syndrome (OMIM 225500 (<http://www.ncbi.nlm.nih.gov/Omim/>)). Majority of cases were typically seen in one particular population from the Amish community of Lancaster County, Pennsylvania, USA.¹ The birth

Figure 1 Elder and younger siblings.

Figure 2 (a) Bilateral hexadactyly on both hands and left foot with fusion of the 4th and 5th digits. (b) Bilateral hexadactyly on both hands and left foot.

prevalence in Amish population is 1/5 000 live births and in non-Amish population, it is estimated to be 7/1000000.^{1 2} Till date, around 150 cases have been described in the literature.³

Family-based genetic studies identified human mutations in two previously unknown genes, EVC and LBN (EVC2) located head-to-head on chromosome 4p16.2.⁴⁻⁶ Such configuration may be a common feature of the human genome and the two genes could be coordinated by the same promoter or shared elements of overlapping promoters. Subsequently, mutations of any of these genes emerge to the same phenotype.⁶ Characteristic tetrad of EVC are: 1) Short limbs and exceptionally long trunk resulting in acromesomelic dwarfism, 2) Bilateral postaxial polydactyly, 3) Dystrophic nails, malformed teeth and hypodontia and 4) Congenital cardiac malformations (60% of cases).^{7 8}

Dental care in childhood includes prevention of caries and plaque control with oral hygiene instruction and dietary counselling. Malocclusion can be corrected with orthodontic treatment and crown or composite build-ups for microdonts. Congenitally missing teeth can be replaced with partial dentures to maintain space and improve mastication, speech and aesthetics. Dental care during adulthood can be done with implants and prosthetic rehabilitation.²

CASE PRESENTATION

Two siblings aged 18 and 14 years complained of unerupted upper and lower front teeth and needed replacement of the missing teeth. Both the siblings gave a history that a few of their primary and permanent maxillary and mandibular anterior teeth had not erupted.

Examination revealed that they had malformation of both lower extremities. Both of them were healthy and normal at the time of birth, but later on their legs progressively deformed resulting in short stature. Dental history

revealed that the older of the two siblings had undergone endodontic treatment for 21 and 16.

Family history revealed that the eldest and middle siblings were affected among the three born to parents with a history of consanguinity. The third child was normal. The patients had an average IQ level. General physical examination revealed that the elder sibling was 137.5 cm and weighed 35 kg while younger sibling was 92.5 cm and weighed 28 kg. Both the siblings had acromesomelic dwarfism and waddling gait (figure 1). Hair, sebaceous and sweat glands were normal.

Thorax appeared long with pectus carinatum, genu valga in the lower extremities with lumbar lordosis, broad hands and feet with postaxial polydactyly. Hexadactyly was noted on the hands in both the children. In the eldest sibling, the 6th digits were well-formed, redundant and widely spaced from the 5th digit. Postaxial polydactyly was noted in the left foot of both the siblings, with fusion of the 4th and 5th digits in the elder sibling (figure 2a,b). Patients could not make a tight fist. Nails were hypoplastic, dystrophic and friable. Ophthalmic, cardiac and genitourinary examination did not show any abnormalities in them.

Extra oral examination revealed that the younger sibling had a straight facial profile and elder sibling had a convex facial profile and broad nose. Both the siblings had low set ears and malar hypoplasia.

Intraoral soft tissue examination revealed that the anterior mandibular labial frenum was attached to the redundant mandibular alveolar ridge in both siblings resulting in the absence of the labial sulcus. In the younger sibling, labial frenum in the maxillary anterior region was attached to the attached gingiva between the maxillary centrals resulting in the absence of the labial sulcus.

Hard tissue examination revealed that in the elder sibling 12, 22, 31, 41, 42, 18, 28, 38 and 48 were missing.

Figure 3 (a) Anterior mandibular labial frenum attached to the redundant alveolar ridge, missing and malformed 32. (b) Attachment of labial frenum in the maxillary anterior region to the attached gingiva between the central incisors and mandibular labial frenum to the alveolar mucosa with missing and malformed teeth.

Figure 4 Orthopantomogram radiograph showing missing teeth and microdont 32 with short roots.

Mandibular left lateral incisor was microdont and conical in shape. Spacing was noted between maxillary centrals and the canines due to missing laterals. Root stumps of 26 and 46 with pulp polyp in the latter were present and 16 and 21 were restored (figure 3a).

In the younger sibling, 12, 22, 31, 32, 41 and 42 were missing with reduced mesiodistal width of the maxillary central incisors. A linear groove was noted in the mid-line of the incisal edge of 11 towards the cemento-enamel

junction on the labial and palatal aspects. The maxillary canines were conical shaped. Dental caries was noted with 36 and 46 (figure 3b).

INVESTIGATIONS

The intraoral periapical and panoramic radiographs confirmed the specified clinically missing teeth in both the siblings. In the elder sibling, 32 was microdont with short roots (figure 4). In the younger sibling, 11 and 21 showed

Figure 5 (a) Intraoral periapical radiograph showing short roots and reduced mesiodistal width with relation to 11 and 21 with a radiolucent line extending from the incisal edge. (b) OPG radiograph showing missing teeth and microdont 11 and 21 with short roots.

short roots, reduced mesiodistal width at incisal edge when compared to cervical portion, with a thin radiolucent line extending from the incisal edge upto the pulp chamber (figure 5a,b).

In both the siblings, the chest radiographs were normal. In the anteroposterior (AP) view of the long bones of lower limbs, the tubular bones were short and thickened with broad distal metaphysis of both femurs. Peaking of the proximal tibia with long lateral and a short medial slope was noted resulting in genua valga, lateral condyle of the tibia was deformed bilaterally along with widening of the tibial shaft. The length of the fibula was shortened (figure 6a). However in the younger sibling, an exophytic growth on the right tibia anteromedially around 2 inches from the proximal physal line was seen and lateral subluxation of patella was noted bilaterally (figure 6b).

AP view of the long bones of the upper limbs showed short and thickened tubular bones, broad diaphyseal ends

of the humerus and mediolateral curvature of both humeri with apex of the angulations pointing medially. Unusually large proximal end of the ulna and the distal end of the radius and unusually small proximal end of the radius and the distal end of the ulna was noticed with bilateral cubitus valgus. Long axis of arm and forearm at the elbow joint was 28 degrees bilaterally (figure 7a,b).

Hand wrist radiograph of elder sibling showed a negative ulnar variance bilaterally, plump distal end of the radius, syncarpalism, and bilaterally capitate and hamate were unusually large. Right hand showed six metacarpals and synmetacarpalism of the 5th and 6th metacarpals (figure 8a); however the younger sibling showed accessory carpal bones near ulnar side on the right and left hand, syncarpalism between capitate and hamate on the left hand and synmetacarpalism bilaterally (figure 8b).

Echocardiography and ultrasonography of abdomen were normal for both the siblings. Based on these findings, a final diagnosis of chondro-ectodermal dysplasia (Ellis van Creveld syndrome) was arrived at.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of Weyers acrodermal dysostosis (Curry-Hall syndrome) (OMIM 193530 (<http://www.ncbi.nlm.nih.gov/Omim/>)), asphyxiating thoracic dystrophy (Jeune syndrome; OMIM 208500 (<http://www.ncbi.nlm.nih.gov/Omim/>)), achondroplasia (OMIM 100800 (<http://www.ncbi.nlm.nih.gov/Omim/>)), chondroplasia punctata (OMIM 215100 (<http://www.ncbi.nlm.nih.gov/Omim/>)) and Morquio's syndrome (OMIM 252300 (<http://www.ncbi.nlm.nih.gov/Omim/>)), were considered.

TREATMENT

For elder sibling, the root stumps of 26 and 46 were extracted and for the younger child the decayed teeth were restored.

OUTCOME AND FOLLOW-UP

Healing of the extraction site was uneventful in the elder sibling and both the siblings were subsequently managed by partial denture prosthesis.

DISCUSSION

Ellis van Creveld syndrome is a rare autosomal recessive disorder with characteristic feature of short stature, short extremities, nail hypoplasia, polydactyly, thoracic abnormalities, congenital heart defects and dental abnormalities.^{9 10} Thirty per cent of the cases are associated with consanguineous marriage.^{2 3 11} The risk of recurrence for siblings is 1 in 4 for each progeny. For children of an affected person the risk does not increase, unless the spouse is also a carrier; in such condition the risk is 50 per cent.¹²

The syndrome can be diagnosed during the prenatal period, starting from the 18th week of gestation, by ultrasonography, or later by clinical examination after birth.³ All embryonic layers are involved; however the signs of ectodermal dysplasia are usually limited to nails, teeth and gums, and sometimes with eye and neural involvement. Mesodermal involvement is associated with abnormalities of the bones, heart and kidneys. Though endodermal involvement is unusual, some patients report with lung and liver abnormalities.¹²

Figure 6 (a) Anteroposterior (AP) view showing shortening of fibula, genu valgum and widening of the tibial shaft. (b) AP view showing shortening of fibula, genu valgum and widening of the tibial shaft, exophytic growth on the right tibia and bilateral subluxation of patella.

Figure 7 (a) Anteroposterior (AP) view showing short and thickened tubular bones and broad diaphyseal ends of the humerus. (b) AP view showing short and thickened tubular bones and broad diaphyseal ends of the humerus.

Most patients have average intelligence. The short stature which may be present at birth becomes more apparent with subsequent growth.^{1 3} Surviving adults remain short with an ultimate stature of 110–150 centimetres. Although the teeth and nails are defective, the skin and sweat glands are normal.⁹ These were consistent with the findings in our cases.

The most consistent clinical feature in chondrodys trophy is due to a defect in ossification resulting in short stature. Shortened long bones of the limbs especially in the middle and distal segments result in acromesomelic

dwarfism, wide diaphyses and metaphyses.^{1 5 8 13} There is progressive shortening along the proximo-distal axis of the limbs with zeugopod (radius-ulna/tibia-fibula) shortening being more marked than the shortening of the stylopod (humerus/femur) and in the autopod shortening of the distal phalanges being more noticeable than that of the proximal phalanges.¹⁴ The limb shortening is usually mesomelic.¹¹ Other features include genu valgum, curvature of the humerus, talipes equinovarus, talipes calcaneovalgus and pectus carinatum with a long narrow chest.^{1 3} Similar findings were seen in our cases.

Figure 8 (a) Hand wrist radiograph showing syncarpalism, synmetacarpalism and right hand showing six metacarpals. (b) Hand wrist radiograph syncarpalism, synmetacarpalism and accessory carpal bones near ulnar side on the right and left hand.

Tubular bones of the hand are shortened with bifid or fused supernumerary metacarpals. Proximal and middle phalanges are short with epiphyses being cone-shaped.¹³ Polydactyly and occasionally syndactyly of the fingers and toes is observed.⁹ The polydactyly involves the ulnar side and is typically seen as postaxial hexadactyly of the hands, and about 10% of cases in the feet.^{8 13} Both the siblings showed similar features and postaxial hexadactyly was seen in the left foot.

The hand radiographs show shortening and thickening of the bones of the extremities. The terminal phalanges reveal hypoplastic bones and dystrophic nails. The polydactyly may be just extra soft tissue or, show bifid metacarpal with duplication of the phalanges and intercarpal fusion between hamate and capitate.⁸ These findings were consistent with our cases.

Oral manifestations of the syndrome include the fusion between the upper lip with maxillary gingival margin

resulting in absence of muco-buccal fold or the sulcus anteriorly, notching of the alveolar ridges,¹ abnormal tooth shape, size and number.^{9 13 14} The clinical variability of the oral abnormalities in Ellis van Creveld syndrome could be due to the fact that it is the genetic effect on the oral structure and teeth occurring during the initiation and morpho-differentiation stages of tooth development.¹⁵ Our patients too, showed such characteristic intraoral changes.

Radiographically, it is almost impossible to differentiate Ellis van Creveld syndrome from similar chondrodysplasias such as Jeune syndrome, achondroplasias, Morquio's syndrome and chondroplasia punctata. Patients may have identical features in hands, pelvis and long bones. Mainly, the diagnosis for Ellis van Creveld syndrome is made based on the clinical changes such as, nail hypoplasia, fusion of upper lip and gingiva, oligodontia and neonatal teeth and cardiac anomalies if present.¹

Ellis van Creveld syndrome needs to be distinguished from a number of closely related conditions. Polydactyly, genu valgum, dwarfism and oral manifestations like hypodontia, abnormal frenum are common features of Ellis van Creveld syndrome, Curry-Hall syndrome and Jeune syndrome. Clinical features in Curry-Hall syndrome are similar to Ellis van Creveld syndrome, but of a milder phenotype which includes normal stature and cardiac defects; however thoracic dysplasia is generally absent.⁸ Additional features of Curry-Hall syndrome include presence of osseous cleft of symphysis of the mandible,¹⁶ while fifth carpal in distal row of wrist and multiple ossification centres in hamate is absent.¹⁷ Jeune syndrome usually presents with limb shortening which is rhizomelic rather than mesomelic,¹¹ abnormally small, narrow thorax, short ribs and pulmonary hypoplasia¹⁸ and absence of nail dystrophy and abnormal frenula.¹⁷

In achondroplasia, rhizomelic shortening of the limbs is seen along with large calvarial bones and small cranial base and facial bones.¹⁹ Chondroplasia punctata presents with severe and symmetrical rhizomelic micromelia, punctate calcifications and alterations to the ossification in metaphyses and epiphyses of the long bones, microcephaly, micrognathia and flattened nasal bridge.²⁰ Morquio's syndrome shows short neck, lumbar kyphosis, hypermobility of metacarpal joints, general osteoporosis, short trunk with proportionately long limbs and coxa valga. The hands show shortening of the metacarpals, inclination of the distal portions of the radius and ulna toward each other and a prominent maxilla along with broad mouth.²¹

Since the patient was lost during the follow-up, the mutation analysis could not be performed.

CONCLUSION

A multidisciplinary approach is always advised which involves an oral physician and maxillofacial radiologist, orthopaedician, cardiologist, ophthalmologist, paediatrician, psychologist and clinical geneticist for suitable diagnosis, management and rehabilitation of such cases. We highlight the appearance of multiple serrated frenum, hypodontia, malocclusion, conical teeth and skeletal changes as constant clinical features. Additional clinical findings affecting other organs may occasionally be observed although these were not identified in our cases.

Learning points

- Ellis van Creveld syndrome is an autosomal recessive disorder associated with consanguinity.
- Genetic counselling is essential in patients with hereditary disorders; risks in consanguineous marriages must be weighed to lay patients.
- If a child is born with such limb deformities, one should carefully examine the oral cavity and rule out multi-organ involvement.
- Antenatal checkups and counselling may prove to be prudent in family planning and help reduce the incidence of such cases.
- Early oral intervention can rehabilitate patients.

Competing interests None.

Patient consent Obtained.

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