Abstract

**Aim** A systematic literature review on oral and craniofacial manifestations of Ellis-Van Creveld syndrome was performed.

**Methods** From 2 databases were selected 74 articles using as key words "Ellis-Van Creveld" AND "Oral" OR "Craniofacial" OR "Dental" OR "Malocclusion". Prisma protocol was used to create an eligible list for the screening. Data were collected in a table to compare the clinical aspects found.

**Results** From the first research emerged 350 articles, and only 72 of them were selected.

**Conclusion** Through this analysis oral and cranio-facial manifestations of Ellis-Van Creveld syndrome were pointed out. Management of Ellis-Van Creveld syndrome requires a multidisciplinary approach involving different clinicians; dentists play an important role in early diagnosis and treatment of the patients.

**KEY WORDS** Ellis-Van Creveld syndrome, chondroectodermal dysplasia, dental anomalies, malocclusion, rare diseases.

Introduction

Ellis-van Creveld syndrome (EVCS) or chondro-ectodermal dysplasia was described for the first time by Simon Van Creveld and Richard Ellis in 1940. Rustin McIntosh published a case report of Ellis-Van Creveld syndrome in 1933 and participated in paper writing a few years later with Ellis and Van Creveld [Muensterer et al., 2013]. This syndrome is a rare autosomal recessive disorder, the birth prevalence is about 7: 1.000.000. EVCS seems to be much more common among the older Amish population of Lancaster Country, Pennsylvania. Genes EVC1 and EVC2 located on chromosome 4p16 are responsible for this syndrome. This syndrome has been described when some paediatricians noticed similar characteristics in some of their patients. The typical clinical manifestations include chondrodysplasia, ectodermal dysplasia (dystrophic nails, hypodontia and malformed teeth), polydactyly and congenital heart disease. Cognitive development is usually normal.

Dental anomalies consist of peg-shaped teeth, prenatal teeth or delayed eruption, hypodontia, taurodontism, micro- or macrodontia and enamel hypoplasia, which may affect nutrition of these patients.

A delay in diagnosis is due to the lack of proper screening.

**Objectives**

The aim of this study is to point out oral and craniofacial manifestations, since the dentist may be the first clinician visiting EVCS’s patient for dental anomalies [Vinay et al., 2009].

Moreover, the second objective is to obtain indications about dental treatments to manage oral manifestations, in order to restore the functions of the stomatognatic system, and to improve aesthetics.

**Methods**

A systematic review was performed on Scopus and PubMed using the key words “Ellis-Van Creveld” AND “Oral” OR “Craniofacial” OR “Dental” OR “Malocclusion”. The following filters were added to create an eligible list for the first screening: publication dates (from January 2008 to December 2018), languages (Italian and English), species (humans), ages (birth to 18 years). The PRISMA protocol (Preferred Reporting Items Systematic review and Meta-Analysis) was used to select the studies for this review (Fig. 1).

From the first research 350 articles emerged, but only 72 were selected. Ten articles were neither accessible through databases nor research in libraries, 30 articles were excluded because they did not include any oral manifestation of this syndrome or were irrelevant because considered only the genetical variables of EVCS; 8 articles were used only for qualitative analysis. For these reasons 48 articles were excluded from the quantitative analysis. Twenty-four articles, including meta-analyses and case reports, were used to collect data for a quantitative analysis [Vinay et al., 2009; Shah et al., 2008; Cesur et al., 2008; Babaji, 2010;
Bhat et al., 2010; Shamas et al., 2011; Aminabadiet al., 2010; Veena et al., 2011; Hegde et al., 2011; Mehndiratta et al., 2011; Jayaraj et al., 2012; Kamal et al., 2013; Sasalawad et al., 2013; Shetty et al., 2015; Hassona et al., 2015; Caparrós-Martinet al., 2015; Shaik et al., 2016; Gokulraj et al., 2016; Gauchan et al., 2016; Tuna et al., 2016; Nethan et al., 2017; Ibarra-Ramirez et al., 2017; Guiguimde et al., 2018; Naqash et al., 2018.

Results

Twenty-four case reports and case series were analysed to identify the most recurrent oral manifestations of EVCS. No cohort studies were found, since the syndrome is a rare paediatric disease. The widest sample was analysed by Tuna et al. in Turkey (8 subjects) [Tuna et al., 2016].


In the examined articles, 44 subjects (27 girls and 17 boys) were described, aged 0 to 21 years (mean age 8.3 years). Oral manifestations were analysed thanks to the clinical assessment of the patients described in each study. The sample comprised 15 patients from consanguineous parents and 19 patients from non-consanguineous parents. Descriptive data (year of publication, width of the sample, age, gender, parental consanguinity, oral-dental findings) are summarised in Table 1.

Discussion

The incidence of this syndrome is estimated to be 7:1,000,000 in the general population, even if some studies estimate 1:244,000 [Gokulraj et al., 2016] or 1:60,000 [Gauchan et al., 2016]. Tuna et al. reported a different incidence in Europe, 1:150,000, and in America: 1:60,000 [2016].

Data analysis shows a higher incidence of EVCS in the Amish population due to consanguineous marriage [Gauchan et al., 2016]. All three embryonic layers are involved in EVCS.

Signs of ectodermal dysplasia are evident in teeth, nails and gums. Signs of endodermal involvement, which is less frequent, affect liver and lungs. Heart and kidneys show a mesodermal involvment [Gokulraj et al., 2016].

EVCS was mapped to chromosome 4p16 and it is caused by mutations in two genes, EVC and EVC2, localised on chromosome 4 [Cortés et al., 2015; Brugmann et al., 2010; Ulucan et al., 2008; Harris and Purcell, 2014].

The syndrome is classified as a ciliopathy, a genetic disorder caused by the abnormal function of cellular cilia [Cortés et al., 2015; Brugmann et al., 2010; Hampl et al., 2017]. Primary cilia are important signalling centres; ciliopathy symptoms include alterations in tooth number, size, shape, position, and dental cells differentiation [Hampl et al., 2017].

The differential diagnosis of this syndrome includes thoracic dysplasia of Jeune, Weyers acrofacial dysostosis, McKusick-Kaufman syndrome (SMK), thoracic cage deformity, chondrodysplasia punctata, asphyxiating thoracic dystrophy [Gokulraj et al., 2016].

Parental consanguinity is a predisposing factor for the syndrome with an incidence of 30% [Tuna et al., 2016]. In our review we found 15 subjects born from consanguineous parents (34.1%), while 19 were not (43.2%). In 10 cases this characteristic is not mentioned. The review analyses a sample of patients described in the selected studies: 27 patients were female (61.4%) and 17 male (38.6%).

Clinical manifestations

Ulucan et al. reported an analysis in which some individuals did not manifest specific features of EVCS [Ulucan et al., 2008]. Typical EVCS’s face is characterised by malar hypoplasia, dolicocephalia, prominent nose and low set ears. Postaxial polydactyly of hands and feet has been reported in almost all of the cases and this feature is sometimes associated with brachydactyly, wide gap between big toe and other two toes, clinodactyly, small phalanges, sausage-shaped fingers, fusion of capitate and hamate and syndactyly. It is reported that all the patients tend to grow differently from non-syndromic patients: they have disproportionate short stature characterised by long trunk, plump and short limbs. Fingernails are usually hypoplastic, dystrophic, friable and sometimes hair abnormalities are observed too. The syndrome is characterised by high mortality in early life. It is usually associated to congenital heart malformations, thoracic cage abnormalities, respiratory insufficiency, and an increased risk of pulmonary hypertension [Tuna et al., 2016]. 29.5% of the patients had congenital heart malformations and the most common is septal defect [Tuna et al., 2016]. Renal disease or small kidneys, liver disease and micropenis are frequent findings. In fact EVCS involves all three embryonic layers.

Oral manifestations

The spectrum of oral manifestation varies widely. Genetic effect on teeth and other oral structures development occurs during a relatively long period, and may be the result of other
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of patients</th>
<th>Age</th>
<th>Sex</th>
<th>Parents</th>
<th>Oral manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shah</td>
<td>2008</td>
<td>1</td>
<td>12</td>
<td>F</td>
<td>c</td>
<td>Agenesis, hypoplastic and malformed teeth, neonatal teeth, fusion of the upper lip to gingiva, absence of mucobuccal fold, enamel hypoplasia</td>
</tr>
<tr>
<td>Cesur</td>
<td>2008</td>
<td>1</td>
<td>14</td>
<td>F</td>
<td>c</td>
<td>High arched palate, agenesis, conical teeth, supernumerary teeth, gum abnormalities</td>
</tr>
<tr>
<td>Vinay</td>
<td>2009</td>
<td>1</td>
<td>7</td>
<td>F</td>
<td>nc</td>
<td>Dysmorphic philtrum, hypertrophic labial frenum, multiple frenum, serrations of the alveolar ridge, hypoplastic teeth, agenesis of deciduous lateral incisors, multiple caries</td>
</tr>
<tr>
<td>Babaji</td>
<td>2010</td>
<td>1</td>
<td>14</td>
<td>F</td>
<td>c</td>
<td>Absence of mucobuccal fold, V-shaped lip, abnormal frenum attachment, retained lower right deciduous canine, agenesis of incisors, hypoplastic and abnormal shaped teeth, multiple caries, supernumerary tooth, retained maxillary primary second molar with single conical roots, taurodontism, incomplete root formations of second molars</td>
</tr>
<tr>
<td>Aminabadi</td>
<td>2010</td>
<td>1</td>
<td>5</td>
<td>F</td>
<td>c</td>
<td>Absence of mucobuccal fold, multiple frenum, conical teeth, oligodontia, thin alveolar ridge, multiple small alveolar notches, enamel hypoplasia, multiple caries, serrated appearance of gingiva, multiple agenesis, supernumerary tooth, taurodontism</td>
</tr>
<tr>
<td>Bhat YJ</td>
<td>2010</td>
<td>1</td>
<td>16</td>
<td>F</td>
<td>c</td>
<td>High arched palate, conical teeth, agenesis of upper lateral incisors, diastema, enamel hypoplasia, fusion of the upper lip to gingiva, delayed eruption, caries</td>
</tr>
<tr>
<td>Shamas</td>
<td>2010</td>
<td>1</td>
<td>16</td>
<td>F</td>
<td>nc</td>
<td>High arched palate, wide tongue, microdontia, agenesis, conical teeth, caries, fusion of the upper lip to gingiva</td>
</tr>
<tr>
<td>Hedge</td>
<td>2011</td>
<td>2</td>
<td>14</td>
<td>M</td>
<td>c</td>
<td>Absence of mucobuccal fold (2 cases), multiple agenesis (2 cases), conical teeth (2 cases), microdontia, caries</td>
</tr>
<tr>
<td>Veena e</td>
<td>2011</td>
<td>1</td>
<td>12</td>
<td>F</td>
<td>nc</td>
<td>Absence of mucobuccal fold, V-notch, natal teeth, conical teeth, agenesis of lower incisors, retained lower deciduous canine</td>
</tr>
<tr>
<td>Mehdiratta</td>
<td>2011</td>
<td>2</td>
<td>2</td>
<td>F</td>
<td>M</td>
<td>High arched palate, dysplastic teeth, anodontia</td>
</tr>
<tr>
<td>Dhandabani</td>
<td>2012</td>
<td>1</td>
<td>8</td>
<td>M</td>
<td>nc</td>
<td>Dysmorphic philtrum and V-notch, hypertrophic frenum, multiple frenula, agenesis of incisors, conical teeth</td>
</tr>
<tr>
<td>Kamal</td>
<td>2013</td>
<td>1</td>
<td>10</td>
<td>F</td>
<td>nc</td>
<td>Hypertrophic frenum, multiple frenula, multiple agenesis, retained lower deciduous incisor, malformed tooth</td>
</tr>
<tr>
<td>Sasalawad</td>
<td>2013</td>
<td>1</td>
<td>13</td>
<td>F</td>
<td>c</td>
<td>Absence of mucobuccal fold, multiple frenula, natal teeth, microdontia, agenesis of incisors, bilateral bony clefts, high arched palate, palatal crossbite, molars with abnormal cusps and accessory grooves</td>
</tr>
<tr>
<td>Shetty</td>
<td>2015</td>
<td>1</td>
<td>17</td>
<td>F</td>
<td>nc</td>
<td>Absence of mucobuccal fold, multiple frenum, ankyloglossia, agenesis of lower incisors, enamel hypoplasia, conical teeth, caries, oligodontia, Class III malocclusion</td>
</tr>
<tr>
<td>Hassona</td>
<td>2015</td>
<td>1</td>
<td>17</td>
<td>F</td>
<td>c</td>
<td>Hypertrophic lower frenum, natal tooth, hypodontia, conical teeth, taurodontism, enamel hypoplasia, impacted upper lateral incisor, high arched palate, anterior open bite, left crossbite, long tongue with streaks devoid of papillae, leukoedema, ethnic pigmentation on gingiva</td>
</tr>
<tr>
<td>Caparros-</td>
<td>2015</td>
<td>5</td>
<td>5,7</td>
<td>M (3)</td>
<td>c(3)</td>
<td>Absence of mucobuccal fold (3 cases), multiple frenum (3 cases), dental anomalies (3 cases), teeth fusion and hypodontia, enamel hypoplasia, serrated alveolar ridge, bifid tip of the tongue and short lingual frenulum</td>
</tr>
<tr>
<td>Martin.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>nc(2)</td>
<td></td>
</tr>
<tr>
<td>Shaik</td>
<td>2016</td>
<td>1</td>
<td>13</td>
<td>F</td>
<td>c</td>
<td>Absence of the mucobuccal fold, multiple frenula, labiogingival adhesions, serrations of the anterior alveolar ridge, agenesis of incisors, conical tooth, decayed tooth, Talon's cusp, taurodontism, impacted lower right lateral incisor, horizontal and vertical bone loss in lower left molar area</td>
</tr>
<tr>
<td>Gokulraj</td>
<td>2016</td>
<td>2</td>
<td>4</td>
<td>F</td>
<td>M</td>
<td>Delayed eruption, obliteration of upper labiogingival sulcus, partial hair lip (2 cases), multiple high frenal attachments (2 cases), agenesis of anterior teeth, conical teeth, depapillation of tongue dorsal surface</td>
</tr>
<tr>
<td>Gauchan</td>
<td>2016</td>
<td>3</td>
<td>New born</td>
<td>F(2)</td>
<td>M</td>
<td>High-arched palate (2 cases), agenesis of incisors (2 cases), conical teeth (2 cases), cleft lip (3 cases)</td>
</tr>
<tr>
<td>Tuna</td>
<td>2016</td>
<td>8</td>
<td>9-21</td>
<td>M</td>
<td>F(2)</td>
<td>Characteristic face, hypertrophic frenum, conical and peg-shaped teeth, hypodontia, dysmorphic philtrum (6 cases), serrated appearance gingiva (7 cases), diastema (7 cases), enamel hypoplasia (5 cases), microdontia (7 cases), taurodontism (3 cases), delayed eruption (7 cases), single-rooted molar (4 cases), high caries rate (2 cases)</td>
</tr>
<tr>
<td>Nethan</td>
<td>2017</td>
<td>1</td>
<td>14</td>
<td>F</td>
<td>not</td>
<td>Absence of mucobuccal fold, multiple frenum, natal tooth, agenesis of incisors, serrated alveolar ridge, edge-to-edge right molars relationship, left cross-bite</td>
</tr>
<tr>
<td>Ibarra-</td>
<td>2017</td>
<td>5</td>
<td>new born</td>
<td>F(3)</td>
<td>M(2)</td>
<td>Hypodontia/oligodontia (4 cases), enamel hypoplasia (4 cases), conical shaped teeth (4 cases), multiple frenum (5 cases)</td>
</tr>
<tr>
<td>ramirez</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guiguimde</td>
<td>2018</td>
<td>1</td>
<td>3</td>
<td>F</td>
<td>nc</td>
<td>Absence of mucobuccal fold, multiple frenum, diastemas, agenesis of incisors, enamel hypoplasia, delayed dental eruption</td>
</tr>
<tr>
<td>Naqash</td>
<td>2018</td>
<td>1</td>
<td>15</td>
<td>F</td>
<td>not</td>
<td>Absence of mucobuccal fold, multiple frenum, diastemas, agenesis of incisors, microdontia, serrated alveolar ridge, partial end-to-end occlusal right relationship, left cross-bite</td>
</tr>
</tbody>
</table>

**TABLE 1** Descriptive data of Ellis–van Creveld syndrome: a qualitative analysis.
genetic and environmental phenotype-modifying factors [Kamal et al., 2013; Tuna et al., 2016]. The undefined phenotype could be characterised by serrated incisal margins, dental transposition, diastema, conical teeth, enamel hypoplasia, hypodontia and natal teeth (Hampl et al., 2017).

This paper examines 24 studies in order to underline the different manifestations of EVCS. Collected data are reported in Table 1 to show a qualitative analysis, and in Figure 2 to show a quantitative analysis of typical oral manifestations in EVCS patients. The most common features are dental shape defects as conical teeth (61.4%), and teeth number defects such as agenesis (47.7%) associated with oligodontia and hypodontia (36.4%) and sometimes with supernumerary teeth. The presence of supernumerary teeth could be associated also with the disruption from the characteristic notchching of the alveolar process [Lubinsky and Kantaputra, 2016]. The agenesis usually interests upper and lower permanent incisives, but could affect also molars.

Multiple frenum, which can be associated to the absence of mucobuccal fold, is present in 45.5% of the patients; this feature can be corrected with a surgical approach, and the same applies to dysmorphic filtrum (18.2%), fusion of upper lip (13.6%) and hypertrophic labial frenum (27.3%).

It could be interesting to consider that enamel hypoplasia (38.6%) and dental anomalies in shape (molars having abnormal cusps or accessory grooves with deep pits and fissures) are predisposing factors for caries onset (22.7% have one or multiple caries). Usually patients show microdontia (22.7%), but a small percentage presents taurodontism with abnormal molar roots anatomy. Other characteristics are diastema (22.7%), delayed eruption (22.7%), neonatal teeth (9.1%), and retained/impacted teeth (11.4%).

Tongue’s alteration can be rarely found (6.8%): in a case series tongue depapillation is seen in 2 patients (4.5%) while only one presented ankyloglossia (2.3%).

Malocclusions are common in this syndrome but are not of any specific type: crossbite is observed in 6.8% of patients, high arched palate in 15.9% and serrated alveolar ridge in 29.5%. Cephalometric evaluation is rarely mentioned. Tuna et al. described different growth patterns in 7 patients: skeletal Class I (n=2), skeletal Class II due to mandibular retrognathism (n=1), skeletal Class III due to mandibular prognathism (n=2) and skeletal Class III due to maxillary retrognathism (n=2) [Tuna et al., 2016].

**Nutrition and oral findings in EVCS**

No case reports and case series about the association between EVCS and nutrition problems were found. However, since oral abnormalities can occur in most subjects, it is likely that children affected by EVCS should cope with severe feeding difficulties.

Wright et al. [2010] described a protocol to manage nutritional habits in syndromic children. They examined 41 children enterally fed (nasogastric or gastrostomy feeding), for at least 6 months, with safe swallow and apparently neurologically capable of eating. One patient (age 2.8 years) was affected by EVCS and was fed through gastrostomy. He successfully ceased artificial feeding in the following 1.9 years.

The authors found out that in children with complex syndromic conditions, the shift from tube feeding to oral food is difficult. Parental anxiety tended to be the major obstacle. However, with psychological, sound medical and dietetic support younger children can be off all feeds within a year. The process is more likely to fail after age 5 years and is not associated with compromised growth [Wright et al., 2011].

**Treatment protocols**

EVCS patients may have congenital heart malformations, requiring antibiotic coverage to prevent infective endocarditis before invasive dental procedures [Hassona et al., 2015; Tuna et al., 2016]. Some authors propose to use prosthetic rehabilitation to improve aesthetics, function and phonetics [Vinay et al., 2009; Shah et al., 2009; Babaji, 2010; Hegde et al., 2011; Jayaraj et al., 2012; Tuna et al., 2016] in patients with agenesis or teeth defects. Patients should be informed about the importance of preventive measures such as proper home oral hygiene, diet control, daily fluoride mouth rinses and professional care. Orthodontic approach is suggested to improve mastication’s quality and to solve the malocclusion [Dinoi et al., 2019; Mummolo et al., 2016; Dinoi et al., 2016; Mummolo et al., 2018; Lauritano et al., 2019]. For all these reasons, in these patients an accurate clinical and radiographic evaluation (orthopantomography) is advisable in order to reach the best clinical decision. Oral health in special need children, in particular in those with EVCS, requires special attention from all specialists (nutritionist, paediatrician, paediatric neurologist, psychologist) [Mansoor et al., 2018; Dangulavanich et al., 2017; Echavarria-Garcia et al., 2018; Alnuaimi et al., 2018; Rodriguez Peinado et al., 2018].

**FIG. 2** Typical oral manifestations in EVCS patients
Conclusion

EVCS is an autosomal recessive disease with a characteristic tetrad: chondrodysplasia, polydactyly, ectodermal dysplasia, congenital heart malformation. Most of the analysed papers propose a multidisciplinary approach for EVCS management, which involves dentist, nutritionist, radiologist, cardiologist, pulmonologist, orthopaedician, urologist, paediatrician, ophthalmologist, paediatric neurologist, psychologist and clinical geneticist. Recognising the oral findings is important for early diagnosis and a correct treatment planning, and in this aspect dentists may play a vital role.

The approach to dental management depends on each particular case. Collaboration between paedodontist, orthodontist, oral and maxillofacial surgeon and prosthodontist is the key to success. An interdisciplinary treatment strategy may include:

• oral prophylaxis and use of antiseptic mouth rinses to reduce microbial load;
• preventive measures of dental caries (dietary control, mouth rinses, and dentifrices with fluoride, dental counselling, plaque control, oral hygiene maintenance, application of fissure sealants and topical fluoride);
• restoration of dental caries and malformed teeth;
• partial dentures (acytic partial denture or fixed partial denture) or implant placement;
• correction of malocclusion;
• surgical correction for soft tissue and skeletal abnormalities;
• regular follow-ups.

References

Muensterer OJ, Berdon W, McManus C et al. Ellis-van Creveld syndrome: its surgical correction for soft tissue and skeletal abnormalities; oral prophylaxis and use of antiseptic mouth rinses to reduce dental caries and malformed teeth; partial dentures (acytic partial denture or implant placement); correction of malocclusion; surgical correction for soft tissue and skeletal abnormalities; regular follow-ups.


Dinoi MT, Marchetti E, Garagiola U, Caruso S, Mummolo S, Marzo G. The 3D Tele.


