Orthopaedic manifestations of chondroectodermal dysplasia: the Ellis–van Creveld syndrome

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Abstract

Background Ellis–van Creveld is a dwarfing syndrome transmitted as an autosomal recessive trait. The constant features of the condition include acromelic–micromelic dwarfism, ectodermal dysplasia involving the nails, teeth and gums, postaxial polydactyly of the hands and congenital heart disease. Congenital heart disease affects 50–60 % of all patients and nearly 50 % of patients die by 18 months of age from cardiopulmonary complications. This study is intended to characterise the orthopaedic manifestations of Ellis–van Creveld based on the authors’ unique opportunity to interview and examine the largest group of patients to date in the literature.

Methods Detailed interviews, physical examinations and/or radiographs were available on 71 cases of Ellis–van Creveld syndrome. Data were collected from physical examinations, radiographs, computed tomography (CT) reconstruction and magnetic resonance imaging (MRI) of

the knee. Pathoanatomy of the knee was reinforced by the direct surgical observation of 25 limbs surgically managed during adolescence and puberty.

Results A number of interesting clinical and radiographic abnormalities were noted in the upper extremities and lower extremities, but by far the most significant orthopaedic finding was a severe and relentlessly progressive valgus deformity of the knee. Although many patients had difficulties making a “fist” with the hand, no patient reported any functional disability. The severe valgus deformity of the knee is the result of a combination of profound contractures of the iliotibial band, lateral quadriceps, lateral hamstrings and lateral collateral ligament, leading to lateral patellar subluxation and dislocation. The lateral portion of the upper tibial plateau presents with cupping and progressive depression of the lateral plateau, along with severe valgus angulation of the proximal tibia and fibula. A proximal medial tibial exostosis is seen in nearly all cases.

Conclusion This is the largest group of Ellis–van Creveld syndrome patients identified in the literature. An understanding of the orthopaedic pathoanatomy of the knee

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deformity is critical to determining the appropriate surgical management. This paper characterises the orthopaedic manifestations of Ellis–van Creveld syndrome and especially identifies the pathoanatomy of the severe and progressive valgus knee deformity.

Level of evidence Level II.

Keywords Pathoanatomy · Chondroectodermal dysplasia · Ellis–van Creveld syndrome

Introduction

Chondroectodermal dysplasia (Ellis–van Creveld syndrome) is a very rare form of skeletal dysplasia seen most commonly in, but not limited to, the Old Order Amish population. It is estimated that <300 cases have been reported in the English-speaking literature. In 1964, McKusick et al. [1, 2] reported 52 cases in the Old Order Amish (of whom 30 died within the first year of life), the largest single group of affected patients reported at that time, and established the genetic transmission as autosomal recessive [3–6]. Others have suggested the transmission as autosomal recessive [7–9]. The origins of this disorder and its particular pedigree were traced to one Samuel King and his wife, who emigrated from Europe in 1744. Recently, the genes which when mutated produce the condition have been identified [10–14]. The focus of the mutant gene is at 4p16 and represents mutations in two separate EVC genes, EVC and EVC2. The incidence has been estimated at 0.9 cases per 100,000 live births [6]. The genes EVC and EVC2 are highly expressed in bone and heart, two organs predictably affected in individuals with Ellis–van Creveld syndrome. Recent evidence suggests that EVC genes are involved in bone growth mediated at the base of primary cilia [15].

In 1670, Kerckring [16] reported a case of a polydactylous dwarf found drown in a river that might have represented one of the earliest cases ever reported of this condition. The infant had seven fingers and nine toes on one side and seven fingers and seven toes on the other. The drawing from the publication suggests a mesomelic form of dwarfism. Unfortunately, the absence of soft tissue findings renders the case speculative at best. In 1933, McIntosh [17] reported what is currently accepted as the first case reported in the modern literature of Ellis–van Creveld syndrome. In 1940, paediatricians Richard Ellis and Simon van Creveld [18] fully clarified the condition, alluding to the 4.5-year-old case described by McIntosh, and have subsequently received eponymous recognition of the condition. Small numbers of cases of Ellis–van Creveld have been reported in many races and in a multitude of countries throughout the world [19–45]. Currently, the Amish

population of eastern Pennsylvania (primarily Lancaster County) still contains the largest concentration of patients with this condition in North America and, likely, outside of North America. Prenatal diagnosis by ultrasound is available [26–49].

The existing literature, albeit assembled from a relatively large number of publications of a small number of patients, paints a picture of a core group of consistent findings that characterise the syndrome across all patients and a larger constellation of findings frequently encountered in many patients but absent or incompletely expressed in others [50–59]. In 1973, Bailey [60] provided a useful overview of the many associated features. A few other clinical findings are only occasionally encountered. The most consistent and typical components of Ellis–van Creveld syndrome include acromelic–micromelic chondrodystrophic dwarfism and ectodermal dysplasia involving the nails, teeth and gums; postaxial polydactyly of the hands and occasionally of the feet; and commonly but not consistent congenital heart disease involving variable defects, most often a single atrium with cleft mitral valves (50–60 % of all patients). The usual average adult height is between 43 and 60 inches (110 and 152 cm.) It has been estimated that nearly a third of the patients die in the first 6 months and up to a half by 18 months of age from cardiac or pulmonary consequences.

A recent, unique opportunity to interview and examine a sizeable group of Amish patients with Ellis–van Creveld syndrome and a few non-Amish cases has prompted an assessment of the orthopaedic manifestations of this condition. Furthermore, an opportunity to directly surgically observe the pathoanatomy of the profound and severe valgus deformity of the knee has provided documentation of the nature of the marked extensive soft tissue contractions and chondro-osseous deformity seen in this condition.

Material—data

General clinical and radiographic characteristics of Ellis–van Creveld syndrome

Approval from our institutional review board was obtained. Detailed interviews, physical examinations and/or radiographs were available on all 71 patients included in this study. All but three of the patients descended from Old Order Amish backgrounds. Radiographic evaluations were available on 47 patients; 80 lower extremities; 31 skeletal surveys, including upper extremities and spine; 13 computed tomography (CT) reconstructions of the knee; and four magnetic resonance imaging (MRI) scans of the knee. Radiographs of the knee were available on all patients, not surprisingly, inasmuch as the knee valgus deformity is the

most obvious and functionally impairing deformity routinely seen in Ellis–van Creveld syndrome (Fig. 1a–g). Online Resource 1 depicts a rotating 3-D computer model of Fig. 1 showing severe genu valgum, cupping of the lateral tibial plateau and patellar dislocation of the left knee.

Typical findings >90 % of patients—non-orthopaedic

Acromelic–micromelic dwarfism

Ectodermal dysplasia

Postaxial polydactyly

Congenital heart disease

Fig. 1 **a** Front and side clinical views of a 13-year-old adolescent male. **b** Anteroposterior (AP) standing radiograph waist-to-floor. **c** Anterior view waist-to-floor illustration of the skeleton showing severe genu valgum. **d** Anterior view waist-to-floor with musculature

showing patellar dislocation. **e** Lateral view with musculature showing iliotibial band and quadriceps contracture. **f** Posterior view with musculature. **g** Posterior detail view with musculature showing biceps tendon contracture

Fig. 2 **a** Front view of a 14-year-old adolescent female. **b** AP standing radiograph waist-to-floor. **c** Anterior view waist-to-floor showing severe genu valgum and lateral tibial defect. **d** Lateral view with musculature. **e** Lateral view with musculature showing severe

iliotibial band and quadriceps contracture. **f** Lateral view of the knee showing the anterior slope of the tibial plateau. **g** Lateral radiograph of the knee

The hair may be sparse or absent or fine and silky. Teeth may be present at birth with wide-spaced, peg-shaped hypoplastic teeth or even absent teeth. The gums are usually serrated and the upper lip is commonly attached to the upper gum in the form of a partial pseudocleft resembling a

harelip but clearly different anatomically. Intelligence is generally normal or just slightly below. The nails are usually described as dystrophic, fragile, fluted and bordered by a peculiar brown rim. Dysplastic nails are seen uniformly in all patients.

For the purpose of this paper, we have arbitrarily divided the manifestations into typical (over 90 % of cases), frequent (50 % or more) and occasional (<50 % of cases).

Surgical observations (14 patients, 25 limbs)

On the basis of direct surgical observation in an attempt to correct the severe valgus deformity of the knee, the

Orthopaedic manifestations		
71 cases		
Clinical manifestations		
Head and neck	Normal (typical)	
Shoulder, arm and elbow	1. Curvature of the humerus and arm	Typical
	2. Increased carrying angle (cubitus valgus)	Typical
	3. Radial head subluxation–dislocation	Frequent
Forearm, wrist and hand	1. Enlarged distal radius	Typical
	2. Stiffness of the PIP joints (thumb and index most frequently, with loss of flexion)	Typical
	3. Marked loss of ability to make “fist”	Typical
Spine and pelvis	1. Increased lumbar lordosis	Typical
	2. Scoliosis	Occasional
Hip and thigh	1. Full flexion/extension, marked external rotation, markedly limited internal rotation	Typical
	2. Overall externally rotated thigh and leg	Typical
	3. Contracted iliotibial band and lateral quadriceps	Typical
Knee and leg	1. Severe, profound valgus deformity of the knee	Typical
	2. Lateral patellar subluxation	Typical
	3. Patellar dislocation	Frequent
	4. Severe contracture iliotibial band, lateral quadriceps, lateral hamstrings and lateral collateral ligament	Typical
	5. Normal knee ligament stability	Typical
	6. Proximal medial tibial exostosis	Frequent
Ankles and feet	1. Broad foot with pronation	Typical
	2. Overriding fifth toe	Frequent
	3. Short third toe and longer fourth toe	Frequent
Radiographic manifestations		
Head and neck	1. Usually normal C-spine	Typical
	2. Bone compression upper cervical cord (two cases)	Rare
Shoulder, arm and elbow	1. Curving of the humerus	Typical
	2. Cubitus valgus	Typical
	3. Radial head dysplasia and subluxation. Early ossification humeral head	Frequent
	4. Enlarged proximal ulna	Typical
	5. Enlarged distal radius	Typical
Forearm, wrist and hand	1. Postaxial polydactyly	Typical
	2. Fusion hamates and capitate	
	3. Diminished ossification of the primary centres of ossification in the hand	Typical
	4. Increased ossification of the secondary centres of ossification	Typical
	5. Polymetacarpalia	Typical
	6. Synmetacarpalism	Typical
	7. Epiphyses embedded into the metacarpal	Frequent
	8. Proximal pseudoepiphysis of the second or first metacarpal	Frequent
	9. Small terminal phalanges	Frequent
	10. Diminished sesamoid maturation	Typical

Table continued

Radiographic manifestations		
Spine and pelvis	1. Lumbar lordosis	Typical
	2. Spur-like or spike-like downward projection of the medial aspect of the acetabulum in young patients	Frequency unknown
	3. Horizontal sacrum	Frequency unknown
Hip and thigh	1. Round, smooth femoral head well located in acetabulum	Typical
	2. Moderate valgus deformity of the upper femur	Typical
	3. Adducted femur	Typical
Knee and leg	1. Increased lateral sloping of the lateral tibial plateau region with “cupping” and depression of the lateral plateau	Typical
	2. Severe valgus angulation tibia	Typical
	3. Proximal medial tibial exostosis, both clinically and radiographically	Frequent
Ankles and feet	1. Postaxial polydactyly	Frequent
	2. Long fourth metatarsal compared to third	Frequent
	3. Polymetatarsalia	Frequent
	4. Syndactyly	Frequent
	5. Short third metatarsal	Frequent
	6. Ossification of the tarsals at birth	Frequent
	7. Single sesamoid	Frequent
	8. Delayed ossification distal phalanges	Frequent
	9. Overriding third and fifth toes	Frequent
	10. Tarsal fusions	Occasional

Fig. 3 **a** AP intraoperative arthrogram of the knee of a 7-year-old boy showing tibial defect. **b** Illustrative reconstruction arthrogram

Fig. 4 X-rays—upper extremity radiographic changes

following observations were routinely encountered in all cases to varying degrees. In 25 consecutive cases in the 10- to 16-year-old age group of patients, the following findings were typical (Figs. 1, 2 and 3; Online Resource 2 depicts the severe osseous pathoanatomy in a rotating 3-D computer model of Fig. 2, whereas Online Resource 3 includes the accompanying soft tissue abnormalities in a 3-D rotating rendition):

1. Lateral subluxation or dislocation of the patella.
2. Severe contracture of the iliotibial band, vastus lateralis and the lateral retinaculum, and capsule of the joint.
3. Contracture of the lateral hamstrings.
4. Contracture of the lateral collateral ligament.
5. Valgus lateralization and insertion of the infrapatellar tendon.
6. Deep “saucer”-like depression of the lateral tibial plateau.
7. Severe valgus of the shaft of the tibia, particularly proximally.
8. Medial proximal tibial exostosis.

Although the ankle and foot are in pronation and the metatarsals and toes have frequent angular and rotation deformities, not a single patient had any foot or ankle

complaint that led to any surgical correction. An unexplained and interesting observation in this group of patients was the frequency of delayed independent walking. Data were available on 43 of 71 patients who walked independently at an average of >15 months (range 11–35 months). The reason for this finding currently remains unclear.

Discussion

Although clinical and radiographic findings were often interesting and abnormal, the abnormalities surprisingly did not produce any functional limitations in the upper extremity, except the inability to produce a “fist” that was mentioned only rarely by an occasional patient on direct questioning, in spite of routinely encountered stiffness in the interphalangeal joints.

Significant restriction of flexion of the proximal interphalangeal (PIP) joints of the hand, often the thumb and index fingers, was seen very frequently (Fig. 4). One would presume that this restriction would result in the impairment of fine motor skills necessary in many occupations in society. The PIP joint stiffness is likely less impairing in the Amish due to occupational types. In the Amish society, nearly 70 % of males are employed in

farming and roughly 30 % in construction and repair trades, such as carpentry, cabinet making, blacksmithing and harness repair or as labourers on farms and construction sites [61]. Unmarried Amish girls often work as store clerks or maids and only rarely work outside the house after marriage [61].

Recent identification of two cases of upper cervical bony cord compression is, at the very least, distressing, but it is unclear whether the bony compression is directly related to the EVC syndrome. Routine lateral flexion/extension radiographs or other more detailed radiographic imaging of the upper cervical spine and base of the skull has not been suggested in the past. These cases warrant an increased awareness at least of the possible linkage to the basic condition in rare cases.

The thoracolumbar spine is usually spared deformity, save for an increased lumbar lordosis, which is seen frequently (Fig. 5). Scoliosis is seen only occasionally and kyphosis has not been seen at all in this group of patients or reported to be related to the syndrome. The fascinating radiographic changes in the acetabulum seen early in patients with Ellis–van Creveld (medial spike-like osseous prolongation) [62–65] appear to disappear with progressive osseous maturation, as the changes are not seen in skeletally mature individuals with Ellis–van Creveld syndrome, nor do they result in acetabular dysplasia.

The femoral head is round, smooth and routinely well positioned in the acetabulum, with the head, neck and proximal shaft positioned in a valgus alignment. The femoral shaft is usually adducted and the overall bony alignment of the head–neck shaft is in moderate valgus. The marked contracture of the iliotibial band and lateral quadriceps, with significant external rotation of the thigh musculature, likely results in the marked clinical external rotation of the hip relative to very limited internal rotation of the hip and was present in nearly all patients. The common peroneal nerve remains adherent to the biceps tendon and is pulled away from its normal course around the neck of the fibula (Fig. 2e), all of which are demonstrated in the rotating 3-D modelling in Online Resource 3.

The soft tissue contractures likely contribute to the bony valgus and external rotation of the femur as well. Flexion/extension ranges of motion of the hip were normal. The severe soft tissue contracture of the iliotibial band and quadriceps is most reflected at the knee level (Figs. 1e and 2e).

Without question, the most striking and functionally impairing orthopaedic deformity affecting patients with Ellis–van Creveld is the severe and relentlessly progressive

Fig. 5 X-ray—lateral spine

valgus deformity of the knee. This progressive valgus results in diminished efficiency in ambulation, with increased energy expenditure, and, in some cases, the inability to maintain ambulation. The extent of the valgus angulations far exceeds that seen by the authors in any other known orthopaedic condition. Thigh–leg angulations over 45° were routinely seen, with the lower extremities crossing over each other during ambulation, as shown in Online Resource 4, which is a gait video of a preoperative Ellis–van Creveld patient.

The peculiar lateral sloping and “cupping” and depression of the lateral tibial plateau was present in all cases [1, 7, 60–73], seen before walking age and progressively increased in dimension thereafter. In addition, the proximal lateral tibial plateau slopes in a variable fashion either laterally forward or, to a lesser extent, posteriorly from one patient to another, or even between

Fig. 6 Illustration of the variable lateral tibial plateau defect

the right and left knees of the same patient (Figs. 6 and 7). Ironically, the medial aspect of the knee joint remains well formed and intact, forming a pivot point against which the tibia may rotate externally or, in some cases, internally, corresponding with the degree of flexion deformity or recurvatum of the knee. Online Resource 5 demonstrates a computer modelling of Fig. 1, morphing between the right and left knees, depicting the variable slope of the lateral plateau, corresponding with flexion deformity and recurvatum, respectively. The medial aspect of the knee joint remains well formed and intact, forming a pivot point against which the tibia may rotate externally or, in some cases, internally. In severe cases, the lateral tibial plateau may sublux posteriorly, exacerbating the knee valgus (Fig. 2c, f), as demonstrated in Online Resource 3. The defect is believed to be a primary bony dysplasia and an inherent component of Ellis–van Creveld syndrome. Secondary weight-bearing changes likely augment the deformity and increase the valgus (Fig. 3). Online Resource 6 provides a conceptual morp-

hing model between normal to a 13-year-old Ellis–van Creveld patient, depicting secondary weight-bearing changes. A proximal medial tibial exostosis (osteochondroma) is seen in most cases. Although speculative at best, it may occur secondary to “traction” on the physis by the relentlessly progressive valgus deformation of the tibia.

The profound soft tissue contracture of the iliotibial band, the lateral quadriceps, the lateral hamstrings and the lateral collateral ligament results in progressive lateral displacement of the patella, with eventual subluxation and dislocation. These soft tissue contractures “tether” the tibia and fibula into further valgus (Fig. 2e). The authors believe that the soft tissue contracture is every bit as important in producing the severe overall valgus as the bone deformity. The failure of most isolated bony surgical attempts at correction substantiates the role of the soft tissue contracture aetiologically [74–79]. Currently, the authors have no plausible explanation for the delay in independent walking frequently seen.

Fig. 7 X-ray—lateral knee and ankle

Conclusion

Although a myriad of clinical and radiographic orthopaedic abnormalities have been identified in association with the Ellis–van Creveld syndrome, the severe knee valgus deformity is the only one to produce significant orthopaedic impairment and disability. Recognition of the soft tissue and bony pathoanatomy of the knee is essential to avoid fruitless surgical attempts at correction.

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References

- McKusick VA, Hostetler JA, Egeland JA (1964) Genetic studies of the Amish, background and potentialities. *Bull Johns Hopkins Hosp* 115:203–222
- McKusick VA, Egeland JA, Eldridge R, Krusen DE (1964) Dwarfism in the Amish I. The Ellis–van Creveld syndrome. *Bull Johns Hopkins Hosp* 115:306–336
- McKusick VA, Egeland JA, Eldridge R, Krusen DE (1978) Dwarfism in the Amish. I. The Ellis–van Creveld Syndrome. In: McKusick VA (eds) *Medical genetic studies of the Amish: selected papers, assembled with commentary*. John Hopkins University Press, Baltimore, pp 93–117
- McKusick VA, Hostetler J, Egeland J, Eldridge R (1978) Genetic studies of the Amish: background and potentialities. In: McKusick VA (eds) *Medical genetic studies of the Amish: selected papers, assembled with commentary*. John Hopkins University Press, Baltimore, pp 1–22
- McKusick VA, Hostetler J, Egeland J, Eldridge R (1978) The distribution of certain genes in the Old Order Amish. In: McKusick VA (eds) *Medical genetic studies of the Amish: selected papers, assembled with commentary*. John Hopkins University Press, Baltimore, pp 51–66
- McKusick VA (2000) Ellis–van Creveld syndrome and the Amish. *Nat Genet* 24:203–204
- Metrakos JD, Fraser FC (1954) Evidence for a hereditary factor in chondroectodermal dysplasia (Ellis–van Creveld syndrome). *Am J Hum Genet* 6:260–269
- Zunin C (1963) Observation on the hereditary transmission of the Ellis–van Creveld syndrome. *Acta Genet Med Gemellol (Roma)* 12:269–275
- Spranger JW, Brill PW, Poznanski AK (2002) Ellis–van Creveld syndrome. In: Spranger JW, Brill PW, Poznanski AK (eds) *Bone dysplasia. An atlas of genetic disorders of skeletal development*, 2nd edn. Oxford University Press, Oxford, pp 130–131
- Polymeropoulos MH, Ide SE, Wright M, Goodship J, Weissbach J, Pyeritz RE, Da Silva EO, Ortiz De Luna RI, Francomano CA (1996) The gene for the Ellis–van Creveld syndrome is located on chromosome 4p16. *Genomics* 35:1–5
- Ruiz-Perez VL, Ide SE, Strom TM, Lorenz B, Wilson D, Woods K, King L, Francomano C, Freisinger P, Spranger S, Marino B, Dallapiccola B, Wright M, Meitinger T, Polymeropoulos MH, Goodship J (2000) Mutations in a new gene in Ellis–van Creveld syndrome and Weyers acrodermal dysostosis. *Nat Genet* 24:283–286. Erratum in *Nat Genet* 25:125
- Galdzicka M, Patnala S, Hirshman MG, Cai JF, Nitowsky H, Egeland JA, Ginns EI (2002) A new gene, EVC2, is mutated in Ellis–van Creveld syndrome. *Mol Genet Metab* 77:291–295
- Ruiz-Perez VL, Tompson SW, Blair HJ, Espinoza-Valdez C, Lapunzina P, Silva EO, Hamel B, Gibbs JL, Young ID, Wright MJ, Goodship JA (2003) Mutations in two nonhomologous genes in a head-to-head configuration cause Ellis–van Creveld syndrome. *Am J Hum Genet* 72:728–732
- Tompson SW, Ruiz-Perez VL, Blair HJ, Barton S, Navarro V, Robson JL, Wright MJ, Goodship JA (2007) Sequencing EVC and EVC2 identifies mutations in two-thirds of Ellis–van Creveld syndrome patients. *Hum Genet* 120:663–670
- Ruiz-Perez VL, Blair HJ, Rodriguez-Andres ME, Blanco MJ, Wilson A, Liu YN, Miles C, Peters H, Goodship JA (2007) Evc is a positive mediator of Ihh-regulated bone growth that localises at the base of chondrocyte cilia. *Development* 134:2903–2912
- Kerckring T (1670) Tab. VIII. (Infant skeleton, abnormal; polydactyly). In: *Spicilegium anatomicum*. Sumptibus Andre, Amstelodami (Amsterdam)
- McIntosh R (1933) In: Holt LE, Howland J (eds) *Holt's diseases of infancy and childhood*, 10th edn. Appleton-Century-Crofts, New York, p 362
- Ellis RWB, van Creveld S (1940) A syndrome characterized by ectodermal dysplasia, polydactyly, chondro-dysplasia and

- congenital morbus cordis: report of three cases. *Arch Dis Child* 15:65–84
19. Lynch JJ, Perry LW, Takakuwa T, Scott LP 3rd (1968) Congenital heart disease and chondroectodermal dysplasia. Report of two cases, one in a Negro. *Am J Dis Child* 115:80–87
 20. Feingold M (1966) Ellis–van Creveld syndrome. *Clin Pediatr (Phila)* 5:431–436
 21. Goldblatt J, Minutillo C, Pemberton PJ, Hurst J (1992) Ellis–van Creveld syndrome in a Western Australian aboriginal community. Postaxial polydactyly as a heterozygous manifestation? *Med J Aust* 157:271–272
 22. Douglas WF, Schonholtz GJ, Geppert LJ (1959) Chondroectodermal dysplasia (Ellis–van Creveld syndrome); report of two cases in sibship and review of literature. *AMA J Dis Child* 97:473–478
 23. Alcalde MM, Castillo JA, García Urruticochea P, Vilaplana R, Molina E, Ortega J (1998) Ellis–van Creveld syndrome: an easy early diagnosis? *Rev Esp Cardiol* 51:407–409
 24. Al-Khenaizan S, Al-Sannaa N, Teebi AS (2001) What syndrome is this? Chondroectodermal dysplasia—the Ellis–van Creveld syndrome. *Pediatr Dermatol* 18:68–70
 25. Prabhu SR, Daftary DK, Dholakia HM (1978) Chondroectodermal dysplasia (Ellis–van Creveld syndrome): report of two cases. *J Oral Surg* 36:631–637
 26. Salvador Amores AM, Grande Baos C, Blanco Caneda ML, Alonso Ortiz T, Moro Serrano M, Arrabal Terán MC (1990) Ellis van Creveld syndrome. *An Esp Pediatr* 32:445–550
 27. Arya L, Mendiratta V, Sharma RC, Solanki RS (2001) Ellis–van Creveld Syndrome: a report of two cases. *Pediatr Dermatol* 18:485–489
 28. Haque F, Ahmad SA (2004) Ellis–van Creveld syndrome. *Indian Pediatr* 41:867–868
 29. Hill RD (1977) Two cases of Ellis–van Creveld syndrome in a small island population. *J Med Genet* 14:33–36
 30. Ferrero NA, Pozo OO, Morresi ES (1961) Chondro-ectodermal dysplasia (Ellis–van Creveld syndrome): report of a case and review of the literature. *J Bone Joint Surg* 43:1230–1236
 31. Alvarez-Borja A (1960) Ellis–van Creveld syndrome. Report of two cases. *Pediatrics* 26:301–309
 32. Goor D, Rotem Y, Friedman A, Neufeld HN (1965) Ellis–van Creveld syndrome in identical twins. *Br Heart J* 27:797–804
 33. Kurian K, Shanmugam S, Harsh Vardah T, Gupta S (2007) Chondroectodermal dysplasia (Ellis van Creveld syndrome): a report of three cases with review of literature. *Indian J Dent Res* 18:31–34
 34. Lichiardopol C, Militaru C (2006) Ellis–van Creveld syndrome. *Rom J Morphol Embryol* 47:363–366
 35. Horák I, Smahel Z (1983) Chondroectodermal dysplasia (Ellis–van Creveld syndrome) report of a case. *Acta Chir Plast* 25:161–175
 36. Akoun E, Bagard M (1956) La maladie d’Ellis–van-Creveld. *Algérie Médicale* 60:669–676
 37. Kunze P (1980) Ellis–van-Creveld syndrome. *Kinderarztl Prax* 48:193–198
 38. Pinelli G, Cottafava F, Senes FM, Becchetti S, Cosso D, Costa M (1990) Ellis–van Creveld syndrome: description of four cases. Orthopaedic aspects. *Ital J Orthop Traumatol* 16:113–121
 39. de Haas WH, de Boer W (1965) Follow-up of one of the first cases of the Ellis–van Creveld syndrome into adulthood. Some developmental aspects. *Arch Interam Rheumatol* 8:197–218
 40. Dayer L (1960) In: *Le Syndrome D’Ellis–van Creveld. Une forme de dysplasie chondro-ectodermique*. S. Karger, Basel and New York, pp 1–59
 41. Monnet MP, Monnet F (1967) Le syndrome d’Ellis–van Creveld. *Rev. Lyonnaise de Med* 5–39
 42. Uehlinger E (1957) Pathological anatomy of chondro-ectodermal dysplasia of Ellis van Creveld. *Schweiz Z Pathol Bakteriell* 20:754–766
 43. Weyers H (1956) Knowledge of chondroectodermal dysplasia (Ellis–van Creveld); 2 case reports. *Z Kinderheilkd* 78:111–129
 44. Nabrady J (1961) Ellis–van Creveld syndrome and neuroectodermal injury. *Ann Paediatr* 196:18–30
 45. Pachaly L, Martinez C (1961) On congenital aortic sinus aneurysms. *Zentralbl Allg Pathol* 102:321–331
 46. Mahoney MJ, Hobbins JC (1977) Prenatal diagnosis of chondroectodermal dysplasia (Ellis–van Creveld syndrome) with fetoscopy and ultrasound. *N Engl J Med* 297:258–260
 47. Horigome H, Hamada H, Sohda S, Oyake Y, Kurosaki Y (1997) Prenatal ultrasonic diagnosis of a case of Ellis–van Creveld syndrome with a single atrium. *Pediatr Radiol* 27:942–944
 48. Tongsong T, Chanprapaph P (2000) Prenatal sonographic diagnosis of Ellis–van Creveld syndrome. *J Clin Ultrasound* 28:38–41
 49. Dugoff L, Thieme G, Hobbins JC (2001) First trimester prenatal diagnosis of chondroectodermal dysplasia (Ellis–van Creveld syndrome) with ultrasound. *Ultrasound Obstet Gynecol* 17:86–88
 50. McKusick VA, Hostettler A, Egeland J (1978) Ellis–van Creveld syndrome. In: McKusick VA (eds) *Medical genetic studies of the Amish: selected papers, assembled with commentary*. John Hopkins University Press, Baltimore pp 125–137
 51. McKusick VA (1972) *Heritable disorders of connective tissue*, 4th edn. Mosby, St. Louis
 52. Holt LE, Howland J (1936) In: *Holt’s diseases of infancy and childhood: a textbook for the use of students and practitioners*. Revised by L. E. Holt Jr. and R. McIntosh. 10th edn. Revised. D. Appleton-Century Company, Inc., New York and London, pp 362
 53. Samat H, Amir E, Legum CP (1980) Developmental dental anomalies in chondroectodermal dysplasia (Ellis–van Creveld syndrome). *ASDC J Dent Child* 47:28–31
 54. Winter GB, Geddes M (1967) Oral manifestations of chondroectodermal dysplasia (Ellis–Van Creveld Syndrome). Report of a case. *Br Dent J* 122:103–107
 55. Mitchell FN, Waddell WW Jr (1958) Ellis–van Creveld syndrome; report of two cases in siblings. *Acta Paediatr* 47:142–151
 56. Taylor GA, Jordan CE, Dorst SK, Dorst JP (1984) Polycarpaly and other abnormalities of the wrist in chondroectodermal dysplasia: the Ellis–van Creveld syndrome. *Radiology* 151:393–396
 57. Biggerstaff RH, Mazaheri M (1968) Oral manifestations of the Ellis–van Creveld syndrome. *J Am Dent Assoc* 77:1090–1095
 58. Varela M, Ramos C (1996) Chondroectodermal dysplasia (Ellis–van Creveld syndrome): a case report. *Eur J Orthod* 18:313–388
 59. Gorlin RJ, Cohen MM Jr, Hennekam RCM (2001) Ellis–van Creveld (chondroectodermal dysplasia). In: Gorlin RJ, Cohen MM Jr, Hennekam RCM (eds) *Syndromes of the head and neck*, 4th edn. Oxford University Press, New York, pp 239–242
 60. Bailey JA II (1973) Disproportionate short stature: diagnosis and management. WB Saunders, Philadelphia, pp 198–213
 61. Cross HE, McKusick VA (1978) Amish demography. In: McKusick VA (ed) *Medical genetic studies of the Amish: selected papers, assembled with commentary*. John Hopkins University Press, Baltimore, pp 29–47
 62. Taybi H, Kane P (1968) Small acetabular and iliac angles and associated diseases. *Radiol Clin North Am* 6:215–221
 63. Gellis SS, Feingold M (1967) Picture of the month. Ellis–van Creveld syndrome. *Am J Dis Child* 114:169–170
 64. Silverman FN (1968) A differential diagnosis of achondroplasia. *Radiol Clin North Am* 6:223–237
 65. Sergi C, Voigtländer T, Zoubaa S, Hentze S, Meyberg-Solomeyer G, Troeger J, Tariverdian G, Otto HF, Schiesser M (2001) Ellis–van Creveld syndrome: a generalized dysplasia of enchondral ossification. *Pediatr Radiol* 31:289–293

66. Murdoch JL, Walker BA (1969) Ellis–van Creveld syndrome. The clinical delineation of birth defects. IV. Skeletal dysplasias. National Foundation—March of Dimes, New York, pp 279–288 (BSOAS V, No. 4)
67. Keizer DP, Schilder JH (1951) Ectodermal dysplasia, achondrodysplasia, and congenital morbus cordis. *AMA Am J Dis Child* 82:341–344
68. Tubbs FE, Crevasse L, Green JR Jr (1962) Congenital heart disease in an adult with the Ellis–van Creveld syndrome. *Ann Intern Med* 57:829–834
69. Smith HL, Hand AM (1958) Chondroectodermal dysplasia (Ellis–van Creveld syndrome); report of two cases. *Pediatrics* 21:298–307
70. Ellis RWB, Andrew JD (1962) Chondroectodermal dysplasia. *J Bone Joint Surg Br* 44:626–636
71. Hirokawa K, Suzuki S (1967) Ellis–van Creveld syndrome: report of an autopsy case. *Acta Path Jpn* 17:139–143
72. Weiss H, Crosett AD Jr (1955) Chondroectodermal dysplasia; report of a case and review of the literature. *J Pediatr* 46:268–275
73. Caffey J (1952) Chondroectodermal dysplasia (Ellis–van Creveld syndrome): report of three cases. *AJR Am J Roentgenol* 68:875–886
74. Zuege RC, Kempken TG, Blount WP (1979) Epiphyseal stapling for angular deformity at the knee. *J Bone Joint Surg Am* 61:320–329
75. Steel HH, Sandrow RE, Sullivan PD (1971) Complications of tibial osteotomy in children for genu varum or valgum. Evidence that neurological changes are due to ischemia. *J Bone Joint Surg Am* 53:1629–1635
76. Shibata T, Kawabata H, Yasui N, Nakahara H, Hirabayashi S, Nakase T, Ochi T (1999) Correction of knee deformity in patients with Ellis–van Creveld syndrome. *J Pediatr Orthop B* 8:282–284
77. Milgram JW, Bailey JA 2nd (1975) Orthopaedic aspects of the Ellis–van Creveld syndrome. *Bull Hosp Joint Dis* 36:11–19
78. Pinelli G, Cottafava F, Senes FM, Becchetti S, Cosso D, Costa M (1990) Ellis–van Creveld syndrome: description of four cases. Orthopaedic aspects. *Ital J Orthop Traumatol* 16:113–121
79. Morsy A, Tsuchiya H, Matsubara H, Kabata T, Tomita K (2007) Ilizarov deformity correction of the lower limbs in Ellis–van Creveld syndrome. *J Orthop Sci* 12:505–509