CHONDROECTODERMAL DYSPLASIA

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In 1940 Ellis and van Creveld described a type of chondrodysplasia occurring in association with ectodermal dysplasia affecting the nails, teeth and hair, polydactyly of the hands and congenital heart disease. They named the syndrome chondroectodermal dysplasia. One of the three cases included in their report had previously been described briefly by McIntosh (1933); this patient lacked a congenital heart lesion, and the hair was unaffected. Since two of the original three cases were in the children of parents who were first cousins, it was suggested that the condition might prove to show recessive inheritance. This has subsequently been confirmed (Metaraks and Fraser 1954). In a comprehensive monograph, Le syndrome d'Ellis–van Creveld, Dayer (1960) recently reviewed thirty-three cases from the literature which could be accepted as examples of the syndrome, and added three personal observations. All of these showed chondrodysplasia, polydactyly of the hands and, with two exceptions, ectodermal dysplasia affecting both teeth and nails. The following two cases show the complete syndrome including congenital heart disease, and bring the total number of cases reported in detail to forty (see Addendum).

CASE REPORTS

Case 1—A male infant was admitted to the Royal Hospital for Sick Children, Edinburgh, at the age of three and a half months, after a transient attack of severe cyanosis and unconsciousness occurring the previous evening. Since birth he had had recurrent cyanosis during feeding and crying, and slight central cyanosis persisted after admission.

The infant was born after artificial rupture of the membranes on account of maternal pre-eclampsia, and weighed 8 pounds 4 ounces (3.75 kilograms). He developed diarrhoea and pyrexia on the tenth day but made an uneventful recovery. A vestigial seventh digit was removed from the ulnar side of each hand soon after birth. He was artificially fed. At the age of five and a half weeks he was admitted to the Northern Ireland Fever Hospital for one week with gastro-enteritis, the congenital malformations being noted, together with the presence of a vestigial erupted tooth which was subsequently shed. At that time the electro-cardiograph showed right ventricular hypertrophy.

Family history—Both parents were from Northern Ireland. The mother, aged twenty-two at the time of the birth, suffered from mild anaemia and pre-eclampsia in the fortieth week of pregnancy, but was otherwise normal. The father was aged twenty-nine, and though not available for examination was said to be normal also. There was no parental consanguinity. Three older children, a girl aged three and a half
and male twins aged two and a half were examined and were well, though each showed a mild degree of hypertelorism. There was no known history of ectodermal dysplasia, chondrodysplasia, polydactyly or heart disease in the immediate family, the mother being able to give information about the infant’s four grand-parents, five uncles, one aunt and six first cousins.

*Examination* (aged four months) showed an active, contented infant with slight central cyanosis. The head circumference was 36.2 centimetres, the weight 5.7 kilograms and the length 55 centimetres (normal 62.5 centimetres). The limbs were disproportionately short in comparison with the normal-sized head and trunk (Fig. 1). The shortening of the limbs affected both proximal and distal segments, but in the lower limbs was most marked distally. The eyes were widely separated, suggesting a slight degree of hypertelorism. Muscle bulk and tone were normal.

*Chondrodysplasia*—Radiographic examination showed all the long bones of the upper limbs to be shortened and thickened, the shortening affecting both proximal and distal segments (Fig. 2). The humeri were curved and expanded distally. The proximal ends of the ulnae and distal ends of the radii were enlarged and the radial heads were dislocated. The terminal phalanges of both hands were represented by minute centres of ossification only. There was partial fusion of the fifth and a sixth metacarpal on the left. In the lower limbs all the long bones were short and thick, but here the shortening affected the tibiae to a greater degree than the femora, and the fibulae more than the tibiae (Fig. 3). There was fusion of tarsal bones, and absence of centres of ossification of terminal phalanges of the first and fifth toes on either side. The spine was normal.

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**Fig. 2**

Case 1. Figure 2—Radiographs of the upper extremities showing bilateral shortening of both proximal and distal segments with thick curved humeri, enlargement of the proximal ends of the ulnae and the distal ends of the radii, dislocation of the radial heads, and polydactyly with partial fusion of the fifth and sixth metacarpals on the left. Figure 3—Radiographs of the lower extremities showing greater shortening of the distal than of the proximal segments, and thickening of the femora and tibiae with disproportionate shortening of the fibulae.

**Fig. 3**

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Polydactyly—Both hands showed a sixth mobile digit attached to the ulnar border, a seventh vestigial digit having been removed previously from each hand (Fig. 4). The fingers were short, but had a full range of movement. The feet showed no polydactyly; there was overriding of the third toe on both sides.

Ectodermal defect—The nails of the fingers and toes were very small, dystrophic and scale-like, and nails were absent on the supernumerary digits. The hair was extremely sparse, even allowing for the age of the patient, and apart from a small pigmented tuft in the occipital region was represented by a little fine down. The eyebrows were very sparse.

Summary of dental report—There were no erupted teeth. The maxillary and mandibular arches were abnormal. The maxillary vestibular groove was absent, the gum pad being fused with the upper lip. The mandibular gum pad was distinct from the lower lip, and was irregularly segmented by transverse grooves with five distinct parts, the most anterior segment being across the mid-line. The transverse grooves passed obliquely from labial to lingual, the anterior segment being wider labially than lingually. The distal part of the gum pad on each side was segmented into two unequal parts by grooves which were less deep and less oblique than those anteriorly. The two sides were individually irregular. The alveolar heights of each segment were unequal.

Radiographic examination showed the four mandibular deciduous incisors to be atypical in size and shape. The central incisors were small and tapering incisally. The incisal edge to a depth of 1 millimetre was less radio-opaque than the remainder of the crown, being sharply demarcated at a straight junction with more radio-opaque cervical part to form a "screwdriver blade" shaped tubercle with straight edges and sharp angles. There was no evidence of root formation, the tooth germ being enclosed by calcified tissue. The size, shape and lack of root development of the central incisors suggested that they belonged to a pre-deciduous dentition. The lateral incisors closely resembled the normal in size, but each was surmounted incisally by a "screwdriver blade" tubercle. The tooth germ was uncalcified apically and root development was possible though not evident.

The deciduous maxillary incisors: the two central and one of the lateral incisor crowns seen were atypical, being peg-shaped, tapering from the cervical to the incisal edge which was narrow and smoothly rounded. There was early root formation.

Cardiological report (Dr R. M. Marquis)—There were normal peripheral pulses in arms and legs. There was no heart failure. Central cyanosis was seen especially well in the tongue. A mid-systolic murmur was audible over the back as well as the front of the chest. There was
no diastolic murmur. Electrocardiography showed left axis deviation and suggestive evidence of both left and right ventricular hypertrophy. Radiography showed a broad supracardiac shadow especially towards the left, a right-sided prominence and slight increase in pulmonary vascularity. It was concluded that there was a congenital heart lesion, probably an ostium primum type of atrial septal defect with a bidirectional shunt.

Other systems—Developmental testing at seventeen weeks of age gave a developmental quotient of 70 to 82. The genitalia were normal, with both testes in the scrotum. Other findings were essentially normal except for scattered moist râles in both lungs, which subsequently cleared. Chromosomes examined in tissue cultures of peripheral blood were indistinguishable from those of a normal male. Amino-acid chromatography of the urine was normal.

Case 2—Boy, born spontaneously at full term and weighing 6 pounds (2.73 kilograms). There had been no maternal infection or radiographic investigation during pregnancy. There was no family history of physical or mental defect, and no parental consanguinity; the patient’s only sibling, an elder brother, was normal. He was artificially fed and had no extra vitamins. During infancy he failed to thrive, had several respiratory infections at about one year of age and did not walk until he was nearly two years old. There were no incidents of note from the age of two to five years (the time of the report). Although markedly undersized, he was then cheerful, cooperative, and of normal behaviour and intelligence.

Skeletal system—His height, 87 centimetres, was that of an average child of two years. His dwarfing was due primarily to the extreme shortness of the limbs, the shortening affecting the distal segments to a greater degree than the proximal (Fig. 5). The upper arms and thighs were bowed. There was no laxity or limitation of movement at any joint. Muscle bulk and tone were normal. The thorax was deformed, with a pigeon-breast deformity and Harrison’s sulcus. The skull was normal in size (circumference 49 centimetres) and in shape, with no bossing or craniotabes.

Radiographic examination of the skeleton (Figs. 6 and 7) showed chondrodysplasia with the following features. The long bones had short, broad and sometimes curved shafts with expansion of the diaphyseal regions. The distal long bones were more markedly shortened than the proximal ones, the terminal phalanges being barely visible. Comparison of the lengths of the long bones with the “normal” values for age given by Maresh (1943) showed that the patient’s long bones represented the following percentages of the normal: humerus 67, radius 59, ulna 48, femur 77, tibia 61, fibula 50 per cent. These figures show that in the arm, the ulna, and in the leg, the fibula, were the bones showing the greatest relative shortening.

There was some fusion of the metacarpals. The proximal ends of the tibial shafts, in the antero-posterior radiograph, showed angulation of the superior surface with a small, hypoplastic epiphysial centre capping the medial face.

The spinal column was abnormally segmented with six lumbar vertebrae, eleven pairs of normally formed ribs and rudimentary first ribs. The skull was normal.

Polydactyly—Each hand had an extra digit arising from the ulnar border, that on the right being double (Fig. 8). The feet had five normal toes without any trace of an extra digit.
Ectodermal dysplasia—The finger nails were tiny, misshapen and thin. The skin was normal apart from a patch of pigmentation adjacent to the right eye; sweating occurred normally. The hair was normal in texture and distribution.

Case 2. Figure 6—Radiographs of the upper extremities showing on each side a curved and thickened humerus, enlargement of the proximal end of the ulna and the distal end of the radius, curving of the radius, and polydactyly with a fused sixth and seventh digit on the left. Figure 7—Radiographs of the lower extremities showing greater shortening of the distal segments. The proximal end of each tibia is thickened and pointed, with the epiphysis displaced medially.

Fig. 8
Case 2—Polydactyly with dysplasia of the nails.

The normal sulcus between the upper lip and the gum was absent. The dental abnormalities may be summarised as slow growth and development of the jaws with an anterior open bite, partial anodontia affecting both dentitions, retarded eruption of deciduous teeth, retarded development of teeth of the permanent series, fusion of tooth germs, feline teeth in the lower...
incisor region and abnormal root formation of D D. The appearance of the incisors is shown in Figure 9.

**Cardiovascular system**—There was no tachycardia, cyanosis or venous congestion, and no enlargement or displacement of the heart on clinical examination. Femoral pulsation was readily palpable and the blood pressure was normal. A systolic murmur of moderate intensity was audible in the third left interspace. Radiographic examination of the chest revealed a cardiothoracic ratio of 62.5 per cent, without predominant enlargement of any one chamber, a normal pulmonary conus and aortic shadow, and orthoanemic lung fields. An electrocardiograph showed sinus rhythm, a regular rate of 120 per minute, right axis deviation, anti-clockwise rotation, normal P waves and QRS complexes. The findings indicated a congenital malformation of the heart, probably a ventricular septal defect.

**Genito-urinary system**—The penis was abnormally small. Both testes were in the scrotum. The kidneys were not palpable. The urine showed no microscopical or biochemical abnormality. **Other systems** were essentially normal.

**Investigations** included normal blood counts, negative Wassermann and Kahn reactions, and negative Mantoux tuberculin test.

**Biochemical examinations**—Serum calcium, serum inorganic phosphate, serum alkaline phosphatase, serum proteins, serum cholesterol, blood urea, electrophoresis, and electrolyte content of sweat were all within normal range.

**DISCUSSION**

The syndrome affects both mesodermal and ectodermal tissues, and the association of ectodermal defects with manual polydactyly and chondrodysplasia is regarded as essential for diagnosis. All the cases included in Table I (adapted from Dayer) fulfilled this criterion, with the possible exception of one case (Akoun and Bagard 1956), that of an infant who died on the ninth day, in which particulars of the gums or nails were not given. The nails were affected in all the other patients, and the teeth in all except one (Niemann, Stehlin and Mancaux 1953), in which the infant was edentulous. Table I gives only the more variable features of the syndrome. The numbering of cases follows Dayer, with the addition of our present two cases. A number of cases which are incompletely documented or lack one of the three cardinal features of the syndrome (Keizer and Schilder 1951; Debré, Lamy, Minkowski and Grumbach 1952; Gallagher, MacGregor and Israelski 1953) have not been included. Of the thirty-eight patients, eighteen were girls and twenty boys.

**Inheritance**—The syndrome has been recorded in five pairs of siblings, including one pair of dizygous twins. Thus, of the thirty-eight patients, ten had a brother or sister affected. In no instance has the syndrome occurred in a parent and child. Isolated elements of the syndrome, however, have occasionally been described in forebears, collaterals or siblings. In one sibship of thirteen children the patient (Case 6) had one brother a polydactylyous dwarf, one sister with simple polydactyly, four siblings with dental anomalies, one with congenital heart disease, one with club foot and four normal; the parents were first cousins.

Consanguinity of parents was present in nine out of thirty-three marriages, as compared with an expected incidence of approximately 1 per cent (Stern 1949). This was a much higher incidence than could be attributed to chance, and this, together with the occurrence of the syndrome in siblings, strongly indicates that chondroectodermal dysplasia has an autosomal
TABLE I
DETAILS OF THIRTY-EIGHT REPORTED CASES OF CHONDROECTODERMAL DYSPLASIA

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S = siblings.  DT = dizygous twins.
recessive mode of inheritance. This may be of practical importance when advising parents of the risk of a subsequent child's being affected (Mettrakos and Fraser 1954).

Ethnic grouping does not appear to play a significant role in etiology, the syndrome having been described in children of Negro, Arab, Jewish, Turkish, Mediterranean and Northern European and American stock.

Chondrodysplasia—This has characteristic features distinguishing it from classical achondroplasia (which it most nearly resembles) and also from Morquio's disease. Although the limbs are invariably shorter than normal, the shortening typically affects the distal segment to a greater degree than it does the proximal. The humeri and femora are often bowed, and may be thickened and expanded distally (as in achondroplasia). The paired bones commonly show unequal shortening, which in some cases has been associated with cubitus valgus or genu valgum. There is enlargement of the head of the ulna and of the distal end of the radius; the head of the radius may be dislocated. Caffey (1952) regarded the appearance of the tibia (Fig. 7) as diagnostic. The shortening is not only more marked than in the case of the femur, but the proximal end of the tibial shaft is widened and pointed; the epiphysial ossification centre is likely to be hypoplastic and displaced medially. The fibula, which in classical achondroplasia is least affected, shows disproportionate shortening—for example, 50 per cent of normal length in our Case 2, compared with 77 per cent of normal length for the femur. (In achondroplasia these relative proportions are reversed.) The phalanges are markedly shortened, and the centres of ossification for the terminal phalanges may be absent. Flexion deformities of the fingers are exceptional. There is frequently fusion of two or more carpal or tarsal bones. Exostoses have been found in some cases. The spine has been normal in all except our second case in which it showed six lumbar vertebrae. In no instance has the skull or facies shown the appearances characteristic of classical achondroplasia.

Polydactyly—The hands are invariably affected, and the feet much less commonly so (in only eight of thirty-eight patients). A sixth, or sixth and seventh, digit has been present on the ulnar side of each hand, but in one of Dayer's cases the supernumerary digit was on the radial side. Our first patient showed a vestigial seventh digit on each hand at birth, and our second had six digits on the left and fused sixth and seventh digits on the right.

Ectodermal dysplasia—The nails and teeth are almost invariably affected, but the hair is usually normal. The hair was described as sparse or fine in ten of thirty-eight patients, including our first patient, in whom the age made the finding rather dubiously significant. The skin is not involved, and sweating is normal.

The nails are small, dystrophic and scale-like; they may be absent on one or more digits. The teeth are markedly irregular, and individual teeth may be pointed, dystrophic or absent. Premature eruption of single, malformed teeth may be noted at birth or shortly afterward, as in our first patient.

Fusion of the maxillary gum pad with the upper lip obliterate the normal gingivo-labial sulcus, has been noted in fourteen of thirty-eight cases, including our two. This malformation, which was described in two of Ellis and van Creveld's original cases, appears to be one of the most frequently associated stigmata.

Congenital heart disease—Evidence of congenital cardiac abnormality has been found in twenty-two of the thirty-eight patients, and is thus the least constant feature of the tetrad. Nevertheless, its occurrence is sufficiently frequent for it to be regarded as a part of the complete syndrome. Although in some of the reported cases the evidence was insufficient to reach a firm diagnosis of the lesion, it is clear that in most it was a patency of the interatrial or interventricular septum or of both. In four instances the heart was trilocular and in one bilocular.

Associated abnormalities—In addition to those already mentioned, a variety of associated abnormalities have been described in individual cases. These include malformations of the genitalia, undescended testicles, cleft palate, cleft lip, strabismus, coloboma of the iris, and
Prognosis—The expectation of life depends primarily on the severity of the heart lesion if one is present. The other components of the syndrome do not present a hazard to life, and do not necessarily limit activity. Pelvic deformities sufficient to make natural delivery hazardous are exceptional.

SUMMARY

1. Two cases are reported showing the syndrome of chondrodysplasia, manual polydactyly, ectodermal dysplasia affecting the teeth and nails, and congenital heart disease.
2. Particulars of thirty-eight cases are tabulated, and the features of the syndrome are discussed.
3. The syndrome is regarded as showing an autosomal recessive mode of inheritance.

ADDENDUM

Since this paper was submitted for publication three additional reports have appeared, two of which represent typical examples of the syndrome. Husson and Parkman (1961) reported the case of a female infant dying at the age of four months with chondroectodermal dysplasia, obliteration of the upper labiogingival sulcus, and congenital heart disease. The heart lesions included anomalous pulmonary venous return, single atrium and a persistent left superior vena cava. There was no known consanguinity. In reviewing the cardiac lesions described in chondroectodermal dysplasia they include another case with anomalous pulmonary venous return described by Darling, Rothney and Craig (1957), which also showed chondroectodermal dysplasia and polydactyly, though details of the extracardiac malformations are not given. Nabradi (1961) described a four-year-old Hungarian girl with ectodermal defects involving the teeth and nails but not the hair, polydactyly, distal shortening of the extremities producing dwarfing, and typical radiological appearances of the long bones. There was presumptive evidence of a sepal defect of the heart. There was no consanguinity, but the mother was considered to show a “forme fruste” of the condition. A necropsy report by Meitner (1961) of a newly born premature infant with multiple congenital malformations of organs of ectodermal, mesodermal and endodermal origin is of interest because these malformations included extreme polydactyly of hands and feet, absence of nails, chondrodysplasia, and trilocular heart. In many respects, however, the case is atypical of chondroectodermal dysplasia.

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