CHONDRODYSPLASIA; MULTIPLE CARTILAGINOUS EXOSTOSES

REPORT OF CASES *

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Until a comparatively recent time, the disease characterized by the formation of multiple cartilaginous exostoses was thought to be a rare affection. Gibney¹ reported the first case in this country in 1875, and in the following year recorded the occurrence of the disease in several members of a family. In 1917, Ehrenfried² reported twelve cases and reviewed the literature on the subject. He found that only twenty-nine cases had been reported in America up to that time, and that about forty-two additional cases were mentioned in the discussions. This report stimulated interest in the subject, and case reports during the past two years have been more numerous.

In the cases described, all degrees of associated distortions and deformities of the skeleton are depicted, from the occurrence of simple multiple bony growths causing no particular disturbance, to the occurrence of marked deformities, shortening of the limbs, dwarfing, and associated neurologic symptoms of such severity as to incapacitate the individual. Boggs³ describes a case of multiple osteochondromata, with great deformity, muscular dystrophy and involvement of the cranial nerves, with blindness.

Ehrenfried found that about 5 per cent. of the reported cases were complicated by malignant osteocartilaginous tumors.

The majority of the cases reported occurred in the period of adolescence and young adult life. A few cases have been reported in children, and Hess in discussing Cowie's⁴ paper, refers to an affected family in which the youngest patient was 2 years of age.

* For permission to study these cases I am indebted to Dr. Roger H. Dennett, Director of the Pediatric Clinic, New York Postgraduate Hospital.

1. Gibney, V. P.: Multiple Exostoses, *Med. Rec.* **10**:300, 1875.

2. Ehrenfried, Albert: Hereditary Deforming Chondrodysplasia; Multiple Cartilaginous Exostoses, *J. A. M. A.* **68**:502, (Feb. 17) 1917.

3. Boggs, T. R.: Multiple Congenital Osteochondromata with Degeneration of the Cranial Nerves, and Muscular Dystrophy, *Bull. Johns Hopkins Hosp.* **24**:310, 1913.

4. *Trans. American Pediatric Society*, 1917. Abstr. in *J. A. M. A.* **68**:235, (July 21) 1917.

Three members of a family came to my attention in the outpatient department of the New York Postgraduate Hospital. Two children were brought to the hospital—one a girl, aged 7 years, with a small bony growth on the front of each leg immediately below the knee, and on each arm immediately below the shoulder joint, and a boy, aged 20 months, with a growth on the left scapula. Suspecting the nature of these growths, inquiry was made regarding similar growths in other members of the family, and it was learned that the father was affected, but that the mother and the other daughter, 5 years of age, were not affected.

REPORT OF CASES

CASE 1.—Tina S., white female, aged 7 years, was born in America, of Italian parents.

Family History.—Mother and father are living and well. They are short in stature, but not a disproportionate shortness. The mother has no visible or palpable abnormalities. The father has bony growths on the legs.

Personal History.—Birth was normal. She was breast fed for seventeen months. The first tooth erupted at 6 months; she sat alone at 7 months and walked at 10½ months. She had measles early in life and pertussis at 6 years.

Present Illness.—When the patient was 3 years of age, hard growths appeared on the front of both legs, about four inches below the knees, and on the front of both arms immediately below the shoulder joints. These protuberances grew out rapidly for a short time; but apparently stopped growing a few months later. They caused no trouble and were not painful.

Physical Examination.—On the medial surface of the upper third of the right humerus, a slight enlargement could be seen. Palpation revealed a spur of bony consistency, not tender, and over which the soft parts were freely movable. The spur pointed downward, so that the finger could be hooked under it; it seemed to be about one inch in length and the globular shaped head indicated that it was pedunculated. On the left humerus, in the corresponding area, a smaller bony mass could be palpated. Two growths of the same consistency and about one or one-half inch in diameter were felt on the medial surfaces of both tibiae, immediately below the tuberosities. Small growths could be felt on both radii, just above the styloid processes, on the clavicles, and several suggestive, though not distinct, enlargements were noted on the phalanges of both hands.

The patient was well developed and well nourished; the head was well shaped and there was no disproportionate shortness of the limbs. The circumference of the head was 19½ inches, and of the chest 21 inches; the height was 43½ inches, and the length of the legs, from the anterior iliac spine to the internal malleolus, was 23½ inches. The middle of the body fell at a point 1½ inches below the umbilicus.

The parents were not aware of any growths, except those on the tibiae and the right humerus. They were causing no trouble whatever and the patient was brought to the hospital only because the protuberance on the arm was noticeable enough to excite comment from those who saw the child.

CASE 2.—Boy, aged 20 months; born in America; a brother of the preceding patient.

Personal History.—Birth was normal; breast fed for nineteen months; he had intestinal disturbances with vomiting and diarrhea early in life, and pertussis when 9 months of age. His first tooth erupted at 6 months; he sat alone at 8 months and walked at 13 months of age.

Present Illness.—A bony enlargement on the back, behind the right shoulder, was noticed when the patient was 5 months of age. It grew out rather rapidly for a few months, then stopped.

Physical Examination.—A mass of bony consistency, about $1\frac{1}{2}$ inches in diameter, could be felt on the right scapula, inferior to the spine. On the third digit of the little finger another growth could be felt. No other protuberances

Fig. 1 (Case 1).—Cartilaginous growths on tibiae and femurs.

could be palpated along the accessible parts of the skeleton. The patient was well developed and presented no other abnormalities. The head measured 20 inches, and the chest 19 inches in circumference. The length of the body was $31\frac{1}{2}$ inches, and the middle point was at the umbilicus. The length of the arms was $12\frac{1}{2}$ inches, and the legs $15\frac{1}{2}$ inches.

CASE 3.—John S., aged 29 years; born in Italy; father of the two preceding patients.

Family History.—His mother is dead. Father and one half-brother live in Italy, and two sisters live in America. To the best of his knowledge, no other members of his family have abnormal bony growths.

Physical Examination.—The patient is $5\frac{1}{2}$ feet in height, is well developed and there seems to be no disproportion between body and limbs. A bony mass can be felt on both tibiae just below the tuberosities.

The only remaining child, a girl, aged 5 years, was submitted to a physical and roentgenologic examination, and was found to be unaffected.

Roentgen-Ray Examination.—Radiographic examination by Dr. William H. Meyer showed multiple osteochondromata on the various long bones, near the epiphyscal lines. The involvement was bilateral in nearly every instance, and the symmetry was marked, although the size of the growths on either side varied considerably in some instances. The bones principally involved were the tibiae, the radii, humerii, femora, clavicles and scapulae. The pelvic bones, the metacarpals and the phalanges were involved to a lesser extent.

Fig. 2 (Case 1).—Spur on left humerus showing the "blown out" lamellar structure.

The part of the bone chiefly involved was in the region of the epiphyseal line, the shaft being comparatively free. There was none of the shortening, curving, and marked thickening of the long bones with globular bubble-like vacuolation at the ends, as was found in the cases described by Ehrenfried. The roentgen ray appearance of the large growths is that of a blown out cystic formation in the lamellar structure, which connects with the lamellæ of the shaft but does not extend up into the shaft for any great distance. The small growths appear as clean-cut exostoses, the defect in the shadow indicating that they are composed of cartilage and bone. The larger growths tend toward spur formation, the spur always pointing away from the nearest joint, a phenomena that seems to be characteristic of this disease.

The most prominent growths on the children were removed and studied microscopically by Dr. Meeker.

PATHOLOGIC REPORT

CASE 1.—Tina S. Nature of specimen: Ecchondrosis.

Gross: Specimen, measuring 18 x 10 x 10 mm., presents a rounded surface showing cancellous bone.

Microscopic: One border of the specimen consists of cartilage with scattered cells in a clear ground substance. Inside this the bone is irregularly deposited with spaces between the trabeculae. A thickened periosteum extends

Fig. 3 (Case 1).—Pedunculated growth on right humerus.

along the sides of the bone, which is most irregular in outline. The picture is typical of the usual growths on bones of children sometimes associated with rickets.

Diagnosis (Fetal): Ecchondrosis, not yet ecchondroma.

CASE 2.—William S.

Gross: Two pieces, measuring 17 x 15 x 16 mm. and 13 x 10 x 20 mm., respectively. Both are bony in consistency, smooth on one side, which is covered by cartilage, and a cut surface showing cancellous bone.

Microscopic: The picture is the same as the sister's specimen. There is the same irregular atypical change from cartilage to bone, the irregular thickened periosteum with irregular bone outline and deposits of cartilage in the periosteum, all atypical of this form of growth.

Diagnosis: Fetal ecchondrosis, not a true tumor.

The terms ecchondrosis and ecchondroma or chondroma are usually used to define cartilaginous new growths. The former is confined to those simple hypertrophies of preexisting cartilage and the latter to cartilaginous growths in any part of the body. The occurrence of these growths, in the cases described, away from the epiphyses, and on the shaft of the bone and on other bones where cartilage does not exist normally, and the microscopic appearance of deposits of cartilage in the

Fig. 4 (Case 1).—Cartilaginous spur on upper end of right tibia and femur.

periosteum, is evidence that the condition is one of chondrodysplasia, rather than a simple hypertrophy, and the term ecchondrosis is not suitable because of its limitations. Ecchondroma indicates a benign cartilaginous growth anywhere in the body, and fits well with the condition here described.

The term suggested by Ehrenfried, hereditary deforming chondrodysplasia, is not applicable at present to these cases, because there is no deformity, but when we take the ages of these children into consideration, we must recognize the possibility of some deformity later in life, inasmuch as the disease is an anomaly of skeletal growth, and it is probable that the condition is still active and will be until skeletal maturity is attained.

Some of the deformities usually found in these patients are shortness of stature, which is practically constant, even to the extent of

Fig. 5 (Case 1).—Cartilaginous spur on upper end of left tibia and flat growth on femur.

dwarfing, the lack of growth being in the legs, not the trunk, short upper limbs, relative shortening of the ulna and bowing of the radius causing the hand to deviate outward.

The account of Case 4 was obtained from the records of the Children's Mercy Hospital in Kansas City, where the patient was admitted in the service of Dr. C. B. Francisco.

CASE 4.—C. J., white, male, born in Missouri, July 4, 1907.

Family History.—Father died of tuberculosis; two sisters and two brothers dead, cause not stated. The mother is living and well and has had one miscarriage. One sister, living and well, has no bony growths, but the two living brothers have had growths removed from the limbs.

Personal History.—Dec. 2, 1913, he entered the hospital with a deformity of the left arm and a growth under the great toe which caused him to walk on the side of the foot. He was operated on and a large exuberant growth was removed from the ventral surface of the great metatarsal bone. Exostoses were also removed from the anterior and posterior surface of the head of the left radius. Jan. 6, 1919, he reentered the hospital with the statement that the small growths noticed in infancy had steadily increased in size. He had many exostoses, the most prominent were those on the upper ends of both tibiae, the right external malleolus, and in the left popliteal space. A growth two thirds the size of a lemon was removed from the popliteal space, and one the size of a walnut from the inner side of the femur.

The Wassermann test was positive.

Injury to blood vessels, such as trauma, and aneurysm, due to friction from bony growths, have been reported, especially injuries to the popliteal artery.

The neurologic manifestations noted are ulnar and radial nerve involvement, cord lesions from endostoses, and in one case acromegalic symptoms from a growth in the sella turcica.

NATIONALITY

The nationality of the patients collected by Ehrenfried shows that these cases occurred more often among the Dutch and the Germans, and only once each in an Austrian, a Canadian, an Englishman and an Italian. Two cases occurred in the negro, and Cox's patient is a native of India.

HEREDITY

The heredity feature is well established, and Ehrenfried states that the condition can be transmitted by an unaffected mother, but there is no evidence that the disease can be transmitted by an unaffected male. In the cases reported since Ehrenfried's review, I have been able to find support for this statement. In Cowie's patient, the disease was transmitted by the affected father. In Hess's three patients, the disease was transmitted by the affected father, and in Gorsaline's five cases, a man inherited the condition from the father, and, in turn, transmitted it to two children by his first wife, and five children by his second wife.

Gorsaline⁵ mentions a case in a man who has a sister, herself unaffected, but with an affected daughter, thus proving that the unaffected mother can transmit the disease.

5. Gorsaline, C. S.: Familial Deforming Chondrodysplasia Multiple Cartilaginous Exostoses, *Am. J. Roentgenol.* 6:271 (June) 1917.

SEX INCIDENCE

Reincke, in 1891, found that the sex incidence was 3 to 1 in favor of the male, and Ehrenfried, in 1917, found it to be about 5 to 2. Since that time I find that in twenty-nine cases, including my own, the males were affected eighteen times and the females eleven times, a ratio of about 3 to 2.

When we attempt to find an explanation for the high incidence among males, and the transmission of the disease by supposedly unaf-

Fig. 6 (Case 3).—Cartilaginous growths on tibia and fibula.

ected females, it would seem that the affection, if mild, would be more readily discernible on the male body and certainly the male would not be so reluctant to make known the condition and present himself for examination. The wider use of the roentgen ray may bring many more cases to light that would otherwise have escaped attention in the days when most of these cases were reported, and the incidence between the sexes may be more equal. However, this is merely speculative, although there is some evidence of it, in the case reports of the past two years.

AGE

All ages have been mentioned in the case reports from the 2 year old patient of Hess to Frieburg's 80 year old man. The patient in this series, aged 20 months, is, I believe, the youngest in whom the disease has been reported. Also the family here reported represent a very mild degree of involvement.

The disease has very different microscopic changes from those found in osteomalacia, osteogenesis imperfecta, rickets and Paget's disease, although these conditions are mentioned sometimes in their relation to chondrodysplasia.

Its relation to that anomaly of skeletal growth known as chondrodystrophy, however, deserves more than passing notice. In spite of the great physical deformities present in both conditions, the mental development, as a rule, is not retarded.

In his monograph on chondrodystrophia fetalis, Kaufman⁶ described three distinct varieties—the hypoplastic, hyperplastic and the malacic. He considered it a dystrophy of the cartilage concerned in the first skeletal formation during the period from the third to the sixth month of fetal life. Some of these patients died in utero, some died in infancy, others in childhood, and some lived to old age, the degree of involvement probably was the factor in determining the fate. In those that lived many variations from the typical achondroplastic dwarf were described. Opie and Allison⁷ described the case of a boy, aged 17, who had outgrowths of cartilage, microscopically similar to those found in chondrodystrophy but with no retardation of the growth of long bones. Kaufman also described two fetuses with involvement of the intracartilaginous bones of the head, but with no interference of the growth of long bones. Chondrodystrophy, therefore, may be present without dwarfing, and with widely varying degrees of involvement.

Schorr⁸ described a type of chondrodystrophy which makes its appearance at puberty, and to which he gave the name chondrodystrophia adolescentium.

From these descriptions it may be seen that chondrodystrophia exists in a variety of forms, involving those bones involved in chondrodysplasia, and with microscopic changes which are very similar and

6. Osler's Modern Medicine.

7. Opie, E. L., and Allison, N.: Hypertrophic Chondrodystrophy in Infancy and Adolescence; Progressive Anomaly of Osteogenesis, *J. Med. Res.* **36**:277, (May) 1917.

8. Quoted by Opie and Allison.

seem to differ only in degree, and there is enough similarity in these conditions to warrant the belief that there is a close relationship between them.

1. Both conditions affect bones of intracartilaginous origin without disturbing those of intramembranous origin.

2. In both conditions isolated inclusions of aberrant cartilage within and beneath the periosteum are found. Where more complete microscopic studies can be made on chondrodystrophic subjects, coming to necropsy, these irregular cartilage masses are found widely distributed in fat and in heads of bones.

3. In both conditions there is a progressive proliferation of epiphyseal cartilage, with bone formation at the edge of the proliferations, as is evidenced by the finding of irregular deposits of bone in the cartilage, in the microscopic study of growths removed.

In chondrodystrophy this proliferation of cartilage tends to widen the bone interfering with longitudinal growth, but the proliferation is in an orderly manner giving uniform enlargement, rather than the production of exostoses. The cartilage proliferation is much more excessive in chondrodystrophy, which may account for the gradual and uniform enlargement, as contrasted with the spontaneous isolated outgrowth with the resulting cartilaginous exostoses of chondrodysplasia.

4. The microscopic changes at the epiphyseal line in the two conditions present a striking similarity. In chondrodystrophy the excess of cartilage cells at the sites of ossification occur in irregular groups instead of the normal orderly arrangement in long rows perpendicular to the line of ossification. The line of ossification is straight and very narrow, and instead of a distinct zone of proliferating cartilage cells being present, they are few and unevenly distributed.

Ehrenfried was able to study a specimen from across the epiphyseal line taken from a patient with chondrodysplasia, and he described an excessive growth of intermediary cartilage, with an irregular zone of calcification, and the cartilage proliferating cells scattered in irregular groups instead of forming a distinct zone in orderly arrangement.⁹

SUMMARY

1. Many variations of hereditary deforming chondrodysplasia may occur, from the existence of multiple small cartilaginous exostoses, giv-

9. For an extensive bibliography and a review of the cases reported in American literature, the reader is referred to the article by Ehrenfried.

ing the patient no trouble, to the existence of great deformities, with dwarfing, paralysis, aneurysm and malignancy.

2. The disease manifests itself in infancy.

3. The condition has much in common with chondrodystrophy of infancy and adolescence, and it is probable that a close relationship exists between them.