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Cartilage-hair hypoplasia

Kenneth A. Vogel
University of Nebraska Medical Center

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CARTILAGE-HAIR HYPOPLASIA

By

Kenneth Allen Vogele

A THESIS

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In Partial Fulfillment of Requirements
For the Degree of Doctor of Medicine

Under the Supervision of Carol Angle, M.D.

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INTRODUCTION

Cartilage-hair hypoplasia is one of a number of syndromes of short-stature which have been recently carved from the catch-all designation achondroplasia. First reported in world literature by Maroteaux et al. in 1963 as a partial form of metaphyseal dysostosis (6), it was revealed as a new condition by Victor A. McKusick in April 1964 (8).

Though McKusick did not describe the first cases, he defined and delimited the disease. During the course of a study of genetic diseases in the Amish, it came to his attention that dwarfism occurred in an unusually high frequency. The dwarfism was mainly of two types. The Ellis-van Creveld type was most frequent in the Amish of Lancaster County, Pennsylvania, whereas the second type, usually referred to as chondrodystrophic or achondroplastic dwarfism, was found there and generally in Amish people throughout the country. The latter has been shown to be clearly distinct from classical achondroplasia. In addition to small size, most cases have abnormally fine, sparse, short, light-colored, and slow-growing hair. Hence, McKusick has given it the name cartilage-hair hypoplasia.

CLINICAL FEATURES

The skeleton. Cartilage-hair dwarfism is of the short-limbed variety. The shortness is present from birth in all cases although some parents do not recognize the retarded growth development until as late as age five (1). While birth weight is normal, birth length usually is nineteen inches or less. Adult heights range from forty-two to fifty-eight inches, placing

all affected adults below the third percentile for that dimension (1).

The head is normal in size and contour (10). There is one report of slightly enlarged head circumference (1). This child also had palpable depressions over the lambdoidal sutures.

Vertebral column height is normal to slightly increased (10). There are usually no spinal curvatures although Maroteaux reports dorsal scoliosis with increased lumbar lordosis in one of his French cases and kyphoscoliosis in the other French case (12). The lumbosacral angle is often increased.

Since the skeletal findings are localized to the tubular bones, one would expect to find minor abnormalities of the rib cage. Widening of the costochondral junction leading to beading of the ribs is seen in some cases as is a Harrison-like groove which has not been explained. A rather marked projection of the upper sternum with depression of the lower sternum is not an uncommon finding (10). Flaring of the lower rib cage has been cited.

The hips appear normal although two cases of Legg-Perthes disease have been described, one in a girl of eleven years (10) and another in a boy of thirteen years (1).

The most striking abnormalities are found in the tubular long bones. Both the upper and lower extremities are markedly reduced in length. This reduction is the sole cause of the dwarfism and is more marked distally in the extremities. McKusick notes an inability to extend the elbows fully (10), attributed by Beals to be the result of flexion contractures (1). The hand is short and

pudgy, and yet the fingers can be brought together without difficulty over their entire lengths. Commonly seen is an amazing loose-jointedness of the fingers and the hand proper, giving the hand a limp feel. "Some affected children 'do tricks' with their loose-jointed fingers, to the amusement of their confreres" (10). Slight bowing of the lower extremities is often present. One case of mild genu valgum has been reported (1). Varus ankles are sometimes found and appear related to the excessive length of the fibula distally relative to the more severely affected tibia (10). The foot is as loose-jointed as the hand causing flattening on weight-bearing. A posterior projection of the heel is often seen (10). The fingernails and toenails are short but of almost normal width on all digits. The surfaces are smooth and the nails are not deformed. The range of motion through all joints is normal with the exception of the elbow joints.

The hair. McKusick first noted hair hypoplasia to be a feature of dwarfism among the Amish in 1964, thus completing the syndrome Maroteaux had partially described one year earlier. Although sparseness, fineness, and silkiness of the head hair, eyebrows, and eyelashes is most noticeable, all body hair is equally affected. "Mothers frequently state that the hair breaks off easily, or at least remains relatively short. Often it cannot be braided in the style customary with Amish girls. Several of the affected persons have been almost completely bald all their life" (10). One is known to wear a wig and one nine and one-half-year-old girl has never had a haircut. Adult males have thin, silky beards. The hair of affected persons is usually lighter in color than that of

unaffected family members. Commonly the hair is almost white at birth but in adulthood becomes light brown (10). Blond hair is not essential, however. Maroteaux et al. picture two of their three Algerian cases, and both have dark hair (12). A retrospective examination of the hair of three of the five cases described by Maroteaux revealed abnormally small caliber (10). McKusick studied the hair diameter of thirty-seven of his affected Amish and eighty-nine of their non-dwarfed siblings and parents (10). Although there was a moderate degree of overlap between affected and normals, the average diameters were 0.024 millimeters and 0.035 millimeters, respectively. The ranges were 0.012 to 0.033 millimeters and 0.020 to 0.054 millimeters, respectively. Part of this overlap may be explained by reduced genetic penetrance suspected in this syndrome.

Motor development. Motor development is not unusual and coordination is normal (1,2).

Intelligence. All researchers state that their cases have normal intelligence with the exception of Beals who reports intelligence quotients in his case of eighty-five and eighty-eight at ages eight and nine, respectively (1). This child repeated second grade but has passed all others up to the tenth grade level.

The gastrointestinal tract. Intestinal disorders are probably common enough to be considered a part of the CHH syndrome. At least two children have been reported to have had the celiac malabsorption syndrome (2,10). McKusick mentions disorders of intestinal absorption with failure to thrive in five cases (10), and Irwin noted occasional diarrhea and gastrointestinal symptoms

suggesting a malabsorption-like syndrome in his case (6). Two diagnoses of congenital aganglionic megacolon have been made by clinical, radiologic, and histopathologic methods (10). One survived an operation at age six and another died at five months of age.

Sexual development. The onset of puberty and the development of secondary sexual characteristics are normal, but pubic and axillary hair is fine and silky. Reproduction is not impaired. Five affected males have married normal females and one affected male has married an affected female. All six unions have resulted in offspring (10).

Miscellaneous physical findings. One of McKusick's probands had a tracheo-esophageal fistula (10). Internal strabismus was found in a French case by Maroteaux (12). Beals noted spontaneous vitreous hemorrhage in his case (1). This dwarf also had a persistent absolute leukopenia of approximately four thousand cells per cubic millimeter and hemoglobin values of 11.9 and 11.3 grams per one hundred milliliters at ages nine and sixteen, respectively. Burgert et al. describe an aregenerative anemia with no reticulocytes and no erythropoietic activity in the otherwise normal marrow of their questionable four-and-one-half-year-old case (2).

Susceptability to chickenpox. Two children have died of chickenpox, one at age six and one at age nine, and a minimum of three other dwarfs had such virulent attacks that smallpox was a serious consideration in the differential diagnosis (10). Since fewer than one death per year per one million persons in the United States is attributed to chickenpox, the unusually great susceptability to this

condition may be a part of the cartilage-hair syndrome.

Chemical findings. No metabolic defect causing cartilage-hair hypoplasia has yet been identified. All laboratory studies are usually normal. In McKusick's series the calcium, phosphorus, acid phosphatase, and alkaline phosphatase tests were normal. However, Beals' case had elevated alkaline phosphatase values of 26.2 and 27.7 King-Armstrong units at ages nine and sixteen, respectively (1), and the case of Burgert et al. had astoundingly high alkaline phosphatase levels of 1,010 and 1,175 King-Armstrong units (2). This marked elevation in enzyme activity was tentatively though insecurely attributed to the malabsorption syndrome which affected the child at the time the examinations were made and was thought to originate in the gut. All studies of renal function have been normal. A single unremarkable urinary phosphoethanolamine level has been mentioned (10). No amino acid abnormality was noted by urine chromatography in at least two cases (1,10), and urinary mucopolysaccharide levels were not quantitatively or qualitatively unusual in two cases (1,10). Growth hormone assay was normal in one dwarf both before and after hypoglycemic stimulation (10). The dichloroacetic-acid-solubilized protein components from the costochondral junction of a five-and-one-half-year-old affected male could not be distinguished from the normal (10). All cases reported by Maroteaux et al. had normal laboratory examinations including at least one normal cholesterol level (12). In addition to many of the more common studies above, Beals' dwarf had a normal fasting blood sugar, and unremarkable serum electrolyte, albumin, and globulin test results (1).

The roentgenologic findings. Radiologically, the cartilage-hair hypoplasia defect is a form of metaphyseal dysostosis, the nature of which can be ascertained only before closure of the epiphysis (3,13). For that reason x-ray diagnosis cannot be conclusively made in the adult, and the findings in metaphyseal dysostosis are seen radiologically only in children. In the CHH variety the osseous abnormality is seen primarily in the tubular bones of the extremities. A striking feature of the metaphyseal dysostoses in general is the smooth edge of the normal-appearing epiphyseal ossification center in contrast to the rough, often scalloped and irregularly sclerotic edge of its contiguous metaphysis. Even though the metaphysis is frayed, Irwin states that its margin is sharp and easily identified (6). The metaphyseal ends are greatly widened and often seen to have cystic areas which McKusick feels represent poorly ossified cartilage or enchondral inclusions (10). Metaphyseal fragmentation is common, but a noteworthy feature is the uniform involvement of the entire width of the metaphyseal junction (10). The growth plate is widened. Dwarfs presenting with the cartilage-hair syndrome reveal flaring, cupping, and cystic changes of the costochondral junction of the ribs (thus, an explanation for the often seen chest deformities) which is similar to the above changes.

The skull. The skull is normal in all respects. In at least ten and probably twelve cases (1,6,10) the foramen magnum was specifically determined to be normal.

The vertebral column. McKusick mentions no definite abnormality of the spine but notes that in certain cases columnarization of the cuboid bones is found, i.e., the vertebral bodies are dispro-

portionately tall for their widths. The interpeduncular distances are normal (10). Beals' case, however, had irregularity of the end plates of the lower thoracic and upper lumbar vertebrae (1). There is an increased angle formed by the lumbar spine on the sacrum leading to the commonly-seen increase in the lordotic curve.

The flat bones. Affected persons have normal pelves except that the anteroposterior dimension of the pelvic inlet is markedly shortened in some (10). The only known married female with cartilage-hair hypoplasia has such a pelvis and has had her three children delivered by Caesarian section. The sacroiliac groove is normal in all cases. The scapulae are normal.

The extremities. The long and short tubular bones are severely affected. However, for unexplained reasons the proximal humerus and femur are not greatly involved, and both the shoulder joint and the hip joint are for the most part spared. It is distally in the extremities that the shortening of the tubular bones is most noticeable. The femur is sometimes bowed outward but never severely (6). Tibial involvement is more severe than fibular disease, especially distally, and this disparity in length is the direct cause of the varus ankle deformity (10). The metacarpals, metatarsals, and phalanges are all markedly shortened. The round bones of the ankle and wrist develop slowly and are small.

The joints. No arthritic joint changes have been discovered.

Bone age. Bone age varies between affected individuals and within the same individual but is always retarded with the exception of the phalanges where the epiphyses close as predicted or even earlier in some cases. The extreme brachydactyly appears

to have its explanation partly in this fact (10). The greatest delay in development is seen in the carpal bones.

In the adult the radiological diagnosis of metaphyseal dysostosis is one of exclusion. The widening of the heads and shortening of the shafts are present, but the epiphyseal plates have closed and the definitive changes seen earlier are no longer available. The size and structure of the skull, spine, and pelvis are seen to be in the range of normal, but the extremities are disproportionately shortened.

The bone histopathology. A brief discussion of normal bone is essential to the understanding of the histopathology of bone in cartilage-hair dwarfism.

The embryological development of a normal tubular bone (13,15). Early in fetal life mesodermal connective tissue cells transform into cartilage cells which are grouped into a cartilage anlage or model of the future long bone. A periosteal bone collar then appears. This bone which formed directly from osteogenic cells in the periosteal membrane is called periosteal bone and is a type of intramembranous bone. Next a center of calcifying cartilage develops which is soon entered by vascular mesenchyme which resorbs the calcified cartilage, and new bone is laid down toward both ends of the cartilage model. This is the beginning of endochondral or intracartilaginous ossification and is called the primary ossification center. As the endochondral ossification advances, the bone increases in length, and as intramembranous ossification progresses, the bone increases in width. Vascular mesenchyme again enters the cartilage model, this time at either end, and the cycle which took

place at the primary ossification center repeats itself. Calcified cartilage is resorbed, and new bone is laid down in the endochondral fashion, and secondary ossification centers are born. With the development of ossification centers at the extremities of the shafts, the four segments of tubular bones can be identified as epiphysis, physis (or growth plate), metaphysis (or zone of transformation of cartilage into bone), and diaphysis in reverse order of appearance.

The anatomic-histologic correlation of normal bone (13). The growing segmented bone has many different cell layers, two of which compose the epiphysis. Covering the epiphyseal ossification center is the articular cartilage which both replenishes joint cartilage which is worn away and increases the longitudinal diameter of the epiphyseal ossification center by endochondral bone formation. Immediately below these layers is a layer of reserve or resting cartilage which is the first of four cellular layers of the physis or growth plate. The resting cartilage acts as a supply of cells and is the precursor for the next zone of actively dividing cells, the proliferating or growth cartilage. The chondrocytes of the growth cartilage divide synchronously to form longitudinal columns of cells. When division ceases, the cells begin to mature by vacuolating and passive swelling, thus forming the vacuolating or hypertrophic cartilage. These cells die to become a thin layer of calcified cartilage which is invaded by vascular mesenchyme from the metaphysis. The dead cells are resorbed and lacunae are formed. The lacunae are soon populated by osteoblasts which form osteoid on which bone is laid, still in the longitudinal rows of the cartilage cells it

replaced. This is the metaphyseal layer of primary spongiosa. Internal osteoclasts remodel the longitudinal bone into cancellous bone, and external osteoclasts marrow the wide metaphysis. This area of remodeling is the zone of secondary spongiosa which rests on the diaphysis. The purpose of the entire process described above is to lengthen the diaphysis which is defined at both ends by the extent of compact bone formation.

The bone histopathology in CHH. According to Rubin, the primary defect in bone formation in the metaphyseal dysostoses (There are four generally recognized varieties--types Janses, Schmid, and Spahr, and cartilage-hair hypoplasia. Rubin speaks more specifically about type Jansen than the others but tends to generalize.) is failure of hypertrophic cartilage in the physis. (13). For some unexplained reason the hypertrophic or vacuolated cartilage persists and there is inability of endochondral bone formation beyond this stage. Rubin notes that from the time endochondral bone formation begins in the fetus until endochondral bone growth ceases, there is an enzyme system for glycolysis in cartilage which is similar to that in muscle. The appearance of this enzyme system coincides with hypertrophy, and the presence of glycogen is preparatory for disintegration. Due to an inhibition or deficiency of the enzymes of the glycolytic cycle which interfere with the progression beyond the hypertrophic stage, calcification of cartilage is impaired. Growth of the cartilage plate is delayed, but appositional and interstitial processes continue. Since the primary block is at the level of vacuolated cartilage which interferes with vertical growth, and since appositional or

horizontal growth continues normally, flaring of the metaphyses is expected, and the irregular cystic defects represent uncalcified collections of dilated cartilage cells. The absorptive processes in the calcified cartilage zone of the physis are not called into play since the sequence of events has not yet reached this stage. Thus, the normal funnelization or remodeling at the metaphysis is lacking mainly as a secondary event and the metaphyses are clubbed. The interstitial bone which does form is normal (13).

Whether the cartilage-hair hypoplasia type of metaphyseal dysostosis fits exactly into Rubin's general model is questionable on the basis of McKusick's examination of the costochondral junction in one five-and-one-half-year-old Amish boy (10). Since this examination is the only histologic study of cartilage in an individual affected with the cartilage-hair syndrome, speculation must also arise as to whether this single example is representative of the disorder. It must be remembered, too, that Rubin speaks of changes in the physis while McKusick cites those seen in the costochondral junction.

The one biopsy specimen studied by McKusick showed a relative paucity of cartilage cells thruout the specimen and failure of those chondrocytes present to form orderly columns. The cartilage cells did not reach the zone of ossification in adequate numbers or in a fully developed hypertrophic condition, resulting in defective ~~endochondral~~ ossification. The bone which did form was normal bone with osteoblasts in abundance and probably adequate osteoclastic activity. Because of the abnormality of cartilage present, McKusick's conclusion was that hypoplasia of the cartilage was the main fault.

He also believed that microscopically the costochondral junction he studied could not be distinguished from a true achondroplastic junction and that the activity of the cartilage correlated well with that of an individual in whom growth had been completed.

Rubin and McKusick each agree that the defect in the metaphyseal dysostoses, including cartilage-hair hypoplasia, is one involving physeal cartilage, Rubin placing it primarily in the zone of hypertrophic cartilage, and McKusick placing it in the zone of proliferative cartilage. Both may be correct.

Since cell division and columnization are present in the zone of proliferation, and both these are relatively absent in McKusick's affected costochondral junction, it might be implied that the primary defect lies in that zone. This is true in classical achondroplasia and similar syndromes only, according to Rubin, and these are radiologically quite unlike the metaphyseal dysostoses (13). No author will state that the ball-in-socket fit of a normal epiphysis into the cupped and widely flared but smooth metaphysis of the achondroplastic can be confused with the findings in the metaphyseal dysostotic individual. Rubin notes that the socket-like metaphysis occurs because of failure of interstitial or vertical cartilaginous growth with normal subperichondrial or horizontal growth at the edges of the physis or growth plate (13). Though an apparently similar finding (decreased interstitial with normal appositional cartilaginous growth at the growth plate) is seen in cartilage-hair hypoplasia, no cupping of the rough, scalloped metaphysis is found.

The reason for the smooth achondroplastic metaphysis is probably

because those cartilage cells which do proliferate, though few, also degenerate and form the zone of calcified cartilage which is physiologically changed to normal bone. The metaphyseal dysostotic metaphysis, on the other hand, is rough and cystic. Proliferation here is also delayed, but even more importantly, the chondrocytes do not progress normally from the vacuolated zone to the calcified zone. There is what appears to be a second delay. Some hypertrophic chondrocytes degenerate, and bone is laid down. Others appear as cystic areas among the scattered areas of calcification and ossification which form the upper limit of the layer of primary spongiosa.

The difference may well be that the primary defect in cartilage-hair hypoplasia truly is (as Rubin claims) in the zone of hypertrophic cartilage, and that if a defect does in fact exist in the zone of proliferative cartilage, it is of lesser importance, at least so far as radiologic findings are concerned.

That the roentgenologic appearance of the tubular long bones in the various metaphyseal dysostoses, including CHH, is similar is unequivocal. Likewise, there can be little doubt that the microscopic appearances are also similar. Type Jansen has been touched upon (5,13), and type CHH has been discussed (10,13). A biopsy has probably never been taken of a type Spahr physis (14). Dent and Normand describe the biopsy from a costochondral junction from a patient with type Schmid (4), noting that the cartilage was hypertrophied and showed excessive degenerative changes or vacuolization. There was no orderly parallel columnization of chondrocytes in the zone of provisional calcification. A fairly

abrupt transition of cartilage into well-calcified, lamellated bone with well-formed trabeculae and Haversian systems was described, and osteoblasts were plentiful. Little osteoid formation was present. The capillaries and osteoclasts between cartilage and bone seemed adequate.

The metabolic defect in the metaphyseal dysostoses has not yet been identified. Whether it has anything to do with an inhibition or deficiency of the enzymes of the glycolytic cycle as Rubin suggests remains speculative and unverified.

The hair histopathology. Normal hair and hair of unaffected siblings of cartilage-hair dwarfs has a pigmented core. This central pigmentation is lacking in the hair of dwarfs. Since the presence or absence of a pigment core seems to be related to hair diameter, the lack of pigment in the hair of affected persons may be a function of small hair caliber (10). The actual hair diameters have been previously presented.

GENETICS

Inheritance in this syndrome has been studied solely by McKusick (10) who identified seventy-seven cases in fifty-three sibships, all Amish. Maroteaux et al. described five cases in three sibships, two French and one Algerian (12). Langer has discovered three cases in two sibships, one Finnish and one Italian (10). One non-Amish United States case of German descent was reported by Beals (1) and another United States case by Irwin (6). A probable United States case was described by Burgert et al. (2). The total is eighty-eight cases in sixty-one sibships. Consanguinity

was present in most of McKusick's sibships and in Beals' sibship.

Thirty-one of McKusick's cases were males and forty-six were females. In all there are thirty-six males and fifty-one females, and one of unreported sex. The distribution of these dwarfs geographically and by sibship is seen in Table I on page seventeen.

The frequency of affected persons with Amish backgrounds, including some who have parents who have married out of the Amish society, is seventy-seven per fifty thousand base population or one to two per thousand (10). The frequency among non-Amish is, of course, miniscule.

Five affected males have married normal females and have sixteen unaffected offspring. One affected male has married an affected female, and three cartilage-hair dwarfs have been produced in this union. (10).

The occurrence of the cartilage-hair syndrome in a highly inbred population and the features of the familial pattern outlined above suggested an autosomal recessive inheritance pattern to McKusick. To test the likelihood of this hypothesis, segregation analysis was performed using the Lenz-Hogben or a priori correction. The number of affected individuals was significantly less than would be expected on the basis of the recessive hypothesis (72 observed as compared with 98.5 ± 6.8 expected), even when infant deaths were excluded from the analysis. Note that three of the seventy-seven cases had affected parents, and two others were only children.

McKusick presents several explanations for the above deficiency. Very unlikely is contamination of the Amish group by a significant number of cases of some sporadic mimicking condition. The deficiency

TABLE I. DISTRIBUTION OF CASES OF CHH

MCKUSICK'S AMISH CASES IN THE UNITED STATES

Holmes & Wayne Counties, Ohio

- 1. ○ ○ ○ ○ ○ ● ̄ ̄
- 2. ● ○ ○ ○ ○ ○ ●
- 3. ● ○ ○ ● ● ○ ○
- 4. ○ ○ ○ ● ○
- 5. ○ ○ ○ ○ ○ ● ○ ○ ○ ̄ ̄ ̄
- 6. ○ ●
- 7. ● ○ ●
- 8. ● ○
- 9. ○ ○ ○ ○ ○ ○ ● ○ ○ - ○ ○ ̄
- 10. ○ ○ ● ○ ○ ○ ○ ●
- 11. ○ ○ ○ ○ ○ ○ ○ ● ○ ○
- 12. ○ ● ○ ● ○
- 13. ○ ○ ○ ● ○ ○ ○ ○ ○ ○ ●
- 14. ● ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ̄
- 15. ● ● ●*
- 16. ○ ○ ○ ○ ○ ○ ○ ● ○
- 17. ○ ○ ○ ○ ○ ○ ○ ○ ● ○ ○ ̄
- 18. ○ ○ ○ ○ ○ ● ̄
- 19. ○ ○ ● ○ ○ ○ ○ ○ ○ ○ ̄ ̄
- 20. ● ○
- 21. ● ●

Lagrange & Elkhart Cos., Ind.

- 22. ○ ● ○ ○ ○ ● ● ○
- 23. ● - ○ ○ ○ ○ ○ - ○ ○ ○ ○
- 24. ● ● ○ ○ ○
- 25. ○ ○ ○ ○ ● ○ ̄ ̄ ̄ ̄
- 26. ○ ○ ○ ○ ○ ● ○

Lancaster County, Pa.

- 27. ○ ○ ○ ○ ○ ○ ● ○
- 28. ● ○ ● ○ ● ○ ●
- 29. ○ ○ ● ○ ● ○
- 30. ● ○
- 31. ●
- 32. ○ ○ ○ ●
- 33. ○ ○ ○ ○ ● ○ ○ ○ ○ ○
- 34. ○ ○ ○ ○ ○ ○ ● ○ ̄ ̄ ̄ ̄
- 35. ○ ○ ● ○ ○ ○
- 36. ○ ○ ○ ○ ○ ● ○ ○ ○ ○ ○

Amish Elsewhere in U. S.

- 37. ○ ○ ● ●
- 38. ● ○ ○ ○ ○
- 39. ○ ○ ● ○ ○ ● ○ ○ ○ ○ ○ ○ ○ ○
- 40. ○ ● ○ ● ● ○
- 41. ● ○ ○ ○ ○
- 42. ○ ● ○ ●
- 43. ● ○
- 44. ● ○ ○ ○
- 45. ○ ○ ● ○ ○ ○ ● ○ ○ ○ ○ ̄ ̄
- 46. ○ ●
- 47. ○ ○ ● ●
- 48. ○ ○ ○ ○ ○ ○ ● ○
- 49. ● ̄ ̄
- 50. ○ ○ ○ ○ ○ ○ ●
- 51. ○ ○ ○ ● ○
- 52. ○ ○ ● ○ ○ ○ ○
- 53. ● ○ ○ ○ ○ ○

MAROTEAUX'S CASES

- 54. ○ ● ● ○ ● ○ Algerian, background unknown
- 55. ● ○ French, background unknown
- 56. ● French, background unknown

IRWIN'S CASE

- 57. ●+ United States, background unknown

BEALS' CASE

- 58. ○ ● United States, German descent, locale unknown

LANGER'S CASES

- 59. ● ●+ Finland, background unknown
- 60. #+ Italy, background unknown

BURGERT'S CASE

- 61. ●+ United States, background unknown

KEY: ● female, affected ̄ ̄ infant deaths, ? affected / dead
 ○ male, unaffected ○-○ dizygotic twins * both par-
 # sex unknown, affected + other siblings may exist ents affected

is too great to be explained by new dominant mutations, and a masquerading recessive disorder would produce an excess rather than a deficiency. Explanations which can neither be proved nor disproved but are equally unlikely are non-random chromosome segregation in the first meiotic division of oogenesis such that the chromosome carrying the mutant gene more often passes into the polar body (meiotic drive) and differential success of sperm bearing the cartilage-hair hypoplasia gene in effecting fertilization of the ovum (gametic selection). Also to be considered is that some homozygotes are aborted or die in infancy before the disorder is recognized. This possibility must be considered in view of the susceptibility to chickenpox and the prevalence of sprue-like conditions, both of which are known to have caused death in affected children. Though the cartilage-hair dwarf is usually recognized at birth, and an increased miscarriage rate probably does not occur, the existence of unrecognized deceased homozygotes cannot be excluded.

The most likely explanation for the deficiency is thought to be reduced penetrance. Previously presented have been the wide range of heights and hair diameters of affected dwarfs, both blending into the range of low normal. McKusick gives some examples. As noted, there is one sibship in which both parents are obviously affected. Yet their three offspring were all reported to be normal or near normal until xrays revealed typical skeletal findings and hair caliber determinations were found to be in the affected range. Environmental as well as hereditary factors are known to influence expressivity and therefore penetrance, but this family suggests the latter, i.e., that segregation of non-allelic genes is operating to

reduce expressivity in the three children as compared with their parents. Another family of eleven siblings contains one typical dwarf and one thirty-five-year-old female who, though sixty-two inches tall, is suspected to be homozygous for the CHH gene because her hair is very thin and measures but 0.032 millimeters in diameter, her hands are short and pudgy, and her contracted pelvis has caused many obstetrical difficulties.

McKusick further advances two hypothetical explanations for the observed reduced penetrance. The genetic defect may be such that the homozygote has an unusually high requirement of some normal dietary constituent. In the cartilage-hair hypoplasia homozygotes in whom penetrance is incomplete, this requirement may have been met, at least in part. The precedent here is vitamin D-resistant rickets. Or the clinical defect may become manifest only when the homozygous individual is exposed to some adverse environmental factor. Here the precedent is favism or primaquine sensitivity. For the latter to be occurring in the cartilage-hair syndrome, the environmental factor would have to be extremely widespread but not ubiquitous, or it would have to vary in strength. These explanations are unlikely.

"It is possible that even with full pre-pubertal x-ray studies and with hair measurements all affected persons cannot be identified"(10). X-ray and hair diameter studies were done on the ten clinically normal siblings of one of McKusick's affected dwarfs, and both examinations were interpreted as being normal in all.

Considering that CHH is an autosomal recessive trait with reduced penetrance, penetrance has been estimated to be about seventy

per cent. Penetrance may be influenced by sex, since thirty-six males and fifty-one females have been reported.

Assuming fifty thousand as the Amish base population and penetrance as seventy per cent, a gene frequency of about one in twenty is derived. McKusick feels this is a minimal estimate because the environmental and/or genetic factors affecting penetrance are probably concentrated in certain families where offspring of two heterozygous parents, though homozygous for the CHH gene, might appear in every way normal.

Birth order does not affect the occurrence of cases (10). See Table I on page seventeen.

Heterozygotes are not clinically distinguishable from normal individuals. The possibility exists, though, that those individuals with hair diameters in the borderline range may be heterozygous (10).

The Amish live in a rural, theocratic society which is virtually closed to outsiders and which practices Meidung or shunning of excommunicated members. The sect originated in the Canton of Berne, Switzerland, in 1693, and converts were acquired in Alsace, Lorraine, the Palatinate, and neighboring areas of southern Germany and eastern France. Migration to the United States began in about 1720 and continued in waves until about 1850. No practicing Amish remain in Europe. Genealogic records are excellent (9,11).

Greater than two-thirds of parents of affected children trace their ancestry to a John Miller who was wounded by Indians in 1757 and to his wife Catherine Hochstetler. More than seventy per cent of parents trace their ancestry to Jacob Hochstetler who may have been a brother to Catherine and was almost certainly a close

relative. Catherine or Jacob Hochstetler or both appear in the ancestry of eighty per cent of fifty of McKusick's fifty-three sibships. Genealogic tracing was not performed on three sibships. The possibility exists that more than one immigrant was heterozygous for the postulated recessive CHH gene, but either Catherine or Jacob Hochstetler or both were most probably carriers. (10).

The mean coefficient of consanguinity has been determined by McKusick to be 0.0074 which is the equivalent of each parental pair being related as second cousins once removed (10).

There can be little doubt that the fitness of affected dwarfs is less than normal. Only six of twelve affected males and two of ten dwarfed females over the age of twenty-five years have married. Survival is somewhat affected by disease, since eleven of the eighty-eight known cases died under the age of twenty years, and in all, twenty are deceased. Affected individuals are subject to severe bouts of chickenpox and to life-threatening abdominal disorders. Cesarean section is probably necessary for childbirth. Yet two affected females have lived to be seventy-six years of age (10).

DIFFERENTIAL DIAGNOSIS

Differentiating the cartilage-hair hypoplasia from other similar disorders is not easy. Since the diseases which must be distinguished from cartilage-hair dwarfism have, for the most part, no proven metabolic defects, the laboratory is of very little help. Differentiation among disorders must therefore utilize the clinical (including genetic) and roentgenological findings which have been discussed. Rubin's classification of bone diseases, though a gross oversimplification, is a valuable tool. However, the inherent

difficulty in devising any classification at this stage in our understanding of the osseous dysplasias is that it cannot be based on the underlying metabolic disorders, and other more imprecise parameters must be used. (Rubin utilized mainly radiological techniques.)

Unfortunately, not all diseases present in their classical forms (some genetic reasons for this variability have been described), and the diseases of bone are not exceptional in this regard. Those cases exist which cannot be placed in any well-defined category by present methods. These less classical cases might be thought of as falling somewhere in either "tail" of the bell-shaped distribution of their respective disease categories where they often blend with the "tails" of the curves of other disease distributions. Because a differential diagnosis is an attempt to clearly separate various disease entities, it does not lend itself well to such gray areas. For this reason the following discussion will be regretfully but necessarily dogmatic.

Differentiation from the metaphyseal dysostoses. The remaining three recognized types of metaphyseal dysostosis are probably most easily confused with cartilage-hair hypoplasia. In all these entities the dwarfism results from shortened extremities.

Type Jansen. Type Jansen is considerably more severe than cartilage-hair hypoplasia and is relatively more rare, only six cases having been described (10). No two have been found in one family, and whether genetic transmission exists is not known (7). The radiological changes of metaphyseal dysostosis can be found in almost all bones except the vertebrae (5). More adjacent metapathy-

seal bone is involved than in the three other varieties, and the metaphyses flare more widely (13). The height is markedly reduced and is probably always under forty-eight inches (5). The skull is abnormally shaped. Its base is shortened (platybasia), and cranio-stenosis may be present. The facies are strange (13). Mental and motor retardation are universal as are decreased muscle mass and multiple flexion deformities (1). Abnormal laboratory findings such as hypercalcemia, hypophosphatemia, and hyperphosphatasemia are probably common (5).

Type Schmid. The Schmid variety is much more similar to cartilage-hair hypoplasia than is the Jansen type (7). Intelligence is normal, and the dwarfism is mild. Radiologically, the same bones are disturbed by the dysostosis of Schmid ^{and} CHH. However, there is assymetrical involvement at the distal femur in the Schmid type with more striking changes medially leading to extreme bowlegs or genu varum (4). Mild femoral bowing and coxa vara are also common. The fibula is not lengthened disproportionately distally as compared to the tibia, and therefore the ankles are not deformed as in cartilage-hair dwarfism (10). The fingernails are not as short as in CHH owing to less shortening of the terminal phylanges. There are no reported obstetrical complications in the delivery of pregnant Schmid females (4). The Schmid type of metaphyseal dysostosis is thought to be hereditarily determined as an autosomal dominant though the existence of frequent sporadic cases suggests the possibility of a high mutation rate (7, 10).

Type Spahr. The Spahr form of metaphyseal dysostosis has been described in but one family and appears similar to the Schmid variety

in every respect except that it shows an autosomal recessive pattern of inheritance (7, 14).

From classical achondroplasia. Achondroplasia is the disease probably most often confused with the metaphyseal dysostoses. It, too, is a physeal dysplasia with shortened limbs, but the primary defect is failure of proliferative rather than hypertrophic cartilage according to Rubin (13). Achondroplasia is termed a rhizomelic dwarfism, indicating that the shortening is proximal, i.e., at the shoulders and the hips. (Cartilage-hair hypoplasia is mesomelic in that the greatest shortening takes place in the middle joints of the extremities) (13).

Histologically, the differentiation may be difficult as previously noted, but radiologically the epiphyseal "ball" in the metaphyseal "socket" is usually an obvious dissimilarity (3, 7). Metaphyseal flaring is also greater than in cartilage-hair dwarfism (13). Bones other than the long bones reveal changes not seen in the CHH syndrome. There is impaired development of the chondrocranium or base of the skull with disturbed development of the membranous bones that constitute the calvarium (13). The foramen magnum may be markedly shortened in the anteroposterior dimension because of early union of the four primary ossification centers at the base of the skull, leading to a prominent brachycephaly or foreshortening of the base of the skull (10, 13). There may be an absolute increase in skull size secondary to an internal or communicating type of hydrocephalus due to lack of interstitial cartilaginous growth at the intersphenoid and spheno-occipital synchondrosis (13), and thus there is an anatomical explanation for the

reduced intelligence which is the rule in achondroplastics (15). Still, there is suggestive evidence that true megencephaly exists as a non-skeletal effect of the achondroplastic gene (7). The head bulges, the nose sports a scooped-out or saddled bridge, and the jaw protrudes (15).

Very early there is excessive cartilage separating the vertebral ossification centers, and on anteroposterior x-ray views the lumbar interpeduncular distances show caudad tapering leading to narrowing of the spinal canal rather than the usual widening seen in normal individuals (7, 13). This stenosis of the spinal canal has been shown to be due to lack of growth of the pedicles. In adulthood, wedge lumbar vertebrae causing a lumbar gibbus are often noted. But more importantly, a severe lordosis results from horizontal tipping of the sacrum on the spine causing rupture of intervertebral disks and leading to the most common complication of adult achondroplasia--nerve root pressure with paraplegia and loss of bladder control (13).

The iliac wings are shortened, and the sacroiliac groove is notch-like (10). Cesarean section is always necessary for delivery of normal-sized babies (10). The inferior angle of the scapula is squared off (10). Neither the pelvis nor the scapulae are notably involved in cartilage-hair hypoplasia.

The fibula is longer than the tibia as in CHH, but its length is due to overgrowth proximally rather than distally (10). In younger individuals the fingers are pudgy, especially proximally, giving rise to a characteristic "trident hand" when the fingers are maximally adducted (13).

The hereditary pattern is autosomal dominant although approximately seven-eighths of all cases are new mutations (7). A few poorly documented reports of recessive inheritance exist.

From spondylo-epiphyseal dysplasia (Morquio's disease, SED). This entity is a chip from the polymorphous block which was once thought to be achondroplasia. However, it is an epiphyseal dysplasia, and the primary defect is in the formation of articular cartilage (13). Furthermore, it is primarily a dwarfism of the short-trunked variety. Infants are thought to be normal until about one year of age when they begin walking and the bony abnormalities become apparent (13). The ligaments and muscles are relaxed giving a peculiar flaccidity to the joints. Osseous malformations affect mainly the spine and the epiphyses of the tubular bones as the name implies but completely ignore the skull (13).

Roentgenological changes are usually not recognized until after twelve months (13). The ossification centers of the larger epiphyses fragment shortly after this time and appear as separate centers. All epiphyses are irregular and flattened. Though the long bones are shortened moderately (in contrast to the gross retardation of arms and legs in the cartilage-hair syndrome), the spine is severely shortened, and changes there are pathognomonic (13). The outlines of all the bodies and processes are indistinct and irregular. Vertebrae plana or flattening of the vertical dimension is universal. The widths of the intervertebral disks are eventually reduced, and all of the above abnormalities combine to create a thoracic roto-scoliosis (13). The odontoid process is hypoplastic as are the vertebrae at T-12 and/or L-1 (13). The latter leads to a thoraco-

lumbar kyphosis.

Wide "canoe-paddle" ribs are seen (13). There are minor irregularities in the development of the pelvis. Genu valgum and flatfoot are common and together with the spinal changes cause a duck-like waddling gait. The muscle strength is diminished without apparent muscle mass atrophy (13). Early osteoarthritis, especially of the hips and other weight-bearing joints is universal (10). Survival beyond childhood is rare (10).

From the pseudoachondroplastic form of spondylo-epiphyseal dysplasia.

A combination of shortened trunk and limbs, this entity is also not discovered until the age of one or two when the child begins to walk with a waddle. It is an epiphyseal dysplasia with the primary defect in the formation of articular cartilage as is SED. Though the skull is normal and the spinal and tubular^{bone}/changes are like those of spondylo-epiphyseal dysplasia, there are similarities to achondroplasia. The syndrome is thus a phenocopy of the achondroplastic genotype though the actual genotype is probably that of spondylo-epiphyseal dysplasia (13).

The spine is not nearly so affected as in SED, but the tubular bones are more severely shortened, and though the articular changes of SED are radiologically present, the shortness and stockiness of the bones resemble those of achondroplasia. The hands are small and the fingers are chubby. The round bones of the wrist and ankles are wide and stubby. Vertebrae plana, as in Morquio's disease, is present but to a lesser extent. A lumbar lordosis is present. Although late complications are neurological in achondroplasia, they are arthritic in the pseudoachondroplastic form of SED, as in spondylo-epiphyseal

dysplasia itself (13).

From multiple epiphyseal dysplasia (MED). This epiphyseal dysplasia, once consistently diagnosed as achondroplasia, is primarily a failure of the ossification of epiphyseal centers resulting in stippled epiphyses, rather than fragmentation as seen in spondylo-epiphyseal dysplasia (13). Multiple epiphyseal dysplasia is usually noted to be present from birth. In contrast to Morquio's syndrome, shortening of the extremities rather than the spine causes the shortness of stature, i.e., the dwarfism is of the short-limbed variety.

The long tubular bones are shortened and stubby, but the round bones and short tubular bones are affected to a lesser degree though the hands are pudgy. Minimal stippling is seen in the ischia and pubic bones, the anterior ends of the ribs, the sternum, and the distal scapulae. The skull is not affected. Since the vertebral bodies simulate epiphyses in some developmental aspects, one would expect to see them stippled. Particularly in the sacrum this is seen (13). The wrists and ankles are markedly stippled.

Many of those affected with MED are stillborn (7). Half of the living cases develop cataracts (15). More than half die within the first year of overwhelming secondary infection (15).

Flexion deformities of the knees and elbows are very frequent (15). There is pain and stiffness in the knees and hips, and osteoarthritis of the weight-bearing joints in later life is a rule to which there are no exceptions (7, 15).

From the pseudoachondroplastic form of multiple epiphyseal dysplasia.

As implied, this syndrome is also a phenocopy. Affected people are stunted rather than being true dwarfs (13), and the shortening is in

the limbs rather than the trunk. The lower extremities are more severely affected than the upper extremities. Children are thought to be normal at birth but by school-age are brought to the physician because of waddling gait, bowlegs, knockknees, or shortness of stature. Epiphyseal nuclei are found to be irregular, but articulation remains good because the defect is one of poor ossification of the epiphyseal centers and because the articular cartilage is probably normal (13).

From chondroectodermal dysplasia (Ellis-van Creveld syndrome, EvC).

Rubin classifies this syndrome as a physeal dysostosis due to a defect in ectodermal and mesenchymal developmental tissues (13). Its findings, too, were once incorrectly thought to represent achondroplasia.

The abnormalities of the condition are: 1) chondro-osseous defects characterized by shortening of the tubular bones which is greatest distal to the knees and elbows in contrast to both achondroplasia (proximal) and cartilage-hair hypoplasia (middle) (13), erosive changes of the superolateral tibiae producing knockknees (13), bilateral supernumerary sixth metacarpal and digit (9), fusion of the capitate and hamate (9), and extreme hypoplasia of the digits with progressive shortening of the more distal phalanges (13); 2) ectodermal defects including dentia tarda with production of small, defective, irregularly spaced, cone-shaped, malocclusive teeth, small, deformed or absent nails, and hypotrichosis of the scalp (13); and 3) mesodermal defects represented by congenital heart disease, most commonly single atrium, and occasional strabismus, presumably from poor development of the eye muscles (13). The syndrome is

noted from birth.

Roentgenograms of the skull, thoracic cage, and vertebrae have been normal, but minimal pelvic and mandibular changes have been described (9). Articulation thru affected joints is abnormal because of the dysplastic changes of the epiphyses and articular cartilages as well as the mechanical problems created by the chondro-osseous defects, but degenerative arthritis has not been a feature of the disease (13).

McKusick has discovered forty-nine cases in thirty Amish sibships living presently or previously in Lancaster County, Ohio (9). All parents of EVC dwarfs have ancestral ties with Samuel Koenig and his wife who immigrated in 1744. Of the forty-nine Amish cases, thirty-two are dead, most of them presumably from cardiac anomalies.

From hypophosphatasia. This metaphyseal dysplasia and those diseases whose descriptions follow are consistently noted to produce abnormal laboratory findings in contradistinction to the conditions discussed above. In the case of hypophosphatasia there is an inborn metabolic error evidenced by persistently low serum alkaline phosphatase levels resulting from a pathological process presumably localized to the proliferating osteoblasts or hypertrophic chondrocytes (13). Urinary excretion of phosphoethanolamine (possibly a precursor to alkaline phosphatase) is elevated, supposedly because of inadequate supplies of phosphatase to hydrolyze its ester-phosphate bond. Severely affected individuals invariably have elevated serum calcium levels (13). The primary anatomic defect is a failure to form primary spongiosa because of poor calcification of osteoid (13).

In hypophosphatasia the time of discovery of the disorder is a fair clinical indication of its severity. Death is common if hypophosphatasia is noted within six months of birth. Up to two years failure to thrive is a usual presenting complaint, and the gastrointestinal symptoms of vomiting, anorexia, and constipation are often mentioned. From two until the onset of puberty the survivors are found to be healthy but present with such orthopedic problems as unusual gait, painful extremities, of short stature (15).

The radiographic findings in only the more severely affected cases need be of concern in the differentiation of hypophosphatasia from cartilage-hair hypoplasia. Long and short tubular bone films reveal wide epiphyseal-diaphyseal separations due to decreased calcification of the epiphyses and virtual absence of the zone of provisional calcification. The metaphyseal area is radiolucent, often irregular and frayed, and poorly calcified. The diaphysis is normal to decreased in calcification and diameter (13). The round bones of the ankles and wrists are slow to develop but are normal. The pelvis in the newborn appears like that of a premature infant but, except for defects at the iliac crests, seems normal later (13). Vertebral development is slightly retarded but is not unusual in other respects. The skull at first appears to be composed of floating islands of bone. The general radiological picture may be summed up as one of hypomineralization (13).

If survival of the first year occurs, craniostenosis or premature closure of the sutures is not infrequent, and mental retardation occurs (15). Early loss of the deciduous teeth is the rule (15). Pathologic fractures, especially at the metaphyses, are common (15).

From calcium-deficiency or rachitiform diseases of any cause. These conditions are classified by Rubin as metaphyseal dystrophies with exogenous defects causing inadequately calcified spongiosa (13).

Of all the diseases causing dwarfism, vitamin D resistant rickets (low serum phosphorus, increased alkaline phosphatase, and negative urinary Sulkowitch test for calcium) may well be the most common (15). Simple nutritional avitaminosis D (usually low serum phosphorus and increased serum alkaline phosphatase) is comparatively rare as are those cases of rickets in which there is a primary metabolic rather than an environmental defect such as renal tubular acidosis (metabolic hyperchloremic acidosis, alkaline or barely acid urine, poor urinary concentration, low serum phosphorus and potassium levels, and increased alkaline phosphatase) and Fanconi's syndrome (generalized aminoaciduria, renal glycosuria, and renal hypophosphatemia) (15).

Rarely are these conditions noted before six months of age (15). They must begin relatively early to be confused with cartilage-hair hypoplasia, and at early ages the roentgenological picture in the different rachitic disorders is similar no matter what their etiologies may be. The epiphyseal ossification centers become less well defined and smaller, and the metaphyses appear widened, cup-shaped, poorly defined, and frayed (13). The physes appear widened. These changes are best seen about epiphyseal plates which are exhibiting the greatest rate of growth such as the distal femur and proximal tibia. The diaphyses show demineralization which gives them a ground-glass appearance, and moderate to severe bowing of the weight-bearing long bones usually results (15).

The rachitic syndromes, like hypophosphatasia but unlike all other conditions discussed (including CHH), respond to proper medical treatment.

In none of the diseases which may clinically mimic cartilage-hair hypoplasia is fine, silky hair of small diameter a part of the syndrome.

As previously mentioned, the differential diagnosis presented does not and was not intended to describe any but the more common or confusing syndromes which might potentially masquerade as cartilage-hair hypoplasia. Unfortunately the dwarf who presents himself to the practitioner does not always fit into one of the classical syndromes because of environmental and/or genetic alterations. He may be a tarda form or simply a variant of the "text-book case". Furthermore, he may present himself after growth and development are complete and when the radiographic and histologic findings are less useful as diagnostic tools. The physician must then rely mainly on his clinical acumen and the age-old history and physical examination to establish the diagnosis.

TREATMENT

No treatment for cartilage-hair hypoplasia is presently available. McKusick and Mariteaux et al. have reported separate cases which did not respond to high doses of vitamin D (10, 12). Normand and Dent have mentioned three cases of type Schmid metaphyseal dysostosis which showed healing of the metaphyseal lesions during prolonged periods of bedrest (4). One five-year-old girl demonstrated a striking return to normal of all metaphyses after a three-month period of complete inactivity. However, the metaphyses

reverted completely to their original appearances when bedrest was discontinued. Long-term immobilization has not been tried with cases of cartilage-hair hypoplasia. Even if bedrest produced changes in cartilage-hair hypoplasia which were identical to those already produced in the Schmid type of metaphyseal dysostosis, it is quite possible that the inactivity would have to be maintained until closure of the epiphyses for it to be of therapeutic benefit, and there are obvious serious drawbacks to such a program.

SUMMARY

Cartilage-hair hypoplasia is an extremely rare, hereditary, congenital, short-limbed variety of dwarfism. Interestingly, scalp and body hair is also involved and is usually found to be blond, silky, slow-growing and small in caliber. Malabsorption is seen often enough that it is suspected to be a part of the syndrome. There is an unusual susceptibility to chickenpox.

The basic metabolic defect is not known. Abnormal laboratory values are uncommon. Radiologically the osseous defect occurs at the physis and is indistinguishable from the lesion seen in metaphyseal dysostosis. Costochondral biopsy suggests that the primary abnormality is a failure of hypertrophic cartilage although this conclusion is not unquestionable. Inheritance is thought to be by autosomal recessive transmission with reduced penetrance playing a part. No treatment is available.

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