The differential diagnosis of the short-limbed dwarfs presenting at birth

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Summary

Attention is drawn to the fact that in a number of types of short-limbed dwarfism a precise diagnosis can be made in the neonatal period. Examples are given and the prognostic and genetic implications are discussed. It is important to be able to advise parents of the likely outlook for the infant and of the genetic implication. Early diagnosis is therefore not merely an academic exercise.

Introduction

When Rathbun (1948) first described neonatal hypophosphatasia he discussed three conditions of differential diagnosis. These consisted of osteogenesis imperfecta, achondroplasia and renal hyperparathyroidism. Since then a number of other conditions have been defined on a clinical, radiological and genetic basis (Tables 1 and 2). Such conditions are not excessively rare if sought. Ryan and Kozlowski (1971) found nineteen cases of bone dysplasia in consecutive radiographs of 109 infants dead on delivery. When a case of neonatal hypophosphatasia occurred in the authors' unit they were able to include thirteen conditions in the differential diagnosis. They are here described together with prognosis and genetic implications.

Achondroplasia

Achondroplasia is the prototype of true bone dysplasia (Rubin, 1963) and it is the best described form of neonatal dwarfism. Its incidence per one million people was found to be fifteen in the United States (Potter and Coverstone, 1948), twenty-three in Denmark (Mørch, 1941) and 283 in Northern Ireland (Stevenson, 1957). It is inherited as an autosomal dominant but over 90% of cases are fresh mutations especially with elderly parents (Barr and Forfar, 1973). Harris and Patton (1971) in their series found that the mutation rate was not greater than 1 in 100,000. Its incidence in twins is extremely rare.

Clinically the condition may be recognizable at birth but often it is not, as the features of proximal limb shortening, large head, depressed nasal bridge and prominent forehead may be poorly developed.

Harris and Patton (1971) reviewed seventeen still-born or early neonatal deaths originally diagnosed as achondroplastics and showed that in ten of these cases the diagnosis should have been thanatophoric dwarfism. This supports the view that achondroplasia has been over diagnosed at birth and that the severely affected cases are, in fact, some other type of lethal neonatal dwarfism.

Achondrogenesis

This was first described under the title of anosteogenesis (Parenti, 1936) as it was thought to be a variety of osteogenesis imperfecta. Fraccaro (1952) first used the term 'achondrogenesis' because of marked retardation of ossification. Parental consanguinity (Saldino, 1971) and multiple affected siblings (Houston, Awen and Kent, 1972) have been reported. The role of teratogenic agents is speculative as a case of achondrogenesis following maternal thalidomide ingestion has been described (Jurczok and Schollmeyer, 1962). Hydramnios is a frequent complication of the pregnancy and achondrogenic infants are usually premature and stillborn. It is a rare condition and is characterized at birth by extremely short limbs, large head, swollen abdomen, poor ossification of bones generally and essentially no neck (Fig. 1). Harris, Patton and Barson (1972) described two siblings under the title of 'pseudo-achondrogenesis with fractures' which is representative of a different type of achondrogenesis and resembling the siblings described by Houston *et al.* (1972). This particular variety is now known as 'Harris and Houston' type of achondrogenesis (Fig. 2). The presence of fractures is the point of differentiation between the two types of this condition.

Asphyxiating thoracic dystrophy

Jeune, Béraud and Carron (1955) first described this condition. It is characterized by extremely short ribs, variable degree of shortening of limbs and fingers and occasionally by polydactyly. The thorax is narrow and immobile. Hereditary nephritis leading to death has been reported (Shokeir, Houston and Awen, 1971).

TABLE 1. Clinical differences

Type	Family history	Antenatal	Part of limbs involved	Associated abnormalities	Inheritance
Achondroplasia (mutant)	—	—	Proximal	Enlarged head, depressed nasal bridge, hands and feet short and broad	Autosomal dominant
Achondrogenesis	Parental consanguinity	Hydramnios stillbirth	Both proximal and distal	Large head, essentially no neck, swollen abdomen	Autosomal recessive
Asphyxiating thoracic distal	—	—	Distal	Extremely short ribs, narrow and immobile thorax, polydactyly, hereditary nephritis	Autosomal recessive
Chondrodysplasia punctata	—	—	Proximal and distal	Flexion contracture of joints, cataracts, ectodermal changes, mental deficiency	Autosomal recessive
Chondro-ectodermal dysplasia (Ellis-Van Creveld syndrome)	—	—	Distal	Thoracic dystrophy, polydactyly, congenital heart, ectodermal changes	Autosomal recessive
Diastrophic dwarf	—	—	Distal	Marked talipes equinovarus, resembles arthrogryposis, 'hitch-hiker' thumb	Autosomal
Homozygous achondroplasia	Both parents achondroplastic	—	Proximal	Large head, depressed nasal bridge, frontal bossing, early death	Autosomal dominant
Hypophosphatasia	Parental consanguinity	X-ray diagnostic	Proximal and distal	Soft skull bones, marked angulation and deformities of long bones	Autosomal recessive
Lymphopenic agammaglobulinaemia with short-limbed dwarfism	—	—	Proximal	Features of achondroplasia, lymphopenia, agammaglobulinaemia, early death	Not known
Metatrophic dwarf	—	—	Proximal and distal	Long narrow thorax, caudal appendage, swollen joints	Autosomal recessive
Osteogenesis imperfecta	Blue sclera	X-ray diagnostic	Proximal and distal	Soft skull, blue sclera	Autosomal dominant recessive
Spondylo-epiphyseal dysplasia congenita	—	—	Proximal and distal	Myopia, retinal detachment, cataract, cleft palate	Autosomal dominant
Thanatophoric dwarf	Parental consanguinity	Hydramnios, weak fetal movements, stillbirth, X-ray diagnostic	Proximal	Redundant skin folds, limbs abducted and externally rotated, large head with frontal prominence	Autosomal recessive

TABLE 2. Radiographic differences

Type	Spine	Limbs	Pelvis	Thorax, ribs	Skull
Achondroplasia (mutant)	Narrow interpedicular distance of lower lumbar vertebrae	Proximal bones short, ball and socket appearance of metaphyses	Narrow sacrum and sciatic notch	Thorax long and narrow	Large vault, small base and foramen magnum
Achondrogenesis	Poorly mineralized and ossified	Marked shortening, poorly mineralized	Poorly mineralized	Short ribs, clavicles disproportionately long	Poorly mineralized, otherwise normal
Asphyxiating thoracic dystrophy	Normal	Variable shortening	Hypoplastic iliac hook-shaped sciatic notch	Extremely short horizontal ribs	Normal
Chondrodysplasia punctata	Punctate calcifications of intervertebral discs	Both proximal and distal shortening, punctate calcifications of joint capsules and epiphyses	—	Normal	Craniostenosis
Chondro-ectodermal dysplasia (Ellis-Van Creveld syndrome)	Normal	Short distal bones, hypoplastic terminal phalanges, carpal and tarsals fused into solid masses	Reduced height of bones	Short ribs	Normal
Diastrophic dwarf	Hypoplastic cervical vertebrae	Hypoplastic first metacarpal	Acetabular dysplasia	Long thorax	Normal
Homozygous achondroplasia	Flattening of vertebrae	Markedly short	Small iliacs	Short ribs	Large, small base
Hypophosphatasia	Normal	Appearance of severe rickets	Normal	Marked costochondral beading	Little or no bone material
Metatrophic dwarf	Flat vertebrae	Metaphyses markedly flared, enlarged and irregular	Crescent-shaped iliac crests	Long thorax, short ribs	Normal
Osteogenesis imperfecta	Shallow vertebrae	Thick-thin bones, stunted, deformed	Normal	Deformities	Poorly ossified
Spondylo-epiphyseal dysplasia congenita	Hypoplastic odontoid	Short, bowing of femora	Small iliac wings	Bell-shaped thorax	Normal
Thanatophoric dwarf	Flat vertebrae, deep discs	Markedly short, bowing of femur	Short iliacs	Short ribs, wide anterior ends	Enlarged, short base, premature fusion of coronal and lambdoidal sutures

Chondro-ectodermal dysplasia

This condition was described in 1940 by Ellis and Van Creveld. It is a complex dysplasia in which skeletal defects are associated with ectodermal anomalies affecting hair, teeth and nails, and congenital heart disease is common. The shortening of limbs in this condition is the reversal of achondroplasia in that it is the distal parts of the limbs which

are shortened rather than the proximal (Fig. 3) and polydactyly of fingers and toes is commonly found.

Chondrodysplasia punctata

These infants are recognizable at birth as dwarfs with short limbs. Radiologically punctate calcifications are found in the epiphyses, joint capsules, trachea, larynx, hyoid, intervertebral discs and in

FIG. 1. A stillborn infant with achondrogenesis showing oedematous soft tissue, virtual absence of ossification of bones and micromelia.

rhizomelic type proximal limb bone shortening (Fig. 4).

Diastrophic dwarf

This term was coined by Lamy and Maroteaux (1960) for achondroplastic-like dwarfs with twisted lower extremities and varying degrees of scoliosis. The other abnormalities described are contracture of joints, dislocation of hips, knees, radial heads and superficial resemblance to arthrogryposis. The long bones are short. The thumbs are displaced proximally and the first metacarpal bone is hypoplastic. The hypoplasia of the mid-cervical vertebrae is a characteristic radiographic feature.

Homozygous achondroplasia

This is extremely rare and is lethal. The affected infant dies within the first few days or weeks of life. The overall body proportions of the infant are midway between those of a thanatophoric dwarf and those of an infant with classical achondroplasia

FIG. 2. 'Harris and Houston' type of achondrogenesis.

FIG. 3. Three-day-old infant with chondro-ectodermal dysplasia.

FIG. 4. A newborn infant with rhizomelic type of chondrodysplasia punctata.

(Fig. 5). The clinical diagnosis is made without difficulty as a homozygous achondroplast is the offspring of two achondroplastic parents.

Hypophosphatasia

This is an autosomal recessive condition.

The term 'hypophosphatasia' was used for the first time by Rathbun (1948) to designate an osteoblastic condition with low serum alkaline phosphatase. There are three salient features—abnormal mineralization of bone, increased urinary excretion of phosphoethanolamine and diminished alkaline phosphatase activity. Fraser (1957) described three different categories depending on the age of onset: newborn, infants and children. The newborn type is the most severe (Figs 6 and 7) and carries the worst prognosis. Hypercalcaemia is a common complication presumably due to accumulation of calcium in the blood as it fails to be incorporated into bone because of absent or low alkaline phosphatase activity. Dent (1956) maintained that the hypercalcaemia in hypophosphatasia was due to hypersensitivity to vitamin D. This hypercalcaemia can be complicated by nephrocalcinosis which can contribute to some of the fatal outcome.

FIG. 5. Two-day-old infant with homozygous achondroplasia.

Lymphopenic agammaglobulinaemia with short-limbed dwarfism

McKusick and Cross (1966) first described a patient with Swiss-type agammaglobulinaemia and a skeletal disorder resembling achondroplasia but they thought the skeletal disorder had no relationship to the agammaglobulinaemia. A few months later Davis (1966) described a newborn female infant with achondroplasia and Swiss-type agammaglobulinaemia. He concluded that because of the rarity of both conditions their concurrence was due to genetic association and not simply to chance. The subsequent recognition of isolated cases of this nature (Fulginiti *et al.*, 1967; Alexander and Dunbar, 1968) have given support to Davis's assumption.

Metatrophic dwarf

This term 'metatrophic' (which means 'variable')

FIG. 6. Day-old infant with neonatal hypophosphatasia showing large head, narrow thorax, bowing of legs and cutaneous dimples on outer aspects of legs.

FIG. 7. Day-old infant with neonatal hypophosphatasia showing demineralization simulating severe rickets.

FIG. 8. Metatrophic dwarf showing expansion of all metaphyses, dumb-bell shaped long bones and flattening of vertebrae.

FIG. 9. Osteogenesis imperfecta congenita.

FIG. 10. Spondylo-epiphyseal dysplasia congenita showing shortening of ribs and long bones, flattening of thoracic vertebrae posteriorly and hypoplastic odontoid.

FIG. 11. Thanatophoric dwarf.

was defined by Maroteaux, Spranger and Wiedemann (1966) for a condition characterized by variation in the clinical picture with age. Initially they superficially resemble achondroplastics with limbs shorter than trunk; later, the proportions reverse with more shortening of the trunk than limbs and bear resemblance to Morquio's disease. The skeletal radiographs show expansion of all the metaphyses, shortening of long bones which become dumb-bell shaped and flattening of vertebral bodies (Fig. 8).

Osteogenesis imperfecta congenita

This condition in the majority of cases results from sporadic mutation and is inherited as autosomal dominant. The severe neonatal type indicates a recessive mode of inheritance. It is characterized by multiple fractures of long bones which consequently become deformed, angulated and short (Fig. 9).

Spondylo-epiphyseal dysplasia congenita

This condition was first described by Spranger and Wiedemann (1966). It selectively affects vertebrae, epiphyses of long bones and occasionally adjacent

metaphyses. The associated clinical abnormalities are: severe myopia, retinal detachment, cataracts, deafness and cleft palate. Roaf, Longmore and Forrester (1967) reported four cases of a syndrome comprising bone dysplasia, retinal detachment and deafness. These were probably cases of spondylo-epiphyseal dysplasia. There are six types of spondylo-epiphyseal dysplasia distinguishable on clinical, genetic and radiological grounds. It is inappropriate to discuss all here. The skeletal radiograph (Fig. 10) shows the abnormalities that are found in the congenital variety.

Thanatophoric dwarf

Maroteaux, Lamy and Robert (1967) first reported this condition which is the commonest cause of neonatal deaths amongst short-limbed dwarfs. The title means 'death bearing'. Harris and Patton (1971) reviewed seventeen stillborn and early neonatal deaths originally diagnosed as achondroplasia and showed that in ten of these the diagnosis should have been thanatophoric dwarf. The clinical appearance is characteristic (Fig. 11) and consists of very short

limbs, redundant skin folds, limbs held in abduction and external rotation, a large head and depressed nasal bridge.

Conclusions

It is now possible to make an early and precise diagnosis in a number of different types of short-limbed dwarfs. This is of importance for prognosis and genetic counselling.

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References

- ALEXANDER, W.J. & DUNBAR, J.S. (1968) Unusual bone changes in thymic alymphoplasia. *Annals of Radiology*, **11**, 389.
- BARR, D.G.D. & FORFAR, J.O. (1973) *Textbook of Paediatrics*. Churchill Livingstone, London and Edinburgh.
- DAVIS, J.A. (1966) A case of Swiss type of agammaglobulinaemia and achondroplasia. *British Medical Journal*, **2**, 1371.
- DENT, C.E. (1956) Bone structure and metabolism. In: *Ciba Foundation Symposium*, p. 266. Churchill, London.
- ELLIS, R.W.B. & VAN CREVELD, S. (1940) Syndrome characterized by ectodermal dysplasia, polydactyly, chondrodysplasia and congenital morbus cordis: report of 3 cases. *Archives of Disease in Childhood*, **15**, 65.
- FRACCARO, M. (1952) Contributo allo studio delle malattie del mesenchima osteopoitico: l'achondrogenesi. *Folia hereditaria et pathologica* (Milano) **1**, 190.
- FRASER, D. (1957) Hypophosphatasia. *American Journal of Medicine*, **730**.
- FULGINITI, V.A., HATHAWAY, W.E., PEARLMAN, D.S. & KEMP, C.H. (1967) Agammaglobulinaemia and achondroplasia. *British Medical Journal*, **2**, 1371.
- HARRIS, R. & PATTON, J.T. (1971) Achondroplasia and thanatophoric dwarfism in newborn. *Clinical Genetics*, **2**, 61.
- HARRIS, R., PATTON, J.T. & BARSON, A.J. (1972) Pseudo-achondrogenesis with fractures. *Clinical Genetics*, **3**, 435.
- HOUSTON, C.S., AWEN, C.F. & KENT, H.P. (1972) Fatal neonatal dwarfism. *Journal of the Canadian Association of Radiologists*, **23**, 45.
- JEUNE, M., BÉRAUD, C. & CARRON, R. (1955) Dystrophie thoracique asphyxiante de caractère familial. *Archives françaises de pédiatrie*, **12**, 886.
- JEUNE, M., BÉRAUD, C. & CARRON, R. (1962) Zur frage des gehauften Auftretens von Extremitätenmissbildungen bei Neugeborenen. *Geburtshilfe und Frauenheilkunde*, **22**, 400.
- JURCZOK, F. & SCHOLLMMEYER, R. (1962) Zur Frage des gehauften Auftretens von Extremitätenmissbildungen bei Neugeborenen. *Geburtshilfe und Frauenheilkunde*, **22**, 400.
- LAMY, M. & MAROTEAUX, P. (1960) Diastrophic nanism. *Presse Médicale*, **68**, 1977.
- MCKUSICK, V.A. & CROSS, H.E. (1966) Ataxia telangiectasia and Swiss type agammaglobulinaemia. *Journal of the American Medical Association*, **195**, 739.
- MAROTEAUX, P., LAMY, M. & ROBERT, J.M. (1967) Le nanisme thanatopore. *Presse Médicale*, **75**, 2519.
- MAROTEAUX, P., SPRANGER, J. & WIEDEMANN, H.R. (1966) Der metatropische Zwergwuchs. *Archiv für Kinderheilkunde*, **173**, 211.
- MØRCH, E.T. (1941) *Chondrodystrophic Dwarfs in Denmark*. Ejnar Munksgaard, Copenhagen.
- PARENTI, G.C. (1936) La anosteogenesi (una varietà della osteogenesi imperfetta). *Pathologica*. Genova, **28**, 447.
- POTTER, E.L. & COVERSTONE, V.A. (1948) Chondrodystrophy foetalis. *American Journal of Obstetrics and Gynecology*, **56**, 790.
- RATHBUN, J.C. (1948) 'Hypophosphatasia'. New developmental anomaly. *American Journal of Diseases of Children*, **75**, 822.
- ROAF, R., LONGMORE, J.B. & FORRESTER, R.M. (1967) A childhood syndrome of bone dysplasia, retinal detachment and deafness. *Developmental Medicine and Child Neurology*, **9**, 464.
- RUBIN, P. (1963) Achondroplasia versus pseudoachondroplasia. *Radiologic Clinics of North America*, **1**, 621.
- RYAN, J. & KOZLOWSKI, K. (1971) *Australian Radiation Records*, **15**, 213.
- SALDINO, R.M. (1971) Lethal short limbed dwarfism: achondrogenesis and thanatophoric dwarfism. *American Journal of Roentgenology*, **112**, 185.
- SHOKEIR, M.H.K., HOUSTON, C.S. & AWEN, C.F. (1971) Asphyxiating thoracic chondrodystrophy. Association with renal disease and evidence for possible heterozygous expression. *Journal of Medical Genetics*, **8**, 107.
- SPRANGER, J. & WIEDEMAN, H.R. (1966) Dysplasia spondyloepiphysaria congenita. *Helvetica paediatrica acta*, **21**, 598.
- STEVENSON, A.C. (1957) Achondroplasia: an account of the condition in Northern Ireland. *American Journal of Human Genetics*, **9**, 8.