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Syndrome of the month

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Dyggve-Melchior-Clausen syndrome

Peter Beighton

Dyggve-Melchior-Clausen syndrome (DMC) is a rare, dwarfing, skeletal dysplasia characterised by a coarse facies, bulky jaws, short trunk, and barrel chest. Significant radiographical changes include platyspondyly and dysplasia of the epiphyses and metaphyses of the proximal limb bones. Dislocation of the hips and malalignment of the spine and knees are variable features. Inheritance is autosomal recessive; the presence or absence of mental retardation might be an indication of heterogeneity.

History

The DMC syndrome was delineated by Dyggve *et al*[1] in 1962 when they investigated three sibs from a consanguineous union in Greenland who were residing in an institution for the mentally handicapped in Copenhagen. In view of the remsemblance of the phenotype to the mucopolysaccharidoses the authors used the term 'Morquio-Ullrich disease' and speculated that the condition might be an inborn error of metabolism. With hindsight, the diagnosis of an earlier example of DMC can be made from the clinical description and radiographical features of a sporadic affected girl depicted in a montage photograph of 'family 12' in a review of hereditary chondrodysplasias in Norway.[2 3]

Holger Dyggve (1913–1984) was a Danish paediatrician and head of the Andersvaenge Slagelse Institute for the Mentally Retarded in Copenhagen.

Johannes Melchior was born in 1923 and became professor of paediatrics at the University of Copenhagen in 1971. He made many academic contributions in the field of metabolic neurological disorders of childhood.

Jorgen Clausen was appointed as professor of biochemistry at the University of Roskilde, Denmark in 1975. He has published numerous articles on immunochemistry and inborn errors of metabolism.

The eponymous triad 'Dyggve-Melchior-Clausen' was introduced by Naffah and Taleb[4] in 1974 and in the following year Spranger *et al*[5] documented the radiological features of 15 patients. The issue of heterogeneity was raised in 1976 when Spranger *et al*[6] drew attention to an earlier case report by Smith and McCort,[7] which had been entitled 'osteochondrodystrophy' and suggested that this disorder was a form of DMC in which mentality was normal. Patients have continued to be reported and at present about 50 affected persons have been documented.[8–13]

Clinical features (figs 1 and 2)

Short trunked dwarfism and craniofacial abnormalities

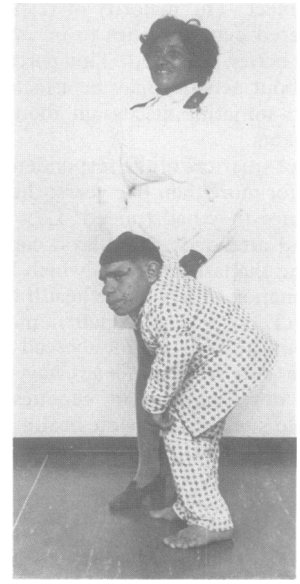

Figure 1 An adult male aged 27 years. Dwarfism and mental retardation are severe.

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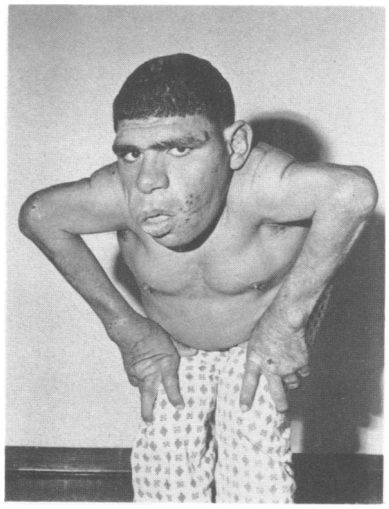

Figure 2 The patient has a short neck, bulky jaws, and a receding forehead.

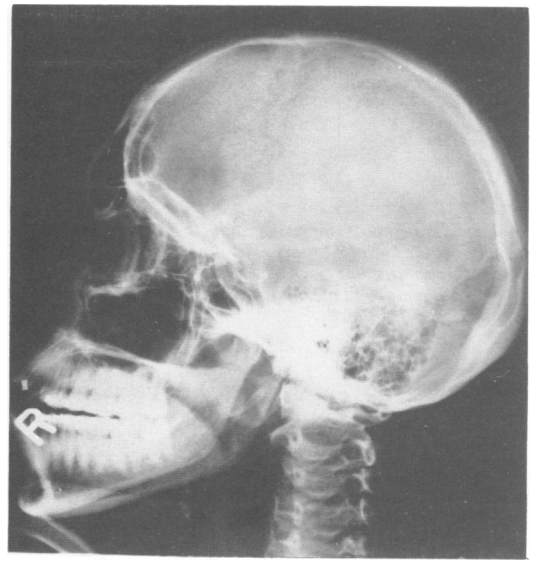

Figure 3 Lateral skull radiograph of an affected adult female at the age of 19 years. The jaws are prominent and there is relative microcephaly.

become evident in infancy and by early adulthood the clinical manifestations are fully established. Mental retardation is a variable feature which results in delayed developmental milestones if present in an affected infant.

In the fully established case, dwarfism is severe. Rhizomelic limb shortening and platyspondyly contribute to the short stature; the vertebral changes predominate and the trunk is shortened relative to the limbs. The neck is short, the thorax barrel shaped, and the spine may be malaligned. Dislocation of the hips and genu valgum are variable features. The hands and feet are broad and in some affected persons the digits are clawed.

The face is coarse with prominence of the jaw and relative microcephaly, but the eyes and teeth are normal. The degree of facial coarsening is variable; in some persons it is severe, while in others the facies are comparatively normal. There are no internal ramifications and in particular there is neither cardiac involvement nor hepatosplenomegaly.

The main clinical problems are mental retardation, which is an all-or-none feature, and orthopaedic complications consequent upon subluxation of the hips and malalignment of the spine and knees. Odontoid hypoplasia may lead to atlantoaxial instability and potentially lethal spinal cord compression. Apart from these problems there is a good prognosis for general health and survival into adulthood is usual.

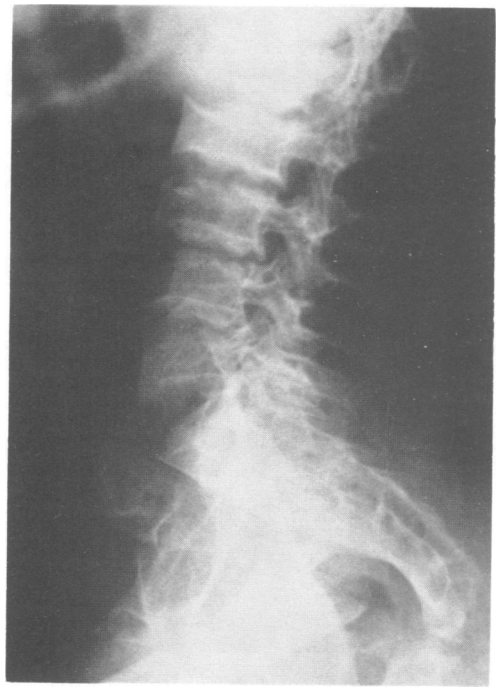

Figure 4 Lateral radiograph of the lumbar spine. The vertebral bodies are flattened and the end plates are irregular and sclerotic.

Radiographical features (figs 3 to 6)

As with the clinical features, the radiographical

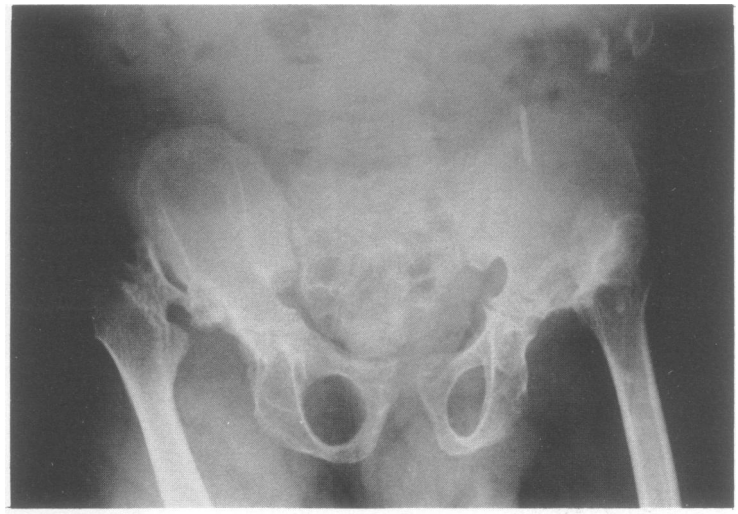

Figure 5 Anteroposterior radiograph of the pelvis at the age of 24 years. The ilia are small with irregular crests, the pubic symphysis is wide, and the hip joints are dysplastic and dislocated.

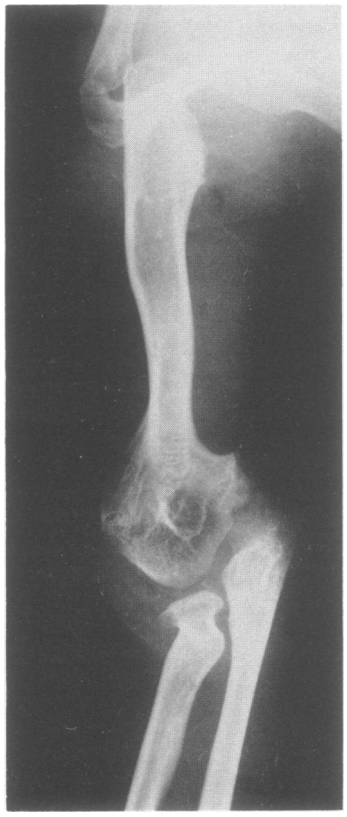

Figure 6 Anteroposterior radiograph of the arm in adulthood. The humeral shaft is short, the head is hypoplastic, and the lower end is broad and misshapen. The radial head and olecranon are dysplastic.

manifestations are inconsistent and there is considerable inter- and intrafamilial variability.

SKULL

Microcephaly is often present and the facial bones are disproportionately large with respect to the cranium. Pneumatisation of the paranasal sinuses may be pronounced.

SPINE

The vertebrae are flattened, with irregularity and sclerosis of their end plates. Notching of the anterosuperior and inferior aspects of the vertebral bodies is evident in the lumbar region in childhood. The odontoid process is often hypoplastic.

PELVIS

The iliac crests have a characteristic lacy appearance in childhood but by adulthood these changes have metamorphosised to a non-specific marginal irregularity. The ilia themselves are small, the acetabulae are sloping and dysplastic, and the pubic symphysis is wide.

LIMBS AND EXTREMITIES

Involvement of the limb bones is predominantly proximal; the heads of the humeri and femora are dysplastic and the shoulder and hip joints may be subluxed. The shafts of these bones show variable shortening and the lower ends are expanded. The radial heads and olecranons may be malformed, but

the bones of the distal portions of the limbs and of the hands and feet are comparatively normal. Ossification in the carpus is delayed and, when mature, the carpal bones are often irregular. Supernumerary ossification centres and cone shaped epiphyses are present in the tubular bones of the hands and feet; shortening of these bones is variable.

Pathogenesis

Routine cytogenetic, biochemical, and haematological investigations in DMC yield normal results. Initial reports of mucopolysaccharidurla could not be confirmed and fibroblast uptake of radioactive sulphate is normal.[5] Altered leucocyte proteinase and sulphate levels have been documented,[14] as have abnormal serum α2 macroglobulins.[15] The pathogenetic significance of these observations is uncertain. Beck *et al*[16] could detect no abnormality of sulphatase and protease activity in proteoglycan degradation in DMC fibroblasts.

Differential diagnosis

The dwarfism, coarse facies, and clawing of the digits in DMC are reminiscent of the mucopolysaccharidoses and this group of disorders warrants exclusion by appropriate biochemical investigations. At present, there are no specific laboratory tests which permit diagnostic confirmation of DMC.

The spondyloepiphyseal dysplasia (SED) group of conditions resembles DMC in terms of short trunked dwarfism and predominant radiographical involvement of the vertebral bodies and proximal epiphyses. The radiological appearances permit differentiation; in particular, the lacy configuration of the iliac crest in childhood in DMC is pathognomonic, while the residual irregularity of the crest in adulthood sets DMC apart from SED.

Genetics

The abnormal gene has a wide geographical distribution and it has been encountered in families from Greenland,[1] the Lebanon,[4 8 10] North America,[7 9] Morocco,[12] South Africa,[10] Western Europe,[5 6] and Brazil.[11 17]

There have been several reports of affected sibs with normal parents[5 6] and some instances of parental consanguinity.[1 10 11] In a formal segregation analysis of 23 reported sibships with both forms of DMC, Toledo *et al*[11] confirmed autosomal recessive inheritance in DMC. Obligate heterozygotes are clinically normal, and there are no available laboratory techniques for determination of possible heterozygosity of family members. There have been no reports of microdeletions in DMC and the chromosomal localisation of the faulty gene has not yet been determined.

It is likely that DMC is heterogeneous, the presence or absence of serious mental retardation being the discriminating factor.[6] In a review of published reports, Spranger *et al*[6] identified three familial instances and three sporadic cases of DMC with normal intelligence and 12 familial and nine sporadic instances of DMC with profound mental retardation.

In view of the serious clinical complications of DMC, prenatal diagnosis would be warranted. At present, however, there are no suitable biochemical techniques and the skeletal changes during early intrauterine development are probably too mild to be detected ultrasonographically.

I am grateful to Gillian Shapley for typing the manuscript. The research upon which this article is based was supported by grants from the South African Medical Research Council, the Maurerberger Foundation, the Harry Crossley Foundation, and the University of Cape Town Staff Research Fund. Fig 1 appeared in Beighton P. *Inherited disorders of the skeleton*. 2nd ed. Edinburgh: Churchill Livingstone, 1988. Figs 2 to 6 are from Bonafede RP, Beighton P. *Clin Genet* 1978;**14**:24–30.

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