Genetic Heterogeneity in Skeletal Dysplasias

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ABSTRACT

Certain skeletal dysplasias represent excellent examples of genetic heterogeneity. Clinical recognition of their individual characteristics is a fundamental prerequisite for an understanding of their pathogenetic mechanisms and for the identification of their basic molecular defects.

Introduction

Few areas in nosology offer as many examples of etiologic heterogeneity as the skeletal dysplasias. Increasing interest during the last few years in these conditions has resulted in the identification of a number of new types of chondrodysplasias, of which most are genetically determined. For many, the mode of inheritance is well known and the clinical and radiological manifestations have been clearly defined. However, failure to recognize their heterogeneity has been a major obstacle in the delineation of their biochemical and histopathological characteristics, as well as in the understanding of their pathogenetic mechanisms.

Identification of genetic heterogeneity may be achieved by clinical, radiologic, histopathologic, genetic or biochemical methods. Our ability to use one or more of these approaches depends upon the degree of knowledge attained in a given condition or group of conditions. Thus, while in some situations the only available alternative for the distinction of similar phenotypes is the use of subtle differences in the clinical and radiologic manifestations, in others the underlying histopathologic lesion or the pattern of inheritance are distinctive enough to allow for this differentiation. Evidence of characteristic biochemical changes or abnormalities is, unfortunately, available only in a small proportion of the skeletal dysplasias.

Chondrodysplastic Dwarfisms

Clinical and roentgenologic studies play a major role in the differential diagnosis of the chondrodysplasias manifested at birth. Only a few years ago micromelic dwarfism in a newborn was practically synonymous with the diagnosis of achondroplasia. Today, in the neonate, at least a dozen different types of chondrodysplastic dwarfisms can be distinguished from this condition (table I).

Harris and Patton, reviewing 17 cases originally diagnosed as achondroplasia between 1951 and 1969, were able to demonstrate that 10 out of 11 infants who were still-births had, in fact, a different type of chondrodysplasia: thanatophoric dwarfism. This condition, first described as a separate entity from achondroplasia by Maroteaux, Lamy and Roberts in 1967, represents a severe form of short-limbed dwarfism. As its name implies (from the Greek: death-bearing), it usually results in death at or

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TABLE I

**Congenital Short-limbed Dwarfism**

<table>
<thead>
<tr>
<th>Lethal</th>
<th>Nonlethal</th>
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</thead>
<tbody>
<tr>
<td>Achondrogenesis (Fraccaro-Parenti type)</td>
<td>Achondroplasia</td>
</tr>
<tr>
<td>Achondroplasia, homozygous</td>
<td>Asphyxiating thoracic dysplasia*</td>
</tr>
<tr>
<td>Camptomelic dwarfism</td>
<td>Chondrodysplasia punctata (Conradi-Hünerman type)</td>
</tr>
<tr>
<td>Chondrodysplasia punctata (recessive form)</td>
<td>Chondrodysplasia punctata (Conradi-Hünerman type)</td>
</tr>
<tr>
<td>Hypophosphatasia congenita</td>
<td>Dochondroectodermal dysplasia</td>
</tr>
<tr>
<td>Thanatophoric dwarfism</td>
<td>Diastrophic dwarfism*</td>
</tr>
<tr>
<td>Short rib-polydactyly syndrome</td>
<td>Metatropic dwarfism</td>
</tr>
<tr>
<td>Majewski type</td>
<td>Nievergelt type</td>
</tr>
<tr>
<td>Saldino-Noonan type</td>
<td>Langer type</td>
</tr>
<tr>
<td></td>
<td>Metatropic dwarfism</td>
</tr>
<tr>
<td></td>
<td>Spondyloepiphyseal dysplasia congenita</td>
</tr>
</tbody>
</table>

*Occasionally lethal

shortly after birth. Clinical and radiological manifestations allow for its accurate differentiation from the other types of micromelic dwarfism in the newborn.17,19,28,29 Commonly, the head is disproportionately large as compared to the facial structures, with frontal bossing and depressed nasal bridge. The limbs are extremely short, while the trunk is of normal length with a narrow thorax and protuberant abdomen. Polyhydramnios is of common occurrence.31 The roentgenologic findings, though in some ways similar to achondroplasia, are characteristic of the condition. The vertebral bodies are markedly flattened in their midportions while the pedicles and posterior segment of the bone are better developed. This gives the vertebrae an H-shaped or inverted U appearance in anteroposterior projections. The spinal canal is small and shows greater narrowing in the lumbar region. The pelvis is small with decreased height of the iliac wings; the acetabular angles are flat, and the sacrosciatic notches are notably reduced. There is marked shortening of the tubular bones and metaphyseal flaring. Bowing of the femora, which gives the diaphysis a resemblance of a telephone receiver, is a characteristic feature. The ribs are short and have widened anterior ends.

In the past, inability to separate thanatophoric dwarfism from achondroplasia led to much confusion, both in genetic counseling and in the delineation of the histopathology of these conditions. Early pathologic studies26 described complete disorganization of endochondral bone formation in achondroplasia. However, Rimoin, et al25 have demonstrated that classical achondroplasia is associated with structurally regular, well-organized endochondral ossification while thanatophoric dwarfism is characterized by generalized disruption of endochondral ossification. It is now apparent that most histopathologic studies of "achondroplasia" were, in fact, performed in children with thanatophoric dwarfism.

Genetic counseling based on an incorrect diagnosis necessarily had to result in the delivery of erroneous advice. It has been well established that achondroplasia obeys an autosomal dominant mode of determination, and that over 80 percent of the cases represent new mutations.28 Therefore, in cases with positive family history, the risk for recurrence is 50 or 75 percent, depending on whether one or both parents are affected; in sporadic cases (new mutations), the risk is negligible.

Most cases of thanatophoric dwarfism have been sporadic,11,14,17,19,20 including a discordant case in female twins.18 The regularity and consistency of the phenotype, together with some reports showing familial aggregation5,14,27,32 point toward a genetic mode of determination. Parental consanguinity found in the siblings studied by Chemke5 and in the triplets reported by Sabry27 is suggestive of autosomal recessive inheritance, while increased parental age as mentioned by Thompson and Parmley31 would favor an autosomal dominant mutation. The postulation of polygenic determination24 has been strongly disputed.12 Regardless of our present inability to depict
the precise mode of inheritance of thanatophoric dwarfism, it is important to recognize that recurrence of the condition in subsequent pregnancies is a distinct possibility.

Spondyloepiphyseal Dysplasias Tardas

There are other groups of skeletal dysplasias in which the pronounced similarity of their clinical and radiological manifestations does not allow for a clear differentiation on a phenotypical basis. In these situations the recognition of the pattern of inheritance may be of great help. An excellent example of this situation is the spondyloepiphyseal dysplasias tardas in which X-linked recessive, autosomal recessive and autosomal dominant forms have been clearly identified.21 Though they can be separated on the basis of their variable involvement of the spine and tubular bones,3 overlapping of the clinical and radiological characteristics may obscure their distinction (table II).

Hurler-Hunter Syndrome

Biochemical differentiation of phenotypically similar skeletal dysplasias can be best illustrated by some of the mucopolysaccharidoses. Hunter15 in 1917 and Hurler16 in 1919 described two similar conditions which, in the following decades, became known as “gargoylism” and later as the Hurler-Hunter syndrome.7 Affected children presented with chondrodysplastic dwarfism, coarse facial features, deafness, cloudy corneas, restriction of joint movement, hepatosplenomegaly, abdominal hernias and, usually, mental retardation.

Variability in the phenotypic expression of the syndrome became apparent through the years and differences in the pattern of inheritance within families were also observed. A number of patients exhibited the primary features of the Hurler-Hunter phenotype, but lacked the corneal haziness and showed milder manifestations of the condition. These patients were all males and their pedigree patterns were consistent with an X-linked recessive mode of determination.23 In contrast, in the more severe cases there was no sex predilection and their family patterns were suggestive of autosomal recessive inheritance.

Though these features permitted the categorization of many patients into either of these two conditions, sporadic cases with milder or atypical characteristics posed a serious diagnostic problem to the clinician. This was especially true in couples seeking genetic counseling after the death of an affected child when the only available data were historical in nature.

The isolation of dermatan sulfate from the liver of two patients with Hurler syndrome4 and the detection of increased levels of acid mucopolysaccharides in the urine8 firmly established the biochemical nature of the disease. However, this did not permit differentiation between the two syndromes, as patients with either one eliminated the same type of mucopolysaccharides in the urine, i.e., dermatan sulfate and heparan sulfate.22

A major breakthrough in the identification of the Hurler and Hunter syndromes occurred in 1967 when Danes and Bearn8 observed metachromatic granules in cultured skin fibroblasts of patients with mucopolysaccharidosis.
polysaccharidosis and their heterozygote parents. They showed that metachromasia could be evidenced in both parents in the autosomal recessive form (Hurler syndrome), whereas in the X-linked variety (Hunter syndrome) only the mother who carried the mutant gene demonstrated this phenomenon.

Further studies proved that the accumulation of mucopolysaccharides is caused by deficient degradation of these substances and that in vitro correction of the abnormality could be achieved by culturing fibroblasts of an affected individual together with cells from a normal person or from a patient with a different type of mucopolysaccharidosis. The diffusible factor responsible for this correction in the Hurler syndrome was finally identified by Neufeld and her group as α-L-iduronidase, while the defect in the Hunter syndrome was shown to be a deficiency in sulfatiduronate sulfatase. The application of these findings now permits the accurate identification of these two conditions.

The examples presented emphasize the need for adequate clinico-pathological delineation of the skeletal dysplasias as a prerequisite for the investigation of their pathogenetic mechanisms. Awareness of the common occurrence of genetic heterogeneity together with sufficient data differentiating each particular type will be the best basis for the investigations that may hopefully lead in the future to the identification of their basic biochemical abnormalities.

References

26. Rubin, P.: Dynamic Classification of Bone Dys-