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MED, *COMP*, multilayered and NEIN: an overview of multiple epiphyseal dysplasia

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Abstract This overview covers the group of disorders that presents radiographically as multiple epiphyseal dysplasia (MED). The disorders include "classic MED" (Ribbing and Fairbank types): MED that is caused by mutations in the cartilage oligomeric matrix protein (*COMP*), type IX collagen, and matrilin 3 genes (*MATN3*); and MED with multilayered patella, brachydactyly, and clubbed feet resultant from mutations in gene defect diastrophic dysplasia (*DTDST*). The recently identified gene/molecular abnormalities in these disorders have made more exact identification possible in many cases, although clinical testing is not always available. However, there are specific radiographic findings that allow the accurate diagnosis to be made, thus potentially guiding which molecular defect(s) should be investigated. The modes of inheritance of these distinct MED conditions are not identical. When a specific diagnosis is made, proper genetic counseling as well as prognostication, management issues and complications can be delineated to the patient and family. This review will include the mechanics of diagnostic and molecular triage for these disorders.

Keywords Multiple epiphyseal dysplasia · Pseudoachondroplasia · Diastrophic dysplasia · *COMP* gene · Collagen abnormalities · Type IX collagen · Matrilin defect

Introduction

With the recent identification of the disease gene and molecular defect (mutation) in many of the skeletal dysplasias, clarification of the clinical and radiographic aspects of a number of these disorders has occurred. In some cases, there has been an expansion of the clinical phenotype to include other diagnostic entities that result from mutations in the same gene. The radiographic expression of multiple epiphyseal dysplasia (MED) is a good example of this. A diagnosis of MED implies that radiographically there is a generalized abnormality of epiphyseal ossification without significant vertebral involvement. This could include a delay in ossification and abnormalities in epiphyseal size and contours. In classic MED, the defect is primarily an ossification defect, as the anlagen of the epiphyseal centers appear to be normal [1]. However, in classic MED there is also an early onset of degenerative arthrosis of the large weight-bearing joints, suggesting that other mechanisms in addition to epiphyseal abnormalities are occurring. Often asymptomatic, superimposed avascular necrosis of a capital femoral epiphysis develops. Let us look radiographically at cases of MED to help the clinician make a definitive diagnosis.

Discussion

Multiple epiphyseal dysplasia (MED) was separately described by Ribbing and Fairbank in the 1930s. It is still classified into the Ribbing (mild) and Fairbank

(severe) types, but there is a continuum of clinical severity between these types. When there is epiphyseal ossification delay and dysplastic-appearing epiphyses primarily confined to the hips, the diagnosis is MED, Ribbing type. If the involvement is more generalized, involving all or most of the large epiphyseal centers, the diagnosis of the more severe Fairbank MED is used. The epiphyses of hands and feet appear almost spared, but carpal (and tarsal) center ossification can be abnormal, with delay in ossification of these "epiphyseal equivalents." Ivory epiphyses can be seen. No significant brachydactyly is present. The term multiple epiphyseal dysplasia was chosen because spinal involvement was not originally recognized. When there is vertebral involvement in MED, it typically consists of early-onset Schmorl disease of multiple thoracolumbar vertebrae, usually beginning when the patient is in his 20s or 30s with mild/moderate clinical spine problems (Figs. 1 and 2).

Recently, the employment of molecular genetic techniques has established that classic MED consisting of both MED Ribbing and Fairbank types can result from dominant mutations in five genes. These include the cartilage oligomeric matrix protein gene (COMP), the three genes that compose the type IX collagen molecule (COL9A1, COL9A2, COL9A3) [2], and in a small number of patients the matrilin-3 (MATN3) gene [3].

A number of patients diagnosed clinically and radiographically as MED have a molecular defect in COMP. This is the same abnormality discovered earlier in pseudoachondroplasia. Pseudoachondroplasia is usually a much more severe condition than classic MED. It is easily diagnosed clinically by the presence of certain features and radiographically by the finding of mini-epiphyses at the hips, epimetaphyseal involvement of

Table 1 Radiographic MED with "COMPY" changes (suggesting COMP mutations)

Pelvis
- Very small capital femoral epiphyses
- Hypoplastic, poorly formed acetabular roofs

Knees
- Metaphyseal widening and irregularity

Hands
- Brachydactyly
- Proximal metacarpal rounding

Spine
- Indentations of superior and inferior ring epiphyseal regions (early age)

most long bones (especially at the knees), vertebral changes including superior/inferior rounding of vertebral bodies and a central anterior "tongue." The acetabular roofs appear to be poorly formed, but are formed normally in cartilage and are simply late to ossify. The hands reveal brachydactyly, especially of the metacarpals, with proximal rounding of the metacarpals persisting into late childhood (Fig. 3).

In reviewing a group of cases of very mild pseudoachondroplasia with a COMP defect that actually mimics MED-Fairbank (MED–COMP), we have noted a number of radiographic signs, which we shall designate as "COMPY." They include: in the pelvic region, quite small capital femoral epiphyses and hypoplastic (unossified) acetabular roofs; at the knees, metaphyseal widening and irregularity; in the hands, brachydactyly and persistence of proximal metacarpal rounding; and in the spine exaggeration (at an earlier age than normal) of the superior and inferior indentation anteriorly of the ring epiphyseal region seen on the lateral spine projection (Fig. 4) (Table 1). These findings are associated with the other typical findings of MED and when present suggest the likelihood of a COMP defect. Not all of these "COMPY" changes are present in most cases, and sometimes only a singular abnormality will act as a clue [4, 5].

Because molecular testing in MED can be costly and time-consuming and available for only some molecular defects on a research rather than as a clinical service test, attempting to establish the MED locus by the radiographic features of MED is of significant value. This may allow for a triage plan for cost-effective clinical testing, and you with your consulting geneticist can decide which test or tests to perform, in what order, or that there is no need for molecular confirmation of the diagnosis. Presently, COL IX and MATN3 testing are only available on a research basis, while COMP testing is a clinical test (http://www.genetests.org).[1]

Fig. 1 MED-Ribbing (mild) type. Hips in a 9 year old that show epiphyseal dysplasia (slightly small, dense capital femoral epiphyseal ossification) and normal acetabular roofs

[1]COMP analysis: cost, about $1800; turnaround time, 3–4 weeks

Fig. 2 MED-Fairbanks (severe) type. **a** Hips in a 5 year old that demonstrate moderately small ossified femoral epiphyses and normal acetabular roofs. **b** Hips in an 11 year old reveal small, flat, irregular femoral epiphyseal ossification and normal acetabulae for age. **c** Hips in a 19 year old with residua of epiphyseal dysplasia. These are non-spherical epiphyses, coxa vara and normal, but shallow acetabular roofs. **d** Knees in a 16 year old show hypoplastic epiphyseal ossification with irregularity. **e** Hand and wrist in a 10 year old reveal carpal ossification delay (small normally formed carpal bones) with no brachydactyly and mild epiphyseal ossification delay. **f** Hands and wrists in a 19 year old with normal hands, no brachydactyly and slightly small-appearing carpus. **g** Proximal humerus in an 8.5 year old with moderately small humeral epiphysis. **h** Lumbar spine in an 11 year old shows normal vertebrae. **i** Thoracolumbar spine in a 25 year old. These are Schmorl node indentations of multiple vertebrae with disc space narrowing (degenerative arthrosis)

Fig. 3 Classic pseudoachondroplasia (moderate and severe cases). **a** Hips and pelvis in a 6 year old. Note the miniepiphyses and marke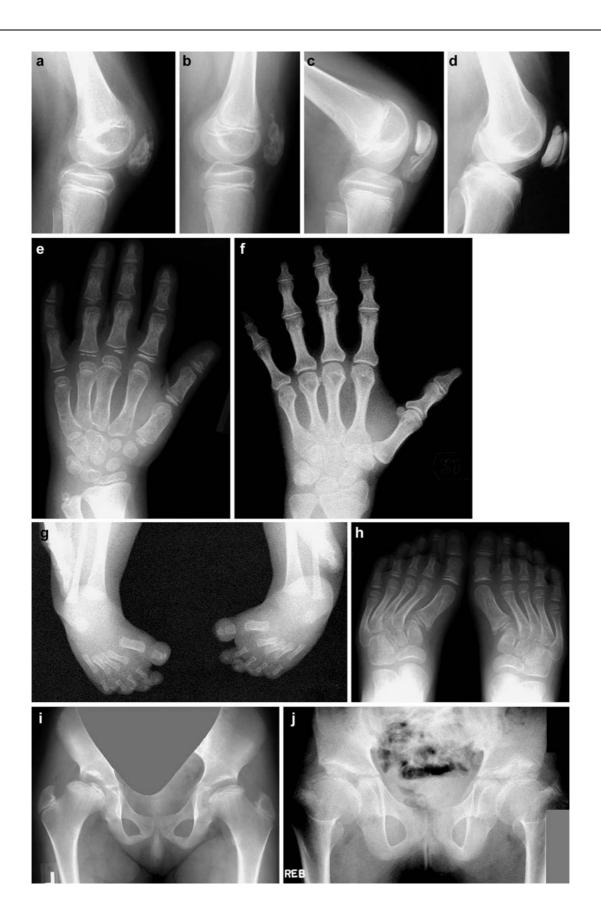d acetabular roof hypoplasia (ossification defect). **b** Hips and pelvis in a young adult with epiphyseal dysplasia (small, flat, irregular) femoral epiphyses and hypoplastic slanted acetabular roofs. **c** Knees in a 6.5 year old. There are very small, irregularly ossified epiphyses and sloped widened metaphyses. **d** Hand and wrist in a 5.5 year old reveal brachydactyly, persistently rounded (immaturely formed) proximal metacarpals, metaphyseal widening and irregularity with epiphyseal ossification delay, and small irregular carpal ossification. **e** Hands and wrists in a 10 year old. There is persistent rounding of proximal metacarpals for age, epiphyseal ossification delay with metaphyseal changes, mild brachydactyly, mild cone-epiphyses, and small irregular carpal bones. **f** Lumbar spine in a 2.5 year old. There is an anterior tongue, superior/inferior rounded vertebrae, with apparent disc space widening. **g** Spine in a 5.5 year old with normal height vertebrae with superior/inferior rounding. **h** Upper extremity in a 2.5 year old with proximal humeral metaphyseal slanting and irregularity, abnormally etched elbow metaphyses, distal radial/ulnar metaphyseal widening, marked generalized epiphyseal ossification delay, and long bone shortening

Fig. 4 Radiographic findings suggesting MED with a *COMP* defect (COMPY). **a** Hips in a 5 year old show moderately small epiphyseal ossification with poor acetabular roof formation and delayed greater trochanter apophyseal ossification. **b** Knees in a 2.5 year old demonstrate moderately small epiphyseal ossification and widened metaphyses. **c** Knee in a 6 year old with moderately small irregular epiphyses and metaphyseal widening. **d** Knees in a 10 year old. There is epiphyseal irregularity and hypoplasia and shows metaphyseal widening with medial and lateral slant. **e** Spine in a 6 year old shows mild superior/inferior vertebral rounding. **f** Spine in an 8 year old with earlier than expected appearance of anterior ring epiphysis indentations

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Fig. 5 Radiographic findings suggesting MED with a *DTDST* mutation. **a** Lateral knee (right) in a 7.5 year old shows multiple ossification centers of patella with longitudinal cleft. **b** Lateral knee (left) in a 7.5 year old with multiple patella centers fusing. **c** Lateral knee in a 10 year old with enlarged double-layered patella with extra ossification centers and normal-size knee epiphyses. **d** Lateral knee in an 18 year old with double-layered patella, but relatively normal knee epiphyses. **e** Hand and wrist in a 7.5 year old. There is brachydactyly, epiphyseal ossification delay, flat epiphyses, several ivory epiphyses, and small carpal centers. **f** Hands and wrists in a 27 year old with significant generalized brachydactyly. **g** Feet and ankles in a 3 month old with bilateral severe clubfeet. **h** Feet in a 7.5 year old There is varus forefoot deformity with characteristic twisted metatarsals. **i** Hips in a 7.5 year old reveal thin, crescent-shaped epiphyseal ossification and normal acetabulae. **j** Hips in a 10 year old with thin, crescent-shaped epiphyseal ossification, normal acetabulae, and short wide femoral necks

Table 2 Radiographic criteria for MED with diastrophic dysplasia gene (*DTDST*) mutations

Lateral knee radiograph
• Multilayered patella
Feet:
• Clubbed foot or metatarsus adductus
• Twisted metatarsals
Hands:
• Brachydactyly

Table 3 Diagnostic and molecular triage

Radiographic (and clinical) findings of classic MED
 No molecular testing necessary (not clinically available)
Radiographic "COMPY" MED findings
 COMP mutation analysis
Indeterminate radiographic and clinical findings
 COMP mutation analysis
Radiographic diastrophic dysplasia gene-type MED findings
 DTDST mutation analysis (may/may not be clinically available)

An additional entity that radiographically can look very similar to classic MED is a condition best called "MED with clubbed feet, brachydactyly and multi (double) layered patella." In the early delineation of the phenotypic spectrum of diastrophic dysplasia, some investigators noticed that a number of cases had only MED-like changes with clubbed feet. They were referred to as diastrophic variants. Because there were not enough clinical and radiographic changes in those cases for investigators to be certain of their diagnosis, the cases were eliminated from the group of diastrophic dysplasia cases analyzed in the manuscript titled *Diastrophic Dysplasia*, the death of a variant [6]. With the recent discovery of the gene defect in *DTDST*, it has been shown that these MED patients have mutations in the *DTDST* sulfate transporter gene [7–9].

A patient with radiographic manifestations of MED should be evaluated for multilayered patellae (only seen in the lateral view of the knee), brachydactyly (even without a "hitchhiker" thumb [round first metacarpal]), and clubbed feet with twisted metatarsals. All of these manifestations are not always present, but even a single finding suggests the possibility of a *DTDST* gene abnormality (Fig. 5; Table 2). When the diagnosis is correctly made, the information is especially important

for genetic counseling purposes, as this form of MED is inherited in an autosomal recessive manner. This is in contrast to MED that is caused by mutations in *COMP*, *COL* IX or *MATN*3, which are all inherited in an autosomal dominant fashion. Mutation analysis for the *DTDST* gene is clinically available only in Europe (http://www.genetests.org).

In conclusion, to date about half of patients with MED changes do not have mutations in any of the known genes [International Skeletal Dysplasia registry-authors' experience]. There are some other forms of MED that do not appear to represent any of these molecularly defined entities. Such forms are usually diagnosed by associated clinical clues such as deafness or immune deficiency [10]. The radiographic diagnosis of MED allows us to identify a group of disorders with significant clinical and molecular heterogeneity that is just beginning to be appreciated. Distinguishing the various forms from a radiographic perspective can be used to guide genetic testing (triage) and aid in appropriate counseling for recurrence risk and natural history (Table 3).

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