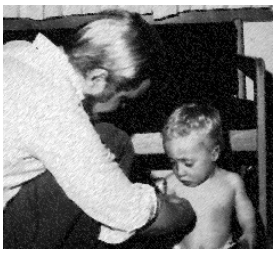

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MULTIPLE EPIPHYSEAL DYSPLASIA
NATURAL HISTORY

INTRODUCTION:

The following summary of the medical expectations in Multiple Epiphyseal Dysplasia is neither exhaustive nor cited. It is based upon the available literature as well as personal experience in the Midwest Regional Bone Dysplasia Clinics (MRBDC). It is meant to provide a guideline for the kinds of problems that may arise in children with this disorder, and particularly to help clinicians caring for a recently diagnosed child. For specific questions or more detailed discussions, feel free to contact MRBDC at the University of Wisconsin – Madison [phone – 608 262 6228; fax – 608 263 3496; email – modaff@waisman.wisc.edu].

Unlike many bone dysplasias, Multiple Epiphyseal Dysplasia may be delayed in presentation and frequently diagnosis is not made until an individual is between 2 and 10 years of age. Diagnosis is sometimes even delayed beyond these ages. First indicators of the presence of this disorder are waddling gait, difficulties running, limping, joint stiffness, joint pain (particularly of the hips and/or knees), activity-precipitated fatigability, and/or subtle slowing of growth velocity.

Multiple Epiphyseal Dysplasia is a descriptive diagnosis, simply implying that an individual has an intrinsic bone dysplasia limited to the ends (epiphyses) of the long bones and with little or no spine involvement. In general, there is profound delay in epiphyseal maturation and deformity of epiphyses. The best described of the various clinical forms of multiple epiphyseal dysplasia is sometimes termed the Fairbank type. Most of the information outlined here is most specifically applicable to those with this type of multiple epiphyseal dysplasia. It is now recognized that the clinical variability seen in Multiple Epiphyseal Dysplasia is paralleled by even greater molecular heterogeneity. The latter is summarized under Genetics and Molecular Biology, below.

MEDICAL ISSUES AND PARENTAL CONCERNS TO BE ANTICIPATED

PROBLEM: **GROWTH**
EXPECTATIONS: Initial growth in infancy and early childhood is often normal. Minimal to moderate short stature is usual, with adult heights ranging from about 135 cm to 155 cm. A

substantial minority of affected individuals are of normal stature. Head growth is normal.
MONITORING: There are no growth charts available. Plotting linear growth on regular growth standards may provide some guide to whether growth velocity is being maintained.
INTERVENTION: There is no known specific treatment. Growth hormone etc. is not likely to be effective since this disorder is secondary to intrinsic abnormality of bone growth. Limb lengthening has been used occasionally but remains controversial.

PROBLEM: **HIPS**
EXPECTATIONS: Hip pain is often the first presenting symptom. Stiffness, abnormal gait (waddling) and limping may also be the first recognized characteristics in early childhood. In addition to the intrinsic and constant abnormalities of the hip, Perthes disease develops in a substantial minority. In fact, Multiple Epiphyseal Dysplasia is the most common cause of bilateral Perthes disease. Hip degeneration and premature osteoarthritis is nearly uniform, often arising in early adolescence.
MONITORING: Periodic clinical history regarding severity of pain and functional difficulties should be sought. Radiologic assessment can be reserved for those with symptoms.
INTERVENTION: Limitations of repetitive weight bearing activities and other activities that result in repetitive stress on the hips, such as rope jumping, trampoline use etc., can slow degenerative arthritic change. Low impact or no impact aerobic activities should be encouraged. Collision sports and other activities that result in a high risk for joint injury should be proscribed since such trauma can further predispose to degenerative arthritic changes. Because all collagens require vitamin C as a co-factor for post-translational modification, it may be beneficial to supplement (a vitamin C rich diet in childhood; an additional 1000 mg of vitamin C per day in adolescence and adulthood), particularly in those with demonstrated mutations in type 9 collagen. Glucosoamine may also be of some benefit in delaying onset of or decreasing severity of osteoarthritis, but this remains controversial. Pain management is the same as in idiopathic osteoarthritis. If Perthes disease develops this is treated with traditional methods (a period of non-weight-bearing and physical therapy followed by abduction bracing). Use of a motorized scooter for long distance mobility is warranted whenever osteoarthritic problems become severe – sometimes as early as adolescence. Many will have total hip replacement, often in the 30s or 40s.

PROBLEM: **OTHER LARGE JOINT SYMPTOMS**
EXPECTATIONS: More generalized osteoarthritis is common, particularly in the knees and the shoulders. As with Perthes developing in the hips, osteochondritis dessicans may develop in the knees.
MONITORING: Clinical monitoring. Radiologic assessment may help predict the severity of problems that can be expected – for example, the shape of the proximal humerus and humeral head is an excellent sign to assess likelihood of and severity of shoulder arthritis later in life; likewise the degree of fragmentation of the femoral head allows prediction in late childhood of how severe osteoarthritic changes will become in the ensuing decades.
INTERVENTION: The usual treatments for osteoarthritis are applicable, but may need to commence in adolescence and young adult life (see above, under Hips).

PROBLEM: **LEG POSITIONAL ABNORMALITIES**
EXPECTATIONS: Beginning after orthograde weight bearing, nearly all develop some knee and leg position abnormality, but these are usually relatively mild. Either varus deformity (bowleg) or valgus deformity (knock-knee) may develop. Progressive deformity may arise and may be sufficiently severe in some older children to warrant surgical intervention.
MONITORING: Monitor clinically for alignment, development of chronic knee pain, limitation of ambulation (usually secondary to pain).
INTERVENTION: Surgery should be reserved for those with severe and symptomatic mal-alignment. Various techniques may be appropriate including use of 8-plates, hemiepiphyseal stapling, angular osteotomies, etc.

PROBLEM: **SMALL JOINT CHANGES**
EXPECTATIONS: Hands may be short with particularly short fingers. There is often mild generalized hypermobility (particularly in those with *COMP* mutations).
MONITORING: Function is usually fine, but some individuals may experience moderate fine motor difficulties or fatigue secondary to efforts to stabilize intrinsically unstable small joints.
INTERVENTION: Usually none is needed. Minor adaptations for fine motor activities in school may be needed.

PROBLEM: **ADAPTIVE**
EXPECTATIONS: In general short stature is not so severe that major environmental adaptations are needed.
MONITORING: Assess for age appropriate needs.
INTERVENTION: School adaptations, stools, etc. if needed.

GENETICS AND MOLECULAR BIOLOGY

Multiple Epiphyseal Dysplasia is relatively common, arising in around 1 in every 10,000 individuals. Multiple epiphyseal dysplasia is usually caused by an autosomal dominant gene abnormality. This means that an adult with this disorder will have a 50% chance to pass this poorly functional gene on to each child.

Infrequently an individual with this disorder will be born to average statured parents. Sometimes this arises because if a new chance change (mutation) in a single egg or single sperm giving rise to the affected individual. More often it is because there are autosomal recessive forms of Multiple Epiphyseal Dysplasia. Given the complexities of accurate diagnosis of subtypes of this disorder, diagnostic evaluation in a bone dysplasia center prior to any counseling regarding recurrence risk is essential.

Thus far changes in 6 different genes are known to cause Multiple Epiphyseal Dysplasia. These include:

1. *Cartilage Oligomeric Matrix Protein (COMP).* Mutations in *COMP* also cause a

somewhat more severe disorder, Pseudoachondroplasia. Probably around 15-30% of all Multiple Epiphyseal Dysplasia results from *COMP* changes.

2. *Col9A1, Col9A2, Col9A3.* These three genes, together, code for the type 9 collagen trimer. Together, these are likely the second most common cause of Multiple Epiphyseal Dysplasia, accounting for 10-20% of instances.
3. *Matrilin-3 (MATN3).* This is a rare cause of fairly mild Multiple Epiphyseal Dysplasia.
4. *DTDST.* This is the one clearly identified cause of autosomal recessive Multiple Epiphyseal Dysplasia. Mutations in this gene also cause diastrophic dysplasia and a number of other far more severe bone growth disorders. Perhaps 15% of all Multiple Epiphyseal Dysplasia is accounted for by changes in *DTDST*.
5. Around ½ of all individuals with Multiple Epiphyseal Dysplasia will have no identifiable change in any of these known genes. It is for this reason, in particular, that Multiple Epiphyseal Dysplasia remains a clinical and radiologic diagnosis.

There are subtle radiographic differences among the known molecular causes of Multiple Epiphyseal Dysplasia. For example, those with *COMP* mutations have more hip involvement, those with *col9* mutations have more abnormality at the knees and those with *DTDST* mutations have a characteristic double patella. These and other differences can be used to guide molecular diagnostic assessment. More importantly, while features of the different forms of Multiple Epiphyseal Dysplasia overlap, certain distinctions based on the gene causing the disorder are evident:

1. Those secondary to *COMP* tend to be of smaller stature, while those secondary to *MATN3* are associated with normal stature.
2. *Col9* mutations tend to result in milder and later onset joint manifestations than other forms.
3. Myopathy seems to be associated with Multiple Epiphyseal Dysplasia caused by changes in *MATN3* or *col9A3*.
4. Joint stiffness, rather than loose jointedness, is usually seen when Multiple Epiphyseal Dysplasia is caused by mutations in *DTDST*.
5. Clubfoot is common in association with *DTDST* Multiple Epiphyseal Dysplasia but is virtually never seen in any other forms.