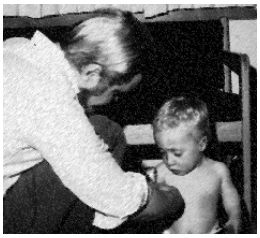

Richard M. Pauli, M.D., Ph.D.,
Midwest Regional Bone Dysplasia Clinics
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DIASTROPHIC DYSPLASIA
NATURAL HISTORY

INTRODUCTION:

The following summary of the medical expectations in Diastrophic 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].

Diastrophic Dysplasia is a severe dwarfing disorder. Although it does result in small stature, in fact, the more problematic issues in this disorder are joint related. It arises because of a gene change that results in abnormalities of the extracellular matrix that, in turn, give rise to abnormalities of the joints – deformation under loading (such as weight bearing), abnormal mobility, and early and severe degenerative changes.

Our understanding of the medical issues in Diastrophic Dysplasia is, to a large extent, dependent upon studies done in Finland. This is the most common dwarfing disorder in those of Finnish descent. Unfortunately, it is not certain whether everything learned from evaluation of affected Finns is applicable to affected individuals in other countries. Most affected individuals of Finnish descent are homozygous for the same mutation in the both copies of the gene that causes Diastrophic Dysplasia, while most individuals in other populations have diverse mutations. This may result in differences in severity, in variability etc., which currently cannot be taken into account.

MEDICAL ISSUES AND PARENTAL CONCERNS TO BE ANTICIPATED

PROBLEM: **GROWTH**
EXPECTATIONS: Anticipated average height is around 46-48 inches. However, there is extreme variability with some individuals above 60 inches. There are two diagnosis specific growth grids available; unfortunately one is based on a limited number of individuals (n=72) while the other is

exclusively based on Finnish individuals. The latter may not be applicable to all populations (and, indeed, shows considerably higher height ranges than seems typical in the U.S.).
MONITORING: Length/height monitoring should occur at least every six months using one of the available diagnosis specific linear growth grids.
INTERVENTION: As an intrinsic abnormality of bone and cartilage, growth hormone therapy would not be expected to be of any benefit. No growth hormone trials have been carried out. Extended limb lengthening, which may be a consideration in some bone dysplasias, has not been utilized in Diastrophic Dysplasia and likely is contraindicated given response to surgery in general (see below).

PROBLEM: **CENTRAL NERVOUS SYSTEM AND COGNITIVE FUNCTION**
EXPECTATIONS: There are no abnormalities of the brain, no risk for hydrocephalus and no significant risk for cognitive abnormalities.
MONITORING: Anticipate severe gross motor and fine motor delays based on biophysical differences; for example, average age for independent walking is around 24 months. There are crude diagnostic specific standards for motor development available.
INTERVENTION: Physical therapy with *gentle* range of motion activities should begin early in life. Occupational therapy for activities of daily living and for fine motor and adaptive needs, particularly related to hand abnormalities, will be needed later.

PROBLEM: **RESPIRATORY**
EXPECTATIONS: Laryngotracheobronchomalacia is common in infancy. Indeed, the increased mortality that seems to be present in the first year of life may arise solely on the basis of unappreciated airway compromise.
MONITORING: Historical and clinical assessment of respiratory status should be done early in infancy.
INTERVENTION: If stridor or distress seems apparent then involvement of a pediatric pulmonologist should be obtained.

PROBLEM: **PALATE**
EXPECTATIONS: About 30-60% have cleft palates.
MONITORING: Early physical assessment.
INTERVENTION: If present, the cleft should be closed at the usual time. If present, there is a high risk for middle ear dysfunction. Any child with palatal abnormality should have behavioral audiometry and tympanometry beginning at around 9-12 months of age and around every 6 months thereafter. If persistent serous otitis develops, early myringotomy and tube placement is appropriate.

PROBLEM: **DENTAL AND ORTHODONTIA**
EXPECTATIONS: About one-third will have hypodontia. Many will develop bite abnormalities, most commonly a narrow anterior palate, open bite and cross bite abnormalities.
MONITORING: Initial pediatric dentistry and orthodontic assessment by around 5 years of age.

INTERVENTION: Palatal expansion may be an option. Traditional orthodontia will usually be needed. Orthognathic surgery is sometime appropriate in later childhood or early adulthood.

PROBLEM: **EAR ABNORMALITIES**
EXPECTATIONS: Most infants develop cystic changes of the ears. These are of no functional significance. Over time these will transform into stiff, 'cauliflower' ears.
MONITORING: Anticipate such changes for the parents.
INTERVENTION: These *may* arise because of a predisposition to microcartilage damage secondary to minor trauma. Most likely the cystic changes arise from rubbing of the ears against bed sheets. If the parents wish, 'ear cups' may be fabricated to protect the ears for the first few months of life. Cystic changes are less likely to arise after this. If cystic changes develop, they should not be needled, drained etc., which treatments carry risk of further deformation, infection etc.

PROBLEM: **CERVICAL SPINE**
EXPECTATIONS: C-spine bifidity is exceedingly common and apparently of no clinical significance. Nearly all infants will have kyphosis of the cervical spine with an apex in the mid-cervical region. In around 20-30% this will progress and persist through childhood; in the remainder there is spontaneous resolution. In addition, there is intrinsic narrowing of the spinal canal in the cervical region and, in some, mild instability. These three features, together, mean that those with severe kyphosis are at risk for neurologic compromise secondary to cord compression and lower medullary compression, as well as at increased risk for trauma precipitated neurologic abnormality. The greatest risk appears to be in early to mid- childhood, since after that increasing degenerative changes negate the abnormal instability of the cervical spine that is initially present.
MONITORING: Lateral cervical spine radiographs (flexion, neutral and extension) should be completed at 3 mo, 6 mo and every 6 months thereafter until around 4 years of age. In those with marked kyphosis, careful neurologic examination for signs of cervical myelopathy must be completed every 3-6 months. In those with kyphosis, special care to prevent head and neck injury should be discussed with the family.
INTERVENTION: Should any signs of cervical myelopathy develop, cervical fusion with or without decompression will be needed, sometimes urgently.

PROBLEM: **THORACOLUMBAR SPINE**
EXPECTATIONS: Scoliosis or kyphoscoliosis is exceedingly common, with around 7 out of every 8 individuals showing a significant curvature. Kyphoscoliosis may be of very early onset, often within the first two years of life, with around 10% showing a very early, rapidly progressive curve.
MONITORING: Clinical evaluation should be at least every six months, with radiographs whenever any clinical evidence for a curve developing arises. Monitoring must be compulsive (e.g. clinical and radiologic reassessments every 6 months) in those who develop curves, so that timely surgical fusion can be carried out.

INTERVENTION: Aggressive bracing often will be needed, although overall the results of bracing have been discouraging. At best, bracing may delay the time of surgical intervention. Combined anterior and posterior surgical approaches will frequently be needed.

PROBLEM: **HIPS**
EXPECTATIONS: Some newborns will have severe hip flexion contractures. In most, hip flexion contractures, if not present initially, will nonetheless develop early. Hip dysplasia develops in many, often at the time of the assumption of orthograde posture. Sometimes there will be frank dislocation. More often there will be progressive degenerative changes. Avascular necrosis frequently becomes evident.
MONITORING: Evaluate hip mobility in infancy. Orthopedic and radiologic assessment of the hips should occur within the first year of life, again after assumption of orthograde posture and then at least yearly thereafter.
INTERVENTION: Gentle physical therapy for hip flexion contractures may have modest benefit. There is great controversy about the best way of managing the chronic, progressive hip problems (dysplastic changes, progressive limitation of movement). Some advocate aggressive, sequential bony surgeries, while others suspect that such surgery ultimately does not result in marked improvement of function. Limited experience suggests that extensive soft tissue releases (similar to that used in children with cerebral palsy) may be of some benefit. Total hip arthroplasty can be done successfully in adults.

PROBLEM: **KNEES**
EXPECTATIONS: Initially there is instability of the knee. Then, over time, stiffness develops. Because of the presence of hip flexion contractures, knee flexion contractures and equinus deformity of the feet, individuals will often have a metastable "Z-posture" – secondary to flexion at the hip, flexion at the knee and toe walking. Sometimes there is frank, persistent dislocation of the patella. In later childhood degenerative arthritic changes arise.
MONITORING: Evaluation of knee mobility in infancy and throughout early childhood should occur. Orthopedic assessment of the knees should occur within the first 2 years of life, and then at least yearly thereafter.
INTERVENTION: It is not clear what, if anything should be done related to the abnormalities of knee position and function. Extension osteotomies should be considered if the knee flexion contractures are sufficiently severe to limit ambulation. Patellar dislocation might be effectively surgically treated. Total knee arthroplasty can be done successfully in adults.

PROBLEM: **CLUBFOOT**
EXPECTATIONS: More than 90% are born with club foot abnormality, usually severe and usually associated with great toe malposition.
MONITORING: Assess clinically.
INTERVENTION: Often the clubfoot is resistant to usual surgeries and will frequently recur after surgery. Initiate physical therapy for range of motion immediately. Anticipate early orthopedic surgical correction, which will need to be aggressive and radical. Such surgery should only be undertaken by an experienced pediatric orthopedist. Often multiple surgeries will be needed with

various salvage procedures used in an attempt to establish plantigrade feet. Custom fitted shoes are usually needed.

PROBLEM: **HANDS**
EXPECTATIONS: 'Hitchhiker' thumbs are nearly constant. Generalized extension camptodactyly (fingers fixed in extension) is usual.
MONITORING: Clinical assessment
INTERVENTION: Physical therapy with *gentle* range of motion activities begun early in life may be of limited benefit. Occupational therapy for fine motor and adaptive needs related to hand abnormalities will be needed. Various adaptive devices may be needed, although children often show remarkable fine motor abilities despite severe abnormalities of position and mobility. Allowing children to find such alternative adaptive strategies to compensate for their limited finger mobility is appropriate. Surgery is probably always contraindicated and may cause further harm.

PROBLEM: **MIGRATORY ARTHRALGIAS**
EXPECTATIONS: There has been little documentation of this problem, but it seems to be quite common.
MONITORING: -
INTERVENTION: Use of nonsteroidal anti-inflammatory agents appears to be effective. Morning arthralgias may be benefited by use of an egg crate mattress, first morning warm baths, etc.

PROBLEM: **RISKS OF SURGERY**
EXPECTATIONS: Although controversial, experience and the molecular basis of diastrophic dysplasia both suggest that individuals with this disorder can not respond normally to cartilaginous damage. It is conceivable that this is the reason that the results of surgery are often disappointing. Indeed, this suggests that the fewest possible number of bony and cartilaginous procedures should be done.
MONITORING: -
INTERVENTION: Limit the number of surgeries on bone and cartilage to those clearly essential for function.

PROBLEM: **ADAPTIVE**
EXPECTATIONS: Considerable psychological and physical adaptive needs may arise later in childhood.
MONITORING: Assess for age appropriate needs.
INTERVENTION: School adaptations, stools, adaptations for toileting, adaptations for dressing and undressing, occupational therapy monitoring, motorized scooter for long distance mobility, teacher involvement, Little People of America involvement.

GENETICS AND MOLECULAR BIOLOGY

Diastrophic dysplasia is always an autosomal recessive disorder. As for other recessive conditions, there is a 25% risk that siblings of an affected individual will be similarly affected. No other family members should have any substantially increased risk. As noted, the diastrophic dysplasia gene is far more common in Finns (presumably secondary to a founder affect).

It is now known that diastrophic dysplasia is caused by mutations in what is termed the Diastrophic Dysplasia Sulfate Transporter (*DTDST*). Mutations in both copies of this gene result in decreased availability of substrates for sulfation and secondary decreased sulfation of proteoglycans. Other, more severe mutations in this same gene result in other, rare and more severe bone growth disorders including atelosteogenesis type II and achondrogenesis type I-B, while milder mutations cause a recessive type of multiple epiphyseal dysplasia.

Prenatal diagnosis (and preimplantation diagnosis using assisted reproductive technologies) can be accomplished by gene analysis. Ultrasonography is also a highly accurate prenatal diagnostic method.