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KNIEST DYSPLASIA
NATURAL HISTORY

INTRODUCTION:

The following summary of the medical expectations in Kniest 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].

Kniest Dysplasia is an infrequent bone dysplasia, which is particularly characterized by progressive stiffness and enlargement of various joints. In addition, it shares many other medical risks with other disorders of type II collagen (such as Spondyloepiphyseal Dysplasia, Congenita). Individuals will typically have both a short trunk and a constricted chest from birth and arms and legs that appear to be disproportionately long.

MEDICAL ISSUES AND PARENTAL CONCERNS TO BE ANTICIPATED

PROBLEM: **GROWTH**
EXPECTATIONS: Marked short stature is typical; ultimate adult height is usually between 100 and 140 cm (about 39 in to 55 in).
MONITORING: No diagnosis-specific growth grid is available.
INTERVENTION: No known treatment is effective. Growth hormone is not likely to be effective since this disorder is secondary to intrinsic abnormality of bone growth. Limb lengthening, suggested but controversial in other short stature syndromes, is probably not an option since much of the effects of this disorder is on spine growth not primarily the limbs. Therefore one can anticipate even more disproportion if the limbs are lengthened. Limb lengthening may also negatively affect already intrinsically abnormal joints.

PROBLEM: **DEVELOPMENT**
EXPECTATIONS: Intelligence is normal unless complications intervene. Variations in developmental patterns and particularly gross motor delays are to be expected because of the marked short stature.
MONITORING: Routine
INTERVENTION: None

PROBLEM: **NEUROLOGIC COMPLICATIONS**
EXPECTATIONS: There is considerable risk associated with frequent instability of the cervical spine, which, if present, can result in upper cervical cord compression [chronically or acutely] and consequent paralysis or related problems. Individuals with Kniest Dysplasia may have spontaneous 'auto-fusion' later resulting in limitation of neck movement.
MONITORING: Watch for signs of upper cervical myelopathy including lethargy, failure to thrive, marked hypotonia, decreased motor endurance, long track signs [asymmetric strength, asymmetric or increased deep tendon reflexes, sensory changes]. Lateral cervical spine films [flexion, neutral and extension] should be obtained in the first 6 months of life; if abnormal or equivocal, repeat as part of complete assessment every 6 months. Neurologic examination should be completed every 6-12 months if there is no apparent instability on x-rays or every 3 months if instability is present.
INTERVENTION: If instability is present, limit neck movement and uncontrolled head movement including no forced flexion with diaper changing, no swingomatic use, use of rear-facing car seat for as long as feasible. If instability is severe, cervical spine fusion is needed. When needed, this probably should be done before independent walking. There has been a high failure rate of fusions in disorders similar to Kniest dysplasia and consultation with specialists with experience in performing fusions in children with bone dysplasias should be sought.

PROBLEM: **RESPIRATORY**
EXPECTATIONS: Four problems, alone or in combination, may be present and may be life-threatening: a. laryngotracheobronchomalacia; b. micrognathia and the Robin sequence; c. diminished airway caliber; d. chest constriction. Infant deaths in those with Kniest dysplasia probably are secondary to airway insufficiency.
MONITORING: Complete pulmonologic assessment should be carried out in infancy including careful evaluation of the airway. Polysomnography should also be done in the first 6 months of life.
INTERVENTION: Aggressive treatment of lower respiratory infections; use of oxygen, cpap, bipap, tracheostomy, ventilator support etc. as indicated by polysomnography and clinical course are all appropriate. Tracheostomy is not infrequently needed in children with this disorder.

PROBLEM: **PROGRESSIVE JOINT LIMITATION**
EXPECTATIONS: Joints typically become more and more prominent with age. Arthropathy in the hands may begin in childhood and may result in fine motor problems. Knee flexion contractures and hip flexion contractures are common and often both progressive and severe. Most joint changes appear to be associated with narrowing of joint spaces and hence are bony limitations of

movement which will, in general, be unresponsive to physical therapy.
MONITORING: Clinical assessment every 6 months.
INTERVENTION: Long term physical therapy involvement. Occupational therapy interventions if hands are involved. Experience with extension osteotomy surgery and with soft tissue releases is very limited.

PROBLEM: **SPINE**
EXPECTATIONS: Exceedingly high risk for early onset kyphoscoliosis.
MONITORING: Examine the spine clinically about every 6 months. AP and lateral spine x-rays if there is any clinical indication of curve developing.
INTERVENTION: Aggressive and early bracing in childhood is appropriate. Often kyphoscoliosis will require surgical fusion.

PROBLEM: **HIPS**
EXPECTATIONS: Coxa vara is usual. Femoral head ossification is delayed, but the cartilaginous head is actually markedly enlarged, probably contributing to the limitation of movement seen. Virtually all have premature hip degeneration in young adulthood.
MONITORING: Radiologic assessment at around 4 years of age, or sooner if serious hip abnormality is suspected.
INTERVENTION: The aim is to have stable, pain free, functional hips. Surgical realignment (femoral valgus and extension osteotomies) is indicated if intractable pain or marked limits of mobility are present. Even in the absence of these indicators, realignment may make total hip replacement easier later. Limitations of repetitive weight bearing activities can slow degenerative arthritic changes.

PROBLEM: **PREMATURE ARTHRITIS**
EXPECTATIONS: In addition to severe hip changes, problems may also arise in knees, shoulders and hands.
MONITORING: Clinical monitoring.
INTERVENTION: Limitation of repetitive weight bearing may help preserve knees as well as hips. No specific therapies for hand involvement have been reported.

PROBLEM: **FEET**
EXPECTATIONS: Some will have clubfoot deformity.
MONITORING: Assess in infancy.
INTERVENTION: Not particularly resistant to usual orthopedic therapy.

PROBLEM: **CLEFT PALATE**
EXPECTATIONS: About 1/2 of individuals with Kniest dysplasia will have frank clefts.
MONITORING: If present, child is at greater risk for middle ear disease and hearing loss [see below].

INTERVENTION: If present, repair using the usual age and weight criteria.

PROBLEM: **HEARING LOSS**
EXPECTATIONS: Although usually middle ear disease related, some have a more significant sensorineural component. Even if no hearing loss is initially demonstrated, some individuals will develop a mixed and progressive loss at some time in childhood.
MONITORING: Audiometric testing at 12, 18 and 24 months and once yearly thereafter.
INTERVENTION: Episodes of acute or serous otitis should be aggressively treated and myringotomy and tube placement should be used liberally for recurrent or persistent problems. Amplification may be needed if mixed loss is more than very mild.

PROBLEM: **EYE PROBLEMS**
EXPECTATIONS: High myopia is the rule. There is a substantial risk for retinal detachments.
MONITORING: Ophthalmologic assessment within the first 6 months of life and then every 6-12 months. Immediate reevaluation for any recognized change in vision or other indicators of possible retinal detachment. The affected child and the child's parents should be taught the signs and symptoms of retinal detachment.
INTERVENTION: Early surgery for retinal detachment can be vision-saving.

PROBLEM: **ANESTHETIC MANAGEMENT**
EXPECTATIONS: There is a high probability that general anesthesia will be needed for surgical intervention(s). Risks relate primarily to cervical spine instability, midface retrusion which makes intubation even more challenging, limited respiratory reserve, and markedly small airways.
MONITORING/INTERVENTION: Assess cervical spine stability before any anesthesia and, if unstable or uncertain, intubation should be completed by bronchoscopic visualization with external neck stabilization. Insure that appropriately small endotracheal tubes are available (e.g. premie sizes for young children, pediatric size even when caring for adults). Anticipate that delayed extubation may be needed given limited respiratory reserve.

PROBLEM: **ADAPTIVE**
EXPECTATION: Considerable psychological and physical adaptive needs later in childhood. These may be worsened because of the progressive joint limitation that develops.
MONITORING: Assess for age appropriate needs.
INTERVENTION: Examples include reachers, adaptations for toileting, school adaptations, stools, teacher involvement, Little People of America involvement.
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GENETICS AND MOLECULAR BIOLOGY

Kniest dysplasia appears always to be 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. Not infrequently an individual with this disorder will be born to average statured parents; when this happens it arises because of a new chance change (mutation) in only the single egg or single sperm giving rise to the affected individual. Occasional instances of germinal mosaicism have been recognized (and, in some parents, the presence of the abnormal cell line can result in mild clinical features in them, similar to those seen in Stickler syndrome). Nevertheless, overall, average statured parents who have had one child with this disorder have only a minimal risk for it to recur in subsequent children.

Kniest dysplasia is one of a group of bone and cartilage disorders that are termed *Type II Collagenopathies.* That is, each member of this group of disorders (that also includes, e.g. Stickler syndrome, spondyloepiphyseal dysplasia, certain forms of achondrogenesis etc.) arises because of changes in the synthesis of type II collagen, coded for by the *col2A1* gene. Type II collagen is particularly important in the connective tissues of joints, in bone growth, in the airways and in the development of the eye.