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ELLIS VAN CREVELD SYNDROME NATURAL HISTORY

INTRODUCTION:

The following summary of the medical expectations in Ellis van Creveld syndrome 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].

Ellis van Creveld syndrome (also known as chondroectodermal dysplasia) is a rare, multisystem disorder. It probably affects only around 1 in every 150,000 individuals. While it arises in all ethnic and racial groups, it is exceptionally common among the Amish. It is characterized by a long, narrow trunk and shortened arms and legs; extra fingers (postaxial polydactyly), and abnormalities of the oral region and teeth. In infants, non-bony manifestations, particularly congenital heart defects, may be health or life-threatening.

MEDICAL ISSUES AND PARENTAL CONCERNS TO BE ANTICIPATED

PROBLEM: LIFE EXPECTANCY

EXPECTATIONS: There is a residual risk of death in the newborn period or in infancy although this is much less than the previously estimated 50% risk. Aggressive evaluation and intervention regarding cardiac and pulmonary status will minimize these risks. No life tables have been generated but there is no a priori reason to anticipate a decreased life expectancy in those without severe heart and lung problems.

PROBLEM: GROWTH

EXPECTATIONS: Moderate to marked short stature; ultimate adult height between about 3 feet 7 inches and 5 feet 3 inches (110 to 160 cm). The origin of this marked variability is unknown. It

seems that rarely individuals with Ellis van Creveld syndrome will also be growth hormone deficient.

MONITORING: Monitor growth to insure normal velocity. No diagnosis-specific growth standards are available. In those who are particularly small, consider growth hormone testing.

INTERVENTION: Growth hormone has been used occasionally but is not likely to be effective, since this disorder is secondary to intrinsic abnormality of bone growth, except in those with objectively defined growth hormone deficiency. Limb lengthening in adolescence is a theoretical possibility.

PROBLEM: DEVELOPMENT

EXPECTATIONS: Central nervous system abnormalities including hydrocephalus, Dandy Walker malformation and other anomalies have been reported occasionally. Nonetheless, in general, cognitive function is normal unless other life threatening events intervene. Variations in developmental patterns are to be expected because of short stature, limitations of finger mobility, orthopedic complications etc.

MONITORING: Routine unless other clinical features suggest the presence of a CNS structural abnormality, in which case magnetic resonance imaging may be appropriate.

INTERVENTION: None

PROBLEM: CONGENITAL HEART DISEASE

EXPECTATIONS: Occurs in about 40-60% of affected individuals. Most frequently ASD [more than 1/2] > single atrium > VSD > AV communis > other. This is the primary cause of death in infancy, but previous estimates of 50% mortality in this disorder did not take into account modern methods of management of cardiac and respiratory problems.

MONITORING: All affected infants need cardiologic assessment, including echocardiography as neonates.

INTERVENTION: When heart disease is found, usual cardiac care is indicated. Aggressive and careful management of this problem takes precedence over virtually all other issues during infancy.

PROBLEM: RESPIRATORY

EXPECTATIONS: At least three different respiratory problems may complicate infancy and early childhood. A constricted chest may cause chronic or intermittent hypoxemia secondary to restrictive lung disease. Less frequently laryngotracheobronchomalacia may cause stridor, obstructive symptoms etc. A small minority of babies with this disorder seem to have central abnormalities of respiratory control (for unknown reasons).

MONITORING: Initial evaluation in infancy should at least include chest circumference, clinical assessment of respiratory status and polysomnographic evaluation.

INTERVENTION: Depending on findings and the severity of abnormalities interventions that may be appropriate include home monitoring, parental training in CPR, oxygen supplementation, cpap or bipap, tracheostomy.

PROBLEM: EARS AND HEARING

EXPECTATIONS: Conductive hearing loss probably occurs at increased frequency.

MONITORING: Behavioral audiometric screening should be completed by one year of age and then repeated yearly thereafter until school age.

INTERVENTION: Usual methods of treating middle ear disease are appropriate. Occasional individuals will need hearing aids.

PROBLEM: POLYDACTYLY

EXPECTATIONS: There is nearly constant postaxial polydactyly of the hands; infrequently of the feet.

MONITORING: Radiologic documentation of bone relationships should be completed prior to surgical removal.

INTERVENTION: Removal of the extra digits surgically (not by simple ligation) is probably best done between around 2 years and 5 years of age.

PROBLEM: JOINT LIMITATION IN THE HANDS

EXPECTATIONS: This is secondary to abnormality of proportion and growth of the phalanges.

MONITORING: None

INTERVENTION: None. Surgery is clearly contraindicated and may cause considerable harm.

PROBLEM: VALGUS DEFORMITY

EXPECTATIONS: Valgus or knock-knee deformity is secondary to asymmetric proximal tibial growth plate function. It is often quite severe, progressive and functionally debilitating.

Malposition, recurrent subluxation, or dislocation of the patellae often accompany this valgus deformity.

MONITORING: This requires clinical monitoring throughout childhood. Radiologic and orthopedic assessment should be sought if valgus exceeds around 15°.

INTERVENTION: Surgery is appropriate if the valgus results in instability, non-remitting pain, marked abnormality of gait etc. Surgical correction is by proximal tibial osteotomy (with either internal or external fixation). Sometimes corrective osteotomies of the femurs are needed, too.

Surgery should be delayed as long as possible since recurrence is very likely given the primary cause. Repeat surgical intervention is frequently needed.

PROBLEM: OTHER ORTHOPEDIC PROBLEMS

EXPECTATIONS: These may include foot position abnormalities, radial head dislocation, other long bone bowing etc.

MONITORING: Clinical assessment.

INTERVENTION: Usually none.

PROBLEM: NAIL ABNORMALITIES

EXPECTATIONS: Usually markedly hypoplastic without significant growth. Only relevance is cosmetic.

MONITORING: None.

INTERVENTION: None. Most often, artificial nails can not be adequately fitted.

PROBLEM: FRENULA, MIDLINE PSEUDOCLEFT OF THE UPPER LIP, ALVEOLAR AND GINGIVOLABIAL ABNORMALITIES, BIFID TONGUE TIP

EXPECTATIONS: Upper gingivolabial fusion is the most common abnormality. While almost always present, this and other orofacial features infrequently are of clinical importance. They seem not to interfere with eating, speech development etc. However, gingivolabial adhesions/continuity may prevent appropriate prosthodontic fittings.

MONITORING: Determination by pediatric dentist and/or prosthodontist of need for intervention.

INTERVENTION: Plastic surgical reconstruction if indicated.

PROBLEM: TEETH ABNORMALITIES

EXPECTATIONS: Can include natal teeth (that usually should be removed), absent teeth (hypodontia), malformed teeth, enamel and dentin abnormalities, predisposition to caries. Missing teeth are particularly important with respect to articulation and to appearance and self-image.

MONITORING: Early involvement with a pediatric dentist is essential.

INTERVENTION: Routine care should include aggressive use of sealants, fluoride. Fitting for prosthetics should be done as needed (including in childhood).

PROBLEM: RENAL

EXPECTATIONS: Low incidence of structural abnormalities of the kidneys. Low incidence of renal tubular abnormalities.

MONITORING: Early renal ultrasound. Urinalysis and urine for amino acids to assess for general renal tubular function.

INTERVENTION: Rarely needed.

PROBLEM: ADAPTIVE

EXPECTATIONS: Considerable psychological and physical adaptive needs later in childhood.

Hypodontia may create psychological barriers if not appropriately treated. Many children seem to be bothered more by teeth and nail abnormalities than their limited growth.

MONITORING: Assess for age appropriate needs.

INTERVENTION: Small stature may be sufficient to warrant adaptive interventions for toileting, school adaptations, stools, teacher involvement, Little People of America involvement. Psychological support as needed.

GENETICS AND MOLECULAR BIOLOGY

Ellis van Creveld syndrome appears always to be caused by an autosomal recessive gene abnormality. This means that parents of an affected child will have a 25% chance that each subsequent child will be similarly affected. No one else in the family should have significantly increased risk.

Genes responsible for Ellis van Creveld syndrome have been identified. The two characterized genes, *EVC* and *EVC2* (the latter also called *LBN*), are dissimilar genes both of which, however, are located very near one another on chromosome segment 4p16 and seem to have coordinate function. Individuals with mutations in *EVC* are clinically indistinguishable from those with mutations in *EVC2*. About 70% of affected individuals will have demonstrable mutations in one or the other of these genes (about equally divided). That nearly 1/3 of unequivocally affected individuals have no identifiable mutation in either gene suggests that an additional gene (or genes) is still to be identified.

Heterozygotes (carriers) of mutations in *EVC* or *EVC2* are usually without clinical features. However, sometimes they display characteristics of a milder disorder which was previously described and named Weyers dysostosis. Therefore, rarely parents of an affected child will have related, more subtle clinical abnormalities.