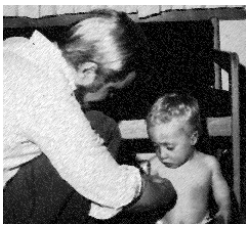

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CAMPOMELIC DYSPLASIA
NATURAL HISTORY

INTRODUCTION:

The following summary of the medical expectations in Campomelic 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].

Campomelic Dysplasia has been considered to be a lethal process. It should, rather, be thought of as a 'sublethal' condition. This change in thinking is partly because of marked improvement in care, particularly for the respiratory complications that this disorder can cause. In addition, there were initial ascertainment biases – more severe (and lethal) instances were recognized while milder ones were often not diagnosed or were diagnosed with a related disorder called ischio-pubic-patellar syndrome. Primary characteristics of Campomelic Dysplasia include, among many, bowing of the femora and tibiae, pretibial skin dimples, hypoplasia of the scapulae, and, in chromosomal males, sex reversal.

MEDICAL ISSUES AND PARENTAL CONCERNS TO BE ANTICIPATED

PROBLEM: **SURVIVAL**
EXPECTATIONS: Most infants with this disorder die, apparently secondary to respiratory insufficiency. Various factors contribute to those risks (see below). Many die in the first days of life, some over the course of the first year. Few of those who survive beyond the first year are free of severe sequelae. Those found to have chromosomal translocations rather than point mutations (see under Genetics and Molecular Biology below) seem to have higher probability of survival.
MONITORING: Anticipatory guidance and counseling of the family.

INTERVENTION: In depth discussions with the family are essential, including consideration of generation of an Advance Directive, copies of which should be placed at all clinics and hospitals where the infant may be cared for.

PROBLEM: **RESPIRATORY PROBLEMS**
EXPECTATIONS: Many factors contribute to severe respiratory risks. The chest is often markedly constricted. The airways are diminished in size and there may also be severe laryngotracheo-bronchomalacia. The mandible is often very small and subsequent retroglossia can cause upper airway obstruction. And there may be abnormalities of central respiratory control (central apnea) because of abnormalities of the cranial base. All may contribute to immediate neonatal risk of death and, in survivors, to long term sequelae.
MONITORING: Evaluation *in survivors of the neonatal period* should include: polysomnography; bronchoscopy in those with apparent severe airway involvement.
INTERVENTION: May include symptomatic management with oxygen supplementation, use of cpap or bipap, tracheostomy, long term ventilator support, etc. Surgical chest expansion/rib interposition has not been shown to be of benefit. Airway infections should be aggressively treated. All infants with this diagnosis should be considered for RSV prophylaxis. Immunizations should be given, particularly for infections that could further compromise limited respiratory reserve.

PROBLEM: **ANESTHESIA RISKS**
EXPECTATIONS: Many infants may require surgery. Risks include those related to the airway and to the cervical spine.
MONITORING: The cervical spine should be assessed for stability with plain lateral x-rays (flexion, neutral and extension) prior to administration of anesthesia. Flexible bronchoscopy should be done prior to intubation.
INTERVENTION: Weaning and extubation need to be carried out cautiously.

PROBLEM: **CENTRAL NERVOUS SYSTEM AND DEVELOPMENT**
EXPECTATIONS: Many have structural anomalies (most commonly arhinencephaly, which, incidentally, will be associated with absence of olfaction). With or without structural aberrations, survivors may show serious developmental abnormalities, with profound variability from survivor to survivor. It is not clear what contributes to developmental abnormalities (primary vs. secondary to sequelae of hypoxia etc.). At least some survivors are cognitively normal, however.
MONITORING: A periodic formal developmental evaluation throughout infancy and early childhood is appropriate.
INTERVENTION: Infant stimulation should begin early. Other interventions should be initiated as indicated by the periodic developmental evaluations.

PROBLEM: **CHONDROCRANIUM AND CRANIOCERVICAL JUNCTION**
EXPECTATIONS: The skull base is clearly small, but little assessment has been documented.

Structure suggests that there may be risk for craniocervical junction compression with secondary hypotonia and/or abnormalities of central respiratory control. There may also be risk for cervical spine instability.
MONITORING: Plain x-rays of the cervical spine (flexion, neutral and extension lateral views) should be completed in the first six months and, in general, about every 6-12 months thereafter. Survivors should have magnetic resonance imaging of the craniocervical junction.
INTERVENTION: If craniocervical compression is documented, consider suboccipital decompressive surgery. If there is severe c-spine instability, surgical fusion may also be needed.

PROBLEM: **GROWTH**
EXPECTATIONS: All survivors are of small stature (sometimes markedly so).
MONITORING: No diagnosis specific growth grids are available. Intrinsic growth deficiency may be complicated by the cardiorespiratory problems that many have. Hormonal therapy in general is not appropriate.
INTERVENTION: -

PROBLEM: **SPINE**
EXPECTATIONS: Scoliosis and kyphosis are exceedingly common in survivors.
MONITORING: Clinical monitoring at each visit. Thoracolumbar spine x-rays should be obtained if progressive scoliosis or kyphosis is detected clinically.
INTERVENTION: Usual treatment. Note, however, that bracing may be problematic because of effects on respiration, curves are usually high and difficult to treat with a brace, and complications including pseudarthroses and paralysis are fairly common after surgical treatment.

PROBLEM: **HIP DISLOCATION**
EXPECTATIONS: Common.
MONITORING: AP and frogleg hip x-rays in infancy.
INTERVENTION: Usual, non-surgical orthopedic treatment is usually effective.

PROBLEM: **LOWER LEGS AND FEET**
EXPECTATIONS: Tibial bowing is often not sufficiently severe to require surgery. There may be complex alignment abnormalities of the ankle. Clubfoot is virtually constant.
MONITORING: Clinical orthopedic assessment.
INTERVENTION: Early initiation of passive range of motion and usual surgical intervention are appropriate for the clubfoot deformity.

PROBLEM: **RADIAL HEAD DISLOCATION**
EXPECTATIONS: Exceedingly common, it may result in limited elbow movement.
MONITORING: -
INTERVENTION: No treatment is indicated.

PROBLEM: **HEARING**
EXPECTATIONS: This is an under-documented but serious concern. It likely arises because of a combination of structural aberrations and recurrent middle ear dysfunction, particularly in those with cleft palate. It may be a significant contributor to speech and language delays in survivors.
MONITORING: All infants should have newborn screening of hearing. Periodic behavioral testing should begin by around 9-12 months of age.
INTERVENTION: Amplification (aids) should be fitted in those with significant hearing loss Middle ear abnormalities (infection, fluid) should be treated aggressively, including having a low threshold for myringotomy and tube placement.

PROBLEM: **CLEFT PALATE**
EXPECTATIONS: Present in about 1/3 of infants with this disorder. Micrognathia is also quite common and at least in some the combination is appropriately designated as the Robin sequence.
MONITORING: -
INTERVENTION: Closure based on the usual criteria of age and weight is appropriate if general health status allows.

PROBLEM: **CARDIOVASCULAR ANOMALIES**
EXPECTATIONS: Present in about 1/4 of infants with this disorder.
MONITORING: Echocardiography and cardiologic assessment should be completed in infancy.
INTERVENTION: Usual medical management if anomalies are discovered.

PROBLEM: **RENAL ANOMALIES**
EXPECTATIONS: Affected children may have congenital anomalies or acquired problems including secondary to vesicoureteral reflux.
MONITORING: Complete renal ultrasound in infancy, and probably yearly thereafter in survivors.
INTERVENTION: Usual medical management if problems identified.

PROBLEM: **GASTROESOPHAGEAL REFLUX**
EXPECTATIONS: Present in many, this may complicate feeding. It may increase risk for aspiration in pulmonologically fragile infants.
MONITORING: By medical history. Further assessment (swallow and reflux studies etc.) should be undertaken in those with a worrisome history.
INTERVENTION: Consider both medical (reflux precautions, pharmacologic management) and surgical (fundoplication) treatment.

PROBLEM: **SEX REVERSAL**
EXPECTATIONS: Many phenotypic females are found to be 46 XY. Indeed, in around 70% of individuals with a 46 XY chromosome makeup there is complete sex reversal. In females who are 46 XY there is a high risk of gonadoblastoma. Some 46 XY males have structural genital

abnormalities (such as hypospadias and/or micropenis).
MONITORING: Chromosomal evaluation.
INTERVENTION: Early gonadectomy in all 46 XY females.

GENETICS AND MOLECULAR BIOLOGY

Campomelic dysplasia is caused by abnormal functioning of a gene called *SOX9.* This gene codes for a transcription factor that is particularly important in bony cartilage and the testes. Both point mutations and various chromosomal rearrangements and deletions of chromosome 17, where this gene resides, have been found in individuals with campomelic dysplasia. Chromosomal assessment and array based comparative genomic hybridization of the 17q region probably should be completed in all affected individuals, since those with microscopically demonstrable chromosomal abnormalities seem to be less severely affected and may have a better chance for long term survival than those with point mutations within the *SOX9* itself. The phenotypic features of campomelic dysplasia arise secondary to inactivation of one copy of the *SOX9* gene.

Most instances arise because of new changes (mutations) affecting *SOX9.* Not surprisingly, then, recurrence risk is low, estimated to be 5% or less in subsequent pregnancies of couples who have had one affected child. Infrequent recurrences appear to arise secondary to germinal mosaicism in either parent, to rare chromosomal rearrangements in a parent or to exceedingly mild manifestations in a parent.