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JEUNE ASPHYXIATING THORACIC DYSTROPHY (JEUNE SYNDROME) NATURAL HISTORY

INTRODUCTION:

The following summary of the medical expectations in Jeune 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].

Jeune Syndrome is a rare, specific, multisystem disorder. The term ‘asphyxiating thoracic dystrophy’ has been used both as a synonym for Jeune Syndrome and, particularly in the surgical literature, as a generic diagnostic term for any instance of a severely constricted chest. Use in this latter sense should be abandoned.

Clinically individuals with this disorder have small, constricted chests, mildly shortened limbs and, in around 20% of affected individuals, postaxial polydactyly. Radiographic assessment allows for confirmation of diagnosis, with the following characteristics typically found: bell shaped thorax; handlebar clavicles; horizontal, bulbous and very shortened ribs; mildly shortened long bones; characteristic pelvic configuration including flared and hypoplastic ilia, flat acetabula with double spike-like projections; coning of epiphyses of the hands (at a later age).

There is marked variability of severity, ranging from early lethality to very modest medical problems. At the severe end of the spectrum, Jeune Syndrome blends into what was thought to be a separate and independent, uniformly lethal process called Short Rib Polydactyly type III. In fact, these have shared molecular cause and can be thought of as a continuum of manifestations of the same cause.

MEDICAL ISSUES AND PARENTAL CONCERNS TO BE ANTICIPATED

PROBLEM: LIFE EXPECTANCY

EXPECTATIONS: No formal mortality studies have been done. Overall it appears that ½ to ¾ of those diagnosed with Jeune Syndrome die secondary to complications of the disorder. Most of

those deaths are in the first 2 years of life and most are secondary to respiratory complications.

MONITORING: see under Respiratory

INTERVENTION: see under Respiratory

PROBLEM: GROWTH

EXPECTATIONS: Small stature is usual but is usually not severe. There is considerable variability and some may reach normal range of stature.

MONITORING: No diagnostic specific growth grids have been generated.

INTERVENTION: There is no known treatment.

PROBLEM: RESPIRATORY

EXPECTATIONS: Many, perhaps 75%, have severe restrictive pulmonary disease secondary to a constricted chest. However, others have only mild or minimal respiratory difficulty. In those who do not have life-threatening problems in infancy, the pulmonologic problems are non-progressive and should not cause subsequent problems.

MONITORING: Early comprehensive pulmonologic assessment is critical. Adequacy of ventilation needs to be assured. Pulmonary function testing should be completed at around 6-7 years of age and then every 3-4 years until maturity.

INTERVENTION: In some, the restrictive lung disease is sufficiently severe that emergent treatment is needed, including intubation, ventilator support, tracheostomy etc. Long term tracheotomy may allow for both survival and improvement of overall pulmonary function (primarily by elimination of dead space).

In those with severe insufficiency, various chest expansion procedures have been used, including, for example, use of a vertical expandable prosthetic titanium rib (VEPTR). In the severely affected this may be lifesaving. However, complication rates are very high and there have been no adequately controlled studies to demonstrate that, on net, use of this procedure is appropriate. If used, then additional surgery for lengthening will be needed around every 6 months until maturity. There is, of course, no justification for any thoracic expansion procedures in children with stable pulmonary status, since these problems are not progressive and children do not 'outgrow' their chest size.

PROBLEM: RENAL

EXPECTATIONS: Around 30% of surviving individuals develop renal abnormalities. Most often these are described as cystic dysplasia or nephronophthisis. Usually this has been recognized in later childhood. Renal failure may eventually result.

MONITORING: Creatinine, BUN, urinalysis and renal ultrasound at time of diagnosis. Yearly creatinine, BUN and urinalysis thereafter. Blood pressure assessment at every health care contact

INTERVENTION: Referral to nephrology for management if renal involvement becomes evident.

Renal transplantation probably is an option, although little is available in the literature concerning this.

PROBLEM: HEPATIC

EXPECTATIONS: A smaller proportion of affected individuals have evidence for liver problems – dysgenesis, cirrhosis or fibrosis. It is not clear how often this becomes a health threatening issue.

MONITORING: Complete blood tests including direct and indirect bilirubin, and liver enzymes yearly. Referral to a hepatologist for management if liver abnormalities become evident.

INTERVENTION: Ursodeoxycholic acid treatment has been used in those with identified liver disease.

PROBLEM: OPHTHALMOLOGIC

EXPECTATIONS: Rod-cone dystrophy (retinitis pigmentosa) has been described in a number of individuals with Jeune Syndrome. It is not clear how common this complication is, but it is probably infrequent. It has arisen as early as at 5 y of age. It may lead to night blindness, tunnel vision etc.

MONITORING: Ophthalmologic assessment at the time of diagnosis and then every 3 years thereafter. Electroretinography should be completed at around 6-7 y of age.

INTERVENTION: If progressive rod-cone dystrophy arises, various adaptations, school modifications, involvement of a low vision specialist etc. will be needed.

PROBLEM: INTESTINAL MALABSORPTION

EXPECTATIONS: While described, malabsorption is probably infrequent.

MONITORING: Clinical

INTERVENTION: -

GENETICS AND MOLECULAR BIOLOGY

Jeune Syndrome is an autosomal recessive disorder. This means that affected children are born to unaffected parents, and that a couple who has had one child with Jeune Syndrome will have a 25% chance that each subsequent child will be affected. Variability even within the same sibship can be very great – so that one child might be quite mildly affected and another within the same family may have life-threatening complications.

Recently two causal genes were identified – *IFT80* and *DYNC2H1*. Curiously both of these make products that are critical for ciliary function. How ciliary dysfunction results in the clinical manifestations of Jeune Syndrome is currently unknown. Additional genes that when poorly functional cause Jeune Syndrome will likely be identified in the future.