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SHWACHMAN SYNDROME NATURAL HISTORY

INTRODUCTION:

The following summary of the medical expectations in Shwachman Syndrome (Shwachman-Diamond Syndrome, Shwachman-Bodian-Diamond 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 individuals with this disorder, and particularly to help clinicians caring for a person recently diagnosed. 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].

Shwachman Syndrome is a rare, multisystem disorder, estimated to arise in around 1 in 75,000 individuals. Although it can be a severe, and potentially life-taking disorder for some, symptoms improve with age and a full, relatively healthy life results. That is exemplified by the best known of individuals with this diagnosis – Scott Hamilton, the American Olympic figure skater.

Although sometimes individuals with this process are first identified because of bony changes, in fact the bone abnormalities are not considered one of the sentinel features of Shwachman Syndrome. In order for this diagnosis to be considered, an individual must demonstrate *exocrine pancreas dysfunction + bone marrow dysfunction + one other characteristic of Shwachman Syndrome*. While the third feature often is bone abnormalities, dysplastic bone changes are not obligatory.

In those in whom Shwachman Syndrome is suspected, the following tests should allow for diagnosis and delineation of what kinds of features are present:

1. 72 h fecal fat and/or serum trypsinogen and/or serum isoamylase and/or pancreatic stimulation test;
2. Complete blood count, differential and platelet count;
3. Skeletal survey.

Some also recommend pancreatic MRI. In all individuals suspected to have Shwachman Syndrome sweat testing should be completed to rule out cystic fibrosis. Gene testing for Shwachman Syndrome is now available (see below under Genetics and Molecular Biology).

MEDICAL ISSUES TO BE ANTICIPATED

PROBLEM: LIFE EXPECTANCY

EXPECTATIONS: The calculated mean survival is about 35 years. This is likely an underestimate. However, there is considerable risk for life-taking complications at all ages. In infancy, primary concerns that may be life-threatening include malabsorption, infection and restrictive pulmonary disease secondary to thoracic dystrophy. In older individuals premature deaths may arise secondary to hemorrhage, infection or malignancy. For unknown reasons, males seem to be more severely affected and more frequently suffer premature death. Many affected individuals will have long and productive lives.

MONITORING: -

INTERVENTION: Counseling of patients and their families should include sensitive discussion of this reality. Prevention of premature deaths principally relates to management of the various non-bony problems that are outlined below.

PROBLEM: METAPHYSEAL DYSPLASIA

EXPECTATIONS: Around 60% of all individuals have bony changes readily evident on x-rays. These include characteristic lucent inclusions of the proximal metaphysis of the femur, minor metaphyseal changes at the knees, flared and cupped ribs (in about 1/2). Delayed bone age is also common. Rarely complications arise because of these dysplastic changes. Thoracic dystrophy with life-threatening restrictive lung disease occurs very infrequently in infants. Slipped capital femoral epiphysis occasional arises in older children.

MONITORING: The metaphyseal dysplasia itself requires no monitoring. Obviously, if respiratory distress is present in infancy it needs to be assessed urgently.

INTERVENTION: Only secondary complications need to be managed, usually in the same way that they are cared for in individuals without Shwachman Syndrome.

PROBLEM: GROWTH

EXPECTATIONS: Most often individuals are of normal size at birth, although around 30% are mildly small for gestational age. Growth typically slows in the first 1-2 years of life but then resumes normal or near normal growth velocity thereafter. A substantial minority have delayed onset of puberty. Mild small stature can be anticipated, with average ultimate adult heights of 5'6" in males and 5'0" in females.

MONITORING: No diagnosis specific growth grids are available. Superimposed failure to thrive secondary to nutritional issues related to pancreatic insufficiency should be ruled out.

Reassurance regarding delayed puberty is appropriate.

INTERVENTION: No effective treatment of the intrinsic growth abnormality is available.

PROBLEM: SCOLIOSIS

EXPECTATIONS: Clinically relevant scoliosis or kyphoscoliosis arises in around 10% of affected individuals.

MONITORING: Yearly clinical scoliosis screening should be completed from early school age through adolescence. If a curve is clinically detectable, then scoliosis radiographs should be obtained.

INTERVENTION: Usually needing no treatment, more severe curves can be managed in the same manner as idiopathic scoliosis.

PROBLEM: OSTEOPENIA

EXPECTATIONS: A majority of (and perhaps nearly all) affected individuals have early onset osteopenia, beginning in childhood. This is a low-turnover osteopenia that may be worsened if secondary deficiencies of vitamin D and/or vitamin K are present.

MONITORING: DEXA scan should be done beginning at around 6 y of age and every 1-2 years thereafter throughout childhood. Scanning should continue less frequently in adults.

INTERVENTION: The usual methods of treatment are appropriate with particular emphasis on weight bearing exercise. Bisphosphonates have been used effectively in some individuals.

PROBLEM: PANCREATIC INSUFFICIENCY

EXPECTATIONS: This usually arises in infancy and is most often the presenting feature. About 85% of those ultimately diagnosed have clinically significant malabsorption (while, by definition, all have abnormality of pancreatic stimulation testing). It is characterized by normal ductile function, normal islet function and abnormal acinar function. The resulting pancreatic enzyme deficiency causes steatorrhea, diarrhea and malabsorption. In turn, deficiency of fat soluble vitamins (A, D, E and K) arises. In more than ½ of affected individuals, this improves with age.

MONITORING: Routine care through a pediatric gastroenterologist should be established.

Confirmation of pancreatic insufficiency can be through serum trypsinogen testing or pancreatic stimulation testing. At diagnosis, assessment should including serum levels of vitamins A, D and E; prothrombin and partial thromboplastin times. Probably these should be repeated every 6 months. Pancreatic sufficiency can be reassessed every 2 years using 72 h fecal fat analysis after 48 h discontinuation of enzyme replacement therapy.

INTERVENTION: Enzyme replacement therapy. Supplemental A, D, E and K as needed. Rarely infants with severe deficiency require enteral feedings for a time.

PROBLEM: BONE MARROW CONSEQUENCES

EXPECTATIONS: All have some evidence for bone marrow involvement: neutropenia (usually fluctuating) in 85-100%; anemia (usually mild and not of great clinical importance) in 40-80%; thrombocytopenia (usually mild) in 25-55%, often with a history of easy bruising. The last of these very rarely can be life-threatening with risk of fatal hemorrhage when combined with vitamin K deficiency. About 10-20% of affected individuals will have pancytopenia and it is in this population that prognosis is most guarded. Pancytopenia may progress to aplastic anemia or affected individuals may develop myelodysplastic changes that can progress to acute myelogenous leukemia (AML). Overall risk of malignancy is around 3% to 15%. Curiously, virtually all of those who develop AML are male. Mean age of diagnosis is around 14 y (range –

1 y to 43 y). Historically the outcome of AML in individuals with Shwachman Syndrome has been very poor.

MONITORING: At the time of first diagnosis, monitoring should include bone marrow aspiration and biopsy (with cytogenetic studies). Routine care through a pediatric hematologist should be established. A reasonable screening schedule would include CBC, differential and platelet count every 6 months and bone marrow aspiration, biopsy and marrow cytogenetics every 24 months.

INTERVENTION: Rarely individuals will require platelet transfusions. Bone marrow transplantation has been effective but there seems to be an increased frequency of complications, with only about 2/3 surviving the transplant.

PROBLEM: INFECTION AND IMMUNITY

EXPECTATIONS: Multiple abnormalities that can result in immune problems are demonstrable, including neutropenia, impaired chemotaxis, and B and T cell defects. Susceptibility is to both bacterial and viral infections, with the most often occurring being infections of the ears, sinuses and upper airway. Less often individuals will develop pneumonia, sepsis, osteomyelitis etc.

MONITORING: At diagnosis assessment should include quantitative immunoglobulins, T and B cell subsets, and mitogen stimulation testing. If any abnormalities are found, then referral to a pediatric immunologist should be made.

INTERVENTION: In general, infections are appropriately and effectively treated with aggressive use of antibiotics. In those with profound neutropenia some recommend use of granulocyte colony stimulating factor, but it is possible that this might also predispose treated individuals to malignancy.

PROBLEM: HEPATIC ABNORMALITIES

EXPECTATIONS: Most children with Shwachman Syndrome (50-80%) will have elevated liver enzymes and 10-20% will have hepatomegaly. These features normalize with age and seem never to be of clinical significance.

MONITORING: -

INTERVENTION: -

PROBLEM: DENTAL

EXPECTATIONS: Various features have been reported including dysplastic enamel, delayed eruption of secondary teeth, and excess risk of caries and periodontal disease.

MONITORING: Careful dental care and dental assessment every 6 months.

INTERVENTION: Routine.

PROBLEM: CARDIAC

EXPECTATIONS: Although there are subtle differences in myocardial function in many affected adults, these are not clinically relevant. However, occasional infants will develop myocardial necrosis and in older individuals symptomatic cardiomyopathy occurs infrequently.

MONITORING: These are sufficiently uncommon that no routine monitoring seems appropriate.

INTERVENTION: -

PROBLEM: RARE OR CAUSALLY UNCERTAIN ASSOCIATIONS

EXPECTATIONS: (1) Learning disabilities seem to be present in around 10% of affected individuals and more subtle changes may be even more frequent. (2) Renal dysfunction and renal tubular acidosis are occasionally present. (3) Endocrine abnormalities (thyroid, parathyroid) arise occasionally.

MONITORING: Yearly screening of BUN, creatinine, TSH, calcium, phosphate and PTH is justifiable.

INTERVENTION: Routine treatments for whatever issues arise.

PROBLEM: RISKS OF SURGERY

EXPECTATIONS: Risks of surgery or dental work principally relate to hemorrhagic complications and, to a lesser extent, to postoperative infection.

MONITORING: Assess PT, PTT and platelet count prior to any surgery or invasive dental procedure.

INTERVENTION: Treat any coagulation abnormality as needed. Consider antecedent prophylactic antibiotic coverage (e.g. 5 days prior to surgery).

GENETICS AND MOLECULAR BIOLOGY

Shwachman Syndrome is always an autosomal recessive genetic condition. This means that parents of an affected child have a 25% risk that any subsequent child will also be affected. There is an unexplained excess of affected males.

The causal gene was identified in 2003. It is called *SBDS* [for *Shwachman-Bodian-Diamond Syndrome*]. It appears that all instances of Shwachman Syndrome arise from changes in this gene.

The *SBDS* protein is important in ribosome biogenesis (as is true of genes involved in some other disorders that result in bone marrow failure or bone marrow failure plus bone growth abnormality, such as Cartilage Hair Hypoplasia), as well as mitotic spindle assembly.