70

Utility of both bone marrow and renal transplants in the management of individuals with Schimke immunooseous dysplasia. Petty, EM,[1,2] Castle, VP.[3] Departments of Internal Medicine,[1] Human Genetics,[2] Pediatrics,[3] University of Michigan, Ann Arbor, Michigan.

Schimke immunoosseous dysplasia (SIOD) is a rare autosomal recessive osteochondrodysplasia that presents in infancy or childhood. It is characterized by spondyloepiphyseal dysplasia, growth failure, proteinuria progressing to renal failure, characteristic facial features, lymphopenia with immunodeficiency, occasional pancytopenia, cerebral vascular disease, and autoimmune dysfunction. It is associated with significant early morbidity and mortality with death during childhood in classic cases. The underlying molecular etiology is unknown. There is no effective curative treatment. While dialysis and renal transplantation have successfully managed the renal disease, much of the disease related morbidity and early mortality is due to cell-mediated immunodeficiency that has been refractory to medical therapy. Given the utility of bone marrow transplant (BMT) in the treatment of other immunodeficiency and hypoplastic bone marrow states, we successfully utilized BMT for the management of SIOD in a boy who presented with severe marrow hypoplasia and immunodeficiency. BMT had not been reported for the management of SIOD. The patient was a six-year-old boy who initially presented in infancy with short stature and gastrointestinal problems. He later displayed classic features of SIOD, including progressive renal disease. His renal disease progressed after BMT. He subsequently underwent a related donor renal transplant 18 months after BMT. At 20 months after BMT and 2 months following renal transplant he demonstrates significantly improved immune function, reconstitution of all marrow derived cell lineages, good renal function, and, importantly, an improved sense of overall well being with increased appetite and activity. He had no adverse chronic neurological sequelae. Based on the excellent outcome of our patient to date, we predict that, until better targeted therapies are developed, bone marrow transplantation in addition to renal transplantation may provide the most effective therapy currently available for severe SIOD, decreasing the morbidity in, and increasing the lifespan of, children with this disorder.

71

Osteopetrosis, progressive sensorineural deafness, glaucoma, alopecia and cardiomyopathy in a 13 year old female: New syndrome or mild variant of Yunis-Varon syndrome? B.A. Pletcher[1], L. Suslak[1], S.G. Carruth[1], K. Kolor[1] and L. Boyd[2] [1]Center for Human and Molecular Genetics and [2]Department of Family Medicine, University of Medicine and Dentistry- New Jersey Medical School, Newark, NJ.

This youngster presented at 10 years of age with bilateral genu valgum and rapidly progressive sensorineural hearing loss. Prior history was significant for delayed motor milestones in early childhood, but normal cognitive development. Family history was non-contributory. Initial exam was remarkable for bilateral proptosis and exotropia that was reported to be of recent onset associated with increased intraocular pressures. Mild alopecia was noted on the scalp. Hypodontia was noted with mostly primary teeth present. Cutaneous exam revealed taut, shiny skin on the fingers and diffuse cutis marmorata. Fingers were slightly tapered and there was bilateral genu valgum with a lumbering gait and muscle wasting of the calves. Radiographic studies revealed diffuse osteosclerosis suggestive of a form of osteopetrosis and the patient subsequently went on to have a number of pathologic fractures. A biopsy of the iliac crest revealed increased osteoblastic activity. Multiple CT and MRI studies failed to find any evidence of optic or acoustic nerve compression despite progression to complete deafness, but calcification of the basal ganglia was noted incidentally. Two surgeries for glaucoma resulted in stabilization of intraocular pressures although the proptosis progressed. Studies for metabolic bone disease were normal including: alkaline phosphatase, calcium, phosphorus and 25 OH-vitamin D. Carbonic anhydrase I and II deficiencies were ruled out and a collagen vascular work-up was also normal. At twelve years of age the patient presented for care because of progressive shortness of breath and was found to have a severe, dilated cardiomyopathy. Primary and secondary carnitine deficiencies were ruled out and she stabilized on digoxin and lasix. Although this may represent a unique clinical entity, there are some overlapping features with Yunis-Varon syndrome(YVS), an autosomal recessive condition that generally presents in infancy. Overlapping features include: alopecia, hypodontia, bony sclerosis with pathological fractures as well as one child with YVS reported with dilated cardiomyopathy. However, the prenatal growth retardation, clavicular abnormalities, micrognathia and hand defects that are common in YVS are not seen in this patient. Other considerations include an unrecognized mitochondrial disorder or variant of osteopetrosis. A muscle biopsy will be done in the near future to provide additional diagnostic information.

72

A close relationship to Smith-Lemli-Opitz (RSH) patients positively correlates with an increased incidence of high cholesterol, late-onset diabetes, and infertility; and negatively correlates with alcoholism. A.F. Poss, J.E. Metherall, and J.M. Opitz. Univ. of Utah, Salt Lake City, UT.

Several valuable sets of data came out of the Second International Scientific Symposium on Smith-Lemli-Opitz/RSH Syndrome held in Salt Lake City in July 1999. One part of this is our study of comorbidity factors in heterozygotes from 23 collected pedigrees (over 450 individuals described). We first asked whether the relatively high frequency of SLO/RSH (1/10,000 births) in the population might be due in part to a fitness advantage in the heterozygotes. Our initial hypothesis was based on the idea that heterozygotes produce less cholesterol, thus protecting them from lipotropic disease. Surprisingly, our data indicated an increased incidence of high cholesterol and late-onset diabetes in close relatives of patients. Therefore, there appeared to be no protective effect offered by the altered cholesterol metabolic pathway in SLO/RSH heterozygotes, but instead a trend toward increases in lipid-related disease. We also found that presumed SLO/RSH heterozygotes exhibit previously unrecognized trends such as a positive correlation with infertility and a negative correlation with alcoholism. These data provide new insight for our understanding of the potential role of 7-DHC mutation carrier status, and for future interpretation of similar findings in families suspected for SLO/RSH.

73

Circadian rhythm abnormalities of melatonin and haploinsufficiency of *COPS3* in Smith-Magenis Syndrome. L. Potocki[1], D. Glaze[2,3], S-S Park[1], C.D. Kasork[1], L.G. Shaffer[1], D-X Tan[4], R.J. Reiter[4], J.R. Lupski[1,2] [1]Department of Molecular and Human Genetics, [2]Department of Pediatrics and [3]Neurology Baylor College of Medicine and Texas Children's Hospital, Houston. [4]Department of Structural and Cellular Biology University of Texas Health Science Center, San Antonio.

Smith-Magenis syndrome (SMS) is a multiple congenital anomalies, mental retardation syndrome associated with a hemizygous deletion of chromosome band 17p11.2. The majority of patients have the same sized deletion; however, patients with smaller and larger deletions have been described. Characteristic features of SMS include a significant sleep disturbance. Urinary excretion of 6-sulphatoxymelatonin (aMT6s)—the major hepatic metabolite of melatonin—in conjunction with 24-hour sleep studies in 28 SMS patients reveal an aberrant diurnal rhythm of aMT6s and abnormalities in quality and quantity of nocturnal and daytime sleep. These data demonstrate a disturbed circadian rhythm of melatonin and objectively document the disturbed sleep pattern in Smith-Magenis syndrome. Our findings suggest that these abnormalities may be secondary to aberrations in the production, secretion, distribution, or metabolism of melatonin. One candidate, the gene for subunit 3 (*COPS3)* of the COP9 signalosome is conserved from plants to humans. In plants COP9 transduces light signals into gene expression, and in humans *COPS3* maps within the SMS common deletion interval. We are investigating the hypothesis that *COPS3* haploinsufficiency may be responsible for the abnormal melatonin circadian rhythm in SMS.