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Entering a new treatment age for mucopolysaccharidosis VI disease: a search for better markers of disease progression and response to treatment

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Mucopolysaccharidosis (MPS) VI is a rare autosomal recessive genetic disorder involving mutation and abnormal function of the lysosomal enzyme N-acetylgalactosamine (arylsulfatase B - ASB).[1] Decreased enzyme activity leads to incomplete degradation of the glycosaminoglycan (GAG) dermatan sulfate, and accumulation of breakdown products in cells and tissues. These breakdown products contribute to lysosome damage, cell death, and organ dysfunction. Although a wide spectrum of clinical severity occurs, the typical findings in a patient with significant disease include short stature, skeletal findings of dysostosis multiplex, joint disease, cardiac valve disease, obstructive and restrictive pulmonary disease, frequent respiratory infections and hearing loss, eye disease including corneal clouding and glaucoma, optic nerve disease, mild hepatosplenomegaly, and abdominal hernias. In contrast to other MPS diseases, primary central nervous system (CNS) disease and mental retardation are not a part of the MPS VI clinical spectrum. Until recently, treatment of patients with MPS VI has involved primarily supportive medical and surgical care.[2] Successful hematopoietic stem cell transplant (HSCT) has been described in a few case reports for MPS VI,[3,4] although the risk of transplant is signifi-

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cant and obtaining compatible donors difficult. In 2005, Naglazyme® (galsulfase; recombinant human N-acetyl galactosamine 4-sulfatse, rhASB) was approved by the Food and Drug Administration (FDA) as an intravenous enzyme replacement therapy (ERT) for MPS VI. The phase 3 clinical trial of rhASB[5] demonstrated a significant improvement in endurance on a 12-minute walk test and decrease in urine GAG concentration in a 6-month, randomized, double-blind placebo controlled design that supported similar findings of earlier phase 1/2[6] and 2[7] studies. The therapy was well tolerated and showed a favorable safety profile. Although shoulder joint range of motion and grip and pitch strength measurements were included in the clinical trials, these parameters were not examined as biomarkers of disease severity or progression, as described in the present study.

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In the present article, Cardoso-Santos et al.[8] systematically examine the skeletal abnormalities of joint mobility and decreased grip and pinch strength as markers of MPS VI disease severity and progression and evaluate the relationship of these markers of disease with other recognized disease markers including urine GAG, ASB enzyme activity, or distance walked on a 6-minute walk test. Identification of clinical markers, both biochemical and performance-based, for MPS VI and other MPS diseases has been a challenge. Although urine oligosaccharides[9-11] and heparin[12] have been suggested, urine GAG has been the only widely accepted biochemical marker for GAG storage.

Before looking at the authors' correlations of performance markers with biochemical markers, it is important to re-emphasize the difficulty of performance testing in this population. As the authors note, grip testing using the Jamar dynamometer was not possible because of the small hand size and weak grip strength. Similar difficulties due to size, joint disease, limited strength, and wide spectrum of disease are encountered when trying to use other standard endurance or strength testing apparatus such as treadmills, stationary bicycles, portable indirect calorimeters. This population can best be tested using simple standardized, validated tests that incorporate activities required for daily living such as walking, stair climbing, respiratory function, joint movement, pinch strength testing, overnight oxygen saturation monitoring (as utilized in the clinical trials for ERT). In the present study, the authors show the value of joint measurements using well-validated techniques by consistent operators. As might be expected, shoulder joint flexion showed the greatest limitation, occurred early, but surprisingly did not change with age, which would have implied disease progression. They suggest the most likely explanation – that the severity is such that change with age was not apparent. In contrast, elbow flexion and knee flexion both were abnormal and changed with age. Interestingly, although not changing with age, shoulder flexion showed a strong correlation with 6-minute walk test, the parameter that best demonstrated the beneficial effect of ERT on endurance. Although a proven benefit of Naglazyme for joint range of motion was not established in the short-term clinical trials, it will be important to assess response of shoulder flexion as well as other joint movements to long-term ERT. As a parameter, shoulder joint flexion may ultimately improve on the 6-minute walk test, since the latter test can be impacted over time by secondary processes such as cervical cord compression or failure of the hip joint structure or function that may be less responsive to ERT. Passive assessment of joint mobility may also be helpful in assessing the young child who is not yet old enough to cooperate for a walk test.

Although urine GAG is clearly a good biochemical measure of response to enzyme therapy, urine GAG did not correlate with joint restriction or pinch strength as measures of disease severity in the present study. It is possible that the normal decrease in urine GAG with age may be obscuring this relationship. There may also be a threshold effect for urine GAG above which severe disease is indicated and differences in joint restriction or individual performance measures may not be well correlated with urine GAG. Such a threshold effect was suggested in a survey study of 121 MPS VI patients reported by Swiedler et al.,[13] in which authors noted that high urinary GAG values greater than 200 µg/mg urine creatinine were associated with an accelerated clinical course.

The authors suggest that restriction of shoulder flexion is an early finding in MPS VI disease and severity of restriction does not correlate with age. This finding underscores the importance of very early diagnosis and treatment. Studies in the feline model of MPS VI[14-16] have clearly demonstrated that very early treatment with rhASB resulted in milder abnormalities in bone development, joint pathology, cardiac valves thickening, and tracheal cartilage structure. In addition, animals treated from birth showed negligible antibody against rhASB, in contrast to animals treated after 5 months of age, and had reduced GAG storage in tissues such as aorta or cardiac valves, in contrast to animals with increased antibody. Early introduction of rhASB produces a state of immune tolerance and improved enzyme effectiveness in the cat model; hopefully, similar findings will be demonstrated in humans after early introduction of ERT. Although studies of human infants receiving Naglazyme® are ongoing, one report of a sibling pair with MPS VI by McGill et al.[17] supports these findings. In this pair, a male infant, the younger sibling of an affected girl, was diagnosed with MPS VI and therapy with rhASB was initiated at 8 weeks of age. The older sister started ERT at the same time (3.5 years of age). The male infant is described by Dr. McGill after 3 years of therapy as having no hepatosplenomegaly, full range of joint motion and maintaining good growth. Nonetheless, he has developed some skeletal changes including *pectus excavatum*, rib flaring, and an

early gibbus, has mild corneal clouding and minimal mitral valve dysplasia. The older sibling was noted to have improved scoliosis, reduced hepatosplenomegaly and improved joint mobility. We look forward to a detailed report of this important abstract. The additional measurements of joint mobility as described by the authors in the present study will be valuable in assessing response to therapy in these younger children.

If early therapy is to provide the benefits seen in animal studies and the sibling pair described above, early identification of the infant with MPS VI is critical. In the case of the sibling pair, the known diagnosis in the family allowed early confirmation of the diagnosis in the newborn sib. In the absence of an older sib in the family with MPS VI, it is unusual to make the diagnosis in the first year after birth. Although the information that shoulder flexion is an early and severe sign of MPS VI disease should prompt physicians and other health care members to consider this diagnosis, it is likely that very early diagnosis will depend on initiation of newborn screening programs. Two approaches to newborn screening have been reported as successful: one is based on tandem mass spectroscopy and analysis of multiple enzyme activities in a single blood spot sample[18]; the second utilizes immunoassay of multiple enzymes in a blood spot sample.[19,20] Both methods are in the process of large scale pilot testing in a high volume of newborn samples and initiation on a population-wide basis. Only with newborn screening in place for early recognition of MPS VI can we take full advantage of the recent advances in the treatment for MPS VI. As the authors point out, effective administration and monitoring of treatment clearly requires knowledge of mobility and strength profiles of MPS VI patients, such as provided in the present study.

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