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Original Article

Unexpected coronary artery findings in mucopolysaccharidosis. Report of four cases and literature review

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ABSTRACT

Introduction: The mucopolysaccharidosis syndromes are a group of lethal inherited disorders affecting multiple organ systems by the progressive deposition of glycosaminoglycan. Advances in treatment such as enzyme replacement and hematopoietic stem cell transplantation have significantly improved the outcome of these disorders. An in-depth understanding of the pathophysiology of heart disease in these disorders is essential since death from cardiac causes continues to be common. Epicardial coronary artery luminal narrowing from myointimal proliferation and glycosaminoglycan deposition is well described in severe mucopolysaccharidosis type I [Hurler syndrome, mucopolysaccharide IH] but poorly understood in other "non-Hurler" phenotypes of these disorders. Given the rarity of these conditions, autopsy specimens are uncommon.
Methods: Tissue from epicardial coronary arteries from autopsies of four patients with non-Hurler mucopolysaccharidosis (attenuated type I, type IIIA, type IIIC, and type VI) who had died after hematopoietic cell transplantation (within 1 month in three cases; after 5 years in the fourth) was examined by light microscopy.
Results: Unexpectedly, near-normal coronary arteries were observed in the patient with attenuated mucopolysaccharidosis type I, while the coronaries from patients with type IIIA, IIIC, and VI demonstrated classic histologic features of glycosaminoglycan deposition. The most severe findings were found in the MPS IIIC patient who had 5 years of full donor engraftment after transplantation.
Conclusions: Our current understanding of the cardiac manifestations of the mucopolysaccharidoses fails to explain why near-normal coronary arteries may be observed when abnormalities would be most likely to be expected and, conversely, why significant histopathology is present when it would be least expected. Identification of downstream effects of glycosaminoglycan deposition may identify other metabolites or metabolic pathways that are important in the clinicopathologic manifestations of these diseases.
Summary: The mucopolysaccharidosis diseases are a group of inherited disorders affecting multiple organ systems by the progressive deposition of glycosaminoglycan. Severe coronary artery disease is well recognized in severe type I mucopolysaccharidosis (Hurler syndrome), but unexpected coronary artery disease occurs in other, "non-Hurler" mucopolysaccharidoses. Factors responsible for the development of coronary pathology in the mucopolysaccharidoses remain elusive.

1. Introduction

The mucopolysaccharide (MPS) disorders are a group of inherited lysosomal storage diseases resulting from deficient enzymes responsible for the catabolism of glycosaminoglycan (GAG), complex heteropolysaccharides intrinsic to all mammalian tissues [1,2]. Depending upon the missing enzyme, specific types of GAG accumulate (Table 1). Accumulation of GAG results in the clinical features of these disorders, including dysostosis multiplex and coarsening of skin and facial features, as well as central nervous system (CNS), respiratory, and cardiac insufficiency [1]. The specific MPS types are defined by determination of the missing enzyme activity and urinary excretion of the corresponding GAG, with each type having clinical similarities to, and differences from, the others. Numerous mutations have been identified within each gene responsible for the specific type of MPS [3–10], and although some genotype–phenotype correlations are recognized, much remains unknown. Severe MPS I (Hurler syndrome) is the second most

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Table 1
The mucopolysaccharidoses, their associated enzymatic deficiencies, and stored GAGs

Mucopolysaccharidoses		
Type MPS	Enzyme deficiency	Stored GAGs
MPS I severe, attenuated	α-L-iduronidase	Heparan sulfate, dermatan sulfate
MPS II severe, attenuated	Iduronate 2-sulfatase	Heparan sulfate, dermatan sulfate
MPS III A	Heparan sulfate sulfatase	Heparan sulfate
MPS III B	*N*-acetyl-α-D-glucosaminidase	
MPS III C	Acetyl-CoA: α-glucosaminide *N*-acetyltransferase	
MPS III D	*N*-acetylglucosamine-6-sulfatase	
MPS IV A	Galactosamine-6-sulfatase	Keratan sulfate, chondroitin-6-sulfate
MPS IV B	β-galactosidase	
MPS VI	Arylsulfatase B	Dermatan sulfate
MPS VII	β-glucoronidase	Chondroitin-4-sulfate, chondroitin-6-sulfate

commonly recognized MPS syndrome [5] and, if untreated, results in profound CNS, respiratory, and cardiac involvement from the relentless accumulation of GAG with death occurring within the first decade of life [1].

Cardiovascular involvement in Hurler syndrome includes deposition of GAG in the myocardium, cardiac valves, great vessels, and coronary arteries [11]. The myocardium is hypertrophied by the infiltration of GAG which may lead to systolic and diastolic dysfunction [12]. Cardiac valves (predominantly mitral and aortic) are thickened and become significantly regurgitant or stenotic. Both dilation and coarctation of the aorta have been reported [13,14]. GAG deposition within the epicardial coronary arteries initiates myointimal proliferation that, in turn, produces severe and diffuse narrowing of these vessels (Fig. 1) [11,15]. Cardiac pathologic findings vary depending upon MPS type, which, in part, is thought to be dependent upon the type of GAG stored [1]. For example, cardiac valve involvement is believed to be more severe in MPS I, II, and VI, types that include the deposition of dermatan sulfate [16–19]. While the coronary arteries are severely affected in Hurler syndrome [11], coronary involvement in "non-Hurler" MPS is poorly understood, with both presence and absence of coronary disease alternatively reported in all types of non-Hurler MPS, including attenuated MPS I (Table 2) [14,15,18,20–48].

Over the past 30 years, the previously dismal natural history of the MPS syndromes has been significantly improved by hematopoietic cell transplantation (HCT) for Hurler syndrome [49–52] and the availability of recombinant enzyme replacement therapy (ERT) for attenuated MPS I, MPS II, and MPS VI [53–55]. The cardiac effects of HCT and ERT include preservation of ventricular function and resolution of ventricular hypertrophy, but established cardiac valve pathology appears unaffected by either therapy [56–59]. Arrest or regression of coronary pathology has been shown in a single patient with MPS IH 14 years after HCT [27], but the effects of ERT on established MPS coronary disease appears variable and may, as has been found for the valves, depend upon the severity of disease present when ERT is begun [21,22,28,33].

Determining the risk of coronary artery disease in non-Hurler MPS is currently an important but overlooked task, both because coronary artery disease can be a cause of morbidity and mortality and because the presence of significant coronary narrowing is an important risk factor for individuals undergoing invasive procedures [60]. Individuals with MPS commonly require surgical correction of skeletal manifestations of the disease that do not respond to either HCT or ERT, including orthopedic surgery for hip and knee dysplasia [61,62] and emergency cervical cord decompression from GAG deposition within the dura in association with atlanto-occipital instability [63]. To increase our understanding, we present coronary artery histology from four "non-Hurler" MPS patients who demonstrated unexpected coronary artery pathology and a review of the known coronary artery findings, either by angiography or histology, in cases where the MPS diagnosis has been affirmed by urinary GAG and/or assay of corresponding enzymatic activity.

2. Methods

This study was deemed exempt by the Institutional Review Board of the University of Minnesota as a retrospective chart and pathological specimen review. Deceased patients with non-Hurler mucopolysaccharidoses were identified through the University of Minnesota Bone Marrow Transplant Database. Four patients fulfilled our criteria: one each with attenuated MPS I, MPS IIIA, MPS IIIC, and MPS VI (Table 3). The autopsy report and medical record of each patient were reviewed. Existing histological slides were reviewed, and when necessary, tissue blocks from each patient's cardiac valves, aorta, and coronary arteries were recut and stained with elastic van Gieson, Alcian blue, and trichrome stains.

3. Results

3.1. Case 1

Prior to the availability of ERT, a 19-year-old male was diagnosed with attenuated MPS I at age 18 years, when he presented with developmental delay and new-onset seizures. He was found to have extremely low α-L-iduronidase activity, consistent with MPS type I. He had previously undergone aortic and mitral valve replacement at

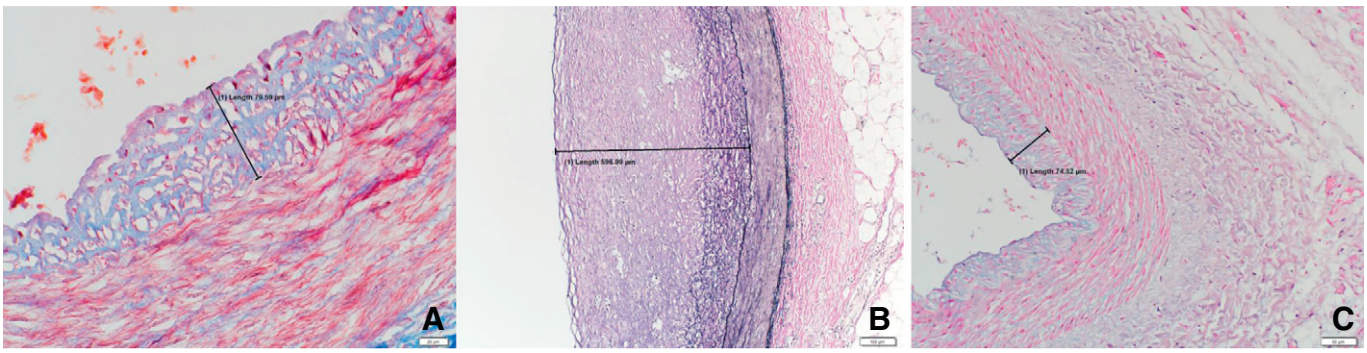

Fig. 1. (A–C) Intimal thickening (bars) is identified within the epicardial coronary arteries of patients with (A) MPS IIIA (thickness 80μm)(Alcian blue, 40×), (B) MPS IIIC (thickness 597 μm) (ELVG, 10x), and (C) MPS VI (thickness 75 μm) (Alcian blue, 20×).