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Carotid intima-media thickness is increased in patients with mucopolysaccharidoses ☆

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ABSTRACT

Background: The feasibility of carotid artery intima-media thickness (C-IMT), an established cardiovascular disease marker, as a cardiac risk marker in mucopolysaccharidosis (MPS) patients was explored.
Objectives: To determine if C-IMT is abnormal in MPS versus unaffected controls, and if C-IMT correlates with coronary artery diameter in MPS.
Material and methods: Measurements of C-IMT via neck ultrasound and echocardiographic parameters, including coronary artery diameters, were obtained from MPS and control patients, and compared.
Results: Sixteen MPS subjects (6 MPS I, 6 MPS II, 2 MPS III, 1 MPS VI, 1 MPS VII) and sixteen age, ethnicity, and gender-matched controls were enrolled. Median MPS and control subject ages were 8.3 ± 4.5 and 8.6 ± 4.3 years, respectively ($p = 0.73$). Mean MPS and control C-IMTs were 0.54 ± 0.070 and 0.48 ± 0.034 mm ($p = 0.0029$). No differences in left main, left anterior descending, or right coronary artery diameters were seen between MPS and controls. A significant proportion of MPS subjects had mitral insufficiency (14/16; $p = 0.0002$), aortic insufficiency (10/16; $p = 0.0021$), and left ventricular dilatation (7/16, $p = 0.037$) versus controls. C-IMT did not correlate significantly with age, height, weight, coronary measurements, or duration of treatment.
Conclusion: C-IMT in MPS patients is increased compared to matched controls, likely reflective of arterial intima-medial glycosaminoglycan accumulation. MPS subjects demonstrated a high percentage of left-sided valvular insufficiency and ventricular dilatation. Additional studies should be performed in MPS patients to determine if C-IMT correlates with arterial elasticity, biomarkers of vascular dysfunction, and higher risk of cardiovascular events.

1. Introduction

The mucopolysaccharidoses (MPSs) are a group of seven inborn errors of metabolism linked by a deficiency in lysosomal hydrolases that catalyze the stepwise degradation of glycosaminoglycans (GAGs). As a result of the enzyme deficiency, GAGs that are normally recycled in a healthy individual cannot be degraded in the MPS patient. Specific MPS symptomatology varies according to the missing hydrolase and location of accumulating GAG species, but is usually multisystemic and always progressive without treatment. Somatic symptoms of GAG storage include airway compromise, hearing loss, cardiac valvular dysplasia, coronary stenosis, visceromegaly, spinal cord compression, vertebral dysplasia, and restriction of joint mobility. When present, neurologic symptoms from central nervous system storage manifest as psychomotor stagnation, then steady regression of skills until all developmental milestones have been lost [1].

The advent of intravenous enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation (HSCT) as treatments for specific types of MPS has dramatically altered the natural history of MPS [2–5]. Although ERT and HSCT are able to mitigate many symptoms of MPS, it is important to emphasize that they are only

Abbreviations: C-IMT, carotid intima-media thickness; MPS, mucopolysaccharidosis; GAG, glycosaminoglycan; ERT, enzyme replacement therapy; HSCT, hematopoietic stem cell transplant; CHOC, Children's Hospital of Orange County; IVS_d, end-diastolic intraventricular septal thickness; $LVPW_d$, end-diastolic left ventricular posterior wall thickness; IDU, α-iduronidase; IDS, iduronate sulfatase; SGSH, N-sulfoglucosamine sulfhydrolase; ARSB, arylsulfatase B; GUSB, β-glucuronidase.

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treatments and not cures. Certain tissues remain resistant to treatment and continue to manifest GAG storage [3,5,6,7]. In addition, with treatment, more MPS patients are now surviving into adulthood and face a different set of potentially life-threatening disease complications. Worsening valvular disease, cardiac dysfunction, and coronary intimal proliferation with stenosis have been reported in stably treated patients [8–11]. A review of the Hunter Outcome Survey, a global registry of MPS II patients, showed that 16% of the Hunter syndrome deaths reported to the survey were a result of cardiac complications; this was most pronounced in the patients older than 20 years of age, where cardiac etiologies accounted for 33% of deaths [12]. While complications related to coronary artery stenosis are being recognized as potentially fatal manifestations of MPS [11,13,14], there are currently no validated markers of cardiovascular or coronary artery disease in this disease population.

We report the results of a pilot study conducted to explore the feasibility of common carotid intima-media thickness (C-IMT) as a cardiovascular risk marker in MPS patients by comparing them with age, ethnicity, and gender-matched unaffected controls.

2. Methods

2.1. Human subjects

Approval from the CHOC Children's Institutional Review Board obtained for this study (Study #090538). Patients were recruited from the Multidisciplinary Lysosomal Program at CHOC Children's. Matched controls included unaffected siblings (n = 2; 1 carrier sibling of MPS I patient and 1 homozygous normal sibling) or unrelated individuals (n = 14). Informed consent was obtained for all patients participating in this study. Anthropomorphic measurements (height, weight, body surface area) were obtained from all patients.

2.2. Carotid intima-media thickness measurement

A Siemens Antares™ Ultrasound Machine with VF 13–5 MHz transducer was utilized for all studies. To eliminate intra-observer variability, measurements were performed by one dedicated ultrasonographer and interpreted by one physician (RD). Using digital calipers, the maximum end-diastolic far wall C-IMT was measured 1 cm proximal to the bifurcation of the common carotid artery. Images were stored digitally for review by interpreting physician. The measurements were performed bilaterally, with three scanning angles (anterior, lateral, and posterior) employed. The six values were averaged to produce the patient's mean C-IMT measurement.

2.3. Echocardiography

A Siemens Acuson Sequoia™ C512 Ultrasound Machine was employed utilizing 4 or 8 MHz transducers, depending on the size and age of the subjects. All subjects underwent complete transthoracic echocardiography, including two-dimensional, color Doppler, and spectral Doppler imaging. The diameters of the left main coronary artery and left anterior descending branch were measured in diastole from both the parasternal long axis right ventricular outflow tract view and parasternal short axis view. End-diastolic proximal right coronary artery and/or distal right coronary artery diameters were taken primarily from parasternal short axis view. Coronary artery diameters were normalized to body surface area; multiple measurements were obtained to ensure accuracy.

2.4. Statistical analysis

All statistical analyses were conducted using *SAS* 9.2 Software (*SAS* Institute, Cary, NC). Univariate statistics (e.g. Means, Standard Deviations, Standard Errors) and tests of the hypothesis of no difference between the Treatment Means of the two study groups (MPS patients & Controls) were computed using the *SAS* TTEST Procedure for continuous variables (Note: $p<.05$ was used as the criterion for statistical significance and no adjustment was made for multiple tests). The *SAS* FREQ Procedure was used to test the correlations for pairs of categorical variables. Similarly, the *SAS* CORR Procedure was used to compute linear correlation coefficients and associated p-values and, by using the *SAS* Output Delivery System (ODS), generate scatter plots for several pairs of continuous variables. Categorical variables were compared utilizing the *SAS* FISHER (2 categories) or the *SAS* CHISQ Test (more than 2 categories to compare).

3. Results

3.1. Human subjects

There were no significant differences in mean age, height, weight, gender distribution, or ethnicity between the MPS and control groups (Table 1). Sixteen patients with MPS were enrolled: six had MPS I, six had MPS II, two had MPS IIIa, and one each with MPS types VI and VII. A summary of their confirmatory testing, type and duration of treatment, and symptoms can be found in Table 2. The four patients with severe MPS I received HSCT at a median age of 1.36 years; none were taking immunosuppressive medications at the time of the study. The six patients with MPS II had received ERT for a median duration of 2.88 years.

3.2. Carotid intima-media thickness and echocardiographic measurements

Mean C-IMT of the whole MPS cohort (0.54 ± 0.070 cm) was significantly greater than the control cohort (0.48 ± 0.034 cm); two-tailed $p = 0.0029$. C-IMT of the MPS I patients was 0.54 ± 0.058 cm, while matched control C-IMT was 0.48 ± 0.039 cm; two-tailed $p = 0.08$. Similarly, C-IMT of the MPS II patients was 0.54 ± 0.10 cm and matched control C-IMT was 0.49 ± 0.034 cm; two-tailed $p = 0.25$. No significant differences in mean C-IMT were observed between MPS patients with aortic insufficiency and those with normal aortic valve function, nor between those who received HSCT and those who did not. Mean fasting triglycerides, low-density lipoprotein, high-density lipoprotein, and total cholesterol obtained for clinical purposes in the MPS cohort were no different between those who had received HSCT and those who did not (data not shown). In addition, there were no significant differences in mean coronary artery measurements (left main coronary, left anterior descending coronary, and right coronary arteries) between the MPS patients and controls, nor were there any significant correlations between any of the three coronary artery diameters and C-IMT. As an aggregate, the MPS cohort did not demonstrate any cardiac hypertrophy, as their mean end-diastolic intraventricular septal (IVS_d), or end-diastolic left ventricular wall ($LVPW_d$) dimensions did not differ significantly from the control cohort. These findings are summarized in Table 3.

Left-sided valvular dysfunction and left ventricular dilatation were significantly more common in the MPS group compared to the control group (see Table 4 for full details). Mitral valve insufficiency was

Table 1
Demographics of the MPS and control cohorts. Age, height, and weight are expressed as mean (standard deviation).

	MPS	Control	p-value
Age (y)	9.0 (4.5)	9.5 (4.3)	0.73
Height (cm)	122 (17)	130 (20)	0.23
Weight (kg)	29.6 (14.5)	29.5 (11.4)	1.00
Gender	9 M 7 F	12 M 4 F	0.46
Ethnicity	10 Caucasian	11 Caucasian	0.63
	4 Hispanic	2 Hispanic	
	2 East Asian	3 East Asian	