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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.

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Conflicts of Interest: Raymond Wang has received speaking honoraria from Shire Human Genetic Therapies, plc. unrelated to this study, and had costs of travel and accommodation for Lysosomal Disease Registry meetings unrelated to this report paid by the Genzyme Corporation.

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.

Keywords

Lysosomal Storage; Mucopolysaccharidosis; Intima-Media Thickness; Cardiac Vascular Outcome; Treatment; Marker

INTRODUCTION

[1.1] 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].

[1.2] 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 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.

[1.3] 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.

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).

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, CIMT 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.

[3.3] 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 observed in 14/16 MPS patients and 0/15 control patients ($p < 0.0001$). Aortic valve insufficiency was observed in 7/16 MPS patients and 0/15 control patients ($p = 0.00068$). Left ventricular dilatation was present in 7/16 MPS patients and 1/15 control patients ($p = 0.037$).

DISCUSSION

[4.1] Carotid intima-media thickness (C-IMT) measurement is an ultrasonographic method that has been validated as a noninvasive marker of cardiovascular disease in many conditions, including hypertension, hyperlipidemia, and diabetes mellitus. In adults, each 0.1 mm increase above the mean has been estimated to increase lifetime myocardial infarction and stroke risk by up to 15% and 18%, respectively [15]. Although pediatric C-IMT does vary with height, weight, gender, blood pressure, and other cardiovascular biomarkers, childhood normal ranges have been published indicating a small increase over the first 20 years of life [16,17]. Corrected for other covariates, pediatric C-IMT is predictive of adult cardiovascular disease [18–20].

[4.2] This study establishes ultrasonographic evidence of carotid arterial wall thickening in this cohort of MPS patients compared to age, ethnicity, and gender-matched controls. The MPS I and II sub-cohorts also had increased mean C-IMT compared to matched controls, but the comparisons failed to reach statistical significance as this study was not powered sufficiently to compare specific MPS types with controls. No apparent long term pro-atherogenic effects of post-transplant immunosuppressive medications were noted in the four patients who had received HSCT, as their C-IMT and fasting lipid and cholesterol profiles did not differ significantly from non-transplanted MPS patients [21]. These observations, in conjunction with histopathology examinations of coronary vasculature in MPS patients, indicate that GAG storage and myointimal proliferation, not atheromatous plaque formation, is responsible for the wall thickening observed in MPS post-mortem specimens [9,13,22,23]. The mechanism for persistence of vascular GAG storage despite treatment is unexpected, as removal of storage material from the intima and media should be facilitated by the close proximity to circulating treatment-derived lysosomal hydrolase. Cardiovascular disease is becoming more prevalent as treatments for MPS are increasing the

longevity of affected individuals but unable to mitigate ongoing vascular storage and other abnormal hemodynamic compensatory mechanisms [24]. While the paucity of MPS long-term survivor data has not yet allowed for direct correlation between the intima-medial storage and cardiovascular events, prior experience with pediatric carotid intima-media thickness as a risk marker for other conditions indicates C-IMT may be useful as a non-invasive predictor of cardiovascular disease for MPS patients.

[4.3] Given the potential for coronary intima-media thickening in MPS and inability of current echocardiographic transducers to accurately measure coronary intima-media thickness, this study also sought to determine if coronary artery diameter could be used to infer arterial intima-media thickness. The lack of correlation between any of the coronary artery measurements and C-IMT indicates that arterial intima-media expansion by GAG does not increase coronary artery width.

[4.4] In addition to increased C-IMT, this MPS cohort also demonstrated a large percentage with left ventricular dilatation, mitral valve insufficiency, and aortic valve insufficiency. The presence of aortic valvular disease in this cohort appeared to be independent of advancing age. Because increased C-IMT has been reported in patients with aortic valve insufficiency, we compared the C-IMT measurements of MPS patients with any degree of aortic insufficiency to those with normal aortic valve function [25]. The absence of significant difference between these two groups implies that the C-IMT thickening in these MPS patients is attributable primarily to arterial GAG storage, and not to regurgitant flow-mediated vascular adaptations.

[4.5] Major limitations of this study were the heterogeneous nature of the MPS cohort and small numbers from each MPS type. Because MPS is a rare disease and patients were recruited from one regional referral center, patients with different MPS types, treatment modalities, and duration of treatment were included to identify any aggregate differences between MPS patients and controls. However, the severity of cardiovascular involvement is known to vary between different subtypes, and the long-term effects of HSCT and ERT upon cardiac disease in MPS remain unclear [8,10,13,14]. In addition, the study was insufficiently powered to effectively determine any effects of treatment upon C-IMT.

[4.6] Given these limitations, more patients of each MPS type will be studied to determine which specific types have the greatest effects upon C-IMT, and how treatment with HSCT or ERT affects C-IMT. Prospective, longitudinal studies are also planned to determine if increased C-IMT in MPS patients correlates, via measurement of arterial elasticity and post-ischemic flow-mediated dilatation, with vascular endothelial dysfunction and subsequent development of cardiovascular events. Canine and murine MPS animal models, both of which manifest endothelial GAG storage [26–28], will also be studied for differences in patterns of arterial endothelial protein expression that may help predict C-IMT thickening and cardiovascular disease in human MPS patients.

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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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Highlights

- Carotid IMTs of mucopolysaccharidosis patients and matched controls were measured
- Carotid IMT of mucopolysaccharidosis cohort was significantly greater than controls
- No correlations seen with carotid IMT and age or duration of treatment
- Carotid IMT is a viable marker of cardiovascular disease for mucopolysaccharidosis

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	

Table 2

Summary characteristics of the MPS group.

Patient	MPS Type	Age (years)	Genotype	Treatment	Duration of Treatment (years)	Cognitive / Orthopedic Phenotype
1	I-HS	10.42	IDU p.P533R/P533R	ERT	5.75	Normal intelligence, lumbar gibbus
2	I-HS	6.73	IDU p.P533R/P533R	ERT	5.75	Normal intelligence
3	I-H	3.24	IDU p.K153X/W402X	ERT+HSCT	2.08	Acetabular dysplasia, behavioral difficulties
4	I-H	7.41	IDU p.T388R/R621X	ERT+HSCT	5	Normal intelligence and linear growth
5	I-H	9.23	*	HSCT	7.75	Learning difficulty, many orthopedic complications, cervical spinal stenosis, carpal tunnel syndrome
6	I-H	6.08	IDU p.W402X/c.35del12	ERT+HSCT	4.83	Learning difficulty, lumbar gibbus, carpal tunnel syndrome
7	II	13.83	IDS p.A338D	ERT	3.58	Normal intelligence, carpal tunnel syndrome, lumbar spinal stenosis
8	II	7.24	IDS c.979insAGCA	ERT	3.08	Slow regression, behavioral difficulties, carpal tunnel syndrome, acetabular dysplasia
9	II	21.21	IDS p.R468Q/normal	ERT	0.67	Symptomatic female (46, XX normal karyotype), joint contractures, coarse facies
10	II	7.68	IDS p.R8X	ERT	2.67	Normal intelligence, carpal tunnel syndrome
11	II	13.75	IDS p.Q80X	ERT	3.08	Severe regression, behavioral difficulties, non-verbal
12	II	3.83	IDS C.1122>T	ERT	0.17	Normal intelligence
13	IIIa	10.56	SGSH c.1144_1145ins6 /1272_1282del111	None	Not applicable	Severe regression, seizures, non-verbal, non-ambulatory, gastrostomy dependent
14	IIIa	8.99	SGSH c.1144_1145ins6 /1272_1282del111	None	Not applicable	Severe regression, behavioral difficulties, non-verbal
15	VI	4.67	ARSB p.L72R/L72R	ERT	1.17	Normal intelligence, severe lumbar gibbus
16	VII	8.83	GLUSB p.W289X/V99M	None	Not applicable	Moderate regression, behavioral difficulties, acetabular dysplasia

* This patient had been diagnosed biochemically with MPS I-H and transplanted prior to first evaluation with the authors.

Table 3

Carotid intima-media thickness and echocardiographic measurements from the MPS and control cohorts, expressed as mean (standard deviation).

	MPS	Control	p-value
C-IMT (cm)	0.54 (0.07)	0.48 (0.034)	0.0029 *
LMCA (mm/m ² BSA)	2.91 (0.78)	2.91 (0.80)	0.98
LAD (mm/m ² BSA)	2.15 (0.30)	2.23 (0.46)	0.58
RCA (mm/m ² BSA)	2.43 (0.46)	2.38 (0.47)	0.79
Aortic Root	2.27 (0.35)	2.10 (0.26)	0.14
IVSd	0.72 (0.14)	0.65 (0.13)	0.17
LVPWd	0.69 (0.10)	0.61 (0.11)	0.059
	MPS, +AI	MPS, -AI	p-value
MPS C-IMT (cm)	0.56 (0.07)	0.51 (0.05)	0.13
	Correlation Coefficient		p-value
C-IMT and age	-0.027		0.88
C-IMT and LMCA	-0.097		0.61
C-IMT and LAD	0.14		0.47
C-IMT and RCA	-0.074		0.70

No significant correlations were observed between MPS patients' C-IMT and their age or coronary artery diameters.

* The C-IMT in MPS patients is significantly increased compared to control patients.

Table 4

Echocardiographic abnormalities noted in the MPS cohort, delineated by MPS type, echocardiographic finding, and severity.

Mitral Valve Insufficiency				
	None	Mild	Moderate	Severe
MPS I	0	4	2	0
MPS II	1	4	1	0
MPS III	1	0	1	0
MPS VI	0	1	0	0
MPS VII	0	1	0	0
	2	10	4	0
	87.5% (14/16)			
Aortic Valve Insufficiency				
	None	Mild	Moderate	Severe
MPS I	4	1	1	0
MPS II	3	1	1	1
MPS III	1	0	0	1
MPS VI	1	0	0	0
MPS VII	0	1	0	0
	9	3	2	2
	43.8% (7/16)			
	MPS	Control	p-value	
Mitral Valve Insuff	14/16	0/15	<0.0001 *	
Aortic Valve Insuff	7/16	0/15	0.00068 *	
LV Dilatation	7/16	1/15	0.037 *	

* Mitral valve insufficiency, aortic valve insufficiency, and left ventricular dilatation are significantly more common in the MPS cohort versus controls.