

Coronary Artery Abnormalities in Hyper-IgE Syndrome

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Received: 8 January 2011 / Accepted: 2 March 2011
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Abstract

Objective Hyper-IgE syndrome (HIES) is a rare primary immunodeficiency caused by autosomal dominant *STAT3* mutations resulting in recurrent infections and connective tissue abnormalities. Coronary artery abnormalities have been reported infrequently. We aimed to determine the frequency and characteristics of coronary artery abnormalities.

Design *STAT3*-mutated HIES patients ($n=38$), ranging in age from 8 to 57 years, underwent coronary artery imaging by computed tomography or magnetic resonance imaging. Images were evaluated for tortuosity, dilation, and aneurysm. Charts were reviewed for cardiac risk factors. To allow blinded image interpretation, an age- and gender-matched non-HIES group was also evaluated ($n=33$).

Results Coronary artery tortuosity or dilation occurred in 70% of HIES patients, with aneurysms present in 37%, incidences much higher than in the literature and in our non-HIES group, in which 21% had tortuosity or dilation and 3% had aneurysms. Hypertension was more common in the HIES group than in the general population and was associated with vessel abnormalities. Atherosclerosis was uncommon and mild.

Conclusions Coronary artery aneurysms and tortuosity are common in HIES, despite a paucity of atherosclerosis, suggesting that *STAT3* plays an integral role in human vascular remodeling and atherosclerosis.

Keywords Hyper-IgE syndrome · *STAT3* · coronary artery aneurysm · atherosclerosis · Job's syndrome · tortuosity

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Electronic supplementary material The online version of this article (doi:10.1007/s10875-011-9515-9) contains supplementary material, which is available to authorized users.

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Introduction

Hyper-IgE syndrome (HIES; Job's syndrome) is a primary immunodeficiency caused by autosomal dominant mutations in signal transducer and activator of transcription 3 (*STAT3*) [1, 2]. HIES is associated with a newborn rash, recurrent skin and lung infections, and elevated serum IgE [3]. Patients also have multiple connective tissue and skeletal abnormalities including typical facies, minimal trauma fractures, hyperextensibility, scoliosis, Chiari I malformations, and focal brain T2 hyperintensities on magnetic resonance imaging (MRI) [3, 4].

Reported arterial abnormalities in HIES include coronary artery aneurysms, bilateral carotid artery aneurysms, and a mycotic aneurysm of the middle cerebral artery [5–8]. In addition, *STAT3* has been found to be involved in vascular remodeling and atherosclerosis in vitro [9]. The reported cases suggest that vascular abnormalities are part of the clinical spectrum of HIES, but the frequency, severity and relationship to age and other clinical factors are unknown. We aimed to systematically and non-invasively characterize the coronary arteries of patients with HIES using computed tomography (CT) and/or magnetic resonance imaging (MRI) techniques, which have been proven to be valuable in evaluating coronary anomalies, coronary artery dilation, and atherosclerosis [6, 10–16]. Additionally, we examined the association of traditional coronary artery risk factors such as hypertension and atherosclerosis with these findings.

Methods

Subjects

Diseased subjects were recruited from a cohort of patients with HIES under study at the National Institutes of Health (NIH). HIES patients were diagnosed based on consistent clinical features and *STAT3* mutation analysis; only those with *STAT3* mutations were included in this study. Patient charts were reviewed for cardiac risk factors, including history of smoking, body mass index (BMI), hypertension, hypercholesterolemia, prior Kawasaki disease, and previous coronary events. Hypertension was defined as an average of three systolic blood pressures ≥ 140 , or an average of three diastolic blood pressure of ≥ 90 , or currently taking antihypertensives. Framingham cardiovascular disease risk scores were calculated for all HIES patients 20 years and older [17]. Charts and primary studies were reviewed for other vascular abnormalities including lacunar, cerebral or brainstem infarcts, non-coronary arterial dilation, and focal areas of hyperintensity on brain MRI. All subjects signed informed consent and were evaluated under Institutional Review Board (IRB)-approved protocols.

To allow blinding of the radiologic interpretation, cardiac CT and MRI scans were examined from non-HIES gender- and age (within 4 years)-matched subjects. These subjects were on IRB-approved coronary artery imaging protocols and had signed informed consent. Thirteen, including those in the pediatric age group, were on a protocol to non-invasively image coronary arteries in individuals with human immunodeficiency virus (HIV) infection. The others were recruited for having at least one coronary artery disease risk factor. Cholesterol levels were known for all non-HIES subjects, and Framingham risk scores were calculated for subjects 20 years or older.

Coronary Artery Imaging

Cardiac CT and MRI were performed to visualize the coronary arteries using previously reported methods (details in “[Supplemental methods](#)” of [Electronic supplementary material](#)) [6, 10, 11, 18]. CT scans were performed for patients at least 30 years old without contraindication including the ability to have intravenous CT contrast and the ability to tolerate a beta blocker to maintain a pulse of approximately 60–70 beats per minute throughout the procedure. MRI scans were performed for the remaining patients without contraindications (such as claustrophobia) or hardware that would interfere with the images (such as Harrington rods placed for scoliosis). The CT and MR scans were analyzed and interpreted by a single radiologist (AMG) who was blinded to whether the subject had HIES or not. Image analyses included measurements of the diameter of the left anterior descending (LAD) and right coronary arteries (RCA) at three points along the vessel (proximal, medial, and distal) to obtain an average diameter of the normal vessel. Additionally, evidence of coronary artery tortuosity and/or dilation was recorded.

The artery was interpreted as being “tortuous” if the main trunk of the vessel bent into an abnormal “S,” “C,” or “U” shape [19]. Tortuosity was graded as moderate or severe by the radiologist who was blinded to disease status. Dilation was recorded when there was a visually apparent dilation of the artery compared to the normal surrounding segments. Three measurements of the dilated segment were taken. We used the following definitions for aneurysm: dilation 1.5 times the diameter of the normal diameter, or dilation greater than 5 mm [12, 20, 21]. The measurements were made with the reader unaware of the subject's diagnosis. Atherosclerosis was defined as coronary wall irregularity resulting in luminal stenosis involving at least one of the three major coronary arteries. The degree of atherosclerotic stenosis was classified as mild (<50% stenosis), moderate (>50% but <70% stenosis), or severe (>70% stenosis).

Statistical Analysis

Several patient characteristics, including Framingham score, total cholesterol, and coronary artery abnormalities, were assessed for association with HIES status. Comparisons between the HIES and non-HIES groups were made for prevalence rates of each cardiac anomaly. Gender differences in the rates of cardiac anomalies in patients were also examined. For univariate analyses, Fisher's exact test was used for dichotomous variables and the Wilcoxon rank-sum test was used for continuous variables. Logistic regression was used for multivariate modeling of associations between cardiac anomalies and risk factors. Statistical analysis was performed using R software (version 2.8.1; R

Foundation for Statistical Computing, Vienna, Austria hyperlink <http://www.r-project.org>). All statistical tests were two-sided and performed at the 0.05 level.

Results

Subjects

Heart CT or MRI was performed on 38 patients from a cohort of 63 patients with *STAT3* mutation-positive HIES (Table 1). The reasons for exclusion included claustrophobia, too young to lie still without sedation, and implanted devices that would degrade the images. One image was

Table 1 HIES and non-HIES characteristics ($n=71$)

	HIES ($n=38$)	Non-HIES ($n=33$)	P value ^c
Female	24/38 (63%)	21/33 (64%)	Matching variable
Age (years)			
Mean	31	32	Matching variable
Range	8–57	13–56	
Age <20	10/38 (26%)	7/33 (21%)	
Ethnicity			
Caucasian	32/38 (84%)	18/33 (55%)	0.005
African American	3/38 (8%)	13/33 (39%)	
Asian	1/38 (3%)	1/33 (3%)	
Unknown	2/38 (5%)	1/33 (3%)	
Framingham score			
<1%	15/28 (54%)	15/26 (59%)	0.75
1–5%	11/28 (39%)	6/26 (22%)	
6–10%	2/28 (7%)	3/26 (11%)	
11–20%	0/28 (0%)	2/26 (7%)	
LDL ^a			
<100	23/38 (61%)	18/33 (55%)	0.62
100–159	15/38 (39%)	14/33 (42%)	
≥160	0/38 (0%)	1/33 (3%)	
HDL ^a			
<40	6/38 (16%)	9/31 (29%)	0.01
40–59	19/38 (50%)	17/31 (55%)	
≥60	13/38 (34%)	5/31 (16%)	
Total cholesterol ^a			
<200	31/38 (82%)	24/33 (73%)	0.21
200–239	7/38 (18%)	5/33 (15%)	
≥240	0/38 (0%)	4/33 (12%)	
Hypertension ^b	16/38 (42%)	11/33 (33%)	0.47
BMI (kg/m ²)			
Mean	25.0	26.4	0.35
Range	16.1–38.8	16.6–46.1	
Tobacco smoking	10/29 (34%)	15/34 (44%)	0.45
Characteristics measured in patients with HIES only			
STAT3 mutation domain			
SH2	17/38 (45%)		
DNA binding	21/38 (55%)		

^a Four HIES patients were on cholesterol lowering medication. Medication records were not available for controls

^b For the HIES patients, hypertension was defined as an average of three systolic blood pressures ≥140, or an average of three diastolic blood pressure of ≥90, or currently taking antihypertensives. For the non-HIES subjects, hypertension was recorded by patient history

^c The P value is calculated using the Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables

excluded due to artifact inhibiting ability to accurately interpret. CT was performed on 14 of the 21 individuals 30 years or older. MRI was performed for the remaining individuals, including all participants less than 30 years old, as well as for four of the patients over 30 years old who also had a CT. Three patients had only limited images appropriate for analysis. The patients' ages ranged from 8 to 57 years old (mean 31 years), and 24 of 38 (63%) patients were female. Ten of the patients were 18 years old or younger.

No HIES patient had a history of Kawasaki disease. One previously reported patient suffered a myocardial infarction and was found to have a large LAD aneurysm and a dilated RCA [7]. Hypertension was present in 15/28 (54%) patients over 18 years of age, and 16/38 (42%) of all patients. No patients had diabetes. The cholesterol levels are described in Table I; four patients were taking medication for their cholesterol. Out of 29 patients, ten (34%) had a history of smoking.

There were 33 non-HIES subjects matched for gender and age within 4 years (age range 13–56 years, mean 32 years, median 31 years; Table I). There were no gender- and age-matched subjects for five HIES patients. The non-HIES subjects had a higher proportion of African Americans (39%) than the HIES group did (8%). Twenty non-HIES subjects had at least one coronary artery disease risk factor, with 11/33 (33%) patients carrying the diagnosis of hypertension, and 13 had HIV infection. Out of 34 non-HIES patients, 15 (44%) were tobacco smokers. There was no significant difference in Framingham scores, BMI, total cholesterol, hypertension, or smoking history between this group and HIES patients (Table I).

Cardiac Imaging Findings

Coronary artery tortuosity or dilation was seen in 26/37 (70%) of evaluable HIES patients seen in 26/37 (70%) of evaluable HIES patients (Figs. 1 and 2; Table II). The prevalence of RCA dilation was 25%, and the prevalence of LAD dilation was 51% (Table II, Fig. S1). Tortuosity was largely isolated to the RCA, with 47% of HIES patients having RCA tortuosity; only one HIES patient had LAD tortuosity. Out of 38 HIES patients, 14 (37%) had 1 or more aneurysms as defined in “Methods.” The prevalence of dilation or tortuosity within the HIES population tended to increase with age (Fig. 3). Cardiac images of non-HIES and non-HIES subjects were intermixed and anonymized, thereby blinding the reader to the disease status in order to reducing bias. Despite diverse diagnoses in the non-HIES subjects, including HIV infection, the prevalence of the above abnormalities was much less (Table II). Looking at the absolute difference in prevalence, non-HIES rate (%)–HIES rate (%), the prevalence for non-HIES subjects was 32% less for tortuosity ($p=0.005$), 45% less for LAD

dilation ($p<0.0001$), 22% less for RCA dilation (0.01), and 34% less for aneurysm ($p=0.0004$; Table II).

Only mild atherosclerosis was seen in the HIES population. For HIES subjects, 21% had atherosclerosis, all of which was mild. Although identification of calcified lesions was possible only for those with a CT scan, none of the 14 HIES patients imaged with CT had coronary artery calcification. Differences in underlying diseases for the non-HIES subjects made comparisons difficult to interpret. However, in this population, 24% had mild, 6% moderate, and 6% severe atherosclerosis disease. In addition, 6 of 19 (32%) had calcified lesions on CT imaging. As HIV or its treatment may lead to an abnormal increase in atherosclerosis, a multivariate logistic analysis adjusted for age, African American race, HIV and HIES status was performed. HIES was associated with a 67% reduction in the odds of atherosclerosis compared to similar non-HIES subjects (odds ratio 0.33; 95% CI: 0.09, 1.22; $p=0.09$).

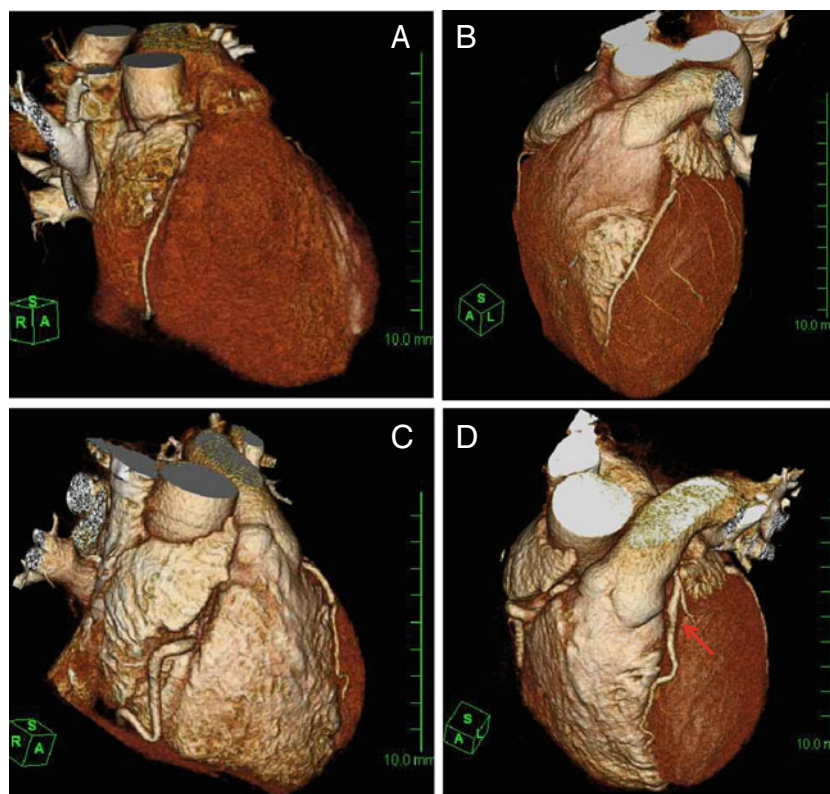
In HIES subjects, the associations between coronary artery abnormalities and other cardiac risk factors (age, BMI, smoking history, LDL, HDL, total cholesterol; hypertension; Framingham score) were examined further with logistic regression. Hypertension was associated with dilation ($p=0.03$) and tortuosity ($p=0.03$). There was significant or near significant association of dilation with increased BMI ($p=0.03$), increased LDL cholesterol ($p=0.10$), increased Framingham score ($p=0.09$), and age ($p=0.11$). Tortuosity had a significant association with age ($p=0.03$). Looking at the three borderline significant factors ($p\leq 0.10$) for dilation in a multivariate logistic model, none were significant, suggesting that the independent effects of these variables could not be distinguished in our dataset; age was not significant in this model. For tortuosity, age and hypertension were not significant in the multivariate model.

Within the HIES population, coronary artery abnormalities (dilation and/or tortuosity) were present in both genders, but appeared more prevalent and the dilation more pronounced in males (Tables SI and SII). This difference may have been because of increased hypertension in males, despite no significant difference in age or obesity (Table SII). There was no association between *STAT3* mutation region (SH2 domain or DNA binding domain) and the presence of arterial dilation, tortuosity, or atherosclerosis.

Other Vascular Abnormalities

Routine imaging of non-coronary vessels was not performed, but other vascular abnormalities were noted from previously obtained imaging. Three patients had lacunar infarcts in the brain. One of these patients had dilation of the left common carotid artery, internal carotid artery, and left carotid bulb; all three had dilated coronary arteries. All but five patients had focal areas of hyperintensity on brain

Fig. 1 CT images of control RCA (a) and LAD (b), tortuous RCA (c), and dilated LAD (d, arrow at dilation) in a 45-year-old man with HIES



MRI. No association was found between the presence or amount of focal brain hyperintensities and coronary artery abnormalities. The presence of other vascular abnormalities was not performed for the non-HIES subjects.

Discussion

Dilation and tortuosity of the coronary arteries are common in *STAT3*-mutated HIES, reflecting the widespread expression and diverse functions of *STAT3*. These coronary artery abnormalities appear to increase with age and are associated with hypertension, which is also more common in HIES. Despite these common risk factors and associated features, there was a paucity of atherosclerosis.

In the general population, the incidence of coronary artery aneurysms ranges from 0.3% to 5.3%, occurring predominantly in the RCA [20–22]. The most common etiology in adults is likely atherosclerosis and its attendant complications such as angioplasty. Other etiologies of coronary artery aneurysms include congenital abnormalities, autoimmune diseases such as Takayasu's arteritis, presumed infections such as Kawasaki disease, and connective tissue diseases such as Marfan syndrome, Loeys–Dietz syndrome (LDS), and vascular-type Ehlers–Danlos syndrome (type IV) [20, 23–25]. In HIES, aneurysms occurred in 37% of patients, with dilation even more frequent, predominantly affecting the LAD, all without significant associated atherosclerosis. Coronary artery tortuosity is also common in HIES, although its incidence in

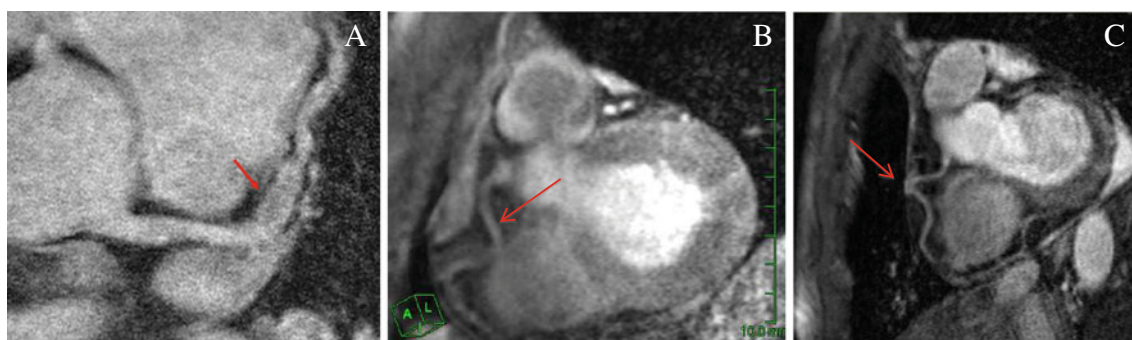


Fig. 2 Cardiac MR demonstrating dilated LAD in a 51-year-old man with HIES (a), and a tortuous RCA in a 24-year-old man (b), and a tortuous RCA in a 32-year-old man (c)

Table II Coronary artery dilation and tortuosity in HIES and non-HIES subjects ($n=71$)

	HIES ^b	Non-HIES subjects	<i>P</i> value ^c
RCA dilation	9/36 (25%)	1/33 (3%)	0.01
LAD dilation	19/37 (51%)	2/33 (6%)	<0.0001
Aneurysm ^a	14/38 (37%)	1/33 (3%)	0.0004
Any tortuosity	18/38 (47%)	5/33 (15%)	0.005
Any defect	26/37 (70%)	7/33 (21%)	<0.0001
Both tortuosity and dilation	12/38 (32%)	1/33 (3%)	0.002

^a Aneurysm defined as: dilation 1.5 times the diameter of the normal diameter or dilation greater than 5 mm

^b Number of patients evaluated varied for each measurement, based on whether an adequate imaging study was available

^c Fisher's exact test is used to compare frequency of binary variables

the general population is unknown. In the general population, similar to aneurysms, tortuosity is mostly associated with atherosclerosis. The proposed mechanism is that of unequal traction and pressure in the lumen leading to degeneration of elastin [26].

The pathogenesis of vascular abnormalities in HIES remains unknown, but disordered TGF- β signaling and matrix metalloproteinase (MMP) dysregulation may play roles. Marfan syndrome and LDS, both associated with disordered TGF- β signaling, share connective tissue abnormalities with HIES including aneurysms, arterial tortuosity, scoliosis, and hyperextensible joints [23, 24]. Familial arterial tortuosity, a rare autosomal recessive disease caused by a mutation in *GLUT10*, is also thought to be involved in TGF- β signaling [27]. Tissue metalloproteinase (MMP) dysregulation may play a role in aneurysm formation as it does in other pro-inflammatory conditions such as Kawasaki disease and vasculo-Bechet's [28–30]. Disordered MMP regulation is also associated with abdominal aortic aneurysms, moyo-moya, coronary artery disease-associated aneurysms, and the aortic aneurysms of Marfan syndrome [31–35]. STAT3 is involved in the regulation of several MMPs, either directly through

interactions with MMP promoters, as has been shown with MMPs 1, 2, 3, and 9, or through STAT3-regulated chemokines and cytokines such as monocyte chemoattractant protein-1 (MCP-1) [36–39]. How MMP3 dysregulation may impact vascular remodeling in HIES requires further study.

The paucity of atherosclerosis in HIES despite coronary artery disease risk factors in a pro-inflammatory immunodeficiency was unexpected [1]. Mouse data implicate STAT3 in the pathogenesis of atherosclerosis [7, 40]; pravastatin treatment of mice prevented atherosclerotic lesions and was associated with decreased levels of phosphorylated STAT3 [41]. Hypertension was the most frequent coronary artery risk factor observed, and was more common in HIES than expected for age, with an overall incidence of 42% despite a mean age of 31 [42]. It is unclear from this retrospective survey whether blood pressure increases as a result of the discovered arterial abnormalities or whether the increased blood pressure causes aberrant remodeling of vessels and subsequent dilation. We suspect that hypertension is a primary effect of *STAT3* mutation, since hypertension is only weakly associated with increased risk of non-HIES aneurysms such as aortic abdominal aneurysm [43, 44].

The clinical implications of tortuosity and dilation of the coronary arteries in HIES are unclear. Coronary artery dysfunction and myocardial events are rare causes of morbidity and mortality in HIES. Only one HIES patient has been reported to have had a myocardial infarction and one other presented with possible angina [5, 7, 8]. Outside of the heart, two patients are known to have had subarachnoid hemorrhages secondary to ruptured intracerebral aneurysms, and one patient died of a mycotic *Aspergillus* cerebral artery aneurysm [45]. In other populations with coronary artery aneurysms, morbidity and mortality are due to thrombosis with subsequent ischemia, infarction and rupture [20–22]. Tortuosity also may alter flow resulting in cardiac ischemia. As survival in HIES is extended with better antimicrobials for life-threatening

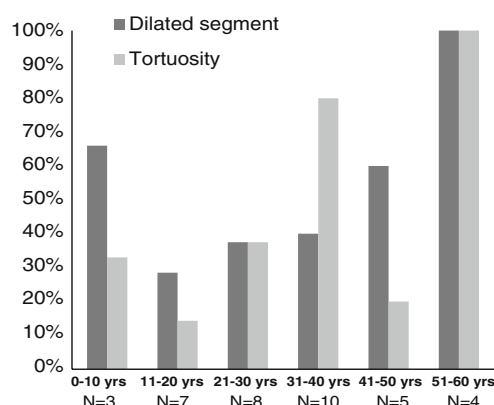


Fig. 3 Percent of HIES patients with coronary artery abnormalities by age group

pulmonary infections, it is possible that these arterial abnormalities will become more clinically significant.

Treatment of the coronary artery abnormalities in HIES remains unexplored. The use of antithrombotic medications needs to be weighed against the risk of pulmonary hemorrhage, a known significant source of morbidity and mortality in HIES [45]. The angiotensin II type 1 receptor antagonist, losartan, appears promising in the treatment of Marfan-associated aneurysms as it antagonizes TGF-beta signaling [46, 47], but the roles of TGF-beta and losartan in HIES require further study.

Our study was limited in assessing atherosclerosis. Non-HIES subjects were selected from other protocols with imaging performed by the same research team, so that the radiologist interpreting the images could be blinded to diagnosis. Although the two patient groups did not have significant differences in Framingham score, hypertension, BMI, and total cholesterol, the non-HIES subjects had diverse diagnoses (including HIV infection), and there were differences in race with controls having more African Americans. Therefore, although the non-HIES subjects allowed comparison of the prevalence of coronary abnormalities with the HIES cohort who were matched for age and gender, their underlying diseases prevented them from acting as ideal controls.

In summary, coronary artery abnormalities including tortuosity, dilation, and aneurysm are common in HIES and occur at young ages. While these abnormalities do not appear to cause marked morbidity or mortality, this may change as overall treatment and survival improves. Future studies will determine the clinical significance of these abnormalities, and examination of vascular tissues and animal models of HIES will help determine the role of MMPs and TGF-beta in STAT3-mediated vascular remodeling. Understanding STAT3's role in vascular remodeling may shed light on more common conditions such as Kawasaki disease. Finally, since *STAT3* mutation appears to protect against atherosclerosis, it may be another target for prevention and treatment of atherosclerotic disease.

Acknowledgement This research was supported by the Intramural Research Programs of the NIAID, NIDDK, and NIH, Bethesda, MD 20892. The views expressed in this article are those of the authors and do not reflect the official policy of the US government.

Elizabeth Mannino Avila was supported by the Clinical Research Training Program, a public-private partnership supported jointly by the NIH and Pfizer (via a grant to the Foundation for NIH from Pfizer).

References

- Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, et al. STAT3 mutations in the hyper-IgE syndrome. *New Engl J Med*. 2007;357:1608–19.
- Minegishi Y, Saito M, Tsuchiya S, Tsuge I, Takada H, Hara T, et al. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. *Nature*. 2007;448:1058–62.
- Freeman AF, Holland SM. The hyper-IgE syndromes. *Immunol Allergy Clin North Am*. 2008;28:277–91.
- Freeman AF, Collura-Burke CJ, Patronas NJ, Ilcus LS, Darnell D, Davis J, et al. Brain abnormalities in patients with hyperimmunoglobulin E syndrome. *Pediatrics*. 2007;119:e1121–5.
- Alomar-Melero E, Martin TD, Janelle GM, Peng YG. Unusual giant right coronary artery aneurysm resembles an intracardiac mass. *Anesth Analg*. 2008;107(4):1161–2.
- Gharib AM, Pettigrew RI, Elagha A, Hsu A, Welch P, Holland SM, et al. Coronary abnormalities in Hyper-IgE recurrent infection syndrome: depiction at coronary MDCT angiograph. *AJR*. 193:478–81.
- Ling JC, Freeman AF, Gharib AM, Arai AE, Lederman RJ, Rosing DR, et al. Coronary artery aneurysms in patients with hyper IgE recurrent infection syndrome. *Clin Immunol*. 2007;122:255–8.
- Young TY, Jerome D, Gupta S. Hyperimmunoglobulinemia E syndrome associated with coronary artery aneurysms: deficiency of central memory CD4+ T cells and expansion of effector memory CD4+ T cells. *Ann Allergy Asthma Immunol*. 2007;98(4):389–92.
- Olive M, Mellad JA, Beltran LE, Ma M, Cimato T, Noguchi AC, et al. p21^{Cip1} modulates arterial wound repair through the stromal cell-derived factor-1/CSCR4 axis in mice. *J Clin Invest*. 2008;118(6):2050–61.
- Gharib AM, Ho VB, Rosing DR, Herzka DA, Stuber M, Arai AE, et al. Coronary artery anomalies and variants: technical feasibility of assessment with coronary MR angiography at 3T. *Radiology*. 2008;247:220–7.
- Datta J, White CS, Gilkeson RC, Meyer CA, Kansal S, Jani ML, et al. Anomalous coronary arteries in adults: depiction at multi-detector row CT angiography. *Radiology*. 2005;235:812–8.
- Arnold R, Ley S, Ley-Zapozhyan J, Eichhorn J, Schenk JP, Ulmer H, et al. Visualization of coronary arteries in patients after childhood Kawasaki syndrome: value of multidetector CT and MR imaging in comparison to conventional coronary catheterization. *Pediatr Radiol*. 2007;37(10):998–1006.
- Greil GF, Stuber M, Botnar RM, Kissinger KV, Geva T, Newburger JW, et al. Coronary magnetic resonance angiography in adolescents and young adults with Kawasaki disease. *Circulation*. 2002;105:908–11.
- Kim WY, Danias PG, Stuber M, Flamm SD, Plein S, Nagel E, et al. Coronary magnetic resonance angiography for the detection of coronary stenoses. *New Engl J Med*. 2001;345:1863–9.
- Miller JM, Rochitte CE, Dewey M, Arab-Zadeh A, Niinuma H, Gottlieb I, et al. Diagnostic performance of coronary angiography for the detection of coronary stenoses. *New Engl J Med*. 2008;359:2324–36.
- Garcia MJ, Lessick J, Hoffmann MH. Accuracy of 16-row multidetector computed tomography for the assessment of coronary artery stenosis. *JAMA*. 2006;296:403–11.
- Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA* 2001;285:2486–97.
- Hoffmann MH, Shi H, Schmitz BL, Schmid FT, Lieberknecht M, Schulze R, et al. Noninvasive coronary angiography with multislice computed tomography. *JAMA*. 2005;293:2471–8.
- Bullitt E, Gerig G, Pizer SM, Lin W, Aylward SR. Measuring tortuosity of the intracerebral vasculature from MRA images. *IEEE Trans Med Imaging*. 2003;22(9):1163–71.
- Cohen P, O'Gara PT. Coronary artery aneurysms: a review of the natural history, pathophysiology, and management. *Cardiol Rev*. 2008;16(6):301–4.
- Swaye PS, Fisher LD, Litwin P, Vignola PA, Judkins MP, Kemp HG, et al. Aneurysmal coronary artery disease. *Circulation*. 1983;67:134–8.
- Burns CA, Cowley MJ, Wechsler AS, Vetrovec GW. Coronary aneurysms: a case report and review. *Cathet Cardiovasc Diagn*. 1992;27:106–12.

23. Judge DP, Dietz HC. Marfan's syndrome. *Lancet*. 2005;366:1965–76.
24. Loeys BL, Schwarze U, Holm T, Callewaert BL, Thomas GH, Pannu H, et al. Aneurysm syndromes in the TGF-beta receptor. *New Engl J Med*. 2006;355:788–98.
25. Watanabe A, Takashi S. The vascular type of Ehlers–Danlos syndrome. *J Nippon Med Sch*. 2008;75(5):254–61.
26. Zegers ES, Meursing BTJ. AJM Oude Ophuis. Coronary tortuosity: a long and winding road. *Neth Heart J*. 2007;5:191–5.
27. Callewaert BL, Willaert A, Kerstjens-Frederikse WS, DeBacker J, Devriendt K, Albrecht B, et al. Familial arterial tortuosity syndrome: clinical and molecular findings in 12 newly identified families. *Hum Mutat*. 2008;29:150–8.
28. Gavin PJ, Crawford SE, Shulman ST, Garcia FL, Rowley AH. Systemic arterial expression of matrix metalloproteinases 2 and 9 in acute Kawasaki disease. *Arterioscler Thromb Vasc Biol*. 2003;23:576–81.
29. Pay S, Abbasov T, Erdem H, Musabak U, Simsek I, Pekel A, et al. Serum MMP-2 and MMP-9 in patients with Behcet's disease: do their higher levels correlate to vasculo-Behcet's disease associated with aneurysm formation? *Clin Exp Rheum*. 2007;25(4 Supplement 45):S70–5.
30. Senzaki H. The pathophysiology of coronary artery aneurysms in Kawasaki disease: role of matrix metalloproteinases. *Arch Dis Childhood*. 2006;91:847–51.
31. Dogan A, Tuzun N, Turker Y, Akcay S, Kaya S, Ozaydin M. Matrix metalloproteinases and inflammatory markers in coronary artery ectasia: their relationship to severity of coronary artery ectasia. *Coron Artery Dis*. 2008;19(8):559–63.
32. Ikonomidis JS, Jones JA, Barbour JR, Stroud RE, Clark LL, Kaplan BS, et al. Expression of matrix metalloproteinases and endogenous inhibitors within ascending aortic aneurysms of patients with Marfan syndrome. *Circulation*. 2006;114(1 Suppl):I365–70.
33. Kang HS, Kim SK, Cho BK, Kim YY, Hwang YS, Wang KC. Single nucleotide polymorphisms of tissue inhibitor of metalloproteinase genes in familial moyamoya disease. *Neurosurgery*. 2006;58(6):1074–80.
34. Lamblin N, Bauters C, Hermant X, Lablanche JM, Helbecque N, Amouyel P. Polymorphisms in the promoter regions of MMP-2, MMP-3, MMP-9, and MMP-12 genes as determinants of aneurysmal coronary artery disease. *J Am Coll Cardiol*. 2002;40:43–8.
35. Scott RM, Smith ER. Moyamoya disease and moyamoya syndrome. *New Engl J Med*. 2009;360(12):1226–37.
36. Schroer N, Pahne J, Walch B, Wickenhauser C, Smola S. Molecular pathobiology of human cervical high-grade lesions: paracrine STAT3 activation in tumor-instructed myeloid cells drives local MMP-9 expression. *Cancer Res*. 2011;71:87–97.
37. Song Y, Qian L, Song S, et al. Fra-1 and Stat3 synergistically regulate activation of MMP-9 gene. *Mol Immunol*. 2008;45:137–43.
38. Tsareva SA, Moriggl R, Corvinus FM, Wiederanders B, Schütz A, Kovacic B, et al. Signal transducer and activator of transcription 3 activation promotes invasive growth of colon carcinomas through matrix metalloproteinase induction. *Neoplasia*. 2007;9(4):279–91.
39. Xie TX, Wei D, Liu M, et al. Stat3 activation regulates the expression of matrix metalloproteinase-2 and tumor invasion and metastasis. *Oncogene*. 2004;23:3550–60.
40. Gharavi NM, Alva JA, Mouillesseaux KP, Lai C, Yeh M, Yeung W, et al. Role of the Jak/STAT pathway in the regulation of interleukin-8 transcription by oxidized phospholipids in vitro and in atherosclerosis in vivo. *J Biol Chem*. 2007;282(43):31460–8.
41. Zhou X, Li D, Yan W, Li W. Pravastatin prevents aortic atherosclerosis via modulation of signal transduction and activation of transcription 3 (STAT3) to attenuate interleukin-6 (IL-6) action in *ApoE* knockout mice. *Int J Mol Sci*. 2008;9:2253–64.
42. Pleis JR, Lucas JW. Summary Health statistics for U.S. adults: National health interview survey, 2007. National Center for Health Statistics. *Vital Health Stat* 2009;10(240)
43. Forsdahl SH, Singh K, Solberg S, Jacobsen BK. Risk factors for abdominal aortic aneurysms: a 7-year prospective study: the Tromsø study, 1994–2001. *Circulation*. 2009;119:2202–8.
44. Corunz J, Sidoti Pinto C, Tevaearai H, Egger M. Risk factors for asymptomatic abdominal aortic aneurysm. *Eur J Public Health*. 2004;14:343–9.
45. Freeman AF, Kleiner DE, Nadiminti H, Davis J, Quezado M, Anderson V, et al. Causes of death in hyper-IgE syndrome. *J Allergy Clin Immunol*. 2007;119(5):1234–40.
46. Habashi JP, Judge DP, Holm TM, Cohn RD, Loeys BL, Cooper TK, et al. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science*. 2006;312:117–21.
47. Brooke BS, Habashi JP, Judge DP, Patel N, Loeys B, Dietz HC. Angiotensin II blockade and aortic-root dilation in Marfan's syndrome. *N Engl J Med*. 2008;358(26):2787–95.

Supplemental Methods

Coronary Artery Imaging: MRI was performed on a Philips 3 T system (Philips Medical Systems, Best, NL) using a 6-element cardiac phased-array receiver coil, and vector electrocardiographic (VCG) gating as previously described.[10] Multidetector CT scans were performed using a 16-detector scanner or 64-detector scanner (Philips Medical Systems, Cleveland, Ohio, USA) or dual-source CT scanner (Siemens, Definition, Siemens Health Care, Forchheim, Germany). The CT protocol was similar to previously described techniques.[6,9,11,16] Briefly, 50-100 mg of oral metoprolol was given 30 to 60 minutes prior to CT when needed to lower the heart rate below 75 beats per minute.

Supplemental Results

HIES Gender differences. Males appeared to have more coronary artery abnormalities and may have more severe abnormalities than females, with a 1.25 mm increase in mean diameter of the dilated LAD (95% CI: 0.37, 2.06; $p=0.01$), and a non-significant 0.93 mm increase in the dilated RCA diameter (95% CI: -0.78, 3.18; $p=0.26$). Additionally, 57% of males had both dilation and tortuosity compared to only 17% of females ($p=0.03$).

Supplemental Table 1. Dilation and tortuosity prevalence by HIES status and by sex for subjects with HIES (N=38).

	Female □ n = 24	Male □ n = 14	□ P-value*
RCA dilation	3/22 (14%)	6/14 (43%)	0.11
RCA dilated diameter □ Mean, mm (SD)	□ 4.78 (1.02)	□ 5.98 (1.11)	□ 0.26
LAD dilation	10/24 (42%)	9/13 (69%)	0.17
LAD dilated diameter □ Mean, mm (SD)	□ 4.03 (0.56)	□ 5.25 (1.04)	□ 0.01
Any dilation	10/23 (43%)	10/14 (71%)	0.17
Any tortuosity	10/24 (42%)	8/14 (57%)	0.50
Any defect	16/23 (70%)	10/14 (71%)	1
Both tortuosity and dilation	4/19 (17%)	8/14 (57%)	0.03

*Fisher's exact test is used to compare frequency of binary variables and the Wilcoxon rank-sum test is used for RCA and LAD diameters

Supplemental Table 2. Coronary artery risk factors by gender in HIES patients who had coronary artery imaging (N=38).

HIES patients	Female □(n=24)	Male □(n=14)	P-value*
Age□Mean (SD)	□29.6 (13.5)	32.3 (15.8)	0.75
Age ≥ 40	5/24 (20.8%)	5/14 (35.7%)	0.45
Obese (BMI ≥ 30)	6/24 (25.0%)	4/14 (28.6%)	1.0
Hypertension ⁺	6/24 (25.0%)	10/14 (71.4%)	0.008
High Cholesterol [†]	0/24 (0%)	4/14 (28.6%)	0.01
Tobacco smoker (past or present)**	6/17 (35.3%)	4/12 (33.3%)	1.0

*Fisher's exact test is used to compare frequency of binary variables and the Wilcoxon rank-sum test is used for age

+ Hypertension was defined as systolic blood pressure ≥ 140 , diastolic blood pressure ≥ 90 , or taking antihypertensive medication

† High cholesterol was defined as LDL ≥ 160 or total cholesterol ≥ 240 or taking lipid lowering drugs.

**Only patients with known smoking history included

Supplemental Figure 1. Diameter of dilated and normal segments of RCA and LAD in HIES and non-HIES subjects.