Premature Cardiovascular Disease Is Common in Relatives of Patients With Premature Peripheral Atherosclerosis

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**Background:** Numerous clinical conditions have been proposed to explain the premature onset of symptomatic peripheral vascular disease (PVD) in young adults, but the role of genetic factors has not been defined. This study was performed to determine the prevalence of cardiovascular disease among family members of patients with premature PVD.

**Methods:** The prevalence of early cardiovascular events occurring in first-degree relatives of 90 subjects with premature PVD (onset ≤49 years) was determined. The prevalence of occult atherosclerosis was determined by duplex ultrasonography in a cohort of 20 asymptomatic siblings. Reference groups included first-degree relatives of 80 subjects with premature coronary artery disease (CAD) and first-degree relatives of 48 healthy subjects.

**Results:** Cardiovascular events occurred at age 55 years or younger in 28% of the parents of PVD subjects, in 23% of parents of CAD subjects, and in 7% of the parents of healthy controls ($P<.001$). Cardiovascular events occurred in 24% of siblings of PVD subjects, in 14% of siblings of CAD subjects, and in 7% of siblings of healthy controls ($P<.001$). Duplex ultrasonography detected early plaques in the lower extremity circulation of 10 (50%) of the asymptomatic siblings of PVD subjects.

**Conclusions:** Early, symptomatic cardiovascular disease is more common in first-degree relatives of individuals with premature PVD than in relatives of healthy individuals or of probands with premature CAD. Occult vascular disease in the lower extremity is prevalent among asymptomatic siblings of probands with premature PVD. These observations indicate that susceptibility to premature PVD has a familial basis.

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SUBJECTS AND METHODS

STUDY SUBJECTS

This project was approved by the institutional review board of the medical center. We studied 90 nondiabetic men and women presenting to our institution between 1993 and 1998 with symptoms of lower extremity atherosclerotic occlusive disease beginning at age 49 years or younger. The presence of PVD was confirmed in these individuals using standard noninvasive tests (ankle pressure indices) or arteriography. Peripheral vascular disease was considered to be present if the ankle pressure index was less than 0.8 or if there was a luminal stenosis in an axial artery measuring greater than 50% diameter loss by arteriogram. The predominant locations of occlusive arterial lesions (aortoiliac, femoropopliteal, or both) were noted. After demographic data were recorded, each participant was evaluated for atherosclerotic risk factors (history of smoking, hypertension, and hyperlipidemia). Detailed medical histories were obtained regarding the presence of overt coronary artery disease (CAD) (angina, previous MI, previous coronary catheterization, previous coronary revascularization) and cerebrovascular disease (transient ischemic attacks, stroke, previous carotid endarterectomy). Complete family histories were obtained by personal interview with each proband. All vascular events in family members were recorded, including prior strokes, MIs, intermittent claudication, and revascularization procedures of the heart (coronary artery bypass grafting/percutaneous transluminal coronary angioplasty [CABG/PTCA]), carotid artery, or lower extremity. The age at onset of the vascular event was noted for each affected individual. Vascular events occurring at age 55 years or younger were defined as premature. This age threshold is in keeping with the criteria of the National Cholesterol Education Program18 for men and is more conservative for women.

REFERENCE POPULATION

Two independent groups of nuclear families were used as reference groups for the PVD cohort. One group included first-degree relatives of 80 patients who developed symptomatic CAD before the age of 50 years. These patients were recruited through a large interventional cardiology program in Dallas, Tex, and through 6 cardiac rehabilitation programs in the Dallas/Fort Worth area. Coronary artery disease was defined as a documented MI, angiographic evidence of a greater than 75% luminal stenosis in at least one major epicardial coronary artery, or coronary revascularization (CABG/PTCA). None of the patients with CAD had symptoms of PVD. A second group included first-degree relatives of 48 healthy white men and women who were at least a decade older than the probands (≥60 years) and who did not have symptoms of cardiovascular disease. These subjects were recruited from the community and were participants in a study of healthy families. Detailed family histories, including the age at which vascular events (if any) occurred, were obtained using a standardized questionnaire.

VERIFICATION OF HISTORICAL DATA

To document the reliability of the family history data obtained from the probands, we contacted all living first-degree relatives of a random subset of the probands in each group. Historical data for all members of each respective family were verified by telephone interview, and discrepancies were noted.

DUPLEX ULTRASONOGRAPHY

The prevalence of early, asymptomatic lower extremity atherosclerosis (occult disease) was evaluated in 20 siblings of 16 patients with premature PVD and in 23 apparently healthy volunteers who were employees at our institution. The 20 siblings represented the first 20 asymptomatic family members of the PVD probands who were willing to participate, and no specific selection criteria were used. None of the siblings or control subjects had symptoms of PVD, CAD, or cerebrovascular disease. The lower extremity arterial circulation (including the aorta, common iliac arteries, external iliac arteries, common femoral arteries, superficial femoral arteries, and popliteal arteries) of each subject was imaged with duplex ultrasonography. A 5-MHz probe was used to visualize the entire intimal surface of these arteries. Arterial plaque disease was defined as a focal area of luminal encroachment having mixed echoes or a calcified appearance, with an irregular surface. The degree of luminal encroachment associated with individual lesions was calculated according to standardized criteria22 and expressed as a percentage of luminal narrowing. Flow velocities were also determined in all areas, providing an assessment of hemodynamic significance for each plaque.

ASSAY OF PLASMA LIPIDS AND LIPOPROTEINS

Fasting plasma lipid and high-density lipoprotein cholesterol (HDL-C) concentrations were assayed in the 20 siblings of premature PVD patients who underwent duplex ultrasonography. Plasma cholesterol and triglyceride concentrations were determined in duplicate by enzymatic assay using commercial reagents (Cholesterol/HP; Boehringer Mannheim, Indianapolis, Ind, and triglycerides/GPO-TRINDER, Sigma Diagnostics, St Louis, Mo). The HDL-C concentration was measured in the supernatant after precipitation of apolipoprotein B–containing lipoproteins with sodium phosphotungstate (0.555 mmol/L). Intra-assay variation was less than 3% for plasma cholesterol and triglyceride, and less than 5% for plasma HDL-C.

STATISTICAL ANALYSES

Continuous data are expressed as mean ± SD. Comparisons of mean values (age at onset, plasma lipid concentrations) for continuous variables were performed using unpaired t tests. Dichotomous data (atherosclerotic risk factors, presence of atherosclerotic disease) were compared in family members of PVD patients, CAD patients, and control subjects using χ² tests. A P value of .05 was used as the nominal threshold for significance. The relative risk for premature vascular disease in siblings of PVD and CAD probands was calculated using prevalence data from the siblings of the healthy control subjects as a population reference.
The mean age of the PVD probands in this study was 48 ± 5 years. Patient demographics and atherosclerotic etiology and from 5 siblings with whom the probands had adverse events before the age of 40 years, and were thus considered to warrant intervention.

RESULTS

CLINICAL CHARACTERISTICS

The mean age of the PVD probands in this study was 48 ± 5 years, and the mean age at onset of PVD symptoms was 42 ± 5 years. Patient demographics and atherosclerotic risk factors are shown in Table 1. Seventy (78%) of these patients had atherosclerosis predominantly affecting the aortoiliac segment, 6 (6%) had predominantly femoropopliteal disease, and 14 (16%) had both. The mean ankle pressure index determined in the more ischemic leg was 0.43 ± 0.2. Forty patients (44%) had CAD; this diagnosis was based on a history of CABG/PTCA in 28, on results of coronary catheterization in 9, on documented MI in 2, and on typical symptoms of angina pectoris in 1. Eleven (12%) patients had symptomatic cerebrovascular disease, including transient ischemic attacks in 5 and strokes in 6. Fifty-nine (66%) patients had previously undergone at least one lower extremity revascularization procedure; 31 (34%) had stable symptoms that did not warrant intervention.

The mean age at onset of symptoms was similar in the premature CAD and PVD groups (Table 1). The number of patients with a history of smoking was significantly higher (P = .02) in the PVD group than in the CAD group, and a far greater proportion of patients with PVD were active smokers at the time of the study.

FAMILY HISTORIES

Family histories provided information on 176 parents and 259 siblings of the PVD probands. Of these, 8 parents and 10 siblings died from trauma or malignant disease before the age of 40 years, and were thus considered to be uninformative. In addition, data were excluded from 3 other siblings who had cardiomyopathy of unknown etiology and from 5 siblings with whom the probands had lost contact. The results of the pedigree analysis are shown in Table 2. Forty-seven (28%) of the 168 parents with available historical data were reported to have had vascular events before the age of 55 years, including 35 with premature CAD (17 fatal MI, 15 nonfatal MI, 3 CABG/PTCA), 6 with premature PVD (3 intermittent claudication, 3 lower extremity bypass), and 6 with strokes. Three of the parents with PVD and 2 with strokes also had a history of premature CAD. Fifty-seven (24%) of the 241 siblings with available historical data had reported vascular events, including 38 with premature CAD (25 MI, 10 CABG/PTCA, 3 coronary catheterizations), 19 with premature PVD (15 intermittent claudication, 4 lower extremity bypass), and 1 with premature stroke. One of the siblings with premature PVD also had premature CAD.

Family histories provided information on 160 parents and 199 siblings of the CAD probands, and on 96 parents and 184 siblings of the healthy controls. The prevalence of premature vascular events was more than 3-fold higher in siblings of premature PVD patients than in siblings of healthy controls (Table 2). Using data from the healthy control group as a population reference, the recurrence risk for vascular disease in siblings of premature PVD probands was calculated to be 3.6. Remarkably, premature vascular events were significantly more common in siblings of premature PVD patients than in siblings of premature CAD patients (Table 2). The recurrence risk for vascular disease in siblings of premature CAD probands was 2.2. Vascular events were also significantly more common among parents of patients with premature PVD than in parents of healthy controls.

VERIFICATION OF FAMILY HISTORY DATA

Ninety first-degree relatives (24 reported as asymptomatic and 66 as asymptomatic) of 40 PVD probands were contacted by the investigators, and 87 (97%) confirmed the information given by the proband. Two siblings denied having the symptoms reported by the respective probands (MI, claudication), and 1 sibling reported as asymptomatic proved to have had an MI at age 49 years. One hundred sixty-one first-degree relatives of 46 of the CAD probands and 74 first-degree relatives of 20 healthy control probands were contacted by the investigators. All relatives (100%) confirmed the information provided by the proband.
PREVALENCE OF OCCULT DISEASE IN ASYMPTOMATIC INDIVIDUALS

Complete lower extremity duplex ultrasound examinations were successfully performed in 20 asymptomatic siblings (11 men, 9 women) of 16 probands with premature PVD, and in 23 control subjects (9 men, 14 women). The mean ages of the sibling and control groups were similar (48 ± 4 vs 45 ± 4 years; P = .08). Thirteen (65%) of the 20 siblings had a history of smoking, as did 4 (17%) of the controls. None of the subjects in either group had a history of diabetes mellitus or hypertension. The mean plasma lipid and HDL-C levels among the 20 siblings were as follows: plasma total cholesterol, 5.15 ± 1.0 mmol/L (199 ± 40 mg/dL); low-density lipoprotein cholesterol, 3.02 ± 0.80 mmol/L (117 ± 31 mg/dL); HDL-C, 1.19 ± 0.34 mmol/L (46 ± 21 mg/dL); and triglycerides, 2.39 ± 1.28 mmol/L (212 ± 113 mg/dL). Eight of the 20 siblings had plasma triglyceride concentrations above the 90th percentile for age and sex. Two of these individuals were also hypercholesterolemic (total plasma cholesterol level exceeding the 90th percentile for age and sex).

The results of duplex ultrasonography are shown in Table 3. A total of 19 arterial plaques were identified in 10 of the siblings: 3 were located in aortas, 6 were in iliac segments, 5 were in common femoral arteries, 4 were in superficial femoral arteries, and 1 was in a popliteal artery. The one arterial plaque identified in a control subject was located in a common femoral artery. Arterial lesions were identified in 8 of 13 siblings who smoked, and in 2 of 7 siblings who had never smoked.

Table 3. Occult Disease in 20 Asymptomatic Siblings Studied With Lower Extremity Duplex Ultrasonography Compared With 23 Age-Matched Controls

<table>
<thead>
<tr>
<th>Duplex Result</th>
<th>Siblings</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, No. (%)</td>
<td>10 (50)</td>
<td>22 (96)</td>
</tr>
<tr>
<td>Single arterial segment involved, No.</td>
<td></td>
<td></td>
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<tr>
<td>1%-19% Stenosis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>20%-49% Stenosis</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>≥50% Stenosis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Multiple arterial segments involved (most advanced lesion identified), No.</td>
<td></td>
<td></td>
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<tr>
<td>1%-19% Stenosis</td>
<td>2</td>
<td>0</td>
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COMMENT

The pathophysiology of premature PVD remains enigmatic. Previous studies have identified several factors associated with PVD, but none of these risk factors accounts for the unusually early onset of the disease in some individuals. Several lines of evidence indicate that susceptibility to premature atherosclerosis of the coronary and cerebral vasculature is heritable, but the role of genetic factors in the development of premature PVD has not been evaluated. As a first step toward determining whether patients with premature PVD have an increased genetic susceptibility to atherosclerosis, we assessed the prevalence of vascular disease in the families of probands who developed severe, symptomatic PVD before the age of 50 years. Our results provide strong evidence for familial aggregation of vascular disease in the first-degree relatives of these patients. First, detailed family histories indicate that premature, symptomatic cardiovascular disease is far more common in first-degree relatives of premature PVD probands than in relatives of healthy individuals, or even of probands with premature CAD. Second, occult vascular disease in the lower extremity, which is rare among healthy individuals, was common among asymptomatic siblings of probands with premature PVD. Taken together, these observations indicate that susceptibility to premature PVD has a strong familial basis.

Family histories provided the first line of evidence for clustering of vascular disease in the families of patients with premature PVD. A family history was obtained from each proband by personal interview with one of us (R.J.V.), and the probands were asked explicitly about the occurrence of CAD, stroke, and PVD in each of their first-degree relatives. Since these data are inherently subjective, the information received from the probands was verified by telephone interview with each living first-degree relative in a substantial fraction of the families. This validation procedure indicated that the information provided by the probands was correct in more than 97% of cases in each of the 3 groups. Thus, the family history data in this study appear to be highly reliable and provide a strong basis for the conclusion that premature symptomatic vascular disease is significantly more prevalent in family members of patients with premature PVD than in family members of healthy individuals in the general population.

To confirm that atherosclerosis is more common in the families of patients with premature PVD, we obtained an objective assessment of the prevalence of arterial lesions in these individuals. To this end, duplex ultrasonography was used to image the lower extremity arterial circulation in 20 asymptomatic siblings of premature PVD patients and in 23 apparently healthy control subjects of similar ages. This procedure is potentially more sensitive than angiography in detecting early atherosclerosis in the peripheral vascular circulation because minor plaque disease can be detected from direct examination of the intimal surface. Duplex ultrasound has been used successfully in a large population analysis to screen for asymptomatic arterial disease in the lower extremity. In the present study, duplex scanning revealed clear evidence of arterial plaque disease in half of the siblings of premature PVD patients. In contrast, only 1 of the 23 asymptomatic control subjects had a detectable lesion. This result provides direct evidence that peripheral atherosclerosis is far more common among first-degree relatives of premature PVD patients than among healthy individuals selected at random.

The development of atherosclerosis is thought to involve both environmental and genetic factors. Although atherosclerotic vascular diseases do not show obvious Mendelian inheritance patterns in most families, they do tend to cluster in families. This familial aggregation is...
frequently interpreted as evidence of genetic susceptibility. The familial aggregation of vascular disease observed in the present study may therefore reflect the clustering in these families of genes that confer susceptibility to atherosclerosis. Since families share environmental factors as well as genes, however, it is also possible that the familial clustering of atherosclerosis observed in the present study is due to shared environmental factors such as tobacco smoking, sedentary lifestyle, socioeconomic class, and lipid-rich diet. Tobacco smoking is strongly associated with PVD, and the prevalence of smoking was twice as high in the siblings of premature PVD patients who underwent duplex ultrasonography as in the general population. The fact that occult atherosclerosis was also observed in 2 individuals who had never smoked suggests that the increased prevalence of vascular disease in first-degree relatives of premature PVD patients is not simply due to smoking. Accordingly, a hypothesis consistent with our data is that individuals who develop PVD at an early age are genetically susceptible to the effects of environmental factors such as smoking. To further define the relative roles of smoking and inheritance, duplex ultrasound examinations will be required to compare asymptomatic smokers with a family history of premature vascular events and asymptomatic smokers without a corresponding family history.

The higher prevalence of active smokers in the PVD group compared with the CAD group (Table 1) suggests that smoking cessation was more successful in the latter group. Patients with PVD are known to have a tendency toward heavy smoking, and few will stop smoking permanently even when enrolled in formal smoking cessation programs. Former smokers in our CAD group included all individuals who smoked in any capacity. Many had smoked for less than 5 years. Although we do not have direct evidence such as carboxyhemoglobin levels to determine the extent of smoking in our study subjects, we suspect that there were more heavy smokers in the PVD group than in the CAD group.

A striking and unanticipated finding of this study was the high prevalence of elevated plasma triglyceride concentrations in siblings of premature PVD patients. Eight of the 20 asymptomatic siblings had plasma triglyceride concentrations above the 90th percentile for age and sex. Increased plasma triglyceride concentrations have been associated with PVD in several previous studies. In general, however, these studies have focused on senescent rather than premature PVD. Interestingly, a high percentage of patients with type III hyperlipidemia have PVD. Therefore, heritable susceptibility to premature PVD may be mediated in part through genes that confer hypertriglyceridemia.

Despite being a relatively large analysis of familial aggregation in patients with premature PVD, limitations did exist in this study. One potential limitation is that family histories were obtained by direct interview from the premature PVD probands, but by questionnaire from the reference groups. However, direct validation procedures performed in a substantial fraction of the families in each of the 3 groups confirmed that the family history data were reliable. Thus, it is extremely unlikely that the increased relative risk of premature vascular disease among relatives of PVD patients is an artifact of the data collection process. A second potential limitation is that the reference groups were not matched for all risk factors, particularly smoking. While this limitation does not alter the observation that premature atherosclerosis is more common in families of patients with PVD, we cannot formally exclude the possibility that this increased prevalence is simply a result of much heavier tobacco use in these individuals. Furthermore, since the prevalence of known risk factors such as hypertension, dyslipidemia, and homocysteinemia was not matched between the groups, it is not possible to determine whether the familial clustering of premature PVD reflects additional genetic risk that is independent of these factors. While the possible contributions of dyslipidemia and homocysteinemia to the development of premature PVD have been evaluated, the role of hypertension has not been adequately studied. However, since published reports have documented that fewer than half of the patients in this population have hypertension, this condition must constitute a minor risk factor. A third limitation is that the majority of the premature PVD probands in this study were white men. Therefore, the results may not be applicable to women with premature PVD or to patients of other racial backgrounds. The demographics of our probands reflect the nature of our referral population. Others have reported similarly high proportions of white male patients with premature PVD, suggesting that premature PVD may be a problem that is in large part confined to white men. However, a community-wide survey of patients with premature PVD and one other report from our own institution have documented that women are also affected by this disease. The former report also documented that premature PVD is not restricted to whites.

While the results of the present study do not indicate the relative contributions of genes and environment to the pathogenesis of premature PVD, our data have important clinical implications. The family history information obtained from premature PVD probands indicates that nearly 1 in 4 of the siblings of these patients will have a vascular event before the age of 55 years. As many as half of the asymptomatic individuals of these patients may be expected to develop occult disease at a young age. Greater efforts at risk factor modification should be directed at family members, especially those with evidence of early disease, who may be identified by sensitive noninvasive tests such as duplex ultrasonography.

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