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Parental history and the risk of subsequent vascular events in patients with clinically manifest vascular disease: The effects of sex of the parent and vascular disease location

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ABSTRACT

Background: Parental history of cardiovascular disease is a risk factor for first vascular events. It is unknown whether this also holds for subsequent events in patients with vascular disease. Also, the role of the location of parental vascular disease and the sex of the affected parent is unidentified.
Methods: In a cohort of 4529 patients with symptomatic vascular disease enrolled in the Second Manifestations of Arterial Disease (SMART) Study, the relation between parental cardiovascular history under the age of sixty, sex of the parent, location of parental vascular disease (heart, brain, lower extremities) and subsequent myocardial infarction (MI), stroke, vascular death and peripheral artery disease (PAD) was determined by Cox-proportional hazard analyses.
Results: During a median follow-up of 4.9 years (interquartile range 2.5–7.0), MI was experienced by 220 patients, stroke by 112, PAD by 297, whereas 371 patients died. A positive parental history of cardiovascular disease, without knowledge of vascular disease location and sex of that particular parent, was not associated with subsequent events (HR1.0; 95%CI 0.8–1.3). For specific types of parental history regarding sex and vascular location, having a father with a history of PAD was related to an increased risk of incident PAD (HR3.1; 95%CI 2.1–4.6).
Conclusions: A positive parental history of cardiovascular disease without information about vascular disease location and sex does not increase the risk of recurrent vascular events in patients with symptomatic vascular disease. Vascular patients with a father with PAD have an increased risk of subsequent peripheral artery disease compared with vascular patients without such a family history.

1. Introduction

A positive parental history of cardiovascular disease is related to an increased risk of first cardiovascular events in offspring without vascular disease [1–4]. The clinical use of assessing parental history of myocardial infarction has been proven: a family history of myocardial infarction before the age of sixty is incorporated in several cardiovascular risk scores, used for stratifying patients with a high risk of first cardiovascular events [5–7].

In clinical practice, assessing a parental history of cardiovascular disease is an integral part of a patients' history, irrespective of the fact whether a patient already experienced a vascular event. Intuitively it seems that patients with a history of vascular disease and a positive parental history of cardiovascular disease have an increased risk of recurrent vascular events compared with patients without a parental history of cardiovascular disease. For patients with premature cardiovascular disease, defined as a cardiovascular event before the age of 51 years in men and 56 years in women, there is a positive relation between a parental history of premature cardiovascular disease and the risk of developing a subsequent cardiac, peripheral artery or cerebrovascular event (HR 1.31, 95%CI 1.01–1.72) [8,9].

The question arises whether it is useful to assess a parental history of cardiovascular disease in all patients with clinically

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manifest vascular disease and to what extent. There is growing evidence that by simply dividing a parental history of cardiovascular disease into positive or negative, the potential value of parental history in risk assessment is not fully utilized [10]. For example, a parental history of peripheral artery disease is related to an increased risk of peripheral artery disease, whereas a parental history of cardiovascular disease in general is not related to incident peripheral artery disease [4].

The sex of the parent with a vascular history may also be worth assessing as it is hypothesized that maternal transmission is related to a higher vascular risk than paternal transmission in offspring, although studies report contradicting findings [11–13]. A possible explanation for an assumed differential transmission of cardiovascular risk from mothers and fathers is the fact that the intrauterine period is determined by the mother. There is increasing evidence that the intrauterine environment has very important and long lasting effects on risk of cardiovascular events and premature mortality in offspring [14,15].

The objective of the present study is to evaluate the relation between a positive parental history of cardiovascular disease and subsequent vascular events in patients with clinically manifest vascular disease and to investigate whether, in case of a positive parental history, the location of parental vascular disease and sex of the parent confer different risks.

2. Methods

2.1. Study population

The patients included in this study originated from the Second Manifestations of ARTerial disease (SMART) study. The rationale and design of the SMART study have been described previously [16]. In short, the SMART study is an ongoing single-center prospective cohort study that was designed to establish the presence of additional arterial disease and risk factors for atherosclerosis in patients with manifest vascular disease or a vascular risk factor. The Ethics Committee of the University Medical Centre Utrecht approved the study and all participants gave their written informed consent.

For this study data were used of 4700 patients who were newly referred to the University Medical Centre between 2001 and 2012 with a history of arterial atherosclerosis (i.e. coronary artery disease (CAD), cerebrovascular disease (CVD), peripheral artery disease (PAD) or abdominal aortic aneurysm (AAA)). Patients were enrolled after a stable situation of their disease was reached. Patients with a terminal malignancy were excluded, as well as those not independent in daily activities, not sufficiently fluent in Dutch language or referred back to the referring specialist immediately after one visit. Of the 4700 patients included in the analysis, parental history information was not available in 171 patients and these patients were excluded.

CAD was present in 2898 patients, CVD in 1289, PAD in 692 and AAA in 313. A total of 663 patients fell into more than one category at baseline. CAD was defined as myocardial infarction, angina pectoris or coronary revascularization (coronary bypass surgery or coronary angioplasty). Patients with CVD had experienced a transient ischemic attack, cerebral infarction, cerebral ischemia, amaurosis fugax, retinal infarction or a history of carotid surgery. PAD was defined as a symptomatic and documented obstruction of distal arteries of the leg or interventions (percutaneous transluminal angioplasty (PTA), bypass or amputation). Patients with AAA had a supra- or infrarenal aneurysm of the aorta (distal aortic anteroposterior diameter $\geq$3 cm, measured with ultrasonography) or a history of AAA surgery.

2.2. Baseline examination

All patients underwent a standardized extensive vascular screening. Patients received a uniform questionnaire on medical history, current medication, symptoms of cardiovascular disease and presence of cardiovascular risk factors. Furthermore, patients underwent laboratory assessments and non-invasive screening for manifestations of atherosclerotic disease and risk factors.

2.3. Parental history of cardiovascular disease

The questionnaire inquired for parental history of stroke, myocardial infarction, coronary artery stenosis and peripheral artery stenosis. A positive parental history was defined as at least one parent with cardiovascular disease before the age of sixty, as this definition is frequently used in current literature [5–7]. Subsequently, parental history was divided in four categories: parental history of CAD, parental history of stroke, parental history of PAD and parental history of cardiovascular disease, a combination of the first three categories. Furthermore, a subdivision was made distinguishing the sex of the affected parent.

Because multiple definitions of a positive parental history of cardiovascular disease exist, we performed additional analyses in 3011 patients with the alternative definition of CVD $<$55 years in men and $<$65 years in women, according to the NCEP [17] and JNC7 guidelines [18].

2.4. Follow-up

During follow-up, patients were asked biannually to complete a standardized questionnaire on hospital admissions and outpatient clinic visits. When a vascular event was suspected, hospital discharge letters and results of relevant laboratory and radiology examinations were collected. Death was reported by relatives of the participant, the general practitioner or the treating specialist. All possible events were independently evaluated by three members of the endpoint committee, comprising physicians from different departments. Study outcomes included myocardial infarction, coronary interventions, stroke (ischemic and hemorrhagic), carotid interventions, peripheral artery disease (amputation, operation, PTA or stenting of leg or iliac artery), vascular mortality, a composite of the previous mentioned vascular outcomes and all-cause mortality. The definitions of the several events are shown in Table 1.

Follow-up duration (years) was defined as the period between study inclusion and first cardiovascular event or death from any cause, date of loss to follow-up or the preselected date of 1 March 2012. In total, 141 of the 4529 participants (3%) were lost to follow-up due to migration or discontinuation from the study.

2.5. Data analysis

Data are presented as percentages for categorical variables, as mean with standard deviation (SD) for normally distributed variables and as median with interquartile range [IR] for non-normally distributed variables. Cox proportional hazards model analysis was used to estimate the effect of parental history of cardiovascular disease on the risk of subsequent vascular events. Patients with both myocardial infarction and stroke during follow-up contributed to both the myocardial infarction and stroke analyses, but with follow-up time matching the respective outcomes. If patients had multiple events of the same type, the first recorded event was used in the analyses. For the composite vascular outcome, the date of reaching the first vascular outcome was set as the composite outcome date. Results were expressed as hazard ratios (HR) and 95% confidence intervals (95%CI).