Family history of cardiovascular disease as a risk factor for coronary artery disease in adult offspring

La storia familiare di malattia cardiovascolare come fattore di rischio di cardiopatia coronarica nella progenie

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ABSTRACT: *Family history of cardiovascular disease as a risk factor for coronary artery disease in adult offspring. K. Hoseini, S. Sadeghian, M. Mahmoudian, R. Hamidian, A. Abbasi.*

Background and aims: There is controversy about the role of positive family history as an independent risk factor for coronary artery disease. The aim of this work was to investigate the influence of family history on presentation of coronary artery disease in adult offspring, and on its severity.

Methods: In a retrospective cross-sectional study at Tehran Heart Center (University of Tehran Medical Sciences), 6399 patients with established coronary artery disease who underwent coronary angiography for standard indications were assessed. Coronary artery disease was defined as atherosclerotic involvement of more than 50% in at least one major coronary artery.

Results: 953 patients (14.9%) had a verified positive family history of coronary artery disease, of whom 193 patients (20.2%) and 215 patients (22.5%) had paternal and maternal positive history, respectively. The mean age of clinical onset of ischemic heart disease in patients with a positive history was significantly lower than patients with no history (p < 0.001). Left main coronary lesion was significantly more frequent in patients with positive history (p = 0.017). Multivariate logistic regression analysis demonstrated that presentation of coronary artery disease in the form of acute coronary syndrome was significantly more prevalent in the background of positive family history (odds ratio, OR = 1.44, 95% confidence interval, CI: 1.14-1.83, p = 0.002), especially above 45 years old.

Conclusion: These findings indicate that positive family history is a major risk factor for coronary artery disease which strongly predisposes to the atherosclerotic process at younger ages; therefore, these patients should be evaluated and managed more intensively for other risk factors.

Keywords: Family history, coronary artery disease, adult, risk factors.

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Introduction

Coronary artery disease is becoming more prevalent in developing countries, particularly in urban areas, and it is a leading cause of mortality, morbidity and disability with high health care cost in Iran [1, 2]. Coronary artery disease is significantly determined by genetic background [3]; however, there is much controversy about the role of positive family history as an independent risk factor [4-8]. Thus, some authors refuse to take family history into account for coronary artery disease in offspring, while others assume it as an independent predictor with a strong influence on coronary artery disease in the next generation, focusing on earlier case finding and more intensive management of the modifiable risk factors. Actually, patients whose first-degree relatives develop early coronary artery disease are at higher risk of developing coronary artery disease than the general population [9, 10].

The objectives of this study were to investigate: 1) the influence of positive family history of coronary artery disease on the presentation of coronary artery disease in adult offspring, and 2) the relationship of pattern and severity of coronary atherosclerosis with positive family history.

Methods and Materials

This retrospective cross-sectional survey was conducted in Tehran Heart Center (Medical Sciences/University of Tehran) on 6399 patients with established coronary artery disease (based on angiographic features) who were hospitalized from June 2004 to March 2006, and underwent coronary angiography based on standard indications. Coronary angiography was performed by a consultant cardiologist who visited the patient at the clinic. All patients' data including age, risk factor profile for coro-

nary artery disease and the family history of coronary artery disease was obtained by the same cardiologist in the clinic and was registered on a special form designed for angiography database. Family history was obtained from all patients by systematically asking about coronary artery disease or stroke/TIA diagnoses occurring in first-degree relatives (mother, father, and siblings) and second-degree relatives (aunts, uncles, and grandparents). For each part, response options included "yes," and "no."

The findings of coronary angiography were reported by an attending cardiologist. Coronary artery disease was defined as atherosclerotic involvement more than 50% in at least one major coronary artery. Severity of coronary artery disease was assessed on the basis of number of involved coronary arteries in the angiogram.

Statistical analysis

We used descriptive statistics to characterize the patients (i.e., mean± standard deviation (S.D.) and frequency (percent) for numerical and categorical variables, respectively), and chi- square test, student *t* test and multivariate logistic regression to analyze the relationship of family history and other risk factors in respect to the documented coronary artery disease. A p Value < 0.05 was considered statistically significant. All the statistical analysis was carried out via Statistical Package for Social Sciences version 16 (SPSS Inc, Chicago, Illinois, USA).

Results

Patients' characteristics are shown at Table 1. There were 953 patients (14.9%) with a verified positive family history of coronary artery disease of whom 193 patients (20.2%) and 215 patients (22.5%) had paternal and maternal family history, respectively; 257 patients (26.9%) and 118 patients (12.4%) had a positive history in brother and sister, respectively. Hypertension (p = 0.024) and dyslipidemia (p < 0.001) were reported more often in patients with positive family history, but there was no statistically significant difference between the patients with and without family history with regard to having diabetes mellitus (p = 0.8).

Patients were divided to three different groups according to the status of their family history including: 1) patients with positive family history and the presence of other risk factors (group I, n = 953); 2) patients without family history (group II, n = 661); and 3) patients with only positive family history (with no other risk factor) (group III, n = 138) (Table 2).

Analysis of the patients' characteristics showed that the mean age of subjects who had only positive family history was 59.21 (± 13.21) years at the clinical diagnosis of ischemic heart disease, while the patients without family history (group II) had a mean age of 64.58 (± 12.84) years. This difference was statistically significant (p < 0.001) (Table 2). The difference of mean age between groups I and II, between groups II and III, and between groups I and III was significant (p < 0.001).

There was no significant association between positive family history (group I) and single vessel, two vessel and three vessel disease, but left main lesion (p = 0.017) was significantly more common in group I compared to group II and III (Table 2).

In regard to the acute presentation of coronary artery disease, (acute coronary syndrome including ST-elevated myocardial infarction, non ST-elevated myocardial infarction and unstable angina) the frequency of acute myocardial infarction among groups I, II and III was found to be 78.6%, 21.4% and 23.4%, respectively (p < 0.001). Although the frequency of unstable angina was not significantly different (p = 0.067), when we considered acute myocardial infarction and unstable angina as a single category (i.e. acute coronary syndrome), this difference was statistically significant (p = 0.027). A multivariate logistic regression analysis demonstrated that presentation of coronary artery disease as acute coronary syndrome was significantly more often in the context of positive family history (odds ratio, OR = 1.44, 95% confidence interval, CI: 1.14-1.83, p = 0.002), particularly above 45 years old (OR = 1.6, 95% CI: 1.18-2.15, p = 0.002).

Table 1. - Clinical and demographic characteristics of patients			
	Verified positive family history of CAD (n= 953)	**Un-verified positive family history of CAD (n= 5446)**	**P value**
Age (yr), mean±S.D.	59.27 ± 11.1	64.35 ± 12.5	<0.001
Sex, n (%)			
Male	441 (46.3)	2619 (48.1)	
Female	512 (53.7)	4809 (51.9)	0.305
Smoking, n (%)	250 (26.2)	1203 (23.5)	0.071
Dyslipidemia, n (%)	371 (38.9)	1819 (33.4)	<0.001
Diabetes mellitus, n (%)	612 (64.2)	3474 (63.8)	0.812
Hypertension, n (%)	439 (46.1)	2297 (42.2)	0.024
CAD: coronary artery disease			

Table 2. - Patients' age and the severity of coronary lesion by categories of family history

	Group I, FH (+) (n= 953)	Group II, FH (-) (n=661)	Group III, only FH (+) (n=138)	P value
Age (yr), mean±S.D.	57.43 (± 11.16)	64.58 (± 12.84)	59.21 (± 13.21)	<0.001
Lesion severity				
LMS, n (%)	52 (5.5)	21 (3.2)	2 (1.5)	0.017
SVD, n (%)	215 (22.6)	167 (25.2)	45 (32.3)	0.390
2VD, n (%)	248 (26)	182 (27.6)	40 (29.2)	0.690
3VD, n (%)	438 (46)	291 (44)	51 (37)	0.127

FH: family history; LMS: coronary left main branch lesion; SVD: single-vessel disease; 2VD: two-vessel disease; 3VD: three-vessel disease.

In another univariate analysis, acute coronary syndrome was significantly more frequent in male patients with positive family history of coronary disease in their mothers (95.3% in males vs. 89.6% in females; OR = 2.37, 95% CI: 1.03-5.41, p = 0.018).

Discussion

According to data analysis in the present study, a significant age difference within groups I, II and III suggests that positive family history accelerates the atherosclerotic process, as genetic diathesis predisposes subjects to atherosclerosis at younger ages. As shown in Table 2, isolated positive family history (group III) predisposes by itself to coronary atherosclerosis at younger age in comparison with the lack of family history (group II). Also, it seems reasonable that accumulation of the effects of positive family history and other risk factors significantly predisposes to atherosclerosis at younger ages (group I vs group II).

An interesting concept is that other risk factors such as hypertension and dyslipidemia were more frequent in patients with a positive family history. This emphasizes the impact of genetic factors on the atherosclerotic process, as the family history reflects the genetic, biochemical and behavioral components (including lipid profile [11] and hypertension [12]. In subgroup analysis, we found no significant relationship between coronary artery disease (including acute coronary syndrome) in a given patient and positive history in brothers and sisters.

A multivariate regression analysis documented that acute presentation of coronary artery disease including acute coronary syndrome was more frequent in genetically predisposed patients, especially above 45 years old, in comparison with negative family history. Positive family history (i.e. genetic diathesis) predisposes persons to accelerated atherosclerotic process and its underlying risk factors at younger ages which is consistent with previous studies [5, 11]. A positive family history was a strong independent risk factor for development of atherosclerosis according to Sesso et al. [4], Scheuner et al. [5], Lloyd-Jones et al. [6] and Shea et al. [7], although it does not correlate with the severity of atherosclerotic lesion(s).

The information obtained in patients with isolated family history (group III) and those with negative family history (group II) emphasize the above-mentioned results, suggesting in addition that positive family history is a strong fundamental independent risk factor for acute coronary syndrome.

According to Sesso et al. [3], various definitions of family history of acute coronary syndrome in the existing literature neglect the separate effect of paternal and maternal history and whether there are comparable effects on the risk of cardiovascular disease [13-17]. In the present study, we suggest that acute coronary syndrome is significantly more frequent in male patients in the background of maternal positive history, compared with paternal positive history. However, further investigations are needed on this point.

Conclusion

Although we are aware that this study was a cross-sectional descriptive survey and that positive family history was collected on the basis of patients' verbal statement, leading to possible inaccuracy of collected data, these findings indicate positive family history of coronary artery disease as a major risk factor which strongly predisposes persons to the atherosclerotic process and to its underlying risk factors at younger ages; these patients should be evaluated and managed more intensively for the modifiable risk factors because of the greater risk for developing coronary events.

Further studies are needed in order to investigate the correlation between paternal and maternal transmission and various degree and severity of coronary artery disease.

Riassunto

Background: È argomento tuttora controverso se la storia familiare positiva rappresenti un fattore di rischio indipendente di cardiopatia ischemica (CAD). Lo scopo del presente lavoro è valutare l'influenza della storia familiare di CAD sulla sua futura presentazione e severità in età adulta.

Metodi: Uno studio retrospettivo cross-section condotto al "Tehran Heart Center" (Università di Medicina di Tehran) ha valutato 6399 pazienti con CAD accertata e sottoposti a coronarografia secondo le comuni indicazioni. La CAD era definita dal restringimento aterosclerotico di più del 50% di almeno una arteria coronaria maggiore.

Risultati: 953 pazienti (14.9%) presentavano una accertata familiarità positiva per CAD; di questi, 193 (20.2%) e 215 (22.5%) presentavano rispettivamente una anamnesi positiva paterna e materna. L'età media della presentazione clinica della CAD nei pazienti con familiarità positiva era significativamente più precoce (p<0.001). Una lesione del tronco comune della coronaria sinistra era più frequente nei pazienti con familiarità positiva (p=0.017). L'analisi multivariata di regressione logistica ha mostrato che la presentazione della CAD sotto forma di sindrome coronarica acuta era significativamente più frequente nei pazienti con storia familiare positiva per CAD (odds ratio, OR = 1.44, 95% intervallo di confidenza, CI: 1.14-1.83, p = 0.002), in particolare dopo i 45 anni di età.

Conclusioni: La storia familiare positiva per CAD è un fattore di rischio indipendente che fortemente predispone al processo aterosclerotico in età precoce, suggerendo in tali soggetti una valutazione e gestione più scrupolosa degli altri fattori di rischio cardiovascolare.

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