Title: The effect of family history on the occurrence of cerebrovascular diseases in the offspring in an Iranian cohort population

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To appear in: Basic and Clinical Neuroscience

Received date: 7 December 2016

Revised date: 27 December 2017

Accepted date: 18 Decenber 2017

Published Date : 18 April 2018

Running title: Cerebrovascular diseases risk and family history

Abstract

Background: Family history is known as a risk factor for the development of cerebrovascular diseases (CVD), but it remains a controversial issue. Here, we aimed to evaluate the relationship between parental history and risk of CVD in offspring in our population.

Methods: Isfahan Cohort Study (ICS) included total 6,504 healthy participants which were randomly selected through a two-stage cluster sampling from three districts. Participants were followed prospectively for 10 years. The CVD patients were diagnosed by a neurologist. Clinically validated history of CVD was established for definition of parental history of CVD. Types of history were categorized to: paternal, maternal, both parent and no history.

Results: The prevalence of CVD is generally higher among in female offsprings compared with male (P<0.001). The relative risk of CVD with maternal history was not significant (CI= 0.95-2.29). By adjusted model, history of CVD in both parents was affected on the risk of CVD in the boys (RR=2.13, P=0.033, CI 95%). By crude model analysis, maternal history of CVD (P=0.047), history of CVD in both parents (P=0.032) and maternal history of hypertension (P=0.005) were determined as risk factors of CVD in offspring. Indeed, the mean age of CVD in offspring lowers based on this order: history of hypertension in parents, paternal history of CVD in both parent, maternal history of CVD and no history (P<0.001).

Conclusions: In female offspring with present history of CVD from maternal side, early and regular screening for CVD development is necessary. This at risk population should be considered as target group for screening and preventive measures.

Key words: family history, cerebrovascular diseases, offspring

Abbreviation:

BMI: Body Mass Index; CI: Confidence Interval; CHD: Coronary heart disease; CVD: Cerebrovascular diseases; DM: Diabetes Mellitus; HTN: Hypertension; ICS: Isfahan Cohort study; OR: Odd ratio; RR: Relative risk

Introduction:

Cerebrovascular diseases (CVDs) are multifactorial diseases that effected by several environmental factors such as: diet, life style, smoking and other predisposing diseases. Although role of genetic in CVD has been discussed but the effect of parental history of

CVD on the risk of disease in offspring is not well known (Seshadri *et al.* 2010). The relationship between family history and risk of stroke is considered in many studies (Chung *et al.* 2016; Tian *et al.* 2017). This familial background has been supported by various studies in twins and animals (Jood *et al.* 2005; Aparicio & Seshadri 2017). A substantial heritable component of CVD with familial aggregation within certain families has been identified which results in earlier development of CVD (Bak *et al.* 2002; Seshadri *et al.* 2006). The risk of stroke in middle-aged to old age is partly associated with a family history of stroke. This familial history imposes the risk for both hemorrhagic and ischemic stroke and neurobehavioral outcomes after discharge especially in young women (Kim *et al.* 2004). Even though a history of coronary heart disease (CHD) in parents well known as a risk factor for the occurrence of disease in their offspring, but a perfect relation about CVD still has not been established (SHOLTZ *et al.* 1975; Jousilahti *et al.* 1996). It has been demonstrated that positive family history of stoke is associated with increased risk of stroke in females compared with males with more association with maternal side (Tentschert *et al.* 2003; Seshadri *et al.* 2010). The reason for this relationship is unknown, but genetic factors seem to have the most important role (Huang *et al.* 1994). However, according to Folssman et al., the impact of family history on CVD in offspring is so heterogeneous (Floßmann *et al.* 2004). This heterogeneity could be attributed to different studied population, insufficient details or bias (Øygarden *et al.* 2015). Thus, it seems that each population should determine the inheritance pattern of this disease entity to provide better preventive, diagnostic and therapeutic options for at risk subgroup. Knowing the detailed family history of CVD with special attention to sex difference can help to develop preventive programs or risk assessment predicting models. Thus, in this study we aimed to evaluate and compare the impact of maternal or paternal history of CVD on the risk of CVD development in their offspring in our population.

Methods and Materials:

Isfahan Cohort study (ICS) is a ten year longitudinal prospective and ongoing population-based study, which was commenced in 2001 (January 2 to September 28) (Sarrafzadegan *et al.* 2011). ICS followed up 6504 individuals, aged 35 years or more, 51% women, gathered from rural and urban areas in three districts including: Najafabad, Arak and Isfahan cities. Among them, 6323 of them were initially free from CVD. Stroke was defined as a rapid onset focal neurological disorder with probable vascular cause which lasts more than 24 hours, based on WHO stroke definition. A combination of stroke and IHD was used for definition of CVD. The final diagnosis was made by a panel of specialists in neurology and cardiology based on hospital records, while verbal autopsy was done for those who died during follow up (Sarrafzadegan *et al.* 2013). Self-reported history of CVD was used for the definition of parental history of CVD. Types of parental history of CVD were categorized as: no parental history of CVD, both parental history of CVD or hypertension. For statistical analysis relative risk and 95% confidence interval (CI) of hypertension, diabetes mellitus, hyperlipidemia, obesity and smoking and association of these risk factors with parental history of CVD were measured. All participants who had CVD during follow-up were selected as the case group and those who did not have CVD were selected as control group.

Both groups were matched in time of follow-up (density sampling), so that the effect of time on the risk was similar.

Statistical analyses were performed using *SPSS* ver.17. Multivariable analysis was performed to determine effect of parental history of hypertension on occurrence of hypertension. Both crude and adjusted model were applied for analysis of data in this study. Adjustment was performed based on age, gender and body mass index (BMI) of offspring.

Results:

This study results showed that the overall prevalence of CVD in the female offspring of people with a CVD history is more than male offspring (*P*< 0.001). The gender-specific distribution of CVD regarding type of parental history is demonstrated in table-1. Data regarding prevalence of parental history of CVD among men and women is depicted. Several risk factors and some general demographic data regarding CVD in the offspring are demonstrated in Table-1. By crude analysis, presence of: Diabetes Mellitus (DM) (3.07, CI: 2.49-3.79), age more than 60 years (3.04, CI: 2.54-3.63), BMI> 30 (1.25, CI: 1.02-1.53) and female gender (0.78, CI: 0.66-0.93) were significantly related with CVD in offspring. By adjusted model, age more than 60 (3.22, CI: 2.68-3.85), presence of DM (1.76, CI: 1.76-2.80), BMI> 30 (1.49, CI: 1.21-1.84), maternal history of hypertension (HTN) (1.45, CI=1.11-1.89) and female gender (0.70, CI: 0.58-0.84), just history of CVD in both parents influenced risk of CVD just in male offspring (RR= 2.13, *P*= 0.033, CI 95%).

Although the relative risk of maternal history of CVD was higher than paternal history but the difference was not significant (CI= 0.95-2.29). Just presence or absence of parental history of HTN (each type) is not effective on development of CVD in offspring. By crude model analysis, maternal history of CVD (*P*= 0.047), history of CVD in both parents (*P*= 0.032), maternal history of HTN (*P*= 0.005), and history of diabetes mellitus (*P*< 0.001) and smoking (*P*= 0.026) were determined as risk factors for occurrence of CVD in offspring. Also female gender (*P*= 0.005), age more than 60 years (*P*< 0.001) and obese (BMI> 30) (*P*= 0.028) offspring are more susceptible for CVD. Also, high level of serum total cholesterol (>200 mg/dl), (*P*= 0.62), high serum level of LDL (>150 mg/dl) (*P*= 0.77) and low HDL (<30 mg/dl) (*P*= 0.57) did not affected on the risk of CVD in offspring, while high level of serum triglyceride (>200 mg/dl) (*P*= 0.045) is relatively effective on the risk of CVD in offspring (Table1). Though, only maternal history of HTN have a significant effects on the occurrence of CVD, but adjusted analysis for sex, age and BMI, showed that, the age of CVD occurrence in patients with positive family history is lower than normal population (57.9±10.9 vs. 61.9±11.1, *P*= 0.031) (Table2). However, there was no significant difference between paternal and maternal family history in the age of the onset of CVD in the offspring (*P*= 0.835). On the other hand the mean age of CVD occurrence in offspring with paternal, maternal and both history of HTN is significantly lower than offspring without parental history of HTN (*P*= 0.013).

Discussion:

The main finding of this study indicated that women with a maternal history of CVD are more susceptible to CVD. Thus maternal side history seems to be an alarm which needs

regular screening for CVD involvement. In addition to the parental history, some risk factors in offspring such as presence of DM, age more than 60 years, female gender and obesity (BMI> 30) are associated with higher risk of CVD which could be explained by the impact of traditional risk factors of CVD in general population. These factors in addition to maternal history of HTN and just history of both parents are associated with slightly greater CVD risk in male offspring. The accumulation of these risk factors together in the family may lead to the occurrence of CVD in the earlier ages of offspring.

The subject of association between family history and CVD has been addressed in several publications with results (Barrett-Connor & Khaw 1984; Hunt *et al.* 2003; Woodward *et al.* 2007). In prospective, community based, two-generational Framingham study cohort, the impact of parental stroke was greatest on occurrence of early stroke before the age 65 years. Genetic epidemiology of stroke is relatively unstudied and sex- specific aspects of this relationship have been poorly clarified (McBride *et al.* 2014). The results of this investigation demonstrated marked gender- specific differences of the relationship between parental and or maternal history of CVD and occurrence of CVD in offspring. Our data indicated that maternal side of CVD imposes greater risk for offspring especially in female gender. Although there are heterogeneous publications regarding the impact of family history on CVD in offspring, our results is consistent with some of previous published studies (Hunt *et al.* 2003; Qureshi *et al.* 2012). The incidence of CVD in women is more affected than men by parental history of the disease. Therefore, knowledge about parental history is better predictor for female offspring. This finding is consistent with previous study that indicated a sex-specific relationship between maternal history of CVD, left ventricular hypertrophy and hypertension in female patients with CVD events (Tentschert *et al.* 2003).

We suggest that the expanded assessment of family history in development of CVD in offspring such as evaluation of family history in maternal or paternal grandfathers, grandmothers and other relatives may be helpful for better stratification of risk factors in offspring. By the way, the conferred risk of CVD in female offspring with positive family history of CVD is higher. But it should be kept in mind that this higher conferred risk could not be introduced to the person as a cause of life long stress and these data could be applied correctly for targeted screening in general practice for primary prevention. In order to accurately assess inheritance traits for children, the environmental factors and lifestyle in the family should also be taken into account.

Conclusions:

Cerebrovascular diseases are affected by familial history. In female offspring with parental history of CVD from maternal side, initial and regular screening for CVD risks is necessary. This susceptible population should be considered as a target group for screening and preventive measures.

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Table1: The relationship of CVD risk factors and family history of participants based on parental history. The first *P*-values in each raw, is related to the presence of familial history and second is related to kind of family history.

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Offspring variable	without History	With History			P
	N=434	Father (N=297)	Mother (N=209)	Both (N=51)	
Sex (Male)	196 (45.2)		243 (43.6)		<0.001
		156 (52.5)	71 (34.0)	16 (31.4)	<0.001
Age at Baseline	49.3±10.9*		47.6±9.55		0.010
		47.0±9.51	48.4±9.74	47.8±8.95	0.281
BMI	26.9±4.52		27.6±4.46		0.020
		27.4±4.28	27.8±4.70	28.1±4.48	0.386
Smoking	90 (20.7)		117 (21.1)		0.895
		71 (24.1)	38 (18.2)	8 (15.7)	0.171
Diabetes	54 (12.4)		60 (10.8)		0.414
		26 (8.8)	26(12.4)	8 (15.7)	0.208
Hypertension	134 (30.9)		158 (28.4)		0.390
		73 (24.6)	68 (32.5)	17 (33.3)	0.105
Low-HDL	198(45.6)		264 (47.4)		0.578
		137 (46.1)	104 (49.8)	23 (45.1)	0.681

High- LDL	204 (47.0)		267 (47.9)		0.771
		132 (44.4)	113 (54.1)	22 (43.1)	0.079
High T ch	252 (58.1)		332 (59.6)		0.625
		165 (55.6)	137 (65.6)	30 (58.8)	0.078
High TG	251 (57.8)		357 (64.1)		0.045
		194 (65.3)	127 (60.8)	36 (70.6)	0.344

Table 2: The hazard ratio of CVD based on family history, paternal and maternal history were compared to both parent familial history (left column) and none familial history (right column). Model 1, 2 and 3: data adjusted with Gender, Age & Gender and Age & Gender & BMI, respectively

Family history	HR (95% CI)	*P*- value	HR (95% CI)	*P*-value
Crude				
None			1	
Paternal	0.47 (0.25-0.89)	0.021	0.96 (0.64-1.45)	0.843
Maternal	0.72 (0.38-1.36)	0.318	1.46 (0.97-2.21)	0.068
Both	1	-	1.98 (1.09-3.61)	0.025
Model 1				
None			1	
Paternal	0.46 (0.24-0.87)	0.017	0.96 (0.63-1.44)	0.838
Maternal	0.72 (0.38-1.36)	0.311	1.47 (0.97-2.22)	0.068
Both	1	-	1.99 (1.09-3.62)	0.025
Model2				
None			1	
Paternal	0.48 (0.25-0.91)	0.024	1.11 (0.73-1.68)	0.624
Maternal	0.70 (0.37-1.32)	0.268	1.56 (1.03-2.35)	0.036
Both	1	-	1.20 (1.21-4.01)	0.010
Model3				
None			1	
Paternal	0.48 (0.25-0.92)	0.026	1.05 (0.69-1.59)	0.817
Maternal	0.69 (0.36-1.30)	0.251	1.41 (0.93-2.15)	0.104
Both	1	-	2.05 (1.12-3.74)	0.019