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Fathers may play a bigger role than mothers in hypertensive patients complicated with coronary heart disease.

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Abstract

Hereditary factors contribute 40-60% to Essential Hypertension (EH) development. In some ethnic groups, mothers play a bigger role than fathers in passing risk factors of EH onto their offspring. To find whether mothers or fathers play a bigger role in EH development in Chinese Han people, clinical and genetic family history data of 518 hypertensive Chinese were collected through interview questionnaires after obtaining informed consents. Morbidity of the patients' parents and offspring were analysed. The mothers showed no statistical difference from the fathers in terms of contribution of passing EH risk factors to subsequent generations (P>0.05). However, after dividing the patients into groups according to the presence or absence or absence of complications, the fathers showed a higher incidence (33.1%, n=118) than the mothers (22.0%, n=123) in the EH group with coronary heart diseases. (P=0.027, OR=1.8, 95% CI=1.2 to 2.4) Thus, fathers may be more likely to pass risk factors of EH with coronary heart disease to their offspring.

Keywords: Hypertension complications, Family history, Statistical analysis BD.

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Introduction

The pathogenesis of Essential Hypertension (EH) is considered to be the consequence of genetic and environmental factors. A twin research found that about 1/3-1/2 Blood Pressure (BP) variations resulted from genetic factors [1,2]. Significantly, interfamilial correlations of hypertension and complications exist in first-degree relatives. Hypertension is highly prevalent among first-degree relatives of individuals with familial coronary artery diseases [3]. However, the specific maternal and paternal influences on hypertension development in their offspring remain unclear. Thus, we want to know whether male or female hypertensive parents are more likely to contribute to EH development in their children. Destefano et al. [4] investigated hundreds of hypertensive families, including African Americans, Greek Caucasians, and American Caucasians. In these racial groups, influence of the mother was greater than that of the father. Kuznetsova et al. [5] studied 159 European families and found that maternal genetic factors based on the left ventricular mass index play a bigger role in EH development in their children than paternal factors. These studies suggest that mothers may have a greater influence on their children's BP and heart complication compared to fathers. Kapuku et al. [6] compared hypertensive people from different races and determined that oxidative stress markers might impact BP variations, implying a racial difference in oxidative stress-related mechanisms of cardiovascular diseases. Little is known whether maternal and paternal factors play different roles in Chinese Han hypertensive patients with complications. To investigate these impacts, an inquiry on 518 Chinese Han hypertensive families was performed.

Materials and Methods

After obtaining informed consents and ethical approval, clinical and family data of EH patients were collected from 2013 to 2015 during their visit to Ningbo First Hospital, Zhejiang Province, China. They were diagnosed with EH in our hospital's clinic according to the management guideline of hypertension [7] and evaluated for their risk factors and complications by laboratory tests and imaging examinations. Clinical data on EH and complications of their parents and offspring were also collected. After the subjects had rested for more than 10 min, a trained observer obtained three consecutive BP readings with a mercury sphygmomanometer, with an interval of 30 to 60 s between measurements. Through a standardized interview, the observer also collected information on each participant's personal and familial medical history, smoking and drinking habits, physical activity, and use of medications.

We divided the probands into groups in two ways. Firstly, all patients were divided into three groups according to their BP level. Patients whose BP levels are 140-160/90-100 mmHg belonged to stage 1; those whose BP levels are 160-180/100-110 mmHg belonged to stage 2, while those with BP levels above 180/110 mmHg belonged to stage 3 [8].

Secondly, all the 518 patients were divided into four groups according to the presence or absence of complications, including Cerebral Hemorrhage (CH), Cerebral Infarction (CI), and Coronary Heart Disease (CHD). Thereafter, we compared their parents' and offspring's morbidity. First, morbidity between the groups with and without an EH family history were compared. Second, morbidity between the different groups of the fathers and mothers were compared. Third, we also compared the offspring's morbidity between the sexes of the probands.

The software application SPSS19.0 (Inc., Chicago, IL, USA) was used for the statistical analysis. Categorical variables were presented as proportions and analysed by the Chi-square test or Fisher's exact test, as appropriate. Normality of the continuous variables was analysed by the Kolmogorov-Smirnov test or Analysis of Variance (ANOVA). Variables of normal distribution were presented as the mean ± Standard Deviation (SD) and analysed by an independent sample t-test or ANOVA. Variables of non-normal distribution were presented as the median (interquartile range) and tested by the Mann-Whitney U test or Kruskal-Wallis H test. Binary logistic regression and linear regression analyses were used to examine independent predictors. $P<0.05$ was considered to indicate statistical significance. OR value and 95% CI were calculated if necessary.

Results

A total of 518 Chinese Han patients diagnosed in our hospital's outpatient department from 2013 to 2015 were randomized. Their age ranged from 40 to 65 y, with an average of 52.7 y. Average systolic and diastolic BP levels were 155 mmHg and 98 mmHg, respectively. Of the patients, 19.5% have smoking habits, and 22.8% have drinking habits. According to the BP level classification, there were 55 probands belonging to stage 1, 360 to stage 2, and 103 to stage 3. All groups were statistically compared to the normal BP group. According to the complications classification, 73 were complicated with CH, 167 with CI, and 172 with CHD. All groups were also statistically compared to the normal BP group and simple hypertension group. There were 264 fathers and/or mothers of EH patients who had hypertension. Out of the 309 male patients, 77 (24.9%) fathers and 67 (21.7%) mothers suffered from EH. Of the 209 female patients, 36 fathers (17.2%) and 45 (21.5%) mothers suffered from EH. EH patients classified under stages 2 and 3 with a family history showed significant differences when compared to those without a family history ($P<0.01$). However, no significant differences were found in other groups (Table 1).

To further clarify whether a difference exists between the EH parents, morbidity of the fathers and mothers were analysed and compared. However, no statistical difference was found (Table 2). Available data were then divided into two groups according patients' sex, carrying out the statistical analysis on their offspring's hypertension occurrence rate. It also showed no statistical difference (Table 3). The complication groups were divided into these four subgroups: a) both parents suffered from EH, b) only the father or c) the mother suffered from EH, and d) neither parent suffered from EH. Thereafter, we compared the probands' morbidity rate between groups with and without complications. Groups with cerebral diseases showed no significant differences. However, only the group with CHD showed that the fathers had a higher incidence (33.1%, n=118) than the mothers (22.0%, n=123) in the EH group with CHD ($P=0.027$, OR=1.8, 95% CI=1.2 to 2.4, Table 4).

Table 1. Family history analysis on different hypertensive groups.

		Y/N	Y1/N1*	Y2/N2*	χ^2	P1/P2
Stage 1	55	14 (25.5%)/41 (74.5%)		4 (19.0%)/17 (81.0%)	0.345	0.775
Stage 2	360	192 (53.3%)/168 (46.7%)		4 (19.0%)/17 (81.1%)	9.338	0.002
Stage 3	103	19 (18.4%)/84 (81.6%)		4 (19.0%)/17 (81.1%)	9.688	0.002
Complicated with CH	73	28 (38.4%)/45 (61.6%)	24 (32%)/51 (68%)	4 (19.5%)/17 (81.5%)	0.656/2.708	0.492/0.1
Complicated with CI	167	64 (38.3%)/103 (61.7%)	24 (32%)/51 (68%)	4 (19.5%)/17 (81.5%)	0.894/3.002	0.344/0.083

*1: Patients with hypertension only; *2: Normal control; Y: Family history is positive; N: Family history is negative; CH: Cerebral Haemorrhage; CI: Cerebral Infarction.

Table 2. Mother's morbidity compared to father's.

		Father		Mother		χ^2	P
		Patients	Normal	Patients	Normal		
Total	518	118 (22.8%)	400 (77.2%)	123 (23.7%)	395 (76.3%)	0.135	0.713

Stage 1	55	6 (10.9%)	49 (89.1%)	9 (16.4%)	46 (83.6%)	0.695	0.405
Stage 2	360	92 (25.6%)	268 (74.4%)	85 (23.6%)	275 (76.4%)	0.367	0.545
Stage 3	103	19 (18.4%)	84 (81.6%)	28 (27.2%)	75 (72.8%)	2.233	0.135
Only hypertension	75	18 (24%)	57 (76%)	22 (29.3%)	53 (70.7%)	0.545	0.46
Complicated with CH	73	15 (20.5%)	58 (79.5%)	19 (26%)	54 (74%)	0.613	0.433
Complicated with CI	167	39 (23.4%)	128 (76.6%)	46 (27.5%)	121 (72.5%)	0.773	0.379
Complicated with CHD	173	39 (22.5%)	134 (77.5%)	28 (16.2%)	145 (83.8%)	2.24	0.135

CH: Cerebral Haemorrhage; CI: Cerebral Infarction; CHD: Coronary Heart Disease.

Table 3. *Offspring's morbidity in different sex hypertensive patients.*

		Male (309)		**Female (209)**		**χ2**	**P**
		Patients	**Normal**	**Patients**	**Normal**		
Total	518	13 (4.2%)	296 (95.8%)	12 (5.8%)	197 (94.2%)	0.673	0.412
Stage 1	55	0 (0%)	33 (100%)	1 (4.5%)	21 (95.5%)	1.528	0.4
Stage 2	360	10 (4.6%)	206 (95.4%)	6 (4.2%)	138 (95.8%)	0.044	0.835
Stage 3	103	3 (5%)	57 (95%)	5 (11.6%)	38 (88.4%)	1.536	0.273
Only hypertension	75	0 (0%)	31 (100%)	5 (11.4%)	39 (88.6%)	3.664	0.073
Complicated with CH	73	1 (2.1%)	46 (97.9%)	2 (7.7%)	24 (92.3%)	1.315	0.287
Complicated with CI	167	6 (5.7%)	99 (94.3%)	4 (6.5%)	58 (93.5%)	0.38	1
Complicated with CHD	173	5 (4.5%)	106 (95.5%)	1 (1.6%)	61 (98.4%)	0.994	0.422

CH: Cerebral Haemorrhage; CI: Cerebral Infarction; CHD: Coronary Heart Disease.

Table 4. *Parent's role in hypertensive patients to improve to complications.*

		With complication	**Without complication**	χ^2	**V**	**P**
	Both parents	4	29	0.704	3	0.872
	Only father	11	74			
	Only mother	15	75			
Complication CH	Neither	43	267			
	Both parents	16	17	5.136	3	0.162
	Only father	23	62			
	Only mother	30	60			
Complication CI	Neither	98	212			
	Both parents	6	27	9.717	3	0.021*
	Only father	33	52			
	Only mother	21	69			
Complication CHD	Neither	112	198	4.916	1	0.027*

CH: Cerebral Haemorrhage; CI: Cerebral Infarction; CHD: Coronary Heart Disease, $p<0.05^*$

Discussion

Brown [9] indicated that racial difference in the hypertensive mechanism is widespread and complicated. Destefano et al. [4] surveyed 69 African American EH patients, 153 American Caucasian patients, and 122 Greek Caucasian patients, discovering that their mothers had a higher morbidity than their fathers with a significant difference. Howeverthere are few related comparison research studies on Chinese fathers and mothers passing on genetic factors to EH patients. Thus, we collected clinical and family data of 518 Chinese Han patients. Based on our findings, no significant difference was found between paternal and maternal morbidity. However, all the 518 patients included in this study are only limited to the residents of Zhejiang Province, China, instead of including all Chinese Han patients. We analysed 518 hypertensive family data and compared the data of the mothers to the fathers but found no statistical difference. According to the sex of the EH patients, we respectively analysed their children's EH data, but there was still no statistically different finding. These mainly indicate that Chinese parents might show equal influence in passing on the risk of EH to their children.

Genetic factors play a key role in the mechanism of EH. However, whether fathers or mothers contribute more risks to their children is not totally clear. Zureik et al. [10] showed no relationship between maternal longevity and BP measurements in either their cross-sectional or longitudinal analyses. On the contrary, they suggested that paternal premature death was associated with accelerated progression of systolic BP and higher occurrence of hypertension in their offspring. Marcovecchio et al. [11] found that mothers, not fathers, were associated with BP changes with albumin excretion in their young offspring with type 1 diabetes. Mothers also had a urine micro protein related to BP in adolescents with diabetic nephropathy in type 1 diabetes. Further, mothers affected with high BP, particularly high diastolic BP, were associated with higher urinary albumin creatinine ratios. Van et al. found that maternal eNOS genotype influences the BP and behavior of grown mice offspring [12]. Compared study between parents all above might help find some mechanisms of the disease. Maternal influence on BP suggests an involvement of the mitochondrial DNA in the pathogenesis of hypertension, and more mitochondrial DNA mutations related to EH have been reported [13-17]. These indicate that mitochondrial DNA may contribute 35.2% to the pathogenesis of EH [18].

Nevertheless, in the Kaplan-Meier survival study of Thorn et al. [19], diabetic nephropathy in type 1 diabetes was associated with paternal cardiovascular disease mortality. Paternal history of diabetes and hypertension contribute to the prevalence and phenotype of polycystic ovary syndrome [20]. Maternal not paternal family hypertensive history was associated with cardiovascular risk factors in children with high waist circumferences [21]. In contrast, maternal history of myocardial infarction appeared to predict cardiovascular diseases as strongly as paternal history at older ages [22]. Thus, maternal and paternal influence may play different roles in the development of hypertensive complications.

For further analysis of our EH data, the complication groups were re-divided into subgroups, and an advanced comparison analysis on the morbidity between the mothers and fathers was again conducted in the EH group with complications. In the two complication groups of CH and CI, no difference was found. However, fathers were more likely to impact EH patients with CHD complications (Table 4). Some risk factors, such as paternal and maternal BMI, are involved in cardiovascular diseases [23]. Kinra et al. [24] analysed 8402 family history of patients with CHD and found no differences in the genetic factors between the parents by a cohort study. However, based on our findings, fathers may be more likely to pass risk factors to EH patients with CHD. These results indicate that paternal factors may be linked to BP changes in patients with CHD complication [10]. Further studies are then required to clarify the genetic and epigenetic mechanisms underlying the paternal-offspring correlations for hypertension with CHD.

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Competing Interests

The authors declare that they have no competing interests.

References

1. Snieder H, Hcoshfield GA, Treiber FA. Heritability of blood pressure and hemodynamics in African-and European-American youth. Hypertension 2003; 41: 1196-1201.
2. Charles AM, Mark JC, Richard JD, Patricia BM. Genetics of essential hypertension. Human Mol Gene 2004; 13: 169-175.
3. Claire H, Vincent W, Valerie J, Last VM. High prevalence of major cardiovascular risk factors in first-degree relatives of individuals with familial premature coronary artery disease-The Genecard Project. Atherosclerosis 2007; 194: 253-264.
4. Destefano AL, Gavras H, Heard-Costa N, Bursztyn M, Manolis A, Farrer L. Maternal component in the familial aggregation of hypertension. Clin Genet 2001; 60: 13-21.
5. Tatiana K, Jan AS, Agnieszka O, Andrew R, Katarzyna S, Sofia M. Maternal and paternal influences on left ventricular mass of offspring. Hypertension 2003; 41: 69-74.
6. Kapuku G, Treiber F, Raouane F, Halbert J, Davis H, Young-Mayes S. Race/ethnicity determines the relationships between oxidative stress markers and blood

pressure in individuals with high cardiovascular disease risk. J Human Hypertens 2016; 1-6.

7. 2013 ESH/ESC guidelines for the management of arterial hypertension. European Society of Hypertension and European Society of Cardiology. Eur Heart J 2013.
8. Paul AJ, Suzanne O, Barry LC, William CC, Cheryl DH, Joel H. Evidence-based guideline for the management of high blood pressure in adults. Report from the panel members appointed to the Eighth Joint National Committee. JAMA 2014; 311: 507-520.
9. Morris JB. Hypertension and ethnic group. Br Med J 2006; 332: 833-836.
10. Zureik PG, Sandrine B, Dominique C, Se´bastien C, Jacques B, Pierre D, Michel ES, Serge H. Parental longevity and 7-year changes in blood pressures in adult offspring. Hypertension 2005; 46: 287-294.
11. Marcovecchio ML, Tossavainen PH, Acerini CL, Barrett TG, Edge J, Neil A. Maternal but not paternal association of ambulatory blood pressure with albumin excretion in young offspring with type 1 diabetes. Diab Care 2010; 33: 366-371.
12. Bruce NVV, Linda LC. Maternal endothelial nitric oxide synthase genotype influences offspring blood pressure and activity in mice. Hypertension 2007; 49: 556-562.
13. Zhongqiu L, Hong C, Yanzi M, Yan W, Ling X, Shaoce Z. The tRNAMet 4435A>G mutation in the mitochondrial haplogroup G2a1 is responsible for maternally inherited hypertension in a Chinese pedigree. Eur J Human Gene 2011; 19: 1181-1186.
14. Zhongbin L, Yuqi L, Li Y, Shiwen W, Min XG. Maternally inherited hypertension is associated with mitochondrial tRNAIle A4295G mutation in a Chinese family. Biochem Biophys Res Commun 2008; 36: 906-911.
15. Shiwen W, Ronghua L, Andrea F, Zongbin L, Yaping Q, Yuqi L. Maternally inherited essential hypertension is associated with the novel 4263A>G mutation in the mitochondrial tRNAIle gene in a large Han Chinese family. Circ Res 2011; 108: 862-870.
16. Yuqi L, Ronghua L, Zongbin L, Xin-Jian W, Li Y, Shiwen W. Mitochondrial transfer RNAMet 4435A>G mutation is associated with maternally inherited hypertension in a Chinese pedigree. Hypertension 2009; 53: 1083-1090.
17. Ronghua L, Yuqi L, Zongbin L, Li Y, Shiwen W, Min-Xin G. Failures in mitochondrial tRNAMet and tRNAGln metabolism caused by the novel 4401A>G mutation are involved in essential hypertension in a Han Chinese family. Hypertension 2009; 54: 329-337.
18. Qiong Y, Sung KK, Fengzhu S, Jing C, Martin GL, Ramachandran SV, Daniel L, Faina S. Maternal influence on blood pressure suggests involvement of mitochondrial DNA in the pathogenesis of hypertension: The Framingham Heart Study. J Hypertens 2007; 25: 2067-2073.
19. Lena MT, Carol F, Johan F, Kim PF, Riika K, Per HG. Clustering of risk factors in parents of patients with type 1 diabetes and nephropathy. Diab Care 2007; 30: 1162-1167.
20. Chen C, Haolin Z, Yue Z, Rong L, Jie Q. Paternal history of diabetes mellitus and hypertension affects the prevalence and phenotype of PCOS. J Assist Reprod Genet 2015; 32: 1731-1739.
21. Martha RM, Celia AG, Luis ESM, Elizabeth ME, Esperanza CM, Maria EDE, Fernando GR. Family history of hypertension and cardiovascular risk factors in prepubertal children. Am J Hypertens 2010; 23: 299-304.
22. Howard DS, Min L, Michael Gaziano J, Kathryn MR, Robert JG, Julie EB. Maternal and paternal history of myocardial infarction and risk of cardiovascular disease in men and women. Circulation 2001; 104: 393-398.
23. Idoia L, Jonatan RR, Francisco BO, Helle ML, Jaanus H, Toomas V. Intergenerational cardiovascular disease risk factors involve both maternal and paternal BMI. Diab Care 2010; 33: 894-900.
24. Kinra S, Davey SG, Okasha M, McCarron P, McEwen J. Is maternal transmission of coronary heart disease risk stronger than paternal transmission? Heart 2003; 89: 834-838.

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