

Association Between Family History and the Onset Age of Essential Hypertension in Han Population in Shanghai China

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Abstract: Genetic factor is one of important influencing factors of essential hypertension, and family history (FH) is an important marker of genetic factors. To explore the association between family history and the onset age of essential hypertension in Han population in Shanghai China. According to 1:1 matched pairs design, 342 cases of hypertension and 342 controls were selected and investigate their nuclear family members in the case-control study. The diagnostic information of hypertension in all relatives of these two groups was investigated. The method of genetic epidemiology research was used to explore the effect of family history. The average prevalence of hypertension was 23.32%. The prevalence of hypertension of first-degree relatives was 33.99%; the prevalence of second-degree relatives was 17.60%; the prevalence of third-degree relatives was 13.51%. All prevalence of hypertension of case group relatives were significantly higher than that of control group relatives. The average onset age in population with positive FH is 48.74±11.16 years old, and the average onset age in population with negative FH is 54.38±9.87 years old. The difference about two FH groups showed statistically significant ($t=4.589$, $P<0.001$). The average onset age of offspring with father, mother, grandpa, grandma, maternal grandpa or maternal grandma positive was respectively 48.42± 11.16, 49.16±11.12, 39.55±11.95, 39.88±11.90, 43.67±9.77 or 43.64±10.21 years old; and the average onset age of children with father, mother, grandpa, grandma, maternal grandpa or maternal grandma negative was respectively 51.90± 10.81, 51.17±11.04, 51.07±10.59, 51.08±10.60, 50.50±11.09 or 50.57±11.06 years old. The difference about two groups showed statistically significant. Family history has a positive effect on the occurrence of hypertension, and lead to earlier age of onset of offspring. The effects are different among parent and grandparent in Han in Shanghai China.

Keywords: Hypertension, Family History, Onset Age, Effect

1. Introduction

Essential hypertension (EH) is a multifactorial disease caused by genetic and environmental factors, The interaction of genes and genes, genes and environment lead to the risk of different populations and individuals suffering from the disease. Some studies suggest that there are two major factors affecting the incidence of hypertension: one is the genetic factor; the other is environmental factors [1-11]. EH is a complex disease influenced by genetic and environmental factors, in addition to genetic factors, several evidence suggest

that stress contributes to the genesis of EH. There are many studies on genes or chromosomal loci that are linked to EH, but the results are controversial [12-19]. This difference is probably due to the small sample size of single study and the different source of the population. According to the current research data at home and abroad, it is recognized that hypertension is caused by environmental and genetic factors. Complex diseases with common effects and the influence of genetic factors on hypertension is about 20% -55% [20-21].

It is now believed that the genetic factor of hypertension is made up of a number of pathogenic genes that have a small but

cumulative effect. But so far, the susceptibility genes for hypertension have not been finalized. The challenges of finding essential hypertension genes mainly may be genetic heterogeneity and effects from confounding factors, because of population stratification. The genes associated with essential hypertension may be a group and micro effect mode, each of which plays a different role in different stages of the formation and development of hypertension and interacts with each other. The interaction between genes and genes, genes and environment, environment and environment leads to different risk of hypertension among different populations and individuals. By the dose effect relationship of quantitative characters, the critical threshold of the occurrence of the disease is reached, and the genetic susceptibility to essential hypertension is determined simultaneously.

This study uses methods of genetic epidemiology study, based on the investigation of the essential hypertension patient family and the control family, to explore the association between family history and the onset age of essential hypertension in Han in Shanghai China.

2. Methods

2.1. Determination of the Core Family in Case Group

All cases were randomly selected from hypertension registry and follow-up management system, the diagnosis of blood pressure is based on outpatient or inpatient diagnosis in clinical hospitals. The diagnosis of hypertension is based on outpatient or inpatient diagnosis (the clinic blood pressure) in clinical hospitals. All case were confirmed by hospital and verified by follow-up in the community, and they were able to correctly respond to the investigators for health information of themselves and their nuclear family members. Every precursor patient gave informed consent to participate in the study which was approved by the local ethics committee.

2.2. Determination of the Core Family in Control Group

According to 1:1 matched pairs design, all controls population had no hypertension, and controls are required the same sex as cases, same race, living in the same community, and the difference of age is not more than 5 years old and at the same age group. Every control gave informed consent to participate in the study. They were able to correctly respond to the investigators for the health information of themselves and their nuclear family members.

2.3. Standard of Case Diagnosis and Inclusion

All precursor patients were over 18 years old, who has been diagnosed by the hospital as essential hypertension, excluding secondary hypertension, such as renal artery stenosis, pheochromocytoma, hyperaldosteronism and other diseases.

2.4. Family Survey Method and Content

All researchers were conducted by trained public health investigators, using a self-designed and unified questionnaire

for the hereditary family of essential hypertension. Questionnaires were completed by direct inquiry including, the investigate contents include: age, sex, race, age of onset, diagnosis time, hospital name, family members and so on. The family investigation mainly includes: spouses, parents, siblings, children, uncle, aunt and cousin. The criteria for judging whether all the respondents had essential hypertension (all relatives of the case and the control population): whether they had been diagnosed with essential hypertension in the hospital before this investigation. If they had been diagnosed with essential hypertension in the hospital, it is "Yes"; if they had not been diagnosed, it is "No".

2.5. Statistical Analysis Method

Statistical analyses were performed using the statistical software package (IBM SPSS statistics version 21). When P values <0.05 , the difference is considered statistically significant.

3. Results

3.1. Characteristics of Population

In this study, 342 (male 171, female 171) precursor cases and 342 (male 169, female 173) control population were investigated, average age in the case group was 62.4 ± 10.7 years old, and average age in the control group was 61.7 ± 10.7 years old. Among these investigated people, they are all Han races, so no racial analysis will be conducted. The difference of age and sex between case group and control group were not significant ($t_{age}=0.894$, $p_{age}=0.372$; $\chi^2_{sex}=0.119$, $p_{sex}=0.730$). Total number of nuclear family members investigated was 8814 (4454 in case group, 4360 in control group), and the average nuclear family member was 12.88 (case group is 13.02; control group is 12.74).

Among 4104 investigated population in the elder member of a family (include father, mother, grandpa, grandma, maternal grandpa and maternal grandma), there were 839 relatives were definitely diagnosed with hypertension. The prevalence of hypertension was 20.44% in the elder relatives of this investigation. Among 3265 non-hypertensive relatives, there may also be some patients with potential or recessive hypertension who have not been clearly diagnosed. There is no reverse effect on the results of this study, so no further discussion will be conducted.

3.2. Family History

There were 2055 hypertensive patient has been clearly diagnosed in the hospital among this investigated population in this study, the average prevalence was 23.32%. The prevalence rate of hypertension of first-degree relatives was 33.99%; prevalence rate of second-degree relatives was 17.60%; prevalence rate of third-degree relatives was 13.51%. This result showed that the order of hypertension prevalence rate was as follows: first-degree relatives $>$ second-degree relatives $>$ third-degree relatives.

All prevalence rates of hypertension of case group relatives

were significantly higher than that of control group relatives. The result showed a phenomenon of familial aggregation in the distribution of hypertension. See table 1.

Among these family members and relatives in case and control group, there were 575 hypertension in parent population, the prevalence was 42.03%; 549 in sibling population, the prevalence was 39.96%; 100 in offspring population, the average prevalence was 11.64%; 291 in paternal siblings population (brother and sister of father), the prevalence was 18.27%; 255 in maternal siblings population (brother and sister of mother), the prevalence was 16.89%; 46 in paternal cousin population, the prevalence was 13.11%; 239 in maternal cousin population, the prevalence was 13.59%. The difference of hypertension prevalence in three degree relative populations between case group and control group were significant. See table 1.

Table 1. The hypertension prevalence rate (%) of relatives in case and control group.

	control group			case group			x ²	p
	total	disease	prevalence	total	disease	prevalence		
first-degree relatives								
parent	684	228	33.33%	684	347	50.73%	14.853	<0.001
siblings	704	217	30.82%	670	332	49.55%	21.557	<0.001
offspring	440	33	7.50%	419	67	15.99%	11.899	0.001
	1828	478	26.96%	1773	746	42.07%	48.167	<0.001
second- degree relatives								
paternal siblings	791	123	15.55%	802	168	20.95%	5.375	0.020
maternal siblings	740	107	14.46%	770	148	19.22%	4.339	0.037
	1531	230	15.02%	1572	316	20.10%	9.635	0.002
third-degree relatives								
paternal cousin	176	14	7.95%	175	32	18.29%	6.330	0.012
maternal cousin	825	97	11.76%	934	142	15.20%	3.897	0.046
	1001	111	11.09%	1109	174	15.69%	7.282	0.007
Total	4360	819	18.78%	4454	1236	27.75%	83.649	<0.001

Table 2. The hypertension prevalence rate (%) of elder member in case and control group.

	Control group			Case group			X ²	p
	No	Yes	%	No	Yes	%		
father	222	120	35.08	170	172	50.32	16.158	<0.001
mother	234	108	31.48	167	175	51.29	27.057	<0.001
grandpa	323	19	5.57	311	31	9.03	3.107	0.078
grandma	323	19	5.57	322	20	5.81	0.027	0.869
maternal grandpa	331	11	3.28	324	18	5.16	1.764	0.184
maternal grandma	324	18	5.25	320	22	6.45	0.426	0.514

3.3. FH Affects Onset Age of Hypertension

If one or more relatives of the first-degree relatives (include father, mother, grandpa, grandma, maternal grandpa and maternal grandma) have been definitely diagnosed with hypertension, family history (FH) is called positive, otherwise is called negative. Among 342 cases in the case group, the result showed that the average onset age in population with positive FH is 48.74±11.16 years old, and the average onset age in population with negative FH is 54.38±9.87 years old. The difference about two FH groups showed statistically significant (t=4.589, P<0.001). Among the first-degree relatives, the efficacy on the age of onset of hypertension in offspring is different for different relatives. See table 3.

Among 4104 investigated population in the elder member of 684 families (include father, mother, grandpa, grandma, maternal grandpa and maternal grandma), there were 575 hypertension cases in parent population (include father and mother), the prevalence of parent was 42.03%; and 89 hypertension cases in grandparent population (include grandpa and grandma), the prevalence of grandparent was 6.51%; and 69 hypertension cases in maternal grandparent population (include maternal grandpa and maternal grandma), the prevalence of maternal grandparent was 5.04%. Because most of the grandparents and maternal grandparents have been died before this investigation, a large number of hypertension cases may be omitted because of unknown or not diagnosed in the retrospective investigation, resulting in the low prevalence of these two groups of population. See table 2.

Table 3 showed that either parents or grandparents or maternal grandparents in the first-degree relatives could affect the onset age of hypertension of children, it's just that the level of effect was different. Grandpa and grandma are particularly influential among the first-degree relatives. The average onset age of children with grandpa or grandma positive was respectively 39.55±11.95 or 39.88±11.90 years old; and the average onset age of children with grandpa or grandma negative was respectively 51.07±10.59 or 51.08±10.60 years old. The difference about two groups showed statistically significant (see table 3). The results suggest that the onset age of hypertension of children with grandpa or grandma positive was about 11 years earlier likely than that of children grandpa or grandma negative.

Table 3. The average onset age of hypertension in case group with different family history.

	Hypertension	N	Onset age (y)		t	p
			mean	SD		
father	Yes	167	48.42	11.16	3.194	0.002
	No	175	51.90	10.81		
mother	Yes	166	49.16	11.12	1.832	0.068
	No	176	51.17	11.04		
grandpa	Yes	26	39.55	11.95	5.768	<0.001
	No	316	51.07	10.59		
grandma	Yes	27	39.88	11.90	5.682	<0.001
	No	315	51.08	10.60		
maternal grandpa	Yes	15	43.67	9.77	2.883	0.010
	No	327	50.50	11.09		
maternal grandma	Yes	18	43.64	10.21	3.086	0.005
	No	324	50.57	11.06		

4. Discussion

It is well known that the genetic factors play an important basic role in the occurrence of hypertension, and family history is a sign reflecting the main role of genetic factors. It's showed that family history plays an important role in the development of hypertension through interaction with acquired risk factors such as body mass index (BMI), and the interaction of family history and BMI is greater than the sum of two independent actions [22]. In this study, the genetic epidemiological results showed that the prevalence of hypertension in three degree relatives was different. The prevalence in the first degree relatives (including parents, siblings and offspring) was the highest (33.99%), the prevalence in the second degree relatives (including paternal siblings and maternal siblings) was the next (17.60%), and the prevalence in the third degree relatives (including paternal cousin and maternal cousin) was lowest (13.51%). The difference of hypertension prevalence among three degree relatives in Han in Shanghai China were significantly ($P < 0.05$). All prevalence rates of three degree relatives of case group relatives were significantly higher than that of control group relatives. It was suggested that genetic factors have obvious influence on the occurrence of essential hypertension, and the genetic potency may be decrease with the increase of degree relatives.

Among 684 families, the prevalence of parent population (include father and mother) was high (42.03%), and the prevalence of case group relatives were significantly higher than that of control group relatives. The prevalence of grandparent population (include grandpa and grandma) or maternal grandparent population (include maternal grandpa and maternal grandma) was lower, and the difference of prevalence between case group and control group. Owing to most of the grandparents and maternal grandparents have been died before investigation, a large number of hypertension cases may be omitted because of unknown or not diagnosed in the retrospective investigation, resulting in the low prevalence of these two groups of population. If we update the data collection methods and increase the sample size in future studies, we may be able to find differences between the two groups.

At present, method of estimating the heritability of polygenic disease is generally accepted to calculate the heritability based on the threshold theory of Falconer, the heritability reported in the relevant literature (20-55%) [20-21]. it indicates that there are also ethnic differences in hypertension susceptibility genes among different ethnic groups. In this study, the result showed that the average onset age in population with positive FH is 48.74 years old, and the average onset age in population with negative FH is 54.38 years old, the difference about two FH groups showed statistically significant. The average onset age of hypertension in cases with positive family history is likely 5 years earlier than that of cases with negative family history. The efficacy on the age of onset of hypertension in offspring is different for different relatives. The average onset age of children with father or mother positive was respectively 48.42 or 49.16 years old; and the average onset age of children with grandpa or grandma negative was respectively 51.90 or 51.17 years old. The average onset age of hypertension in cases with positive parents is likely 2-3 years earlier than that of cases with negative parents. The average onset age of children with grandpa or grandma positive was respectively 39.55 or 39.88 years old; and the average onset age of children with grandpa or grandma negative was respectively 51.07 or 51.08 years old, the average onset age of hypertension in cases with positive grandparents is likely 11 years earlier than that of cases with negative grandparents. The average onset age of children with maternal grandpa or grandma positive was respectively 43.67 or 43.64 years old; and the average onset age of children with maternal grandpa or grandma negative was respectively 50.50 or 50.57 years old, the average onset age of hypertension in cases with positive maternal grandparents is likely 7 years earlier than that of cases with negative maternal grandparents.

5. Conclusion

Family history has a positive effect on the occurrence of hypertension, and lead to earlier age of onset of offspring. The effects are different among parent and grandparent in Han in Shanghai China.

Ethics Approval and Consent to Participate

Ethical approval was granted by Jiading district center for disease control and prevention research ethics committee. All subjects gave informed consent to participate in the study, they would like to participate in investigation and answer all the related questions in the questionnaire.

Availability of Data and Material

The questionnaire and database supporting the conclusions of this article are available, through contact with anle_li@aliyun.com.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

The original idea for the project was conceived by An-le LI. Qian Peng, Yue-qin Shao, Yi-ying Zhang, Xiang Fang participated in the collection of early data, quality control, and gave a lot of administrative support. LI An-le conceptualized the paper, analyzed data and wrote a first draft of the manuscript. All authors contributed to subsequent drafts and approved the final manuscript.

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