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Familial Aggregation of First Degree Relatives of Children with Essential Hypertension

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Abstract

Purpose—Determining familial aggregation is an important first step in narrowing the search for disease-causing genes and hence we determined the familial aggregation of EH among first degree relatives of children with EH.

Materials and methods—We prospectively enrolled children with EH along with their first degree relatives from a tertiary pediatric hypertension clinic in a large ambulatory care center. We utilized rigorous methodology for blood pressure (BP) measurements and diagnoses of EH to reduce the heterogeneity in the phenotype. For those enrolled, parental BP status was confirmed by in-clinic direct BP measurements. We also enrolled control children without EH along with their first degree relatives from the same pediatric ambulatory center.

Results—In our case-control study of 153 families, the odds of having familial EH was more than 3 times higher among the cases than in controls (OR: 3.63, 95% CI: 1.85 – 7.12) with 71% of the cases and 41% of the controls reporting familial EH. One parent with EH was seen in 88% of the cases and 52% of the controls (OR: 6.92, 95% CI: 2.68 – 17.84). The odds of at least one parent (compared to neither) with EH was almost 7-fold higher, and odds of having two parents with EH was 14-fold higher among cases versus controls. The risk of EH did not go back from the first degree relative to the second degree relatives.

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Disclosure statement

The authors report no conflicts of interest.

Conclusions—We identified familial aggregation with an increased liability of childhood onset EH with parental EH. The risk of childhood onset EH is more than doubled in the presence of EH in both parents versus in a single parent. Prediction for childhood-onset EH is improved by obtaining a family history of EH in the first degree relatives.

Keywords

primary hypertension; pediatrics; parental hypertension; sibling hypertension; genetics; risk factors

Introduction

There are three important methodologies to determine the genetic contributors to a disease: studying genetically isolated populations, reducing heterogeneity of the phenotype, and evaluating an early onset of the phenotype. Primary or essential hypertension (EH) is a heterogeneous disease with several biological pathways and environmental contributors to the disease expression. This heterogeneity of EH correlates negatively to the ability to identify its susceptibility genes [1]. In this study we evaluated EH at the onset of the disease in early childhood to reduce, although not eliminate, contribution from environmental factors. We also utilized rigorous methodology for blood pressure (BP) measurements and diagnoses of EH via a strict diagnostic criteria to reduce the heterogeneity in the phenotype.

Several reported studies have looked at how BP tracks from childhood to adulthood and also how BP levels are correlated between sib-sib pairs and also child-parent pairs in adulthood. A few studies have also shown aggregation of BP levels in parent-child dyads and triads [2-6]. However, these studies involving children had looked at BP levels and not EH which is chronic disease. Hence incidence and aggregation of parental EH in children with EH has not been well defined in literature. We also do not know whether adult EH also aggregate in families where a child has EH. If so, it would have implications for better understanding the pathophysiology of childhood onset EH in terms of the factors, both genetic and environmental, that might play a role in its development.

In this study we determined children with EH, an early phenotype obtained by rigorous methodology to reduce the heterogeneity. We then determined the incidence of parental and sibling hypertension and studied the familial aggregation of EH among first degree relatives of children with EH.

Material and methods

Institutional approval

The study was approved by the institutional Committee for the Protection of Human Subjects at the McGovern Medical School at the University of Texas Health Science Center in Houston and Children's Memorial Hermann Hospital, Texas Medical Center. All subjects and parents gave informed assent and consent, respectively for this study. We were careful in maintaining full patient confidentiality, safeguarding the rights and welfare of human subjects, and informing subjects, in a confidential manner, of the results obtained from the

study. All families were given compensation for their participation for multiple visits in order to enroll all first degree relatives.

Patient Population

Patients were prospectively enrolled in this case-control single center observational pedigree study. Subjects, aged 19 years or younger, with either an established or a new diagnosis of essential hypertension were enrolled. Both treated and un-treated consecutive patients seen at the Pediatric Hypertension Clinic at the McGovern Medical School at the University of Texas Health Science Center in Houston that fit the above criteria were eligible for inclusion in the study.

Blood Pressure Protocol

Blood pressure was measured in all children who participated in this study including probands, siblings and controls in a standard manner in the clinic. The hypertension status was confirmed both by clinic measurements and by ambulatory BP monitoring for 24 hours in all proband children as follows: Clinic hypertensive status was confirmed in all subjects at the first visit to the hypertension clinic by averaging the last 3 of 4 blood pressure measurements performed by oscillometric method and confirmed by manual auscultation with a mercury sphygmomanometer by trained personnel using methodology recommended by the Fourth Report[7]. Hypertension was diagnosed when 3 separate measurements of systolic and/or diastolic BP were recorded $>95^{\text{th}}$ percentile for post-conceptual age, adjusted for height, age and gender per Fourth Report [7] were documented in the medical record. All children who were above 5 years of age except those admitted with a hypertensive emergency underwent an ambulatory blood pressure monitoring (ABPM) using Spacelabs oscillometric monitors (Spacelabs, Inc., Redmond, WA) and validated by a standard protocol. The children along with their families were instructed on avoidance of caffeinated beverages or supplements, any medications, herbals or over the counter products, smoking and alcohol for 24 hours prior to and during the ABPM. While on ABPM, the BP was automatically measured every 20 minutes for 24 hours. Both BP and BP load will be used to define the severity of ambulatory hypertension. Subjects with 24-hour systolic BP or diastolic BP greater than the pediatric 95^{th} percentile or BP load (percentage of BP values exceeding the 95^{th} percentile for the 24-hour period) greater than 25% were considered to have ambulatory hypertension [8]. Specifically, more severe ambulatory hypertension was defined as mean systolic or diastolic BP greater than the 95^{th} percentile and BP load greater than 50%. Children with elevated BP in clinic but a 24-hour systolic BP and diastolic BP less than the pediatric 95^{th} percentile and BP load less than 25% were considered to have White Coat hypertension. Children without hypertension in the clinic, but a 24-hour systolic BP or diastolic BP greater than the pediatric 95^{th} percentile and BP load greater than 25% were considered to have masked hypertension. Children with history of elevated BP prior to referral that had normal BP measurements in the hypertension clinic and a 24-hour systolic BP and diastolic BP less than the pediatric 95^{th} percentile and BP load less than 25% were considered to have normotension.

Diagnosis of Essential Hypertension in Probands

Once hypertension was confirmed, all children underwent further evaluation for secondary hypertension per recommendations by the Fourth Working Group Report [7]. Prematurity was defined as gestational age less than 37 weeks. The diagnosis of secondary hypertension was made by extensive evaluation per recommendations by the Fourth Working Group Report[7] including a urinary evaluation, blood tests, renal ultrasound and echocardiogram in all children; renal magnetic resonance imaging for evaluation for renal artery stenosis in all those with stage II hypertension or resistant hypertension; sleep study for those with obesity and/or symptoms, and so on. Criteria for the diagnosis of essential hypertension were: (a) clinic BP elevation above the 95th percentile on 3 previous occasions, (b) positive 24 hour ambulatory BP monitoring (except in those who with history of hypertensive emergency requiring admission or those who were age less than 5 years), (c) absence of secondary causes of hypertension and (d) no concurrent medication with the potential to raise BP (e.g., steroids, central stimulants).

Recruitment Criteria for Study Population

For our family based genetic study, to be considered for further analysis, criteria for recruitment of the study subjects consisted of the following: *Inclusion criteria:* (a) history of diagnosis of essential hypertension per Fourth Report [7] below age of 19 years, (b) no known underlying medical conditions predisposing to hypertension. (c) no concurrent medication with the potential to raise BP at the time of diagnosis (e.g., steroids or stimulant medication) (d) no evidence of white-coat hypertension after an ambulatory BP monitoring (e) living with at least one of their biological parent (f) at least one parent spoke and wrote English or Spanish and (g) age less than 19 years at the time of diagnosis of EH. *Exclusion criteria:* (a) adopted or custody with extended relatives without involvement of either biological parent (b) parents without ability to read or speak English or Spanish language (c) children with white coat hypertension and prehypertension (d) children involved in custody issues (e) children with complete evaluation for hypertension pending or lost to follow-up (f) children born by donor egg or sperm.

Recruitment Criteria for Control Population

We enrolled unrelated controls children, along with their siblings and parents. We recruited the control population from the ambulatory pediatric clinics in the same building as the tertiary pediatric hypertension clinic. We matched the case probands to control probands based on age (age of onset of hypertension of the case probands), gender and self-reported ethnicity. Inclusion criteria were similar to the study population other than as follows no history of elevated BP, or prehypertension/hypertension established upon BP measurements in the child Exclusion criteria were similar to the cases.

Pedigree and Family Structure

A 3-generational pedigree was drawn for each family based on the in-person interview. A pedigree was constructed and all data was store in a computerized database using Progeny software (version 7, Progeny software LLC, Delray Beach, Florida, USA). Probands with a one parent or two second-degree relatives with hypertension diagnosed before age of 50

years were defined as having familial hypertension. Those probands with normotensive parents and grandparents were defined to have non-familial form of hypertension. Only full siblings were considered for analysis.

Ascertainment of EH in family members

All enrolled parents and siblings had BP measurements made in a standard manner for the purpose of this study and if found to be elevated per definition as described above, labeled as having hypertension. If they were normotensive when BP was measured but were concurrently also on an anti-hypertensive medication, they were classified as having EH. The ascertainment of hypertension amongst parents who did not enroll or those who were second degree relatives was by interview of the parent of the proband regarding the history of hypertension. There was no direct BP measurement on the second degree relatives. Information was also gathered on other potential co-morbidities to rule out common causes of secondary hypertension in the family members.

Classification of familial EH

Probands with least one parent or two second-degree relatives with EH diagnosed before age of 50 years were defined as having familial EH. Those probands with normotensive parents and grandparents were defined to have non-familial form of hypertension. EH in first degree relatives was assumed if presence of EH was ascertained in at least one parent. The absence of EH in the first degree relative was assumed if the data on the absence of EH was ascertained for all first degree relatives. In other words, those labeled with no EH were those known to have no EH, not missing data. If there was no parental or sibling measurement of BP in our clinic and if their history was unknown then they were not included in the analysis of familial effect. EH in second degree relatives was ascertained via querying the parent of the child. If the presence of EH was reported for any second degree relative, it was noted as such. A second degree relative was considered to not have EH if that was explicitly stated by the respondent.

Statistical Analysis

Data from the medical records was abstracted and tabulated. Continuous variables were non-normally distributed and comparisons between groups utilized non-parametric tests (Mann-Whitney, Kruskal Wallis. Contingency tests (Fisher exact or chi-square) were used to compare categorical variables across groups. Univariable and multivariable logistic regression models were used to assess the individual and interactive effects of maternal and paternal hypertension on the odds ratios of childhood onset EH. The referent group for the odds ratios was children with no EH in either parent. The adjusted models assessing maternal and paternal effects included EH information on both parents. All analyses was performed in STATA (v.14 College Station). Statistical significance was assumed at a Type I error rate of 0.05.

Results

A total of 153 families (77 hypertension probands, 76 control probands, males 54%, and median age 12 years, range 1-18 years) were prospectively enrolled in the study. The details

of demographics and family structure are given in Table 1. There was no differences in the distributions of gender, age, race or ethnicity and birth weight between the hypertensive and controls probands, except for the weight at clinic visit which was significantly higher among probands with EH than those without (Table 1). Table 2 provides the data on EH status among the first degree relatives of cases and controls. Out of the 153 probands, 86 probands had familial EH, and of those 81 (95%) had a parental history of EH (at least one parent known to have EH) while only 1 (1%) had no parental history of EH (data was incomplete for the remaining 3 probands). When first degree relative assessments were made, out of the 153 probands, maternal and paternal EH status were known for 142 (93%) and 111 (73%) of the probands, respectively. Data on the EH status was missing for just the father or just the mother or both in an additional 40, 9 and 2 families, respectively. The status for both parents in a family was known for 102 of the 153 probands (53 cases and 49 controls), with an additional 9 and 4 probands having a hypertensive mother or a father, respectively, while information on the other parent was missing. These 115 probands represent the “any parent” category in Table 2. Data was then stratified to assess the effect of having only one (mother or father, separately) or two hypertensive parent(s).

Out of the 153 probands, 104 probands had data available for both parents. Among the cases the distribution was as follows: 21%, 26%, 40% and 13% of the cases had both parents, only a mother, only a father, and neither parent with EH, respectively [Figure 1]. In comparison, the distribution was 6%, 18%, 20% and 55%, respectively, among the normotensive controls ($p<0.001$) [Figure 1]. In other words, among couple where neither parent was hypertensive, 20% of them had a hypertensive child, while among couples where both the parents were hypertensive, 79% of them had a hypertensive child ($p<0.001$) [Figure 2]. The percentage of couples with a hypertensive child was 61% and 68% among couples where only the mother was hypertensive or only the father was hypertensive, respectively. About a third out of 155 probands did not have any siblings ($n=50$; 24 cases and 26 controls) and two probands did not have information on their sibling’s hypertension status. Four of the remaining 105 probands had at least one sibling with EH. All four of the probands were positive for familial EH. Only one of these four was a sibling of a normotensive control proband and both his parents were normotensive as well, but second degree relatives were hypertensive. Two siblings of case proband had one parent (a mother and a father respectively) as well as other second degree relatives with a positive EH statuses. The final case proband only had second degree relatives with EH.

Overall, the odds of having familial EH was more than 3 times higher among the cases than in controls (OR: 3.63, 95% CI: 1.85 – 7.12) with 71% of the cases ($n=55$) and 41% of the controls ($n=31$) reporting familial EH. The vast majority of case probands with childhood onset EH ($n=52$, 88%) had at least one hypertensive parent compared to only half the control probands ($n=29$, 52%). This meant that the odds of having at least one hypertensive parent was nearly 7-fold higher in childhood onset EH compared to the control probands (OR: 6.92, 95% CI: 2.68 – 17.84). The adjusted odds of having a hypertensive mother and normotensive father (as opposed to no hypertensive parents) was 6-fold higher (OR: 6.00, 95% CI: 1.84 – 19.53), and the odds of having a hypertensive father and a normotensive mother was 8-fold higher (OR: 8.10, 95% CI: 2.64 – 24.87) among case probands compared to the control probands. The odds of having both parents having hypertension (as opposed to

neither) was 14-fold higher (OR: 14.14, 95% CI: 3.08 – 64.88) in case probands compared to the controls [Figure 1]. There was no evidence of any statistical interaction between maternal and paternal hypertension and its influence on EH in the proband (OR interaction: 0.29, 95% CI: 0.04 – 1.93). The history of EH beyond first degree of relatives is not as helpful as there was no difference in the odds ratio between history of EH in any family member and a first degree relative. Therefore the prediction for childhood-onset EH is improved by obtaining a family history of EH in the first degree relative. There was no significant difference in the EH status in siblings between cases and controls which may reflect the small sample size and needs to be further evaluated by a larger study [Table 2]. We identified an increased liability of EH in children with familial EH in our study. The point estimates for this increased liability were even higher, though not at a statistically significant difference, for liability due to EH in at least one parent, and persisted when data was analyzed for offspring with only one affected parent.

Discussion

Determining familial aggregation is an important first step in narrowing the search for disease-causing genes[9]. Family aggregation may arise because of genetic (shared genes) or environmental similarities or the combination of the two between the family members[10]. Evaluation of EH phenotype in early childhood helped reduce contribution from environmental factors such as substance abuse (smoking, alcohol), chronic stress and aging in our study.

Only few studies have evaluated familial aggregation of EH, since majority of the studies have evaluated the aggregation of BP levels and not EH which is chronic disease. Familial aggregation exists when there is an occurrence of a trait in more members of a family than can be readily accounted for by chance[9] and several studies have shown familial aggregation of blood pressures in adults [11] but only few in children[12]. Predominantly adult studies that have shown the clustering of EH phenotypes within a given family, including familial aggregation of low renin EH[13], insulin resistance [14] and response to treatment and control of blood pressure[15].

We report aggregation of EH among children and their first degree relatives in comparison to normotensive children which is not previously reported in the literature [Figure 1]. A previous study reported presence of EH in 49% of the parents in children with EH versus 24% of the parents in children with secondary EH[16] indicating higher aggregation amongst those children with EH. As described under methodology, parental and sibling BP status was confirmed by in-clinic direct measurements.

We found that there was doubling of the risk of childhood onset EH if both parents had EH versus a single parent with EH (Figures 2). A previous study on BP screening has shown offspring of two hypertensive parents have significantly higher BP than offspring of one hypertensive and one normotensive parent [17].

Thus, we identified an increased liability of EH in children with parental EH [Figures 2]. Additionally, we found that the risk of childhood onset EH was increased in the presence of

EH in both parents versus EH in a single parent. The odds of at least one parent (compared to neither) with EH was almost 7-fold higher, and odds of having two parents with EH was 14-fold higher among cases versus controls. The risk was quite similar regardless of whether it was the father or the mother who had EH. Although EH status in case siblings was higher than control siblings, it did not reach statistical significance most likely secondary to the small sample size and hence the findings need to be evaluated further by a larger study.

We found that the individual and independent parental effects exerted an additive effect on the liability of childhood onset EH on their offspring. There was no evidence of any statistically significant multiplicative interaction in the odds ratio scale between maternal and paternal hypertension. This suggests that there may potentially be separate biological and/or physiological pathways through which the risk is conferred from each parent to the child.

For clinical perspective, obtaining history of EH in the first degree relative may be sufficient to confer the risk for EH in the child. We found that the risk of EH did not go back from the first degree relative to the second degree relatives. Predictors of childhood onset EH includes EH in one or both parents in our study. We identified an increased liability of EH in children with familial EH in our study. Our findings suggest that more, if not all of the risk conferred onto the child can be traced to the history of EH in a first degree relative. Prediction for adult onset EH is improved by obtaining a family history of EH [18]. A parental history of EH is a known risk factor for EH in an offspring [19]. In our study prediction for childhood-onset EH is improved by obtaining a parental history of EH. Furthermore, the history of EH beyond first degree relatives was not as helpful in our study as there was no difference in the odds ratio between history of EH in any family member and a first degree relative.

Our findings suggest that clinicians may be able to identify children who are at risk for developing EH by screening for EH in their parents. These children at risk may benefit from an intensified preventive measures such as weight management and dietary changes early in life to alter risk as renal disease and stroke in adulthood. Annual blood pressures measurements in children with one parent with EH and biannual measurements in children with both parents with EH may be helpful in identifying children with EH thus enabling earlier treatment and preventing long-term morbidity.

We did not enroll children who did not have at least one biological parent and hence the study results cannot be utilized for families involving grandparent as the primary caretaker of the child. The findings are somewhat imprecise due to a wide confidence interval and may be related to the small study sample size. Finally, we did not evaluate children with white coat hypertension or prehypertension in this study.

Our results indicate an aggregation of parental and offspring EH phenotypes. The risk of childhood onset EH is more than doubled in the presence of EH in both parents versus in a single parent. Prediction for childhood-onset EH is improved by obtaining a family history of EH in the first degree relatives.

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Figure 1.
Distribution of parental hypertension status in the normotensive control children and the children with essential hypertension

Figure 2.
Distribution of normotensive children and children with essential hypertension based on the parental hypertension status

Table 1

Demographic distribution of case and control probands from enrolled families

	All	EH	Control	p value
Family Number, n *	153	77	76	
Age, years (median, range) **	12 (1-18)	12 (1-18)	13 (5-18)	0.418
Birth weight, kg (median, range)	3.2 (0.9 – 6.5)	3.2 (0.9 – 6.5)	3.2 (1.0 – 4.5)	0.622
Weight, kg (median, range) **	55 (10-179)	62 (10-179)	49 (17-122)	0.022
Gender, males, n (%) *	78 (53)	45 (59)	33 (46)	0.103
Ethnicity, n (%)				
African American	69 (47)	37 (49)	36 (47)	0.681
Non-Hispanic White	22 (15)	12 (16)	8 (10)	
Hispanic	51 (34)	24 (32)	30 (39)	
Asian	6 (4)	3 (4)	3 (4)	

EH, essential hypertension; n, number; kg, kilograms

* Discrepancy between cases and controls pending enrollment of additional matched controls

** For cases: "Age" and "Weight" correspond to measurements taken at time of diagnosis of EH; For controls: "Age" and "Weight" correspond to measurements taken at enrollment into study.

Table 2

Frequency, n (%), of familial history of essential hypertension in first degree relatives

	N	EH	Control	p-value	Odds Ratio *	95% CI
Familial EH	153	55 (71)	31 (41)	<0.001	3.63	1.85 – 7.12
EH in first degree relatives						
Either parent [‡]	115	52 (88)	29 (52)	<0.001	6.92	2.68 - 17.84
Mother only ^{*,†,***}	57	14 (67)	9 (25)	0.004	6.00	1.84 - 19.53
Father only ^{*,†,***}	65	21 (75)	10 (27)	<0.001	8.10	2.64 - 24.87
Both father and mother ^{*,†,***}	48	11 (61)	3 (10)	<0.001	14.14	3.08 - 64.88
Sibling only	153	3 (4)	1 (1)	0.304	3.13	0.32 - 30.74

EH, essential hypertension; CI, confidence interval;

* Reference group is 34 subjects with no essential hypertension in either parent;

** Categories are mutually exclusive;

[‡] Either both parents are normotensive or at least one parent is hypertensive to be included in analysis;[†] Need to have hypertension information on both parents to be included in analysis