Epidemiology of Childhood Onset Essential Hypertension

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Abstract

The knowledge of epidemiology of a disease is paramount in identifying preventive measures. Currently there is a paucity of literature on the epidemiologic determinants of childhood onset essential hypertension (EH). We evaluated children with EH, ascertained in a rigorous manner, in a large multiethnic population in a tertiary pediatric hypertension clinic. We enrolled children with and without EH and obtained data by in-person interview of their parents and by direct anthropometric measurements including blood pressures. A total of 148 children (76 hypertension probands, 72 control probands, and males 53%, mean age 12.2 ± 4.3 years) were enrolled. Of these 148 children, 51 pairs were matched 1:1 on ethnicity, gender and age (± 2.5 years). In this study we evaluated the demographics, genetic predisposition and a variety of exposures including, socioeconomic, perinatal, lifestyle and environmental, between cases and controls. All measures were similar between cases and controls other than a significantly higher BMI (p = 0.01) and rates of obesity (p = 0.03), and a difference of near-significance in any family history of EH (p = 0.05) higher in cases compared to controls. The odds of obesity was 3.5 times higher among cases than controls. In this study we evaluated a variety of prenatal and postnatal exposures that could potentially contributed to the EH phenotype in childhood. The findings of the study elucidate the epidemiology of EH in children and two important associated risk factors, any family history of hypertension and a higher body weight.
Keywords

primary hypertension; pediatrics; socioeconomic; birth weight; environmental exposures

INTRODUCTION

Childhood onset essential hypertension (EH) has recently become a more visible disease based on several factors, including recommendations for regular evaluation of blood pressure (BP) in the ambulatory pediatric clinics (1) and improved ease of recognition using computerized software for flagging elevated BP (2). Charts similar to growth charts exist to recognize abnormal BP thresholds in children, again making recognition of hypertension easier than before (3). The prevalence of EH in children was reported at around 2% in one study (4). Based on the 2017 American Academy of Pediatrics guidelines on hypertension, the prevalence of hypertension in childhood appears to be increasing in the United States of America (5). Although prevalence of childhood onset EH has been increasing, there is a paucity of literature on its epidemiologic determinants (4, 6–8).

The knowledge of epidemiology of a disease is paramount in identifying exposures and risk factors for disease so that preventive measures can be applied. Further, it is important to capture and treat this population early since cardiovascular changes can occur in the very young. We have previously reported cardiovascular endorgan damage in childhood onset EH, including left ventricular hypertrophy (9, 10), myocardial dysfunction (11, 12) and aortopathy (13). Thus, evaluation of epidemiology of childhood onset EH can help with early prevention strategies to reduce the disease burden in later life. For example, studies in adult onset EH have shown association of epidemiological factors with compliance with therapeutic recommendations for hypertension (14). The investigators found factors such as gender, race, and socioeconomic status, among others, to play a role in adherence to antihypertensive therapy (14). Lastly, in order to better inform pediatricians on clinical management of their patients, one needs to study and report epidemiological findings on a chronic disease such as EH (9).

In this observational case-control epidemiological report, we evaluated several prenatal and postnatal exposures and their relationship to childhood onset EH. We evaluated the maternal and fetal exposures, socioeconomic status, familial risk factors and several environmental exposures in children with EH in comparison to age-, gender- and ethnicity-matched control children without EH.

Study Design:

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 and Children’s Memorial Hermann Hospital, Texas Medical Center, Houston. All children 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 of $20 per clinic visit for 3 visits for their participation in order to enroll all first degree relatives.

**Patient Population:**

All cases and controls along with their biological parents were enrolled into this case-control single center observational study from 2011 through 2014. Cases included both treated and un-treated patients seen at the Pediatrics Hypertension Clinic at McGovern Medical School at the University of Texas Health Science Center in Houston with either an established or a new diagnosis of EH. Controls were from other general pediatric clinics in the same ambulatory clinic area where the Pediatric Hypertension Clinic was located. The children with no prior or current diagnosis of any kind of hypertension and no relationship to the cases were approached for enrollment as controls into the study. Detailed family history and family structure was obtained by using a questionnaire and an in-person interview. Children younger than 19 years of age, with either an established or a new diagnosis of EH, were enrolled.

**Blood Pressure Protocol:**

The BP was measured by a standard protocol and hypertension status confirmed both by clinic measurements and by ambulatory BP monitoring (ABPM) for 24 hours in all children as follows: hypertensive status in the clinic was confirmed in all children at the first visit to the hypertension clinic by averaging the last 3 of 4 BP measurements performed by oscillometric method and confirmed by manual auscultation with a mercury sphygmomanometer by trained personnel using methods recommended by the Fourth Report(1). Hypertension was diagnosed when 3 separate measurements of systolic and/or diastolic BP were recorded >95th% percentile for post-conceptual age, adjusted for height, age and gender per Fourth Report (1) and documented in the medical record. Multiple BP measurements both by cuff and by ABPM were made in a standard manner, thus improving the reliability and validity of the measurements. All children who were above the age of 5 years of age except those admitted with a hypertensive emergency underwent an ABPM using Spacelabs oscillometric monitors (Spacelabs, Inc., Redmond, WA). The children were instructed on avoidance of caffeinated beverages or supplements, any medications, herbal 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. Subjects with 24-hour systolic BP or diastolic BP greater than the pediatric 95th percentile or BP load (percentage of BP values exceeding the 95th percentile for the 24-hour period) greater than 25% were considered to have ambulatory hypertension (15). Both BP and BP load were used to define the severity of ambulatory hypertension. Specifically, more severe ambulatory hypertension was defined as mean systolic or diastolic BP greater than the 95th percentile and BP load greater than 50%. Children with hypertension in clinic but a 24-hour systolic BP and diastolic BP less than the pediatric 95th percentile and BP load less than 25% were considered to have white coat hypertension and were excluded from the study. The BP status of a parent who was not previously diagnosed with EH was evaluated by averaging the last 3 of 4 BP measurements performed by oscillometric method and
confirmed by trained personnel using manual auscultation with a mercury
sphygmomanometer. Parents were labeled as hypertensive if BP was above 140/90 mmHg.
Biological parents previously diagnosed with EH were included as hypertensive.

**Diagnosis of Essential Hypertension:**

Once hypertension was confirmed, all children underwent further evaluation for secondary
hypertension per recommendations by the Fourth Working Group (1). The diagnosis of
primary hypertension or EH in children was made by extensive evaluation per
recommendations by the Fourth Working Group (1) 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 EH were: (a) BP elevation in the clinic 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 less than 5 years old), (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:**

Both treated and un-treated patients seen at the Pediatric Hypertension Clinic that fit the
enrollment criteria were eligible for inclusion in the 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 EH per protocol described above (1) (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 incomplete evaluation of their hypertension or lost to follow-up (f) children
born by donor egg or sperm.

**Recruitment Criteria for Control Population:**

Children who were unrelated to the study population were enrolled into the study. We
recruited the control population from ambulatory pediatric clinics similar to those that
referred the cases. Case matched controls were enrolled during the same time frame from the
general pediatric clinic and underwent the same questionnaires and interview. We matched
the control probands with case probands based on the age (age of control probands matched
to the age of diagnosis of EH in the case probands), gender and ethnicity. Their
normotensive status was confirmed by averaging the last 3 of 4 BP measurements as
described above performed by trained personnel using methods recommended by the Fourth
Report(1). Inclusion criteria were similar to that of the cases in addition to having no prior
history of elevated BP or a diagnosis of hypertension in the child. Exclusion criteria were similar to the cases.

**Demographic and anthropometric data**

All data were collected on all subjects at study entry. After recruitment into the study, each family was evaluated and all information was recorded in a questionnaire along with demographic, socioeconomic and familial factors, including parental education and occupation, family history and co-morbid data. Anthropometric measurements along with BP measurements were made in proband and their parents after enrolment. The age of onset of hypertension, and type of hypertension for each family member was determined by in-person interview of the biological parent along with history of end organ damage such as stroke, congestive heart failure and renal failure. The ethnicity was self-reported and labeled as: whites (non-Hispanic white or European Americans), blacks (African Americans, non-Hispanic blacks), Hispanics, Asians, American Indians, and other. All relevant history, including birth weight, was obtained from the medical records and augmented by an in-person interview of the biological parent. Children with a body mass index between 85th and 95th percentile for children of the same age and gender were classified as overweight (according to the Centers for Disease Control and Prevention growth charts)(16). Those with a body mass above the 95th percentile for children of the same age and gender was classified as obese (according to the Centers for Disease Control and Prevention growth charts)(16). A child, evaluated and diagnosed by a pediatric endocrinologist with type II diabetes, was classified as diabetic (17).

**Exposures:**

At entry into the study, information on exposures were obtained by an in-person interview via a questionnaire, including, socioeconomic (marital status, education, employment status), perinatal (maternal substance abuse, birth weight, birth length), lifestyle (smoking, alcohol) and environmental (lead level, urban) in this study. The biological parents of children who participated in the study provided information regarding the living status and family structure of the proband. At enrollment, we assessed any absent parent within a household via an in-person interview with the biological parent of the child present at the clinic visit. A family history of diabetes, hypertension, stroke, and so on were also obtained. Self-reported exposure to second hand smoking for any period of time after birth was recorded. Also both parental and the proband substance abuse history was obtained. The total duration and the amount of exposures could not be recorded with certainty in this study.

**Statistical Analysis:**

Data from the medical records was abstracted and tabulated. Continuous variables were compared between paired groups using parametric (paired t-tests) and non-parametric (Wilcoxon signed rank tests) tests depending on the distribution of the variable. McNemar and Friedman tests were used to compare paired frequency distributions within categorical variables. All analyses was performed in STATA (v.14, College Station). Statistical significance was assumed at a Type I error rate of 0.05.
Results

We evaluated 423 children in our tertiary pediatric hypertension clinic and diagnosed 275 children with hypertension; further sub-classifying 119 children with EH. Among the 119 children with EH we enrolled 76 children in our study. The remaining 43 of the 119 children with EH were excluded for the following reasons: evaluation pending or lost to follow-up (n = 21), use of foreign language other than Spanish (n = 2), refusal to participate in the study (n = 10), siblings already enrolled (n = 3), adopted (n = 6) and custody issues (n = 1). Among the 76 children with EH, 35 had stage I hypertension and 41 had stage II hypertension on clinic BP measurement. Children (n = 72) who were unrelated to the study population and were normotensive on repeated measures were also enrolled. Thus, a total of 148 children (76 hypertension probands, 72 control probands, males 53%, mean age 12.2 ± 4.3 years, range 1–19 years, median 14 years) were enrolled for this study. Of these 148 children, 51 pairs were matched 1:1 on ethnicity, gender and age (± 2.5 years) and were further evaluated. Demographic data and exposures between the cases and controls are listed in Tables 1 and 2. All baseline measures were similar between cases and controls other than a significantly higher BMI (p = 0.01) and rates of obesity (p= 0.03), and a positive family history of EH (p= 0.05) in cases in comparison to controls. Among discordant pairs, the odds of obesity was 3.5 (95% confidence intervals 1.1 – 14.6) times higher among cases than controls.

Discussion

The epidemiology of childhood-onset EH is not well defined in the current literature. While determining the etiology and risk factors for a disease, both genetic and environmental exposures are studied. Our study indicates the exposures among children with EH and thus provides an epidemiological portrait of the disease in the early stages. The current study has the advantage of having children with EH evaluated in a rigorous manner in a multiethnic population. In our study we enrolled children with confirmed hypertension with their phenotype obtained by a rigorous evaluation, giving a better substrate to understand the beginnings of EH in the humans.

In this study we describe the epidemiological determinants of childhood onset EH. We have previously shown that childhood onset EH can begin as early as 3 years of age, with male gender and black race predominating (8). In this study of age, gender and ethnicity matched cases and controls we have shown that any family history of EH and a higher body weight are also important epidemiological determinants of childhood onset EH.

In our current study we found a higher incidence of any family history of hypertension among children with EH in comparison to children without EH. We have also shown in a previous study that prediction of childhood onset EH and was improved by obtaining history of EH in the biological parents (18). We found that the overall odds of having familial EH (EH in one first degree relative or 2 second degree relatives) was 3 times higher in cases than controls (18). Other studies in the literature also show that any family history of hypertension is associated with more cases of childhood-onset EH in comparison to children with secondary hypertension (19, 20). In our previous studies, when compared to children
with secondary hypertension, children with EH had a stronger family history of hypertension (94% vs. 68%, p < 0.0001) (8).

In our current study with matched controls, we found a significantly higher number of obese children in the EH cohort in comparison to the normotensive cohort. We found that the odds of obesity was 3.5 times higher among children with EH in comparison to children without EH.

Similarly the BMI was significantly higher among children with EH in comparison to normotensive children. Other studies have also linked increase in body weight with childhood EH (7, 20, 21). An increasing body weight has been found to be associated with hypertension among children (22).

In this study we were able to describe the contribution of both environmental and genetic exposures in childhood onset EH. While both genetic and environmental exposures can give rise to a disease, our study indicates a lower contribution from a variety of childhood exposures to EH phenotype in childhood. We evaluated a variety of the prenatal and postnatal exposures that may be associated with elevated BP and did not find any difference in exposures between children with and without EH. We evaluated the genetic predisposition (family history of EH and comorbid conditions) and a variety of exposures including, parental socioeconomic (parental marital and employment status), perinatal exposures (maternal factors, birth weight, birth length), lifestyle (smoking, alcohol) and environmental exposures (lead level, urban) in children with and without EH. We did not find any difference between rural and urban status between cases with early development of EH and the controls. We did not find any difference in socioeconomic factors such a single parent status, parental marital status, and parental employment status between children with and without EH. Socioeconomic stressors have been found to play a role in adult-onset EH, however, we did not find it to play as big a role in childhood-onset EH in this study or in a previous study (23). Thus, the findings of this study indicate important epidemiological risk factors associated with childhood onset EH.

The limitations of the study include a small number of children enrolled and thus we recommend a larger study to confirm our findings. Although majority of the information for this study was obtained from the electronic medical records and direct blood pressure measurements, there were some aspects of patient and family data that were obtained by in-person interview and may be subject to a recall bias.

Conclusions

In this study we determined the epidemiological risk profile in children with EH by evaluating a variety of prenatal and postnatal exposures that could potentially contributed to the EH phenotype in childhood. The findings of the study elucidate the epidemiology of EH in children and two important associated risk factors, any family history of hypertension and a higher body weight. Our findings provide tools for screening of children for the development of chronic hypertension. It also indicates a higher genetic and less contribution from childhood exposures to the early EH phenotype in childhood.
Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We would like to thank Dr. Sanjay Shete, Dr. Michelle S. Barratt, Dr. Dianna Milewicz, Dr. Jon Tyson, Dr. Eric Boerwinkle and Dr. Jacqueline Hecht for mentorship of Dr. Monesha Gupta during her career development award by the National Institutes of Health. We would also like to thank the families who agreed to participate in this study.

Funding

The project described was supported by Grant Number K23HL089391 for “Determination of genetics of childhood onset hypertension” (PI Monesha Gupta) from the National Heart, Lung, And Blood Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, And Blood Institute or the National Institutes of Health.

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Table 1.
Characteristics of children diagnosed with essential hypertension (EH) and 1:1 age, ethnicity and gender-matched controls, n = 51 pairs

|                          | EH * | Controls * | p-values |
|--------------------------|------|------------|----------|
| Total                    | 51 (100) |           |          |
| Male gender              | 21 (51) |           |          |
| Ethnicity                |       |            |          |
| NHW                      | 9 (18) | 9 (18)     |          |
| Hispanic                 | 13 (25) | 13 (25)    |          |
| Black                    | 28 (55) | 28 (55)    |          |
| Other                    | 1 (2)  | 1 (2)      |          |
| Resident in urban setting| 40 (78) | 43 (84)    | 0.593    |
| Age, mean (SD) †**       | 11.9 (3.2) | 12.1 (3.4) | 0.146    |
| Birth parameters         |       |            |          |
| Height, cm, median (IQR)*** | 48.3 (45.7 – 51.0) | 48.3 (45.7 – 53.3) | 0.625    |
| Weight, kg, median (IQR)*** | 3.2 (2.8 – 3.7) | 3.3 (2.8 – 3.8) | 0.901    |
| Prenatal proband exposures†† |       |            |          |
| Maternal smoking during pregnancy | 10 (20) | 8 (16) | 0.405    |
| Maternal hypertension   | 15 (29) | 12 (24)    | 0.251    |
| Maternal diabetes       | 3 (6)  | 4 (8)      | 0.564    |
| Postnatal proband exposures†† |       |            |          |
| Post-natal lead exposure | 2 (4)  | 0 (0)      | 0.157    |
| Post-natal smoke exposure| 12 (24) | 11 (22)    | 0.819    |
| Alcohol consumption by child | 3 (6)  | 1 (2)      | 0.317    |
| Comorbid Conditions †|       |            |          |
| Type II Diabetes        | 1 (2)  | 0 (0)      | 0.317    |
| BMI, median (IQR)       | 19.5 (15.3 – 28.0) | 16.6 (11.27 – 24.8) | 0.019    |
| Obese, n (%)            | 21 (41) | 11 (22)    | 0.031    |

* Data are frequency (percentage) unless noted
** SD: standard deviation; IQR: interquartile range
† Age at diagnosis for cases and at enrollment for controls
†† All non-birth and non-prenatal measures were at time of enrollment for controls
## Table 2.
Familial and socioeconomic characteristics of children diagnosed with essential hypertension (EH) and 1:1 age, ethnicity and gender-matched controls, n = 51 pairs

| Living arrangements           | EH          | controls    | p-values |
|-------------------------------|-------------|-------------|----------|
| Both parents                  | 24 (74)     | 26 (51)     | 0.575    |
| Single parent                 | 27 (53)     | 24 (47)     |          |
| Other/missing                 | 0 (0)       | 1 (2)       |          |

| Family member * with history of | EH          | controls    | p-values |
|--------------------------------|-------------|-------------|----------|
| Hypertension                   | 46 (90)     | 42 (82)     | 0.058    |
| Diabetes (Type II)             | 24 (47)     | 28 (55)     | 0.433    |
| Hypercholesterolemia           | 26 (51)     | 22 (43)     | 0.317    |
| Myocardial infarction          | 21 (41)     | 14 (27)     | 0.433    |
| Stroke                         | 19 (37)     | 12 (24)     | 0.127    |
| Kidney disease / dialysis      | 9 (18)      | 5 (10)      | 0.132    |
| Aneurysm                       | 3 (6)       | 2 (4)       | 0.655    |

### Paternal characteristics **

| Education                      | EH          | controls    | p-values |
|--------------------------------|-------------|-------------|----------|
| Less than high school          | 16 (32)     | 6 (12)      | 0.050    |
| High School (or equivalent)    | 21 (41)     | 25 (49)     |          |
| Some college or higher         | 14 (27)     | 20 (39)     |          |
| Employed (full- or part-time)  | 30 (65)     | 37 (74)     | 0.197    |

### Maternal characteristics **

| Education                      | EH          | controls    | p-values |
|--------------------------------|-------------|-------------|----------|
| Less than high school          | 8 (16)      | 7 (14)      | 0.779    |
| High School (or equivalent)    | 13 (25)     | 14 (27)     |          |
| Some college or higher         | 30 (58)     | 30 (59)     |          |
| Employed (full- or part-time)  | 35 (69)     | 33 (65)     | 0.251    |
| In single parent (mom) household | 8 (67)     | 8 (67)      | 0.687    |

Data are frequency (percentage)

* Family member is any first or second degree relative

** Data missing for paternal (n=3) and maternal (n=2) characteristics