Significance of Heritability in Primary and Secondary Pediatric Hypertension

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Background: Patient weight and family history are significant risk factors for the development of hypertension in children. Multiple genetic factors have been identified in primary (essential) hypertension in adults; however, the delineation of genetic factors in the separate populations of children with primary or secondary hypertension are not well understood. Heritability is the proportion of observed variation in a particular trait that can be attributed to an inherited genetic factor in contrast to environmental factors. In the consideration of hypertension, heritability can be assessed in terms of an underlying continuous gradient of the liability for developing hypertension. With this assumption it is possible to compute heritability using hypertension incidence among relatives as described by Falconer. Heritability values range from 0 (no genetic contribution) to 1 (complete genetic contribution). The aim of this study was to determine the genetic contribution to primary and secondary hypertension in a pediatric population through heritability analysis.

Methods: This was a retrospective case-control analysis of medical records of children (n=276) followed in the Pediatric Nephrology Clinic over a 4-year period from 1999 to 2002. There were 192 children and adolescents with primary hypertension (124 male, 68 female, age 0 to 21 years) and 84 children and adolescents with secondary hypertension (46 male, 38 female, age 0 to 21 years). Each hypertensive group served as the control for the other. Estimates of heritability were made using Falconer’s method. The model assumes independence between the environment and genetic factors and that the joint distribution of liabilities between parent and child are normally distributed. Problems can arise from computing heritability due to dominance within loci, correlations between nongenetic familial effects, or the presence of a major gene.

Results: Of the children and adolescents with primary hypertension, 49% had parents with primary hypertension; and of the children and adolescents with secondary hypertension, 24% had parents with primary hypertension. Of the children and adolescents with primary hypertension, 10% had parents with secondary hypertension; and of the children and adolescents with secondary hypertension, 46% had parents with secondary hypertension. The estimated heritability for primary hypertension was 0.84 (SE=0.21). The estimated heritability for secondary hypertension was 1.14 (SE=0.21). As the value was >1, this indicates that the fit of the liability model is poor and that a few genes, or even one major gene, were significantly involved in the causes of secondary hypertension in the children and adolescents studied.

Conclusions: The results suggest that primary and secondary hypertension do not share the same type of genetic profile. Primary hypertension in children and adolescents is likely due to a large number of additive contributions of genes, although a highly correlated environmental component can not be excluded. The continuous liability model is inappropriate for secondary hypertension because the estimate was substantially greater than one. This study supports the model that secondary hypertension in children and adolescents may be related to just a few genes. Am J Hypertens 2005;18:917–921 © 2005 American Journal of Hypertension, Ltd.

Key Words: Pediatrics, hypertension, heritability.
lungs, central nervous system, endocrine system, and vascular system. Increased awareness and focus on hypertension has led to identification of modifiable factors (such as diet, physical activity, body weight, blood glucose) and nonmodifiable variables (such as age, ethnicity, genetics, and gender) in the adult population.\(^3\)–\(^6\) In children and adolescents, body size (height and weight), gender, and age are important determinants of blood pressure (BP).\(^7\) Body mass index (BMI) has been used as an assessment tool for obesity and more recently as a monitoring parameter for hypertension in adults; however, until recently a consensus was not established for normal BMI values in children and adolescents, and the use of BMI as an indicator in pediatric hypertension was not evaluated.\(^8\)

Increased recognition of pediatric hypertension in recent years has led to renewed focus on the etiology, identification, prevention, and management of hypertension in children and adolescents.\(^7\)–\(^9\) A number of factors associated with primary hypertension in adults have been shown to contribute to elevated BP in pediatric patients. Patient weight and family history are significant risk factors for the development of hypertension in children. Multiple genetic factors have been identified in primary hypertension in adults; however, the delineation of genetic factors in the separate populations of primary and secondary hypertension in children and adolescents are not well understood.

Heritability is the proportion of observed variation in a particular trait that can be attributed to genetic factors in contrast to environmental factors. Heritability is estimated from the correlation among relatives. The degree of heritability in the etiology of a disease assumes an underlying continuous gradient of liability, which is a result of the accumulation of the additive contribution of many genes. The concept has been expanded by Falconer\(^11\) to suggest a latent cutoff point on the gradient of liability above which the disease manifests itself sufficiently to be diagnosed and below which it is not. With this assumption it is possible to compute the association, heritability, using hypertension incidence among relatives. The objective of this study was to determine the genetic contribution to primary and secondary hypertension in a pediatric population through a heritability analysis.

**Methods**

A retrospective, case-control analysis of medical records of children and adolescents with primary and secondary hypertension (n = 276) followed in Pediatric Nephrology Clinic over a 4-year period from 1999 to 2002 was conducted. Demographic data, including height, body weight, age, ethnicity, and gender of the child were collected. Family history of hypertension or renal disease, suspected etiology of hypertension, presentation of disease (e.g., headache, dizziness), date of diagnosis, medication doses, regimen duration, and date of initiation of drug therapy were also obtained. Each hypertensive group served as the control for the other group.

For a qualitative trait, heritability is defined as the proportion of variation attributable to genetic factors. Heritability (h\(^2\)) equals 2 times the slope of relatives’ trait of interest regressed on the target patient (propositi) trait of interest when the relatives are full siblings, parents, or children. When the trait is discrete as in the case of the diagnosis of primary or secondary hypertension, then an assumption is made that there is an underlying continuous distribution of the risk (liability) of developing hypertension. Falconer has proposed a method of estimating heritability with incidence data.\(^11\) Figure 1, based on the work of Falconer, illustrates the relationship between the liability distributions of the general population and the relatives of the affected population. The regression, b, is defined as:

\[
b = (R - G)/(A - G) = (x_g - x_r)/a
\]

G is the mean liability of the general population, A is the mean liability of affected individuals within the general
population, and R is the mean liability of the relatives of the affected patients. The difference between the mean of the general population (G) and the mean of the relatives of the affected population (R) is the impact of the genetic relationship. The difference between the mean liability of the general population (G) and the mean liability of those individuals within the general population that are affected (A) provides a scale for the magnitude of the impact. The ratio of the two differences is the regression (b) of the relative’s degree of liability on the degree of liability of an individual from the general population. Heritability ($h^2$) is 2 times the slope (b) when the relatives are full siblings, parents, or children. The complete calculation is described in the Appendix.

In this retrospective study, relatives of secondary hypertension patients served as general population controls to the relatives of patients affected with primary hypertension, and the relatives of primary hypertension patients served as the general population for the relatives of patients affected with secondary hypertension. This approach was taken because it was assumed primary and secondary hypertension are independent, the patients are served by the same clinic and thus the demographics are similar and the family history forms are identical. Each patient contributed one observation to the analysis in which any parent or full sibling either was or was not affected.

### Results

The medical records of 192 children and adolescents with primary hypertension (124 male, 68 female, age 0 to 21 years) and 84 children and adolescents with secondary hypertension (46 male, 38 female, age 0 to 21 years) were reviewed.

#### Heritability of Primary Hypertension

Of the patients with primary hypertension, 49% had relatives with primary hypertension compared to 24% of the control patients with primary hypertension.

As shown in Fig. 1, the value of $x_g$ is 0.71. Thus, it is assumed that when individuals in the general population with an underlying primary hypertension liability scale value that is $>0.71$ standard units, they will be diagnosed with primary hypertension. The incidence of primary hypertension among relatives of children and adolescents with primary hypertension was 49%, so the threshold cut at the standard score of 0.025 point on the normal distribution. The estimated heritability for primary hypertension was 0.80 (SE = 0.19). The heritability index suggests that 80% of the variance of liability of primary hypertension is attributed to additive genetic factors. Heritability of primary and secondary hypertension, based on family histories of the affected patients, is shown in Table 1.

#### Heritability of Secondary Hypertension

Of the patients with secondary hypertension, 46% had at least one relative with secondary hypertension, and of the patients with primary hypertension 10% had at least one relative with secondary hypertension. The estimated heritability for secondary hypertension was 1.36 (SE = 0.17). The computed value $>1$ suggests that an underlying liability scale of a continuous variable is not appropriate for these data. The liability model assumes the additive effects of a large number of genes. The failure of this assumption suggests that possibly a few genes or even one major gene are significantly involved in the causes of secondary hypertension in pediatric populations.

#### Discussion

In children, BP values are significant predictors of future BP rank and appear to be maintained throughout adolescence and early adulthood. The tracking of BP measurements does not appear to differ between obese and normal-weight adolescents; however, the onset of puberty, sexual maturation, and subsequent change in height and weight appear to influence the extent and rapidity of increase in BP. Although the immediate risk associated with hypertension in childhood is small, evidence of cardiovascular and hemodynamic changes consistent with sustained hypertension have been documented in early adulthood. Children and adolescents with serial and isolated elevated BP values ($>95$th percentile based on height, weight, and age) are more likely to develop high BP as adolescents and adults. Therefore, early identi-

### Table 1. Heritability of primary and secondary hypertension from the family history of the affected patients

<table>
<thead>
<tr>
<th>Family History of Hypertension</th>
<th>Primary Hypertension Heritability $h^2 = 0.80$ (SE = 0.19)</th>
<th>Secondary Hypertension Heritability $h^2 = 1.36$ (SE = 0.17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Secondary Hypertension</td>
<td>Primary Hypertension</td>
</tr>
<tr>
<td></td>
<td>Relatives</td>
<td>Primary Hypertension Relatives</td>
</tr>
<tr>
<td>No</td>
<td>64</td>
<td>98</td>
</tr>
<tr>
<td>Yes</td>
<td>20</td>
<td>94</td>
</tr>
<tr>
<td>Total</td>
<td>84</td>
<td>192</td>
</tr>
</tbody>
</table>

Note: Relatives of the secondary hypertension patients serve as representatives of the general population when calculating heritability of primary hypertension. Relatives of the primary hypertension patients serve as representatives of the general population when calculating heritability of secondary hypertension.
fication of populations at increased risk may be important to allow methods for early intervention designed to decrease end-organ damage in children and young adults.

There is strong evidence for the genetic basis for both essential and secondary hypertension and the genetic link between obesity and hypertension in adults.16–19 Heritability is believed to be between 30% and 50% for essential hypertension and up to 70% in hypertensive siblings.19,20 In our study we found that heritability was 80% for primary hypertension. Of the children and adolescents with primary hypertension, 49% had at least one parent with primary hypertension.

A similar number of parents of secondary hypertensive children and adolescents (46%) had secondary hypertension. The estimate of heritability of the children and adolescents with secondary hypertension was >1. Heritability represents a proportion of variance and cannot be >1, and thus this result indicates problems with applying the heritability analysis to this population. Problems in estimating heritability may be due to dominance within a loci and to correlations between the environment and genetic factors. The genetic component and environmental components are assumed to be independent. Failure to meet this assumption could also result in an overestimation of the genetic component.

In conclusion, the results suggest that the genetic contribution to hypertension is different for primary and secondary hypertension. Primary hypertension may be due to a large number of additive contributions of genes, although a highly correlated environmental component cannot be excluded. The continuous liability model is inappropriate for secondary hypertension because the estimate was substantially >1, suggesting that secondary hypertension in children and adolescents may be related to just a few genes.

Family history patterns can provide an initial estimation of genetic contribution and can offer insights for more detailed assessment of genetic patterns of diseases such as hypertension. Family history patterns are only the start to genetic understanding, however; more detailed genetic studies of hypertension in children and adolescents should prove valuable in defining populations amenable to intervention strategies.

References


Appendix. Complete heritability calculation

<table>
<thead>
<tr>
<th>Family History of Hypertension</th>
<th>Control</th>
<th>Affected</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>na</td>
<td>nb</td>
<td>na + nb</td>
</tr>
<tr>
<td>Yes</td>
<td>nc</td>
<td>nd</td>
<td>nc + nd</td>
</tr>
<tr>
<td></td>
<td>na + nc</td>
<td>nb + nd</td>
<td>nc + nd</td>
</tr>
</tbody>
</table>
qg = nc/(na + nc) = proportion of control patients with a family history of the disease
qa = nd/(nb + nd) = proportion of affected patients with a family history of the disease
pg = 1 - qg
pa = 1 - qa
xg = cutoff standard score for the proportion of the normal curve, qg. Norminv(qg) is a function that returns a standard score from a normal distribution with mean = 0 and SD = 1 given the P value.
a = Cutoff standard score for the proportion of the normal curve, qa. Norminv(qa).
a = Standard score at the point where z (from Fig. 1) is the mean of the area represented by qa; Norminv(1 - (.0039qg^2 + .067qg^3 + .3903 qa - .00003)). The area under the curve at the point where the height is z is not readily available from tables. The following curve is an approximation of the cumulative probability at that point.
b = slope = pg * (xg - xg)/a
h^2 = 2b.
To calculate the standard error of h^2
apg = a (pg - qa)/qa
Wg = pg/a_p_g^2 * nc
Wa = pg/a_w_a^2 * nd
Variance(h^2) = (pg/a_g - b * (apg - xg))^2 * W_g + (pg/a_p_g^2 + W_a
se (h^2) = 2 * Variance^{1/2}
An Excel spreadsheet of the above formula is available from the author.