Association of Blood Groups with Essential and Secondary Hypertension

A Possible Association of the MNS System

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SUMMARY Persons participating in a 5-day diagnostic protocol were routinely typed for ABO, Rh, MNS, Kell, Kidd, Duffy, P, Haptoglobin, phosphoglucomutase-1 (PGM-1), and acid phosphatase (AcP). The study population was composed of 164 normotensive whites, 34 normotensive blacks, 161 whites and 43 blacks with essential hypertension, and 52 whites with secondary forms of hypertension (18 atherosclerotic renovascular hypertensives, 17 patients with fibromuscular disease, and 17 patients with primary aldosteronism). There were no significant differences in phenotype frequencies in ABO, Rh, Kidd, Duffy, P, Haptoglobin, PGM-1 or AcP in any of the comparisons. However, there was a significantly different distribution of MNS phenotypes in comparisons of essential and atherosclerotic renovascular hypertensives with normotensive controls. Essential hypertensives had a lower frequency of the S gene and a higher frequency of s in whites ($X^2 = 12.21, p < 0.005$). Atherosclerotic renovascular hypertensives differed from the normotensive population in the frequencies of both MN ($X^2 = 4.34, p < 0.05$) and Ss ($X^2 = 4.21, p < 0.05$). The finding of disease-blood group associations supports the hypothesis that there may be significant physiological differences between individuals of different blood types. (Hypertension 1: 493–497, 1979)

Key Words • hypertension • blood group • disease-blood group association • MNS system

The importance of genetic factors in familial aggregation of blood pressure level has been shown repeatedly. We have previously reported evidence for genetic mediation of components of the blood pressure control system. Previous investigators have reported higher diastolic pressures in subjects with blood group O than in their siblings with other ABO blood types from a study of 5777 members of 1068 Brazilian families. A population study of Easter Islanders migrating to Chile on the South American continent reported that the MN system may influence the development of increased diastolic blood pressure attributable to the environmental changes, with NN genotypes showing the greatest blood pressure increase. The gene frequencies were not different in the continental and island populations, so the results could not be attributed to selective migration. Their results showed an increased variance in diastolic blood pressure in the Easter Islanders when they migrated to the continent with blood pressures of the two homozygous (MM and NN) groups reacting in opposite ways. As with previous population surveys, secondary causes of hypertension were not investigated in either of these studies.

The purposes of the present investigation were to extend previous observations in order: 1) to investigate...
whether there were indeed differences in the frequencies of genotypes between essential hypertensive and normotensive subjects, and 2) to determine if patients with secondary forms of hypertension differed from patients with essential hypertension or from normotensive control subjects in the frequency of one or more genetic markers.

Methods

Diagnostic Protocol

All subjects participated in a 5-day diagnostic protocol at the Indiana University Hospital. The primary purpose of the study was to measure blood pressure, natriuretic, kaliuretic and humoral responses following volume expansion and contraction in normotensive and hypertensive subjects. Normal subjects were studied at the Clinical Research Center. This protocol has been described in detail elsewhere. The research protocol was approved by the Indiana University Committee for the Protection of Human Subjects and informed consent was obtained. Hypertensive patients had renal arteriography and their renin-aldosterone status determined. Briefly, on the day following the hospital admission day, subjects ate ad libitum and control blood and urine samples were obtained for electrolytes, renin, aldosterone and norepinephrine determination. Blood samples were obtained on this day for genotyping. On the third day subjects received a 2-liter saline infusion. On the following day subjects received a salt restricted diet and 40 mg of furosemide in three oral doses. Before discharge on the final day blood samples were obtained. Blood pressure was taken four times each day in both the recumbent and upright positions. Systolic and diastolic blood pressure for each day represents the average of these eight readings.

Population

The individuals classified as normotensive showed no evidence of elevated blood pressure throughout the study. This population consisted of black and white individual recruited by news media publicity and 30 like-sex white twin pairs who participated as part of other related studies; all were paid for their participation. There were 36 normotensive blacks and 164 normotensive whites. Analyses using only one member of each twin pair were not different from those in which both members were included. Hypertensive subjects were referred to the Indiana University Medical Center for evaluation of their elevated blood pressure by their primary care physician. The diagnosis of essential hypertension was made on the basis of evidence from the protocol described where secondary forms of hypertension could be ruled out. There were 43 black and 161 white essential hypertensives. The diagnosis of renovascular hypertension was made if a stenotic lesion was found on arteriography and renal vein renins were significantly greater on the side of the stenosis. The classification of atherosclerotic or fibromuscular etiology was based on angiographic evidence and/or on tissue obtained at surgery. Primary aldosteronism was diagnosed if the patient exhibited low plasma renin levels and nonsuppressible plasma aldosterone.

The study population included 18 atherosclerotic renovascular hypertensives, 17 patients with fibromuscular disease, and 17 patients with primary aldosteronism.

Blood Typing Techniques

All persons were routinely typed for ABO, Rh, MNS, Kell, Kidd, Duffy, P, Haptoglobin, Phosphoglucomutase-1 (PGM-1), and acid phosphatase (AcP) systems. All genotyping was performed in the laboratories of the Department of Medical Genetics at the Indiana University Medical Center. Serotyping was performed using standard techniques. Other systems were typed using standard electrophoretic techniques.

Data Analysis

The typing results were converted to a numerical code and stored on the PDP-11 in the Department of Medical Genetics. Data analysis was performed using Statistical Package for the Social Sciences on the CDC 6600 computer.

Patients were classified by diagnosis and all analyses were performed separately by race; however, there was an insufficient number of blacks with secondary forms of hypertension, thus only blacks with essential hypertension are reported here. Gene frequencies were calculated using methods described by Cavalli-Sforza and Bodmer.

Results

There were no significant differences in phenotype frequencies in ABO, Rh, Kidd, Kell, Duffy, P, haptoglobin, PGM-1 or acid phosphatase systems in comparisons of essential hypertensives, renovascular hypertensives and patients with primary aldosteronism with normotensive controls. In addition, essential hypertensives did not differ from individuals with secondary forms of hypertension in any of these genetic markers. However, there were significant differences detected in the MNS system in comparing the normal group with essential and atherosclerotic renovascular hypertensive groups.

Tables 1 and 2 report the frequencies of the MNS phenotypes in the essential hypertensives and their controls in the black and white populations. As can be seen, essential hypertensives were significantly different from controls in the distribution of the MNS phenotypes in whites (p < 0.03). A similar difference was not seen in blacks, possibly due to the smaller sample size. In addition to the S and s alleles found in whites, a third allele referred to as Null occurs in the black population. Its occurrence can be inferred only in the absence of the other types. Only one person was homozygous from the Null allele in the black population. In table 1 individuals with hypertension due to atherosclerotic renovascular disease appear to differ in
TABLE 1. Comparison of MNS Phenotype Frequencies in Caucasians

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Normotensive controls</th>
<th>Essential hypertensives</th>
<th>Atherosclerotic renovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>MS</td>
<td>11</td>
<td>6.7</td>
<td>5</td>
</tr>
<tr>
<td>MSs</td>
<td>35</td>
<td>21.3</td>
<td>17</td>
</tr>
<tr>
<td>Ms</td>
<td>11</td>
<td>6.7</td>
<td>21</td>
</tr>
<tr>
<td>MNS</td>
<td>2</td>
<td>1.2</td>
<td>5</td>
</tr>
<tr>
<td>MNSs</td>
<td>44</td>
<td>26.8</td>
<td>35</td>
</tr>
<tr>
<td>MNSs</td>
<td>34</td>
<td>20.7</td>
<td>47</td>
</tr>
<tr>
<td>NS</td>
<td>1</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>NSs</td>
<td>7</td>
<td>4.3</td>
<td>9</td>
</tr>
<tr>
<td>Ns</td>
<td>19</td>
<td>11.6</td>
<td>22</td>
</tr>
</tbody>
</table>

\[X^2 = 17.4\]
\[df = 8\]
\[p < 0.03\]

TABLE 2. Comparison of MNS Phenotype Frequencies in Blacks

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Normotensive controls</th>
<th>Essential hypertensives</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Percent</td>
</tr>
<tr>
<td>MS</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MSs</td>
<td>3</td>
<td>8.3</td>
</tr>
<tr>
<td>Ms</td>
<td>5</td>
<td>13.9</td>
</tr>
<tr>
<td>MNS</td>
<td>2</td>
<td>5.6</td>
</tr>
<tr>
<td>MNSs</td>
<td>6</td>
<td>16.7</td>
</tr>
<tr>
<td>MNSs</td>
<td>12</td>
<td>33.3</td>
</tr>
<tr>
<td>NS</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>NSs</td>
<td>3</td>
<td>8.3</td>
</tr>
<tr>
<td>Ns</td>
<td>4</td>
<td>11.1</td>
</tr>
<tr>
<td>M*</td>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>N*</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\[X^2 = 8.21\]
\[df = 8\]
\[p > 0.10\]

*Persons with these phenotypes would be homozygous for the Null allele of the Ss system.

Table 3 presents the gene frequencies in each of the groups. The four antigens are controlled by two sets of alleles at closely linked loci, and crossing over has been reported only rarely. In this table the gene frequencies for the two systems are reported separately. Atherosclerotic renovascular hypertensives differ from the normotensive population in the frequencies of both MN (\(\chi^2 = 4.34, p < 0.05\)) and Ss (\(\chi^2 = 4.21, p < 0.05\)) genes. Essential hypertensives had a relatively lower frequency of the S gene and higher frequency of the s in the whites (\(\chi^2 = 12.21, p < 0.005\)) when compared to the normotensive population. Similar comparisons were not possible for the black population, because the gene frequencies were calculated differently for the two populations. This was due to the fact that there were no black essentials homozygous for the Null allele necessitating the use of different estimates of the gene frequencies in the Ss system. Other secondary hypertensive subgroups did not differ from the control population in gene frequencies.

Analysis of variance grouping both normotensive and essential hypertensive subjects according to phenotype (MM, MN, NN and SS, Ss, ss) failed to

TABLE 3. Comparisons of Gene Frequencies

<table>
<thead>
<tr>
<th>Marker</th>
<th>Whites</th>
<th>Normals</th>
<th>Essentials</th>
<th>Atherosclerotic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Normals</td>
</tr>
<tr>
<td>M</td>
<td>0.59</td>
<td>0.54</td>
<td>0.41</td>
<td>0.53</td>
</tr>
<tr>
<td>N</td>
<td>0.41</td>
<td>0.46</td>
<td>0.58</td>
<td>0.47</td>
</tr>
<tr>
<td>S</td>
<td>0.34</td>
<td>0.25</td>
<td>0.18</td>
<td>0.13</td>
</tr>
<tr>
<td>s</td>
<td>0.65</td>
<td>0.75</td>
<td>0.82</td>
<td>0.84</td>
</tr>
<tr>
<td>Null</td>
<td></td>
<td></td>
<td></td>
<td>0.22</td>
</tr>
</tbody>
</table>

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reveal any effect of phenotype on average systolic and
diastolic blood pressure throughout the diagnostic
protocol in the white and black populations. In black
hypertensives analysis of variance yielded some indi-
cations that the MN group had lower average
pressures than the homozygotic groups but the mean
values were not different between groups.

The reader should be cautioned that a very large
number of statistical comparisons have been made in
the present investigation and the majority failed to
show statistical significance. As the number of tests
performed increases so does the possibility that one
will obtain a “significant” result by chance alone.

Discussion

Investigators using the described diagnostic
protocol have shown that normotensive first degree
relatives of essential hypertensives have significantly
higher blood pressure (p < 0.05) and significantly
higher plasma renin activity before and after a saline
infusion (p < 0.05) than age-race-sex matched con-
trols.13 Hereditary influences on blood pressure con-
motion mechanisms have been demonstrated under con-
ditions of volume expansion and contraction.14 The
excretion of sodium and potassium following a saline
infusion yielded evidence of significant genetic
variance and plasma renin and aldosterone levels
sampled with the patient in a recumbent state
appeared to be heritable. In addition, studies of nor-
motensive black and white subjects revealed that
blacks and individuals greater than 40 years of age ex-
crated less sodium following a saline infusion than
whites or subjects less than 40 years of age.15 Taken
together these studies indicate that there may be im-
portant physiological differences in individuals
predisposed to become hypertensive compared to nor-
motensive individuals and that such differences may
be under genetic influence. For these reasons, we
investigated the possibility that association of specific
genotypes with characterized forms of hypertension
would provide an additional insight into genetic
mediation of abnormalities of the blood pressure con-

The practice of searching for disease-blood group
association has often been criticized.16 This is because
studies on different populations have often failed to
confirm initial reports. It is likely that such inconsis-
tencies are due to vastly different environments in
study populations. Increases in blood pressure have
been shown to be related to the level of acculturation
and dietary differences in primitive people.17 Changes
in blood pressure have been observed in children sub-
jected to marked environmental changes.18 Dietary
factors, particularly sodium and potassium, have been
implicated in human hypertension.19 It is likely that
the discovery of blood group association may be
dependent on both the population under investigation
and its environment; in the case of hypertension, par-
ticularly dietary habits.

One of the best established blood group associations
is that between blood type O of the ABO system and
duodenal ulceration,20 although even this has not been
confirmed in every investigation.18 The importance of
the gene-environment interaction in disease develop-
ment is unknown, but it may be responsible for the
familial aggregation of apparent nongenetic disorders.
This is confounded by the fact that families share both
genesis and household environments. It is possible that
it is not the presence of a given blood type but rather
the absence of the protective effect of other alleles that
is responsible for disease development. It is beyond
the nature of the current investigation to discriminate
between these alternative hypotheses.

Although numerous studies have revealed genetic
influences on blood pressures, only recently have
genetic influences on physiological mediators been
defined and genetic markers have not been identified.14
The Brazilian study demonstrated an average increase
of 1.7 mm Hg in diastolic blood pressure of persons
with blood group O compared to their siblings with
other blood types.2 The present investigation failed to
demonstrate any association of blood group O with in-
creased blood pressure as reflected in the occurrence of
essential hypertension, nor were there seen quanti-
tative differences in blood pressure among groups.

The current study population is quite different from
that of Nance et al.6 In contrast to their very large rural
population with inadequate medical care, the
current investigation contains both rural and urban
populations with above average medical care.

In 1964, Cruz-Coke et al.6 reported that changes in
blood pressure that occurred in Easter Islanders who
migrated behaved differently in subjects differing in
the MN system. Under the influence of the new en-
vironment, genotypes MM and NN reacted in op-
posite ways, and further analysis of the phenotypic
variation of blood pressure indicated that a substantial
portion (0.246) could be attributed to the effects of
these genes. These findings are not reinforced by the
present investigation, with the exception of individuals
with atherosclerotic renovascular disease. In this case,
there is a reversal of the expected frequencies of the M
and N alleles. One might hypothesize the occurrence
of a gene-environment interaction in the development
of this disease.

Recent investigations of the complement system in
Denmark have shown an association of the C3\textsuperscript{a}-gene
and the occurrence of atherosclerosis.21,22 In addition,
it was found that among treated hypertensive patients
those with C3\textsuperscript{a}-gene showed approximately a sixfold
increase in the incidence of coronary heart disease
over those without it. The authors interpret these find-
ings as indicating that the C3\textsuperscript{a}-allele does not play a
role in the etiology of hypertension, but that its
presence might accelerate the atherosclerotic process.
It has also been hypothesized that human vascular dis-
 ease may be related to other immunological pathways
that are influenced by other risk factors, such as diet
and smoking.20 Such a hypothesis could explain the
different reactions of individuals with different anti-
gen in vastly different environmental conditions.

The observation of the marked changes in the fre-
quency of the S gene is unique to the present investiga-
tion. Nance et al. failed to observe any association of the MNS system and blood pressure level and the Ss typings were not performed in the investigation by Cruz-Coke et al. This may reflect an effect of this blood system on the development of essential hypertension in the study population.

The finding of disease-blood group associations emphasizes the fact that there may be significant physiological differences between individuals of different blood types. They may be of clinical interest and help in understanding the interactions of many of the factors affecting the diseases involved. It is unlikely that there exists any selective advantage, however, since most of the diseases involved exhibit their major effects at the end of the reproductive period.

Acknowledgments

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