Serum Immunoglobulins in Hypertension

E. Victor Adlin, M.D., Jesus Moctezuma, M.D., Allan D. Marks, M.D., and Bertram J. Channick, M.D.

SUMMARY We measured serum immunoglobulins in 52 persons whose blood pressure was higher than 140/90 mm Hg, and 52 normotensive controls matched for age, sex and race. All were selected from a population of actively employed persons undergoing a routine health evaluation. Contrary to previous reports, the hypertensive subjects did not have higher levels of IgG or IgA than the controls. Sixteen hypertensive subjects with mean blood pressure higher than 115 mm Hg did not have elevated IgG or IgA levels when analyzed separately. Serum IgM was significantly lower in the 52 hypertensive subjects (125 ± 67 mg/dl vs 171 ± 85 mg/dl, p < 0.01).

Our subjects failed to show the increase in immunoglobulins reported by others. The most likely reason for this is the mildness of their blood pressure elevation, although the absence of immunoglobulin elevation in the small number with more marked hypertension does not support this explanation. (Hypertension 1: 650-653, 1979)

KEY WORDS • serum immunoglobulins • IgG • IgA • IgM • hypertension

Several investigators have reported that serum immunoglobulins are elevated in patients with hypertension. In 1970 Ebringer and Doyle studied 118 patients with severe hypertension and found IgG levels of 1568 mg/100 ml, compared to 1259 mg/100 ml in 163 normotensive blood donors. Olsen et al. reported that 25 of 84 hypertensive patients had increased levels of either IgG, IgA, or IgM. More recently, Kristensen has described his findings in 164 patients with essential hypertension, in whom both IgG and IgA were elevated when compared to normotensive controls.

The reason for the observed increase in serum immunoglobulin levels in hypertension is not known. Ebringer and Doyle proposed that vascular damage resulting from increased arterial pressure may lead to the release of tissue components that act as antigens. Formation of antibodies against these components of the injured vessels may then be reflected in raised levels of immunoglobulins. An alternative explanation is that immunoglobulin abnormalities precede the onset of hypertension, and reflect alterations in the immune system that might be related to the etiology of the hypertensive disease.

We have studied immunoglobulin levels in a population of essentially healthy, actively employed persons from whom both hypertensive and normotensive individuals could be selected and compared. The hypertensive persons we studied did not have increased immunoglobulin levels. These findings suggest that immunoglobulin elevation is not present in all groups of people with mild to moderate hypertension, and may have implications concerning the significance of immunoglobulin elevation in this disease.

Methods

The subjects of this report are employees of a large insurance company, most of whom were engaged in sedentary or "white collar" work, who voluntarily underwent a routine annual health evaluation. This consisted of an interim history, physical examination, and laboratory studies, performed within the medical department of the company by a physician, nurse and technologist. As part of the examination two blood pressure measurements were performed by a physician, with the subject in the sitting position, and information was recorded concerning the use of antihypertensive or other medications. Each examination was performed by one of two physicians, each...
of whom examined approximately equal numbers of hypertensive subjects and controls.

After blood had been drawn for routine laboratory studies, one milliliter of serum was set aside and frozen. The frozen sera were forwarded to the investigators, together with information on the age, sex, race, blood pressure, medications, and medical history of each subject. The sera and corresponding clinical data were identified by number only.

Subjects were considered to have hypertension if the average of the two blood pressure readings was higher than 140/90 mm Hg. If only systolic or only diastolic pressure was elevated, a mean pressure of 107 mm Hg or higher was the criterion used to define hypertension. Mean blood pressure was calculated as the diastolic pressure plus one third the pulse pressure.

Each subject with hypertension was matched with a control. The control was the person examined closest in time, who was of the same sex, race, age (within 3 years), and had both systolic and diastolic pressure below 140/90 mm Hg without the use of antihypertensive medication. None of the subjects or controls was known to have a chronic illness that might affect immunoglobulin levels, such as liver disease, chronic infection, or collagen vascular disease.

Immunoglobulins were measured in the serum of each hypertensive subject and matching control. IgG, IgA, and IgM were quantitated by radial immunodiffusion using commercially available plates and standards (Meloy Laboratories, Springfield, VA). Each specimen was measured in duplicate, and samples were coded so that the person performing the assay could not identify a sample as hypertensive or control. The sera of each hypertensive subject and his or her matching control were always analyzed together on the same immunodiffusion plates. The coefficient of variation of duplicate determinations, run on different plates, was 13.6% for IgA, 16.5% for IgM, and 12.5% for IgG.

Differences between the hypertensive and control subjects were analyzed by the t test for paired observations.

Results

Between November, 1977 and May, 1978, sera and blood pressure data were collected from 368 persons. Of these, 342 were white, 23 were black, and three were Asian. Because of their small numbers, nonwhite subjects were not included in the study.

Fifty-two of the 342 white subjects had blood pressures higher than 140/90 mm Hg, and each of these persons was matched with a separate control. The characteristics of the hypertensive and control groups are shown in table 1.

Serum IgG and IgA were not significantly different in the 52 hypertensive patients, compared to the matching controls (table 2). Serum IgM was lower (p < 0.01) in the hypertensive patients. The 16 hypertensive subjects with mean blood pressures higher than 115 mm Hg, when analyzed separately, also failed to differ from their matching controls in levels of serum IgG and IgA (table 3). Serum IgM levels were lower than those of the controls, but this difference did not achieve statistical significance.

Twenty-three of the hypertensive subjects were receiving antihypertensive medication at the time of their examination. Twenty-two of these 23 persons were taking a diuretic; in addition, six were receiving reserpine, four methyldopa, one propranolol and one clonidine. As shown in table 4, the treated subjects had lower levels of serum IgM than the controls, but there was no difference in serum IgG or IgA.

<table>
<thead>
<tr>
<th>Table 1. Sex, Age and Blood Pressure of 52 Hypertensive Subjects (BP higher than 140/90 mm Hg) and Matching Controls</th>
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</thead>
<tbody>
<tr>
<td><strong>Age (mean &amp; range, yrs)</strong></td>
</tr>
<tr>
<td><strong>Hypertensive (n = 52)</strong></td>
</tr>
<tr>
<td>36</td>
</tr>
<tr>
<td><strong>Control (n = 52)</strong></td>
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<td>36</td>
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<table>
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<tr>
<th>Table 2. Serum Immunoglobulins in Hypertensive Subjects and Matching Controls</th>
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<tbody>
<tr>
<td><strong>Serum immunoglobulins (mg/dl) ± sd</strong></td>
</tr>
<tr>
<td><strong>No. of subjects</strong></td>
</tr>
<tr>
<td><strong>Hypertensive subjects</strong></td>
</tr>
<tr>
<td><strong>Controls</strong></td>
</tr>
</tbody>
</table>

* p < 0.01.
Because the serum IgM in the 23 subjects receiving antihypertensive medication seemed lower than the IgM of the entire group, these 23 subjects were compared with the 29 hypertensives not receiving medication. Their serum IgM of 102 ± 48 mg/dl was significantly lower than the IgM of 144 ± 75 mg/dl of the 29 untreated hypertensives (p < 0.05, unpaired t test).

Subjects were diagnosed as having hypertension, for the purposes of this study, if their blood pressure was elevated at a single examination. To confirm the validity of this diagnosis, the medical records of the 52 hypertensive subjects were reviewed approximately 1 year after the original evaluation. Forty-two subjects had elevated blood pressure at one or more annual examinations in addition to the one at which immunoglobulins were measured; in the remaining 10 persons the diagnosis of hypertension was not supported by additional elevated blood pressure measurements. In table 5 serum immunoglobulins are shown for the 42 subjects whose blood pressure elevation was documented on two or more occasions. The results are the same: lower IgM levels in the hypertensive subjects, but no other differences in serum immunoglobulins.

Discussion

Serum immunoglobulin levels were not elevated, when compared to the levels of matching controls, in 52 subjects who had mild to moderate blood pressure elevation at the time of a routine annual examination. Unexpectedly, serum IgM levels were significantly lower in the hypertensive subjects. These findings differ from the three previous reports that have described elevations of serum IgG in hypertension. How can we account for the differences between our observations and those of other investigators?

Ebringer and Doyle studied a selected group of patients with severe hypertension, all of whom had mean blood pressure exceeding 130 mm Hg. 1 Our subjects, none of whom had a mean blood pressure higher than 127 mm Hg, represent a milder form of the disease. Olsen et al. also studied patients with severe hypertension, averaging 225/130 mm Hg before treatment. 2 Comparison of our subjects with the hypertensive population in these two studies might suggest that immunoglobulin elevation occurs only in patients with severe degrees of blood pressure elevation.

In a study of patients with both mild and severe hypertension, Kristensen found IgG elevation in patients whose mean arterial pressure was less than 115 mm Hg. 3 This increase was statistically significant in women who were receiving antihypertensive treatment, but not significant in untreated women or in treated women or in treated or untreated men. More pronounced immunoglobulin elevations were found in patients whose mean blood pressure exceeded 130 mm Hg, once again suggesting that immunoglobulin elevation is related to the severity of the hypertension.

On the other hand, if the subjects in our study who had a mean blood pressure greater than 115 mm Hg are considered separately, there still is no increase in immunoglobulin levels compared to the matching controls. Only 16 subjects had this degree of hypertension; nevertheless, this finding fails to support the conclusion that the absence of immunoglobulin elevation in our subjects is attributable to the mildness of their hypertension.

Since our criteria for hypertension were based on a single set of blood pressure determinations, it is possible that some of the hypertensive group would prove to be normotensive on subsequent examination. We were able to confirm the diagnosis of hypertension in 42 of the 52 subjects by the finding of elevated blood pressure at earlier or later annual examinations; omitting the other 10 from consideration did not change the finding of decreased IgM and normal IgA and IgG levels in the hypertensive subjects. The 23 persons who had elevated blood pressure readings while receiving antihypertensive medication can also be considered to have reliably diagnosed hypertension and had similar results of immunoglobulin determination.

Another factor to be considered is selection bias. In the previously reported studies hypertensive patients were drawn from clinical practice, and the controls were blood donors or hospital employees. Factors other than those controlled for may have affected immunoglobulin levels in these differing populations. Our subjects and controls were drawn from a single population, a group of employees undergoing a

Table 4. Immunoglobulins in Hypertensive Subjects Receiving Antihypertensive Medication and Matching Controls

<table>
<thead>
<tr>
<th>No. of subjects</th>
<th>IgG</th>
<th>IgA</th>
<th>IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive</td>
<td>23</td>
<td>1083 ± 450</td>
<td>205 ± 73</td>
</tr>
<tr>
<td>Controls</td>
<td>23</td>
<td>1008 ± 292</td>
<td>204 ± 111</td>
</tr>
</tbody>
</table>

*p < 0.01.

Table 5. Serum Immunoglobulins in Subjects with Elevated Blood Pressure on Two or More Annual Examinations and Matching Controls

<table>
<thead>
<tr>
<th>No. of subjects</th>
<th>Serum immunoglobulins (mg/dl) ± SD</th>
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<tbody>
<tr>
<td>IgG</td>
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</tr>
<tr>
<td>Hypertensive</td>
<td>42</td>
</tr>
<tr>
<td>Controls</td>
<td>42</td>
</tr>
</tbody>
</table>

*p < 0.01.
routine health examination, in order to minimize selection bias.

Serum IgM was significantly lower in the hypertensive subjects, a finding not previously reported. It is possible that a decrease in IgM is characteristic of early mild hypertension, but is not observed in the cases of severe hypertension in which elevation of other immunoglobulins has been described. The lower levels of IgM in the patients receiving antihypertensive medication may suggest that drug therapy has an effect on blood IgM levels or may be related to differences in the severity or duration of the disease in the treated patients.

In summary, we are not able to state why our hypertensive subjects did not have elevated immunoglobulin levels, or why serum IgM was lower than normal. We believe it most likely that immunoglobulin elevation is characteristic of severe hypertension, but is less marked and will be less consistently found in earlier or milder disease, such as was present in the population we studied. The original view of Ebringer and Doyle that IgG elevation is a result of severely increased arterial pressure, rather than a precursor or risk factor for the disease, is consistent with the findings of our study. If further study confirms that IgM levels are decreased in early mild hypertension, however, a predisposing or precursor role for this abnormality might be postulated.

References

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