Etiologic Factors in Renovascular Fibromuscular Dysplasia
A Case-Control Study

Christine N. Sang, Paul K. Whelton, Ulrike M. Hamper, Margaret Connolly, Saadoon Kadir, Robert I. White, Roger Sanders, Kung-Yee Liang, and Wilma Bias

The role of several factors that have been suggested as being of etiologic importance in renovascular fibromuscular dysplasia was examined in a case-control study of 33 patients with angiographically demonstrated fibromuscular dysplasia and 61 renal transplant donor control subjects with normal renal arteries. The factors studied included use of oral contraceptive agents or markers of sex hormone dysfunction, mechanical stress to the renal artery wall, human lymphocytic antigen (HLA) type, cigarette smoking, history of hypertension for more than 5 years, and family history of cardiovascular disease. The risk of fibromuscular dysplasia was significantly (p=0.003) increased (odds ratio=4.1, 95% confidence interval=1.5-10.9) among cigarette smokers. A significant (p<0.001) dose-response relation was noted between cigarette use and the risk of fibromuscular dysplasia developing (odds ratio=8.6 for those who had smoked more than 10 pack-years). Personal history of hypertension more than 5 years was also associated (odds ratio=5.0, 95% confidence interval=1.1-22.8) with a significantly (p=0.036) increased risk for the development of fibromuscular dysplasia. HLA-DRw6 antigen was more common in the 33 fibromuscular dysplasia patients than in the 61 renal transplant donor control subjects (odds ratio=3.00, p=0.067) or a second group of 934 ambulatory control subjects (odds ratio=2.51, p=0.031). Adjustment for cigarette smoking increased the odds ratio to 5.0 (95% confidence interval=1.3-19.6). There was a positive though not statistically significant (odds ratio=1.7, p=0.175) association noted between family history of cardiovascular disease and fibromuscular dysplasia. No evidence of an etiologic association between the occurrence of fibromuscular dysplasia and prior oral contraceptive use, endogenous sex hormone abnormality, or increase in renal mobility was noted. Our results suggest that cigarette smoking and genetic predisposition are of etiologic importance in fibromuscular dysplasia. However, they fail to support the putative role of other previously suggested causal factors such as oral contraceptive use and excessive renal mobility. (Hypertension 1989;14:472-479)
Materials and Methods

Because of the low incidence of renal FMD, a case-control design was chosen to examine the etiologic factors of interest. The case group consisted of 33 patients at The Johns Hopkins Hospital who presented with arteriographically demonstrated FMD of the renal arteries during the 13-year period between 1973 and 1986. Each of the 33 case patients had hypertension at the time of diagnosis, evidence of ischemia on the basis of renal vein renin activity, and a focal or multifocal angiographic lesion that was thought to represent the presence of FMD. During the study period, 565 patients underwent renal vein renin sampling at the Cardiovascular Diagnostics Laboratory, the only source of such studies at The Johns Hopkins Hospital. Of these, 245 (43%) had evidence of renal ischemic disease (renal vein renin ratios greater than 1.5 and renal venous difference greater than 1 ng/ml/hr),13 and FMD was identified originally in 65 (27%). Fifty-two original angiograms were retrieved for blinded rereading by an experienced angiographer. Forty of the 52 angiograms demonstrated a focal or multifocal angiographic lesion consistent with FMD. An attempt was made to involve all 40 case patients in the study. Thirty-three of the 40 (83%) were contacted and all agreed to participate in the study. FMD lesions were arteriographically subclassified as "beaded" or "unbeaded" based on the presumption that a beaded appearance might represent more definite evidence of the presence of FMD and that different etiologic factors might be associated with beaded and unbeaded lesions. Both unilateral and bilateral cases were included. Two control groups were chosen for comparison with the 33 FMD case patients. Sixty-one renal transplant donors who were originally evaluated at The Johns Hopkins and Francis Scott Key Hospitals during the same time period (1973–1986) were selected to serve as the primary control group. Living related renal transplant donors were the only sizeable group of healthy subjects who underwent arteriography, and in whom we could unequivocally demonstrate the presence of normal renal arteries. Eighty-four white women, 62 white men, and 22 black women were demonstrated to have normal renal arteriograms during their evaluation in the study period under question. An attempt was made to contact all 168 to invite them to participate as control subjects. Approximately 100 (60%) were actually contacted and 61 (61%) agreed to return to The Johns Hopkins Hospital for follow-up. Of these, 33 were white women, 8 were black women, and 20 were white men. A large group of 934 ambulatory subjects who were studied at The Johns Hopkins Hospital between September 1, 1985 and July 31, 1986 was chosen to serve as a second control group for the assessment of FMD human major histocompatibility complex (HLA) associations. This group was composed of staff members, students, and other presumed healthy volunteers. All study participants gave informed consent. The study protocol was approved by the Joint Committee of Clinical Investigation at The Johns Hopkins University School of Medicine.

The principal exposure variables of interest were personal history of hypertension greater than 5 years, cigarette smoking, exogenous and endogenous sex hormone exposure, family history of cardiovascular disease, renal mobility, and markers of class I (HLA-A, B, C) and II (HLA-DR) HLA antigens. Historical information was obtained by means of a specially designed questionnaire. This was administered by a trained interviewer who was blinded to the hypotheses being tested. Reference time was emphasized to be time of the original diagnostic arteriogram. Additional data were obtained by a structured medical record review. This was performed by an independent observer who was also blinded to the study hypotheses. Results of interest obtained by both methods were identical and only questionnaire responses are included in the present report.

Two approaches were used to evaluate renal mobility. In the first, a modified renal sonogram, which yielded two-dimensional dynamic images, was used to directly measure renal mobility at the time of follow-up in 1986. This estimate was obtained during the same visit that the questionnaire was administered and the blood for HLA analysis was obtained. Only the women patients were assessed in this section of the analysis, as only one of the case patients was a man, and renal mobility has been shown to differ between men and women.14 Only the kidneys themselves and not the hili or renal arteries were visible; therefore, movement of the upper pole of the kidney was used as a marker of renal mobility. Several measures in the two-dimensional plane were used to assess renal mobility, including maximal displacement, vertical and horizontal coordinates of displacement, and angle of movement. Because each of these values was found to be highly intercorrelated, maximal displacement of the upper pole of the kidneys was the measurement chosen to represent renal artery mobility. This parameter was evaluated during a maximal respiratory cycle (respiratory displacement) in the prone and upright positions, and from the prone to upright positions during end expiration (positional displacement). The mobility of kidneys with FMD in the renal arteries was compared with that of corresponding (left or right) renal donor control kidneys. The second approach was chosen to provide an indirect estimate of renal artery mobility and mechanical stress at the time of each individual’s initial hospital evaluation. Using the arteriogram obtained at that visit, renal artery length was measured from the aorta to the renal hilum. Only the 20 case patients and 15 control subjects who underwent conventional arteriography were included in this portion of the analysis as it was felt that renal artery length could not be measured with sufficient
accuracy in those who had undergone digital subtraction angiography.

Because of the small number (3/33) of black patients in our sample and known racial variations in antigen frequencies,12 only white case patients and control subjects were included in the HLA comparisons. However, as inheritance of HLA markers is sex independent, both men and women were included. HLA-A, B, and C haplotypes were identified by the Amos-modified microlymphocytotoxicity test.16 A locally developed variation of the two-color immunofluorescence test was used to determine HLA-DR and DQ haplotype specificities.17

Frequencies were tabulated to identify the relative proportions for exposure categories among case patients and control subjects. Odds ratios and 95% confidence intervals were used to estimate the association between exposure status and the presence of FMD. Because FMD is rare and our control subjects were representative of the population at risk, the odds ratios estimated from our analyses should closely approximate the relative risk of renal FMD developing among exposed as compared with unexposed persons. For categorical data, the standard Pearson’s χ² and Fisher’s exact test were used to evaluate the statistical significance of observed associations. The nonpaired Student’s t test was used to detect differences in continuous variables. Logistic regression analysis was used to evaluate the association between case patient status and cigarette smoking, number of pregnancies, age of onset of menses, and renal mobility. The logistic regression models for renal mobility were adjusted for smoking and renal size (kidney-to-body surface area ratio). Age adjustment was included in the initial analysis, but age did not influence the results and was not included in the final model. Probability values of these associations are expressed in exact terms, unless less than 10⁻⁴.

Results

Age, race, and sex characteristics of the overall group of 33 case patients, the subgroup of 15 patients with beaded lesions, and the 61 renal donor control subjects are shown in Table 1. Most of the case patients and their controls were young- to-middle-aged white women. All of the beaded cases were white women, while three black women and one white man were included among the unbeaded cases. A majority of the case patients and control subjects were 30–50 years of age.

Table 2. Frequency of Exposure, Odds Ratios, 95% Confidence Intervals, and Corresponding .p Values for Variables Studied

<table>
<thead>
<tr>
<th>Variable</th>
<th>All cases (n=33)</th>
<th>Beaded cases (n=15)</th>
<th>Controls (n=61)</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than 5-year history of hypertension (%)</td>
<td>21</td>
<td>20</td>
<td>5</td>
<td>5.0</td>
<td>1.1–22.8</td>
<td>0.036</td>
</tr>
<tr>
<td>Family history of cardiovascular disease (%)*</td>
<td>70</td>
<td>73</td>
<td>40</td>
<td>1.7</td>
<td>0.8–3.9</td>
<td>0.175</td>
</tr>
<tr>
<td>Cigarette smoking Ever smoked (%)</td>
<td>79</td>
<td>80</td>
<td>53</td>
<td>4.1</td>
<td>1.5–10.9</td>
<td>0.003</td>
</tr>
<tr>
<td>Pack-years among smokers (mean±SD)</td>
<td>18±16</td>
<td>18±20</td>
<td>6±10</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Oral contraceptives (%)*</td>
<td>55</td>
<td>54</td>
<td>46</td>
<td>1.2</td>
<td>0.4–3.3</td>
<td>0.771</td>
</tr>
<tr>
<td>Hysterectomy (%)*</td>
<td>19</td>
<td>13</td>
<td>28</td>
<td>0.6</td>
<td>0.2–2.2</td>
<td>0.482</td>
</tr>
<tr>
<td>Gynecological disorders (%)*</td>
<td>48</td>
<td>53</td>
<td>33</td>
<td>1.9</td>
<td>0.6–5.6</td>
<td>0.244</td>
</tr>
<tr>
<td>Spontaneous abortion (%)*</td>
<td>29</td>
<td>33</td>
<td>29</td>
<td>1.3</td>
<td>0.4–4.2</td>
<td>0.655</td>
</tr>
<tr>
<td>No. pregnancies (mean±SD)*</td>
<td>3±2</td>
<td>3±3</td>
<td>3±3</td>
<td>0.9</td>
<td>0.8–1.2</td>
<td>0.609</td>
</tr>
<tr>
<td>Age of menarche (mean±SD)*</td>
<td>13±2</td>
<td>14±2</td>
<td>13±2</td>
<td>1.2</td>
<td>0.9–1.6</td>
<td>0.281</td>
</tr>
</tbody>
</table>

Values for pack-years among smokers, number of pregnancies, and age of menarche are mean±SD.

*Adjusted for cigarette smoking.
between cigarette smoking and FMD, odds ratios for the remaining exposure variables were adjusted for the influence of cigarette smoking. A personal history of hypertension greater than 5 years before arteriography was associated with an odds ratio of 5.0 (p=0.036). This was not surprising, as renovascular FMD manifests itself as Goldblatt hypertension, and hypertension is usually the first indication of the presence of this disease. A positive family history of cardiovascular disease—hypertension (20/33), heart disease (19/33), stroke (9/33), and peripheral vascular disease (4/33)—was also more common among the FMD case patients than the donor control subjects, but this result was not statistically significant (odds ratio [OR]=1.7, p=0.175). The frequency of prior oral contraceptive use and history of hysterectomy, gynecological problems, spontaneous abortion, number of pregnancies, and age at menarche did not differ significantly between the case and control groups.

Odds ratios, 95% confidence intervals, and corresponding probability values for the group with beaded lesions were similar to those of the overall group. After adjustment for history of cigarette smoking, they were as follows: greater than 5-year history of hypertension (OR=4.76, 95% confidence interval [CI]=0.53–43.74, p=0.091), family history of cardiovascular disease (OR=1.64, 95% CI=0.69–3.92, p=0.262), and cigarette use (ever-smoked) (OR=4.41, 95% CI=1.13–17.22, p=0.032). Oral contraceptive use and gynecological disorders were not found to be significantly related to FMD, although the odds ratio was greater than unity in both instances (OR=1.3, 95% CI=0.35–4.97 and OR=2.9, 95% CI=0.74–11.23, respectively). There was no evidence of a significant association between FMD and oral contraceptive use among either nonsmokers (OR=1.6, p=0.5) or smokers (OR=0.55, p>0.5).

As outlined in Table 3, there was a significant dose-response relation between cigarette smoking and the presence of FMD; the strongest association was noted for those who had smoked more than 10 pack-years of cigarettes (OR=8.6, p=0.001 for all cases and OR=8.0, p=0.009 for the subgroup with beaded lesions).

HLA frequencies and corresponding odds ratios and probability values were calculated for the case patients and both groups of control subjects (renal donors and hospital-based control subjects). As shown in Table 4, HLA-Cw7 was associated with a significantly (p=0.002) increased odds ratio when the renal transplant donors were used as a control group. Although a positive trend was evident, this association did not remain statistically significant when the case patients were compared with the larger group of ambulatory control subjects. On the other hand, HLA-DRw6 was more common among case patients than either the 45 renal donor HLA control subjects (p=0.067) or the 934 ambulatory (p=0.031) control subjects. HLA-DRw6 was further analyzed after adjustment for cigarette smoking, and the adjusted odds ratios were 5.0 (95% CI=1.3–19.6, p=0.007) for "all cases" and 5.5 (95% CI=1.07–30.21, p=0.02) for the subgroup with beaded lesions. A positive though not statistically significant trend toward a difference in HLA-DRw52 was also noted between the case patients and both the renal donor and hospital-based control subjects (p=0.117 and p=0.130, respectively).

<table>
<thead>
<tr>
<th>Cigarette smoking (pack-years)</th>
<th>All cases (n=33)</th>
<th>Beaded cases (n=15)</th>
<th>Controls (n=61)</th>
<th>All cases (n=33)</th>
<th>Beaded cases (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>21</td>
<td>20</td>
<td>48</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1–9</td>
<td>18</td>
<td>27</td>
<td>36</td>
<td>1.2</td>
<td>0.3–4.0</td>
</tr>
<tr>
<td>≥10</td>
<td>61</td>
<td>53</td>
<td>16</td>
<td>8.6</td>
<td>0.1–16.7</td>
</tr>
<tr>
<td>x²</td>
<td></td>
<td></td>
<td></td>
<td>18.8</td>
<td>9.4</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>0.009</td>
</tr>
</tbody>
</table>

CI, confidence interval; p, probability.

<p>| TABLE 3. Frequency Distributions, Odds Ratios, and 95% Confidence Intervals for Three Levels of Cigarette Use |
|--------------------------------------------------------|--------------------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Cigarette smoking (pack-years)</th>
<th>Frequency distributions (%)</th>
<th>Odds ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>All cases (n=33)</td>
<td>Beaded cases (n=15)</td>
</tr>
<tr>
<td>0</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>1–9</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>≥10</td>
<td>61</td>
<td>53</td>
</tr>
<tr>
<td>x²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<p>| TABLE 4. Frequency Distributions, Odds Ratios, and p Values for Human Lymphocytic Antigen Haplotypes in White Fibromuscular Dysplasia Case Patients, Renal Transplant Donor Control Patients and Hospital-Based Control Subjects |
|--------------------------------------------------------|--------------------------------------------------------|</p>
<table>
<thead>
<tr>
<th>HLA haplotype</th>
<th>FMD case patients (n=28) (%)</th>
<th>Renal transplant donor control patients (n=45)</th>
<th>Ambulatory control subjects (n=934)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-Cw7</td>
<td>43</td>
<td>9</td>
<td>7.69</td>
</tr>
<tr>
<td>HLA-DRw6</td>
<td>43</td>
<td>20</td>
<td>3.00</td>
</tr>
<tr>
<td>HLA-DRw6*</td>
<td>43</td>
<td>20</td>
<td>5.0</td>
</tr>
</tbody>
</table>

HLA, human lymphocytic antigen; FMD, fibromuscular disease; OR, odds ratio; CI, confidence interval.
*Adjusted for cigarette smoking.
was of interest because the HLA-DRw52 supertypic group includes DRw6.18

Table 5 presents sonogram-measured displacement of the right kidney during a maximal respiratory cycle in the prone and upright positions and during a change in posture from the supine to upright position for the 20 white women case patients with right-sided FMD lesions and a corresponding group of 23 white women renal donor control subjects with arteriographically normal right renal arteries. Odds ratios were adjusted for history of cigarette smoking and, to standardize for the increased renal mass of the donors, for kidney-to-body surface area ratio. Respiratory displacement was negatively associated with FMD in both the prone and upright positions (p = 0.03 and 0.04, respectively). Postural displacement tended to be greater among FMD case patients (OR = 1.2, 95% CI = 0.9-1.5), but this trend was not statistically significant (p = 0.24).

As the renal sonogram was obtained up to 10 years after initial examination, the possibility of a confounding interaction between FMD treatment and sonographic renal mobility was also explored. No case-control differences were noted for the subset of eight medically treated case patients during respiratory displacement in the prone (OR = 0.4, 95% CI = 0.2-1.0) and upright (OR = 0.5, 95% CI = 0.3-1.0) positions, as well as postural displacement (OR = 1.2, 95% CI = 0.9-1.6).

Digital angiography had been used during the initial evaluation of 13 FMD case patients and 43 renal donor control subjects. For each of the remaining 20 case patients and 15 control subjects, it was possible to obtain an arteriographic measurement of renal artery length. Table 6 presents mean lengths of the right renal arteries for two subgroups (all women and women with right renal artery FMD lesions) of the case patients and control subjects for whom renal artery length could be measured successfully. There was no significant difference between the case patients or control subjects for either of the two subgroups. The pattern for left renal artery comparisons was similar.

Discussion

The vast majority of studies that have explored the etiology of FMD have been case reports or case series. Although these studies have raised a number of interesting etiologic possibilities, they have lacked the study design and statistical power necessary to test the validity of putative etiologic associations. A strength of the present study is that it was constructed to provide at least an 80% power of detecting odds ratios of 1.5 to 2.0 at the 5% level of significance for the principal etiologic variables of interest. Thus, despite the relatively low incidence of renovascular FMD, we were able to test the hypotheses of interest with an adequate degree of statistical power.

The increased frequency of hypertension among our FMD case patients was not surprising. Although the case-control design does not permit characterization of a temporal sequence with certainty, it seems very likely that the hypertension identified resulted from rather than caused the associated FMD. Although not statistically significant, the increased frequency of family history of cardiovascular disease, including hypertension, in our case patients compared with the control subjects is consistent with the hypothesis that a genetic predisposition may be etiologically important. Several isolated case reports of arteriographically proven FMD in relatives of patients with FMD have been published.19-23 Rushton24 performed a pedigree analysis of 20 families in which at least one member was affected with arterial FMD. In 12 (60%) of these families, there was some evidence of an inheritance pattern. Unfortunately, the presence of FMD was not arteriographically proven in any of the relatives.

Our results identify a marked association between cigarette smoking and FMD in a dose-dependent fashion. These findings support the observations of

### Table 5. Displacement±SD, Associated Odds Ratios for a 10-mm Difference in Mobility of Right Kidney Between White Fibromuscular Dysplasia Women Case Patients and Corresponding Renal Donor Control Subjects During a Maximal Respiratory Cycle and Change in Posture

<table>
<thead>
<tr>
<th>Displacement (mm)±SD</th>
<th>Odds ratios</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory displacement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prone</td>
<td>44±17</td>
<td>59±14</td>
<td>0.5</td>
</tr>
<tr>
<td>Upright</td>
<td>25±16</td>
<td>39±19</td>
<td>0.4</td>
</tr>
<tr>
<td>Postural displacement</td>
<td>55±46</td>
<td>41±32</td>
<td>1.2</td>
</tr>
</tbody>
</table>
MacKay et al., who noted a significant association between cigarette smoking and several groups of nonmalignant hypertensive patients including those with FMD. Reanalysis of a study in which patients with FMD were age-matched with essential hypertensive patients also demonstrated a strong association between cigarette smoking and the occurrence of FMD (OR = 3.6, 90% CI = 1.6–8.0). The mechanisms by which cigarette smoke constituents may act to produce FMD have not been elucidated. However, a variety of plausible possibilities can be advanced. Oberai et al. suggest that cigarette-mediated release of platelet-derived growth factor may promote proliferation of collagen and hence thickening of myocardial and renal arteriolar walls. Smoking is also known to affect fibrinogen levels. The activated form of fibrinogen, fibrin, is thought to stimulate cell proliferation and migration within the vessel wall. It is conceivable that this represents the biologic basis for FMD lesion formation.

Our findings do not support the notion that renal mobility is an important etiologic exposure for the development of FMD. There was a modest trend toward increased postural nephropthosis in kidneys with diseased renal arteries, but the association was not statistically significant, was not seen during respiratory displacement, and was not impressive enough to substantiate previous suggestions of a causal relation between nephropthosis and FMD-induced hypertension. With use of a test model for estimation of statistical power (1-β) in the analysis of respiratory displacement in the prone position, our data provided us with a crude and smoking-adjusted power greater than 95% to detect a case-control difference of 30% at a significance level of <0.05. It is worth noting that we should have had little difficulty detecting the 60% difference previously reported by DeZeeuw et al. The possibility that we might have missed an important mobility effect because of the confounding influence of interventional treatment (surgery or percutaneous transluminal angioplasty) must be considered. However, this seems unlikely because no significant difference in renal mobility was noted between those who received medical versus surgical or percutaneous transluminal angioplasty treatment. In addition, the marked similarity of pretreatment estimates of renal artery length make it unlikely that substantial pretreatment differences in renal mobility could have existed.

FMD is predominantly a disorder of young women, and this is a demographic pattern that is common in many disorders thought to be caused by an autoimmune process. Not surprisingly, several authors have suggested that FMD may represent a disorder of the immune system. However, this hypothesis has primarily been derived from findings in single case reports and small case series. Meyers et al. described a case of renovascular FMD with clinical evidence of polyarteritis nodosa. Intimal FMD has also been found in association with other forms of arteritis, such as Takayasu’s disease. Dornfeld and Kaufman identified the presence of immunoglobulin (Ig) M, complement, and fibrinogen in the intimal region of a dysplastic lesion in a renal transplant recipient. Our results suggest that the HLA-DRw6 antigen, a Class II major histocompatibility complex allele, is positively associated with an increased risk of FMD developing in an individual. The pattern of the association noted between FMD and DRw52 suggests that the identification of DRw6 is real and that other DRw52-linked antigens are not associated with FMD. In mice and other experimental animals, immune response genes map within the major histocompatibility complex Class II region. In humans, many autoimmune diseases are associated with Class II antigens. HLA-DRw6 is mainly expressed on the surface of B lymphocytes, monocytes, macrophages, and dendritic cells, but has also been identified on endothelial cells from the umbilical vein of newborns and in glomerular and peritubular capillaries. We are unaware of any reports of the presence of HLA-DRw6 in renal artery endothelial cells. Several reports suggest that HLA-DRw6 may be an important marker of renal allograft rejection antigens. Reekers et al. reported that DRw6-positive renal transplant recipients had lower graft survival at 1 year, both with and without the use of cyclosporine. Reekers et al. have reported that HLA-DRw6 is associated with a higher frequency of autolymphocytotoxins before renal transplantation and after graft failure. Matthews has proposed that membrane-reactive autoantibodies cause endothelial proliferation of vessels and that circulating immune complexes (composed of IgG) and autoantigens predispose to thrombosis and atherosclerotic plaque formation.

Based on the relatively high prevalence of FMD among premenopausal multiparous women, estrogen exposure has frequently been proposed as an etiologic factor in this disease. Hardy-Godon et al. reported cerebrovascular FMD lesions, identified by angiography, in 18% of 65 patients receiving oral contraceptive pills. Many investigators have attributed the histochemical changes and circulatory compromise seen in the vessel walls of young women receiving oral contraceptives to intrinsic morphological changes rather than to embolic phenomena. These local alterations, characterized by endothelial proliferation, intimal thickening, and focal nodular thickening of the intima, media, and adventitia resemble the histopathological changes that have been reported in renal FMD. It has been suggested that the etiologic influence of sex hormones may be mediated by effects on the immune system. Grossman has reported that estrogen enhances antibody response to inhibition of T-suppressor cell activity in mice, and that estrogen and androgen receptors are found on T cells. Hartman et al. have proposed that anti-ovulants contribute to the progression of fibromuscular hyper-
plasia rather than act as a primary causative factor. However, in the present study, there was little evidence to support the etiologic role of an abnormality in endogenous or exogenous sex hormone function. For oral contraceptives, the statistical power (1-β) to recognize a 20% difference in oral contraceptive use between FMD case patients and control subjects, given a type I (α) error of 0.05, was approximately 50%. Although we cannot exclude the possibility of an association, it seems unlikely that we could have missed an important relation.

In summary, results of the present study suggest that genetic predisposition and personal history of cigarette use can be of etiologic importance in patients with renovascular FMD. Recognition of these factors can allow the identification of candidates at high risk for the development of FMD and provides further support for the admonition to avoid cigarette smoking, especially in those with an extended personal or a family history of hypertension. Additional case-control studies involving a larger sample size and multiple control groups would be helpful. Such studies would not only provide an opportunity to confirm the findings of the present report but could further clarify the strength of the risk factors identified.

References


KEY WORDS • fibromuscular dysplasia • renovascular hypertension • cigarette smoking • human lymphocyte antigen typing • nephrophtosis
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