Vascular diseases and their risk factors in IgA nephropathy

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Abstract

Background. Many studies have focused on risk factors for renal insufficiency in IgA nephropathy (IgAN). We recently found metabolic factors, especially uric acid, to predict progression and marked histopathological lesions in IgAN. Since vascular diseases (VDs), in addition to renal insufficiency, affect the overall survival of IgAN patients, we studied the occurrence of and risk factors underlying VDs in IgAN.

Methods. In this study, VDs here comprised the presence of coronary heart disease (CHD) and/or cerebrovascular disease (CeVD). We correlated clinical, metabolic and histopathological findings with the occurrence of VDs in 221 adult patients with IgAN. Seven histopathological parameters were semiquantitatively graded. Logistic regression analysis was used to evaluate independent predictors of VDs in these patients. The occurrence of VDs in IgAN patients ≥30 years of age was studied and compared with that in the general population drawn from the same area.

Results. VDs were notably common in IgAN patients. Patients with IgAN had significantly more frequent VDs, CHD and CeVD than the general population (p < 0.01 to < 0.001). Of ≥30 years of age IgAN patients, 25% had some VD at the end of follow-up, while only 9% of the general population had VDs [odds ratio, OR 4.6 (2.2–9.4)]. Old age, male gender, hypertension, proteinuria, renal insufficiency, hyperuricaemia, hypertriglyceridaemia, diabetes, smoking and high body mass index correlated with the occurrence of VDs in univariate analysis. In all patients initial renal insufficiency and smoking were independently associated with some VD, and hypertriglyceridaemia with CHD.

Conclusion. VDs, especially CeVD, would seem to be particularly common in patients with IgAN. Patients with progressive renal disease run a significantly elevated risk of developing VD. Many previously known risk factors for VD were also associated with the occurrence of some VD in the present study. Vascular changes seen in renal biopsy in patients with IgAN signify an elevated risk of VDs.

Keywords: cerebrovascular disease; coronary heart disease; glomerulonephritis; hyperlipidaemia; IgA nephropathy; serum uric acid

Introduction

Patients with chronic renal failure have increased cardiovascular mortality and morbidity rates. It is, however, unclear whether patients with chronic kidney disease without renal insufficiency are at an increased risk of arteriosclerotic complications. The risk-factor profiles of progressive chronic kidney disease and coronary heart disease (CHD) or cerebrovascular disease (CeVD) share a number of features. Hypertension, diabetes mellitus, dyslipidaemia, hyperuricaemia and old age are associated with poor prognosis in IgA nephropathy (IgAN) as well as constituting risk factors for vascular diseases (VDs) [1]. High prevalences of hypertension and dyslipidaemia may partly explain the high rates of CHD among patients with chronic renal failure [2]. Also, proteinuria would appear to be a risk factor for both CHD and chronic renal failure [3]. It is generally assumed that arteriosclerosis and glomerulosclerosis may have similar pathogenetic mechanisms.

In the present investigation, we studied the prevalence of VDs in patients with IgAN compared with controls matched for age, sex and residential area.
We also looked for clinical and histopathological risk factors for VDs in IgAN patients with and without progressive renal disease, focusing on correlations between VDs and metabolic factors, which have previously been associated with progression and histopathological damage in IgAN.

Patients and methods

Patients, controls and renal pathological evaluation

The original patient population consisted of all 221 adult IgAN patients diagnosed in Tampere University Hospital from January 1980 to December 1990. This is the only centre where renal biopsies were performed in the residential area of Pirkanmaa, with about 440,000 inhabitants. IgAN was diagnosed when there was IgA as the sole or predominant glomerular immunofluorescent (IF) finding in renal biopsy. There were 140 (63%) male and 81 (37%) female patients, and median age was 41 years (range 16–78).

A control group matched for age (at the end of follow-up), sex and residential area was constructed from the Health 2000 Survey (H2000), a large cross-sectional health examination survey carried out in 2000–01 by the National Public Health Institute. The implementation of the survey is described in detail elsewhere [4]. The control group comprised 203 persons ≥30 years of age from the general population.

Paraffin sections for light microscopy (LM) were stained by haematoxylin–eosin, periodic acid–Schiff reaction, Masson’s trichrome and periodic acid–silver methenamine methods. Specimens were considered sufficiently representative for light-microscopic evaluation if they contained four or more glomeruli. Of all IgAN cases, 202 fulfilled this criterion. Mesangial cellularity, glomerulosclerosis, tubular atrophy, interstitial fibrosis and inflammation, hyaline arteriolosclerosis and arterial intimal fibrosis were evaluated. The histopathological parameters were semiquantitatively graded into three groups: normal, mild or marked, as described in detail in our recent study [5].

Post-biopsy follow-up

Follow-up ended at the control visit, including comprehensive clinical examination during the years 1996–97, or if the patient died. The median follow-up time after renal biopsy was 10 years (range, 0.2–17). Causes of death were confirmed from patient records and death certificates kept by Statistics Finland. Thirty patients (14%) died during the follow-up, six of them due to myocardial and three due to cerebral infarction.

Clinical definitions

At the time of renal biopsy 11 IgAN patients had purpura, and 2 of them had complete Henoch–Schönlein syndrome (abdominal pain, arthritis and purpura). Ten IgAN patients (5%) had diabetes mellitus. None had systemic lupus erythematosus or liver cirrhosis.

Serum creatinine values ≤125 μmol/l in men or ≤105 μmol/l in women were considered normal. Progression of IgAN was defined as an elevation of serum creatinine value above the normal limit and over 20% from baseline. In addition, progression was also defined by estimating creatinine clearance (Cr) by the Cockroft–Gault formula as deterioration of Cr under 90 ml/min/1.73 m² and over 20% from baseline. We divided the patient population into those with stable renal disease (s-group) and those with progressive course (p-group).

Blood pressure was measured by sphygmomanometer after rest. Hypertension was defined as systolic blood pressure over 140 mmHg and/or diastolic blood pressure over 90 mmHg, or use of antihypertensive medication in both IgAN patients and controls.

Urine protein excretion (UPE) was based on 24 h urine collection. Proteinuria was defined as UPE ≥1 g/24 h. Serum uric acid was measured in 189 (85%) patients. Hyperuricaemia was defined as serum uric acid >0.45 mmol/l in men and >0.34 mmol/l in women. Two patients were using allopurinol for gout. Serum triglyceride values were studied in 191 (86%) and cholesterol in 188 (84%) patients. Serum cholesterol and triglyceride concentrations were measured enzymatically after an overnight fast at the time of biopsy. Hypertriglyceridaemia was defined as serum triglyceride concentration >1.7 mmol/l, and hypercholesterolaemia as a serum cholesterol concentration >5.0 mmol/l. None of the patients used lipid-lowering medication at the time of biopsy. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in metres, elevated BMI being defined as ≥27 kg/m². Patients were divided into two groups according to their smoking habits: patients who had never smoked, i.e. non-smokers and patients who had smoked earlier or were smokers at that time, i.e. ex-smokers or current smokers.

In H2000, measurements of cholesterol and triglyceride levels and BMI were performed during programmed health examinations after a fast of at least 4 h. The determination of BMI was based on measured height and weight. For more strict definitions of methods of H2000, see the baseline results of H2000 [4].

Vascular diseases and diabetes

The data on VD morbidity in patients with IgAN were based on patient records and careful clinical examination at the control visit or on the last available check in those who died during the follow-up or were not available for the control visit. CHD included a history of myocardial infarction or angina pectoris, CeVD a history of transient ischaemic attack or cerebral infarction and any VD occurrence of CHD and/or CeVD in IgAN. All VDs were clinically diagnosed by a physician. In H2000 information on CHD, CeVD and diabetes mellitus was elicited in the home health interview. Subjects were asked whether a doctor had diagnosed myocardial infarction, angina pectoris, stroke (cerebral haemorrhage or thrombosis), or diabetes.

Statistics

Differences between categorical variables were tested by χ²-test or Fisher’s exact test when appropriate. Stepwise multivariate logistic regression analysis was used in detecting independent risk factors for VDs. Mann–Whitney U-test was used when comparing continuous variables between control and patient groups. Differences in occurrences of VDs between patients with IgAN and the general population were tested by McNemar’s test. P < 0.05 was considered
statistically significant for all tests. The software used for statistical analysis was SPSS for Windows 9.0.

**Results**

**Clinical findings and vascular diseases at biopsy**

Clinical data on patients with IgAN at the time of renal biopsy are listed in Table 1. Clinical data on controls and ≥30 years of age IgAN patients, at the end of follow-up, are summarized in Table 2. Serum creatinine, uric acid, triglyceride and cholesterol concentrations, and UPE rate were all strongly intercorrelated. A summary of histopathological findings is presented in Table 3. Vascular diseases were rare at the time of biopsy; 7 (3%) patients had CHD, 6 (3%) had CeVD and 13 (6%) had some VD at that time.

**Vascular diseases at the end of follow-up**

The median age of patients at the close of follow-up was 50 years (range, 19–85). Progression of IgAN was noted in 41 (19%) patients when using serum creatinine concentration and in 60 (27%) when using Ccr estimate. Of patients without progressive renal disease defined by serum creatinine, 63% were hypertensive and 16% had UPE >1 g/24 h at the end of follow-up. Mean creatinine concentration in that patient group was 93 μmol/l (SD=1.7 μmol/l).

The occurrence of VDs at the end of follow-up is summarized in Tables 4 and 5 according to the course of renal disease. IgAN patients ≥30 years of age were compared with age- and sex-matched controls representing the general population in the same residential area. At the end of follow-up, 51 (25%) of IgAN patients and 19 (9%) control subjects had some VD (P<0.001, odds ratio, OR = 4.6). Of patients with stable renal function 30 (19%) had some VD. Also, CHD and CeVD were significantly more frequent in patients with IgAN with or without progressive renal disease (Table 4).

**Correlations of clinical and histopathological findings with VDs in univariate analysis in IgAN**

The influence of progression of renal disease on the prevalence of VDs is summarized in Table 5. Patients in the p-group suffered from VDs more frequently

### Table 1. Clinical findings in 221 IgAN patients at time of renal biopsy

<table>
<thead>
<tr>
<th>Finding</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥41 years</td>
<td>112 (51)</td>
</tr>
<tr>
<td>Male gender</td>
<td>140 (63)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>116 (53)</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Proteinuria ≥1 g/24 h</td>
<td>65 (29)</td>
</tr>
<tr>
<td>Microscopic HU</td>
<td>205 (93)</td>
</tr>
<tr>
<td>Macroscopic HU in history</td>
<td>62 (28)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>42 (19)</td>
</tr>
<tr>
<td>Ccr &lt;90 ml/min/1.73 m²</td>
<td>60 (27)</td>
</tr>
<tr>
<td>Hyperuricaemiaa</td>
<td>56 (30)</td>
</tr>
<tr>
<td>Hypertriglyceridaemab</td>
<td>69 (36)</td>
</tr>
<tr>
<td>Hypercholesterolaemiaa</td>
<td>113 (61)</td>
</tr>
<tr>
<td>BMI ≥27 kg/m²</td>
<td>65 (29)</td>
</tr>
<tr>
<td>Smokinga</td>
<td>93 (42)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (5)</td>
</tr>
</tbody>
</table>

HU, haematuria; Ccr, Creatinine clearance estimate; BMI, body mass index.

*aMeasured in 189 pts; bmeasured in 191 pts; cmeasured in 188 pts.

### Table 2. Central clinical parameters in controls and IgAN patient ≥30 years of age at the end of follow-up

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls, n = 203</th>
<th>IgAN patients, n = 203</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (2SD), years</td>
<td>53.5 (29.1)</td>
<td>53.5 (29.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum total cholesterol, mean (2SD), mmol/l</td>
<td>6.0 (2.3)</td>
<td>5.4 (2.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum LDL cholesterol, mean (2SD), mmol/l</td>
<td>3.9 (2.4)</td>
<td>3.4 (1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum triglycerides, mean (2SD), mmol/l</td>
<td>1.6 (2.0)</td>
<td>1.7 (2.3)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, mean (2SD), kg/m²</td>
<td>26.8 (9.3)</td>
<td>26.8 (9.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>83 (41)</td>
<td>114 (73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>14 (7)</td>
<td>21 (10)</td>
<td>NS</td>
</tr>
<tr>
<td>Smokinga, n (%)</td>
<td>111 (56)</td>
<td>72 (45)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, non-significant.

*aEx-smoker or current smoker.
than those in the s-group (\(P < 0.001\)). In the p-group 54% of patients had VDs at the end of post-biopsy follow-up. CHD was significantly more frequent in the p-group (\(P < 0.001\)). The occurrence of CeVD was also somewhat higher in this group than in the s-group (\(P = 0.064\)). When using Ccr estimate-based partition, the results of differences in VD prevalences between the s- and p-group were essentially similar.

Results of univariate analysis of associations of clinical and histopathological parameters with the occurrence of VD are listed in Tables 6 and 7. We found statistically significant correlations between all clinical parameters and VDs when evaluating the patients. CeVD did not correlate with male gender, proteinuria, hypercholesterolaemia and hypertriglyceridaemia.

The severity of glomerulosclerosis (\(P < 0.01\)), tubular atrophy (\(P < 0.05\)), interstitial fibrosis (\(P < 0.05\)) and hyaline arteriolosclerosis (\(P < 0.01\)) was significantly associated with the prevalence of VDs. Of patients with some VD only 4% evinced no significant glomerulosclerosis in their biopsy samples (Table 7). Of patients with CeVD, 42%, but only 17% of those without CeVD displayed marked arteriolosclerosis (Table 7).
Associations between clinical parameters and VDs in multivariate analysis in IgAN

All parameters listed in Table 6 were included in the multivariate analysis model. Among all IgAN patients, we found initial renal insufficiency ($P<0.05$) and smoking ($P<0.01$) to be independent risk factors for some VD. Male gender was independently associated with the occurrence of CHD ($P<0.01$). Hypertension was found to be independently associated with CeVD ($P<0.05$). When using Ccr estimate-based definition of renal insufficiency, the results of multivariate analyses were essentially similar. However, hypertriglyceridaemia was then also found to be independently associated with some VD ($P<0.05$).

Since initial renal insufficiency correlated significantly with many biochemical factors measured, we also performed the aforementioned multivariate analysis in the case of patients with normal serum creatinine concentration at the time of renal biopsy separately. In the group of patients with initially normal creatinine concentration, male gender was an independent risk factor for some VD ($P<0.05$), while hypertriglyceridaemia was associated independently with the occurrence of CHD ($P<0.05$). In this patient group we found no parameter associated with the occurrence of CeVD in multivariate analysis.

Associations between histopathological parameters and VDs in multivariate analysis in IgAN

All semiquantitatively graded histopathological parameters were included in the multivariate analysis model. We found the severity of hyaline arteriolosclerosis seen in renal biopsy to be independently associated with some VD ($P<0.05$), while hypertriglyceridaemia was associated independently with the occurrence of CHD ($P<0.05$). The severity of arterial intimafibrosis was significantly associated with the occurrence of CHD.

Discussion

The results of the present study show the prevalence of VDs to be clearly higher among patients with IgAN than in the general population. These patients seem to be at an increased risk of VDs, especially CeVD, even when their renal function remains stable. The risk of VDs is further elevated when patients have progressive renal disease.

There are many studies concerning risk factors for progression of renal disease in patients with IgAN. The overall survival, however, involves all life-endangering diseases, including end-stage renal disease (ESRD), CHD and CeVD. In Finland and many other Western countries, the main cause of mortality is some form of VD. Patients with ESRD seem to have substantially higher CHD death rates than the normal population [6]. The prevalence of CHD may also be higher among patients with milder renal insufficiency [7], but it is not clear whether patients with chronic renal
disease without a progressive course run an elevated risk of VDs.

In the present study, we compared the prevalences of CHD, CeVD and all VDs between patients with IgAN and age-, sex- and residence-matched controls. The data on controls are based on home health interviews on diseases diagnosed by a physician. In addition to ischaemic cerebral attacks, CeVD also included a history of intracerebral haemorrhage in the control group. This may underestimate the difference in CeVDs between patients and controls. The data on VDs were collected in a cross-sectional manner mainly during 1996–97 in IgAN patients and during 2000–01 in controls. This small difference in time is not likely to cause significant bias to the results.

Patients with IgAN had significantly more frequently CHD, CeVD and some VD than the general population. The OR was especially high when comparing prevalences of CeVD. The same phenomenon is clearly seen among patients with stable renal disease, which shows that it is not just renal insufficiency, which explains the elevated risk for VDs in IgAN.

Serum total cholesterol and low density lipoprotein (LDL) cholesterol concentrations were significantly lower in IgAN patients at the end of follow-up, which may be due to more strict lipid control and antihyperlipidaemic medication among renal patients. The laboratory analyses in IgAN patients and controls were performed in different laboratories, which may also affect the differences in lipid levels. Awareness of renal disease may also cause cessation of smoking and more appropriate antihypertensive treatment in IgAN.

Progressive renal disease is an independent risk factor for CHD [6]. In the present study, patients with progressive renal disease suffered significantly more often from some VD or CHD than patients with stable disease. No similar trend could be seen in CeVD. An elevated serum creatinine concentration at the time of renal biopsy predicts a progressive course and ESRD in IgAN [2]. We found initial renal insufficiency also to be an independent risk factor for VDs.

The independent role of male gender as a risk factor for CHD is unquestionable. Among patients with renal insufficiency, the significance of gender is not clear [8]. It is assumed that gender also has a significant role in the context of CeVD [9]. In the present study, male gender was an independent risk factor for CHD, but not for CeVD.

Hypertension is one of the most prominent risk factors for both CHD and CeVD [10,11]. We found hypertension to be independently associated with CeVD in patients with IgAN. Over 90% of patients developing CeVD by the end of follow-up were hypertensive at the time of renal biopsy. Even though hypertension is clearly associated with all VDs, it may constitute an even more notable risk factor, especially for CeVD. It has been proposed that renal function tests may be the most significant sensors also in evaluating the risk of VD in hypertensive patients [12].

We have previously observed that elevated serum triglyceride levels predict a poor course of renal disease in IgAN [13]. An elevated serum triglyceride level is an independent risk factor for CHD in the normal population [14]. In our IgAN patients, hypertriglyceridaemia and hypercholesterolaemia were associated with the occurrence of some VD and CHD. In patients with initially normal serum creatinine concentration, hypertriglyceridaemia was independently associated with the occurrence of CHD.

Some investigators have suggested hyperuricaemia to be an independent risk factor for CHD [15], while there are also opinions to the contrary. We have previously found hyperuricaemia to be an independent risk factor for progression, and to be independently associated with tubulointerstitial damage in IgAN [5,13]. In the present study hyperuricaemia was associated univariately with VD, CHD and CeVD. In multivariate analysis, we found no independent associations between hyperuricaemia and some VD or CHD.

Cigarette smoking is a pathogenetic component of atherosclerosis and a risk factor for atherosclerotic complications. Smoking also involves a risk of impaired renal function in diabetic and non-diabetic renal disease [16]. In IgAN the importance of smoking remains unclear [13,17]. In the present study, smoking was associated with CHD and CeVD and independently with some VD.

Some authors have suggested that mesangial glomerulosclerosis may be analogous to arteriosclerosis [18]. We found glomerulosclerosis, tubulointerstitial damage as well as renal arteriolosclerosis to be univariately associated with the occurrence of VDs in patients with IgAN. As expected, hyaline arteriolosclerosis was the best predictor of the development of some VD. Arterial intimafibrosis was independently associated with CHD.

We conclude that VDs, especially CeVD, are significantly more common in patients with IgAN than in the general population. The risk-factor profile for VDs in IgAN and in the general population is quite similar, while male gender, hypertension, renal insufficiency, smoking and elevated serum triglyceride concentration are independently associated with CHD, CeVD or some VD in all patients with IgAN. Hypertension and hypertriglyceridaemia, which have previously been found to be risk factors for the progression of IgAN, are also independently associated with CeVD or CHD. A progressive course of renal disease predicts VDs in IgAN patients. Vascular changes seen in renal biopsy in patients with IgAN signify an elevated risk of VDs.

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