PART XIX

DIABETES MELLITUS

Chairmen:  C Jacobs
            J F Moorhead
IS RENAL GLYCOSEURIA A BENIGN CONDITION?

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Summary

HLA typing and a range of autoantibodies were evaluated in five families affected
with type A renal glycosuria. HLA typing demonstrates that this inherited
disease is controlled by an autosomal dominant gene located on chromosome six
in close genetic linkage with the HLA complex. All affected family members
have significant titres of autoantibodies to nuclear antigens, native DNA, smooth
muscle, mitochondria, liver antigens, thyroglobulin, thyroid microsomes and
renal tubule brush border with variable association. This suggests that renal
glycosuria is a complex HLA-linked disease with increased susceptibility to
multiple autoantibody production and this urges caution with respect to its
classical definition as a benign condition.

Introduction

Primary renal glycosuria (RG) is an inherited disorder of renal tubule function in
which significant amounts of glucose are excreted in the urine in the simultaneous
presence of normal blood glucose concentration. It is generally considered to be
benign [1]. The fortuitous discovery of significant titres of autoantibodies to
thyroglobulin and thyroid microsomes in a 27 year old woman with RG prompted
us to evaluate both a large range of autoantibodies and HLA typing in this
interesting ‘freak of nature’.

Materials and methods

We studied five unrelated families affected with RG (25 patients) and 40 healthy
relatives. No consanguinity was reported. Control group consisted of 100 subjects:
50 women and 50 men (mean age 38 years; range 16—60 years) with normal
renal function.

The diagnosis of RG was determined by measuring fasting glycosuria, 24-hour
urinary glucose and by performing a renal glucose titration as previously described
by Eljas and Rosenberg [2]. The specificity of the tubule defect for glucose reabsorption was confirmed by evaluation of urinary pH, 24 hour protein and bicarbonate excretion, urinary free amino acid pattern, clearances of creatinine, uric acid, calcium and β-2-microglobulin, and tubular phosphate reabsorption

\[ T_P = (C_{Cr} \times P_{Cr}) - U_P \times V \]

Each subject was submitted to an ammonium chloride load test and to a fluid deprivation test.

HLA typing was performed on peripheral blood lymphocytes by the Standard National Institutes of Health two stage microcytotoxicity test. One hundred and four selected antisera were used to determine 37 specificities: 12 in the A locus, 19 in the B locus and six in the C locus. We investigated a large variety of auto-

antibodies including antibodies to nuclear antigens (standard fluorescent antibody technique), native DNA (Farr’s technique), smooth muscle (indirect immunofluorescent technique (IIT)), mitochondria (IIT), gastric parietal cells (IIT on cryostat sections of human gastric mucosa), pancreatic islets (IIT on cryostat sections of human group O pancreatic gland), thyroglobulin (IIT and tanned red cells haemoagglutination technique) thyroid microsomes (IIT on cryostat sections of thyrotoxic thyroid gland), liver antigens (IIT) and renal tubule brush border (IIT).

Results

Renal glucose titration studies in our patients demonstrated a reduction of both the minimal threshold (TminG) and the maximal reabsorptive capacity (TmG) for glucose reabsorption delineating a type A RG as proposed by Reubi [3]. Endogenous clearances of creatinine, tubular phosphate reabsorption, daily proteinuria and bicarbonaturia and urinary free amino acids were in the normal range. Endogenous clearances of uric acid, calcium and β-2-microglobulin corrected for the creatinine clearance were also normal. This range of investigations excluded other inherited or acquired renal tubular dysfunction. In each family all the affected members carried a haplotype which was not present in the healthy relatives demonstrating that the gene responsible for RG segregates with the HLA complex. The HLA haplotypes linked to RG trait in our families are summarised in Table I. The HLA-A, -B and -C locus antigen frequencies of one affected patient of each family were calculated and compared with the antigen frequencies of 120 normal blood donors. No significant difference was observed between the

<table>
<thead>
<tr>
<th>Families</th>
<th>Affected members</th>
<th>Unaffected members</th>
<th>HLA haplotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family 1</td>
<td>5</td>
<td>3</td>
<td>A1, B5</td>
</tr>
<tr>
<td>Family 2</td>
<td>2</td>
<td>2</td>
<td>A11, BW44, CW4</td>
</tr>
<tr>
<td>Family 3</td>
<td>6</td>
<td>12</td>
<td>BW16</td>
</tr>
<tr>
<td>Family 4</td>
<td>3</td>
<td>6</td>
<td>A2, B15, CW3</td>
</tr>
<tr>
<td>Family 5</td>
<td>9</td>
<td>17</td>
<td>A9, B27</td>
</tr>
</tbody>
</table>
patients and the normal population for any of the antigens studied.

Table II summarises the frequencies of autoantibodies in our families with RG and in controls. All the affected members had significant titres of autoantibodies to nuclear antigens, native DNA, smooth muscle, mitochondria, liver antigens, thyroglobulin, thyroid microsomes and renal tubule brush border in variable association. These autoantibody titres were significantly higher than those of healthy controls but lower than those of patients with symptoms of overt autoimmune disease.

TABLE II. Frequencies of autoantibodies in five families affected with renal glycosuria and in controls

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>Affected members (n = 25)</th>
<th>Unaffected members (n = 40)</th>
<th>Controls (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear antigens</td>
<td>42</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Native DNA</td>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mitochondria</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Smooth Muscle</td>
<td>47</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Liver antigens</td>
<td>21</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Thyroglobulin</td>
<td>32</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Thyroid microsomal</td>
<td>32</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Pancreatic islets</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastric parietal cells</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Renal tubule brush border</td>
<td>42</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

All values are expressed as %

Discussion

The presence of autoantibodies in RG has never been reported and its significance is unclear. Many autoantibodies, such as antinuclear antibodies and thyroid antibodies occur more frequently and in higher titres in certain immune diseases than in healthy subjects and there is some evidence that seroreactions may precede the development of clinical disease [4]. On the other hand extensive population surveys have confirmed that in most instances autoantibodies do not have any obvious relation to the diseases [5]. Although none of our patients have clinical evidence of autoimmune diseases, this association with autoantibodies urges caution against the classical definition of RG as a benign condition. The question must be asked whether such predisposition to multiple autoantibody production increases the susceptibility to autoimmune diseases or whether these immunological abnormalities might represent early manifestation of an underlying autoimmune disease in patients at present clinically healthy. In fact autoimmunity has a late and variable age of onset [6] and the mean age of our patients is relatively low (34 years). It will be most interesting to see whether or
not they will develop symptoms. Moreover there is circumstantial evidence from cross-sectional studies and a limited amount of more straightforward evidence from longitudinal studies that autoantibodies act as risk factors. They appear to be associated with excess mortality from vascular causes and cancer [7]. The presence of autoantibodies in all the affected members of our families suggests a role of genetic factors in predisposing patients with RG to produce autoantibodies. Recently a great deal of information has been obtained about the function of the HLA system in regulating the immune response [8]. In more than 40 conditions it has been found that the susceptibility to disease is associated with a particular HLA-A, -B or -D locus type. The mechanism of this association is as yet unknown but most of these diseases have a definite or suspected autoimmune pathogenesis [9]. On the basis of extensive study on the related H2 system in the mouse it has been postulated that the HLA-D locus is closely linked to other, yet undefined immune related genes. Persons with certain non-specific D alleles may carry a closely linked immune related gene that makes them more likely to produce autoantibodies when challenged by autologous antigens [10].

HLA typing in our families demonstrates that RG trait segregates with HLA and suggests that the inherited disease is controlled by an autosomal dominant gene located on the sixth pair of human chromosomes in a close genetic linkage with the Major Histocompatibility Complex. One interpretation suggests that the location of the abnormal gene near the HLA complex might have a role in explaining the immunological findings in our patients. Alternatively such predisposition to autoantibody production might be due to an, as yet unidentified, metabolic impairment related to RG. In summary, our data suggest that RG is a complex HLA linked disease with an increased susceptibility to multiple autoantibody production. Most of the possible mechanisms for the association of HLA, autoantibodies and RG as well as the probability that such predisposition to autoantibody production may favour a susceptibility to autoimmune diseases remains a matter for future research which will depend on better knowledge of this interesting inherited disease, perhaps too easily considered a ‘freak of nature’.

References
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684
Open Discussion

MOORHEAD (Chairman) Have you performed any twin studies looking for concordance?

De MARCHI No, we have no twins in our families.

PARSONS (London) One of the interesting things is that when you follow-up renal glycosuria patients over years a proportion of them develop diabetes mellitus and I wonder if you find more pancreatic autoantibodies at this stage? Is this one autoimmune problem you didn’t see? You seem to have a lot of families and some of them must be quite old patients with renal glycosuria. Renal glycosuria in the old patients is uncommon, they don’t present in their middle age and beyond. You were describing patients who were quite old, is that true?

De MARCHI In our patients we have no autoantibodies to pancreatic islets but the question of the association of renal glycosuria and diabetes mellitus is very interesting. However, since the biochemical aetiology of renal glycosuria is not fully understood it is not reasonable, in our opinion, to make a definite statement concerning the linkage of the two clinical entities. Nevertheless our findings could contribute to a better knowledge of the question. We have known for several years that type I diabetes mellitus is a disease with a probable autoimmune pathogenesis and in which different types of autoantibodies occur more frequently and in higher titres than in other subjects, exactly as we have found in renal glycosuria. Moreover we have investigated the glycaemic and the insulinaemic curve during glucose tolerance test in patients with renal glycosuria and in controls. The glycaemic curves were normal or greater than those of controls but contrary to what we would have expected the insulin values during the glucose tolerance test were not lower. In fact the insulinaemic curve of patients with renal glycosuria and an ideal body weight were higher than those of controls. These findings suggest that renal glycosuria is a complex metabolic derangement with a disruption of the normal glycaemia insulin feedback. We have to remember that the hyperinsulinaemia could play a role in predisposing patients with renal glycosuria to develop diabetes mellitus because of the failure of the beta cell. Of course this is only a hypothesis and more longitudinal studies are needed to confirm the association between the two clinical entities.