Sjögren’s Syndrome in One of Two Sisters with Idiopathic Renal Hypouricemia

Hisashi Yamanaka, Atsuo Taniguchi, Naoyuki Kamatani and Sadao Kashiwazaki

Concomitance of idiopathic hypouricemia and Sjögren’s syndrome is reported. A 37-year-old Japanese woman with Sjögren’s syndrome and her 39-year-old sister without this syndrome both had extremely low levels of serum uric acid. Markedly increased urinary excretion of uric acid and poor response to the pyrazinamide suppression test revealed that the hypouricemia in these sisters was caused by a defect in the pre-secretory reabsorption of uric acid. It is categorized as idiopathic renal hypouricemia rather than hypouricemia rather secondary to Sjögren’s syndrome. Thus, idiopathic renal hypouricemia should be considered even in cases with autoimmune diseases.

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Key words: case report, renal tubular acidosis, pyrazinamide

Introduction

Hypouricemia, as defined by serum uric acid levels less than 2.0 mg/dl, is rare in U.S.A. [1% (1)] and is 3.38% in the Japanese population (2). Idiopathic hypouricemia, which comprises the majority of hypouricemia among the Japanese, is an isolated defect of uric acid transport in renal tubules; massive uricosuria ensues (3-6). The renal handling of uric acid in humans constitutes four components; glomerular filtration, presecretory reabsorption, tubular secretion and postsecretory reabsorption (7). Accordingly, idiopathic hypouricemia has been classified into subtypes based on the response to pyrazinamide or benzbromarone, pharmacological inhibitors of tubular secretion and reabsorption, respectively (8, 9).

Hypouricemia occurs in various pathological conditions, including Wilson’s disease (10), Fanconi syndrome (11), primary biliary cirrhosis (12) and Sjögren’s syndrome (13) as a result of renal tubular damage. We describe cases of renal hypouricemia in sisters with and without Sjögren’s syndrome.

Case Report

Case 1

A 37-year-old Japanese woman (younger sister) visited our rheumatology unit complaining of an arthralgia in the right third interphalangeal joint. She complained of a dry mouth from the age of 23, and had experienced bilateral painful swelling of parotid glands accompanied by elevated body temperature.

Based on the findings of decreased production of saliva and destruction of a parotid duct as seen on sialography, a diagnosis of Sjögren’s syndrome was made. On the first examination in our out-patient clinic, bilateral parotid glands were swollen but there was no lymph node swelling. Radiographic examination revealed no evidence of rheumatoid arthritis. On ophthalmologic examination, decreased secretion of tears and diffuse keratoconjunctivitis were apparent. All these findings suggested Sjögren’s syndrome.

Case 2

A 39-year-old Japanese woman (elder sister) visited our rheumatology clinic complaining of left ankle joint pain. She had been treated with deoxycholic acid for 6 years for liver disease and/or gall bladder dysfunction. On the initial examination in our unit, there was no swelling of joints, parotid glands or lymph nodes and no positive evidence of rheumatoid arthritis on X-ray examinations.

Laboratory tests revealed extremely low levels (0.7 and 0.5 mg/dl) of serum uric acid in both sisters. Serum urea nitrogen, creatinine and β2-microglobulin levels, and urinalysis were normal. There was a slight decrease in the serum K⁺ (3.5 mEq/L) in the younger sister, but no other abnormalities in electrolytes. Twenty four-hour urine analysis showed a normal creatinine clearance rate and normal amounts the electrolytes excreted. The amount of uric acid excreted into the urine was marginal (470, 610 mg/day), but the fractional clearance of uric acid was markedly elevated (62.8, 76.6%).
Table 1. Pyrazinamide Suppression Test

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<th>S.T. 37 yo</th>
<th>S.Y. 39 yo</th>
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<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Serum uric acid (mg/dl)</td>
<td>0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Cua (ml/min)</td>
<td>39.3</td>
<td>53.8</td>
</tr>
<tr>
<td>Ccr (ml/min)</td>
<td>70.0</td>
<td>67.0</td>
</tr>
<tr>
<td>Cua/Ccr (%)</td>
<td>56.1</td>
<td>60.3</td>
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Serum and urinary levels of uric acid and creatinine were determined before and after the oral administration of 3g pyrazinamide, and the clearance for uric acid (Cua) and for creatinine (Ccr) were compared.

To estimate the degree of tubular defect of uric acid transport, the pyrazinamide suppression test was used (8, 9). In normal subjects, administration of 3 g pyrazinamide completely blocks tubular secretion of uric acid and markedly decreases urinary excretion of uric acid. However, no substantial suppression of the uric acid clearance was observed in either sister (Table 1). These data suggest that the hypouricemia in these sisters is due to a presecretory reabsorption defect of uric acid at the proximal renal tubules.

Slight elevation of erythrocyte sedimentation rates (32, 30 mm/1 hr, respectively), and increased percentages of gammaglobulins (24.1, 24.4%) were noted in both sisters. However, IgM-rheumatoid factor (RAHA ×640), anti-SS-A/Ro antibodies (×4), and decreased secretion of tears (Shirmer test) and saliva (gum test) were present in the younger but not in the elder sister. Human leukocyte antigens were A-2, A-24, BW-61, BW-48, DR-4 and DRW-12 for the younger sister, and A-26, A-11, BW-52, B-13, CW-1, CW-3, DR-4 and DRW-12 for the elder sister. Many of their family members had gastric cancer, but hypouricemia was not confirmed in any of them (Fig. 1). Although the marriage was not consanguineous, both parents were born on the same small island in Japan, and therefore may carry the same mutant allele.

In another series of research, serum uric acid levels in 24 patients with Sjögren’s syndrome were investigated in our rheumatology unit. Serum uric acid levels in the patients with Sjögren’s syndrome were 4.36±1.38 (mean±S.D.) mg/dl, and were practically identical with those in the control female population (4.3±0.8 mg/dl). None of the 24 patients with Sjögren’s syndrome had hypouricemia, with the exception of Case 1, described in this report.

**Discussion**

Hypouricemia in autoimmune diseases including Sjögren’s syndrome has been reported only in cases with an apparent renal tubular acidosis (12, 13). However, Sjögren’s syndrome itself does not include hypouricemia, since serum uric acid levels in 24 patients with Sjögren’s syndrome were equivalent to those in the control female population.

In the two sisters, the diagnosis of Sjögren’s syndrome was definitive in the younger but not in the elder sister. Twenty to thirty percent of subjects with Sjögren’s syndrome are considered to have renal tubular acidosis, according to the literature (14, 15), however, clinical and laboratory findings of renal tubular acidosis were absent in the present sisters, except for a slight decrease in serum K+ concentration in the younger sister. The serum K+ level of the younger sister was examined repeatedly, and remained at slightly lower levels (3.4 to 4.2 mg/dl). Even if the younger sister had subclinical renal tubular acidosis, the hypouricemia in the elder sister cannot be attributed to renal tubular acidosis, since these sisters had the same defect in uric acid transport, as seen with the pyrazinamide suppression test. In addition, the pre-secretory reabsorption defect in uric acid transport in these sisters is not consistent with the assumption that the hypouricemia might be secondary to renal tubular acidosis since renal tubular acidosis in Sjögren’s syndrome usually occurs in distal tubules (15).

Thus, the lack of findings of renal tubular acidosis, no abnormal tubular transport other than uric acid, renal hypouricemia due to pre-secretory defect of uric acid and familial incidence of the disease suggest that the hypouricemia of these sisters should be categorized as idiopathic renal hypouricemia. The extremely low levels of serum uric acid also support the diagnosis of idiopathic hypouricemia, since serum uric acid levels in patients with secondary hypouricemia in autoimmune diseases are usually over 1.5 mg/dl (12, 13).

Hypouricemia itself is a common clinical finding, since idiopathic renal hypouricemia is not an unusual disorder among the Japanese population (2). When physicians see patients with hypouricemia, we suggest that idiopathic renal hypouricemia might be considered not only in patients without underlying diseases but also in those with a primary illness such as an autoimmune disease. Assessment of the daily excretion of uric acid and the pyrazinamide suppression test as well as a survey...
for underlying diseases are recommended for the diagnosis of the etiology of hypouricemia.

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References

Deficiency of the Fourth Component of Complement (C4): A Family Case


In this report, an apparently healthy 38-year-old woman with a remarkably low serum C4 value is described together with other family members who had moderately low serum C4. Plasma C4 typing disclosed that the proband inherited two C4B “null” haplotypes. In addition, Southern blot analysis of the C4 gene indicated that the C4A gene was partially deleted on one of these two haplotypes in the proband. We thus concluded that a de novo deletion on the inherited half-null haplotype was the likeliest cause of the low C4 level.

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Key words: complement, complement genetics, major histocompatibility complex

Introduction

The fourth component of complement (C4) plays an important role in activation of the classical complement pathway. In genetic terms, it is encoded by two tandem loci, C4A and C4B, located in the major histocompatibility complex (MHC) on chromosome 6 (1). Deficiency of C4 is known to occur due to inactivation of these four loci (two paternal and two maternal) to a variable extent depending on the number of inactivated loci (2, 3). “Half-null” haplotypes in which one C4 locus is nonfunctional are common causes of C4 deficiency, while “null” haplotypes in which both C4A and C4B loci are nonfunctional are quite rare (4). We report here an apparently healthy woman with a remarkably low serum C4 value. Biochemical and genetic studies revealed that the likeliest cause was a de novo deletion on a half-null haplotype.

Case Report

A 38-year-old woman was admitted to our hospital because of persistent hypocomplementemia in April 1990. In October 1989, she complained of epigastralgia and vomiting, which was attributed to acute gastric mucosal lesions and reflux esophagitis diagnosed on upper gastrointestinal endoscopy by a local physician. She then began to pass soft stools with mucus and blood, which led her to visit us. Multiple round erosive lesions were observed on colonoscopy, and medical therapy was started under the suspicion of inflammatory bowel disease. Hemolytic complement activity (CH50) was noted to be low (21.5 U/ml, normal range 30^-5) at this time. Subjective symptoms and colonoscopic abnormalities disappeared by January 1990, when CH50 was still low (17.8). It decreased further to 16.9 in March, when some systemic disorders were suspected although she was apparently well.

On admission, she was a well nourished woman with normal physical findings. Personal history and family history were unremarkable. Past history was: “acute glomerulonephritis” at age 12, allergic rhinitis at 34, microscopic hematuria at 35. Complete blood count and routine blood chemistry tests were normal. Erythrocyte sedimentation rate and C-reactive protein value were within normal range (Table 1). Rheumatoid factor, antinuclear antibody, and other autoantibodies were not detected. The urine was normal except 3–5 red cells per middle-power field. Renal function tests (PSP and creatinine clearance) gave normal results. Her CH50 was still low (19.3) with normal C3 (46 mg/dl) and low C4 (5 mg/dl, normal range was 18^-57). Values of C2 and C5-9 were all within normal range. C1 inactivator was reported to be normal in both concentration and activity. From these data, partial C4 deficiency seemed to be the most plausible diagnosis.

We then proceeded to genetic studies. Because the human C4 gene is closely linked to MHC (1), the C4 values and serological MHC types of the patient’s family members were determined (Fig. 1). For convenience, four human leucocyte...
Table 1. Laboratory Data on Admission

<table>
<thead>
<tr>
<th>Hematological Data</th>
<th>Urinalysis</th>
<th>Biochemical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>White Blood Cell Count</td>
<td>7,100/μl</td>
<td>Blood urea nitrogen 11 mg/dl</td>
</tr>
<tr>
<td>Red Blood Cell Count</td>
<td>389×10^6/μl</td>
<td>Creatinine 0.4 mg/dl</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>11.9 g/dl</td>
<td>Serum sodium 139 mEq/l</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>36.6%</td>
<td>Uric acid 2.7 mg/dl</td>
</tr>
<tr>
<td>Platelet</td>
<td>22.3×10^9/μl</td>
<td>Total protein 6.1 g/dl</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Albumin 3.8 g/dl</td>
</tr>
</tbody>
</table>

Serological Data

- C-reactive protein: 0
- Anti-nuclear antibody: 10>
- Anti-deoxyribonucleic acid antibody: 0.8 U/ml
- Anti-extractable nuclear antigen antibody: (Ribonuclease sensitive) 50>
- Anti-thyroglobulin antibody: (-)
- Anti-microsome antibody: (-)

Complement Components (Normal ranges are shown in parentheses)

<table>
<thead>
<tr>
<th>CH50</th>
<th>C6</th>
<th>C3</th>
<th>C4</th>
<th>C5</th>
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<tr>
<td>19.3 U/ml (30-45)</td>
<td>3.6 mg/dl (2.5-4.5)</td>
<td>5.6 mg/dl (5.5-8.9)</td>
<td>3.4 mg/dl (2.7-7.3)</td>
<td>19.2 mg/dl (15-35)</td>
</tr>
</tbody>
</table>

Because C4 is a highly polymorphic protein, allotypes of this family’s plasma C4 proteins were determined by a standard method in order to spot the origin of the defect (5). This analysis disclosed that the proband, her mother, brother, and younger sister had no C4B protein. As for C4A, three allotypes were observed. Knowing that they segregate together with HLA haplotype, we could link C4 alleles to HLA haplotypes as shown in Fig. 1. For instance, C4A*4f must be on haplotype C because it was the only haplotype shared by II-1 and 2 who shared 4f but not the other allotypes. Note that the identity of “4f” is not clear at this point on the basis of electrophoretic motility and this nomenclature is tentative. The proband’s plasma gave one C4A3 band. But it was still unknown whether this band was derived from haplotype A or D, or both.

Next, DNAs of this family were analyzed by Southern blot hybridization. Genomic DNA was isolated from peripheral blood leukocytes or Epstein-Barr virus-transformed cell lines, digested completely with the indicated restriction enzyme, electrophoresed on 0.7% agarose gel, and blotted onto nylon membrane. The blots were hybridized with the C4 or 21-hydroxylase cDNA probe (Bam HI-Kpn I fragment of the PAT-A plasmid and undigested pC21/3c plastmid, respectively) (6, 7), washed, and exposed to an X-ray film.

Figure 2 shows the results of Southern hybridization with the C4 probe. Eco RI digestion gave rise to four (15, 12, 8.4, and 7.1 kb) polymorphic bands (Fig. 2a). Each band was traced to an HLA haplotype using the segregation pattern in this family excluding the proband. For example, the 8.4 kb and 7.1 kb bands...
Fig. 2. Southern blot analysis of C4 gene. The symbol of each lane is the same as used in Fig. 1. Enzymes used are EcoR I (a), Hind III (b), and Taq I (c).

Fig. 3. Southern blot analysis of 21-OH gene. The symbol of each lane is the same as used in Fig. 1. Enzymes used are EcoR I (a) and Hind III (b).

must be on haplotype A, because they appeared in II-2 and 4 but not in I-2 and II-1. Likewise, the 12 kb and 15 kb bands were traced to haplotype D and C, respectively. From these results, the proband, with HLA genotype AD, was expected to have 7.1, 8.4, and 12 kb bands but the 7.1 kb band was missing reproducibly. This result indicated that some part of the C4 gene was deleted on haplotype A. Digestion with Hind III and Taq I did not show enough alleles to reveal this deletion, but a potentially important finding was that the 31 kb Hind III band was linked to haplotypes A and D (Fig. 2b and 2c). Because this band usually represents the C4B gene (8, 9), it indicated the presence of C4B locus on haplotype A. Also notably, haplotype A was demonstrated to have an unusual 6.4 kb Taq I band, although it was not resolved whether this band was C4A or C4B, or both. Despite the absence of the C4B protein production from haplotypes C and D, configuration of the C4B loci on them seemed normal, as indicated by 12 or 15 kb bands with Eco R I, 25 or 31 kb bands with Hind III, and 5.4 or 6.0 kb bands with Taq I (8–10).

The gene for steroid 21-hydroxylase (21-OH), located 3' of each C4 gene (1), was also analysed by Southern hybridization (Fig. 3). Absence of the 15 kb 21-OH A Eco R I band in II-3 indicated that the deletion on haplotype A involved the 21-OH A locus but this could also result from polymorphism on both haplotypes A and D (9). The 20 kb Hind III band could be a rather unusual polymorphic 21-OH B locus on haplotype C (9), and its absence in II-3 did not necessarily implicate a 21-OH gene deletion on haplotype A. Therefore, we could not determine if the deletion on haplotype A involved the 21-OH gene.

From these findings, the low C4 value of the proband was most likely attributed to the null C4 haplotype resulting from a new C4A gene deletion in the background of the inherited nonfunctional C4B gene.

**Discussion**

In this report, an apparently healthy woman with hypocomplementemia as a virtually sole abnormality was described. Frequent causes of hypocomplementemia with low C4 and normal C3 are autoimmune diseases, especially systemic lupus erythematosus (SLE) and angioneurotic edema. But the lack of clinical symptoms and characteristic laboratory findings, e.g. positive autoantibodies or low C1 esterase inhibitor, ruled out these diseases. Glomerulonephritis, although usually presenting with low C3, was considered because of persistent microhematuria and the reported past history of acute glomerulo-
nephritis. But it was also ruled out by a normal renal biopsy done in May 1990. These considerations left genetic C4 deficiency as a possible cause, which was supported by genetic analysis. C4 typing revealed that three C4B null alleles (haplotypes A, C, and D in Fig. 1) had accumulated in this family.

Nonfunctional C4 alleles like the C4B*Q0 alleles found in this family are not uncommon. The frequency of half-null haplotypes was reported to be as high as 30% in Caucasians (4). In the Japanese population, the frequency of A*Q0 and B*Q0 alleles were reported to be 0.067 and 0.158, respectively (11). They can occur as a result of a gene deletion, but most of them are due to functional inactivation of unknown nature with the gross gene configuration kept intact as the C4B*Q0 on haplotypes C and D in the family described here (1).

However, haplotype A had an unusual feature illustrated by the 7.1 kb and 8.4 kb C4 bands on Southern hybridization following Eco R I digestion. Furthermore, this haplotype seemed to have undergone another deletion as shown by the loss of the 7.1 kb band in the proband. There has been no detailed description on the 7.1 and 8.4 kb Eco R I bands in the literature. However, given the results of Southern blotting, the simplest explanation would be that each band represents each of two C4 loci both of which have an unusual polymorphism. The appearance of the 6.4 kb Taq I band is in keeping with this explanation. In any case, it is not perfectly clear what part of the gene was deleted in the haplotype A of the present patient, but the presence of the 31 kb Hind III C4B band pointed to the C4A locus. The possibility of a new deletion in the C4A locus on the 7.1 kb and 8.4 kb C4 bands on Southern hybridization further shown in Fig. 1. Note that while C4 types of I-1 could not be examined, the results with II-1, 2, and 4 clearly indicated that both haplotype A and B had carried a functional C4A locus in I-1. Therefore, it seemed highly likely that the deletion on haplotype A was responsible for the inactivation of C4A locus thereby making the whole haplotype incapable of C4 production in the proband. It should be noted, however, that the possibility that haplotype A in the proband produced a trace amount of C4A3 could not be formally ruled out because such a production would have been masked with C4A3 produced by haplotype D.

It remains unknown if the deficiency of C4 was related to the present patient’s pathologies in the past. The recent erosive lesions of the colon may be attributable to some bacteria or the drugs, including antibiotics given by the local physician. The present patient was in good health except occasional urticaria three years later. The patient’s siblings with a half-null haplotype were also in good health. It is yet to be seen if an SLE-like syndrome or rheumatoid arthritis or insulin dependent diabetes mellitus, which are associated with C4 deficiency (4, 14, 15), will develop in this family. But most likely, partial C4 deficiency is innocent and, therefore, unnoticed in the great majority of affected people.

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References