Exercise-induced acute renal failure associated with renal hypouricaemia: results of a questionnaire-based survey in Japan

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Abstract

Background. A retrospective investigation was conducted to define the clinical features of exercise-induced acute renal failure (ARF) associated with renal hypouricaemia with the aim of clarifying further the clinical features of the disease entity.

Methods. A questionnaire was mailed to 43 institutions in Japan that had experienced case(s) of exercise-induced ARF associated with renal hypouricaemia. Fifty-four patients (48 males and six females) were identified from 38 institutions.

Results. Median age at the first episode of ARF was 17 years (range 11–46). The maximal serum uric acid and creatinine levels were 4.40±2.49 (range 0.4–13.3) and 5.45±3.33 mg/dl (range 1.10–17.7), respectively. The serum uric acid level after recovery was 0.70±0.25 mg/dl (range 0.1–1.4). The short-term prognosis seemed to be good and histological findings in 28 patients showed minimal change or acute tubular necrosis except for one patient with chronic lesions. ARF episodes occurred predominantly in September, October and May, mostly after strenuous exercise such as a short-distance race. The first symptoms were nausea/vomiting in 51 episodes, loin pain in 35, abdominal pain in 22, general fatigue in 16 and low-grade fever in seven. Thirteen patients (24.1%) experienced recurrent ARF at various intervals. Univariate and multivariate analyses failed to demonstrate any risk factor of ARF recurrence, although no female patients experienced ARF recurrence.

Conclusions. The reason for the heterogeneity in ARF associated with renal hypouricaemia remains unknown. Further studies, especially on molecular mechanisms, are required to establish the best guidance against ARF recurrence.

Keywords: ARF; exercise; questionnaire; recurrence; renal hypouricaemia

Introduction

Idiopathic renal hypouricaemia is a clinical disorder attributed to increased renal excretion rates of urate. Although hypouricaemia per se is mostly asymptomatic, the condition is well known to be at high risk of urolithiasis and acute renal failure (ARF) [1,2]. Exercise-induced ARF associated with renal hypouricaemia was first reported in 1989 by Erley et al. [3], and a number of cases have been reported to date [2,4–14]. However, many problems remain unsolved in this complication.

We conducted a national questionnaire survey to clarify further the clinical features of the disease entity. Here we report the results of the analysis of exercise-induced ARF associated with hypouricaemia in wide geographic areas in Japan.

Subjects and methods

A single-page questionnaire was mailed to 43 institutions (members of the ARF Associated with Renal Hypouricaemia Research Group are listed in the Acknowledgements) that had experienced case(s) of exercise-induced ARF associated with renal hypouricaemia. These institutions were identified through a MEDLINE search and check of abstracts in Japanese congresses and meetings on nephrology. Secondary hypouricaemia associated with disorders such as Fanconi’s syndrome, Wilson’s disease and syndrome of inappropriate antidiuretic hormone secretion was excluded. The diagnosis of hypouricaemia was based on a serum uric acid level of <2.0 mg/dl. ARF was defined as a maximum creatinine level 1.5 times higher than the level after recovery. The possibility of rhabdomyolysis was excluded because of the absence of...
haemoglobinuria and myoglobinuria. The questionnaire consisted of the following items: (i) gender of the patient; (ii) age of the patient at ARF episode; (iii) family history; (iv) past history; (v) the first symptom of the ARF episode; (vi) type of exercise leading to ARF; (vii) date of ARF episode; (viii) time lag from exercise to the first symptom and from the first symptom to hospital visit; (ix) maximum levels of serum creatinine and uric acid; (x) baseline levels of serum creatinine and uric acid; (xi) fractional excretion of sodium (FENa) during the ARF episode; (xii) treatment for ARF; (xiii) time lag from the first symptom to renal biopsy; (xiv) histological findings; (xv) results of challenge tests to study renal uric acid handling; and (xvi) guidance for prevention of ARF.

Defects of uric acid handling in the tubules were classified into four categories from fractional excretion of uric acid before and after drug challenge using pyradinamide (an inhibitor of uric acid secretion) and probenecid or benz-bromarone (inhibitors of post-secretory reabsorption), as previously described by Sperling [15].

Data are presented as mean±SD, unless otherwise indicated. Several clinical characteristics and laboratory data were compared between patients with recurrence (recurrence group) and without recurrence (non-recurrence group). Mann–Whitney U-test was used to compare the two groups and analyse the difference between the first and subsequent ARF episodes. Fisher’s exact probability test was used to analyse the relationship between ARF recurrence and guidance for prevention. Univariate analysis and multivariate analyses with logistic regression were used to analyse the relationship between recurrence and five factors: baseline uric acid level (<0.6 mg/dl), gender, age <20 years at the first ARF episode, daily exercise, and guidance from doctors. All data were analysed using Stat View 5.0 (SAS Institute, Cary, NC). A difference is regarded as statistically significant when $P<0.05$.

### Results

Fifty-six patients with renal hypouricaemia were identified from 38 institutions. Of these, two cases were excluded because of an uncertain relationship with exercise; one was a 14-year-old boy with ARF associated with acute gastroenteritis and the other was a 30-year-old man with ARF of unknown trigger. Forty-eight males and six females aged between 11 and 46 years (mean, 19.3±8.1; median, 17.0 years) at the first ARF episode were analysed (Figure 1). The age at the first episode was not described in two patients. Exercise-induced ARF associated with renal hypouricaemia was reported evenly from all over Japan without geographical difference in incidence.

#### Family studies

There were two pairs of affected siblings. Another patient had a brother who had suffered from ARF. However, the brother was not enrolled in this study, because his serum uric acid level had not been measured. Three family members of three families had urolithiasis. Serum uric acid concentrations were measured in 21 pairs of parents, 14 male and seven female siblings, and two daughters. Three mothers, nine male and one female sibling, and two daughters were found to have hypouricemia.

#### Past history

None of the patients had been detected by the national urine screening programme for renal disease in school children, which has been conducted since 1973 in Japan [16]. Two of 54 patients had a history of urolithiasis, one of whom had a silent stone detected incidentally by ultrasound on admission.

#### Defect of uric acid handling

Evaluation for the type of uric acid handling defect was carried out in 35 of 54 patients. The results showed a pre-secretory reabsorptive defect in 26, a post-secretory...
Clinical manifestations of ARF episodes

The sports or events that induced ARF were short-distance races in 36 episodes, association football in two, baseball training in four, basketball in three, marathon running (long-distance running) in eight, and field hockey, swimming, scuffle, push-ups and sit-ups, lacrosse, house cleaning, cycle training and delivery work in one each.

Figure 2 graphically depicts the monthly variation in the occurrence of ARF episodes, which occurred predominantly in September, October and May. When we divided the patients into three groups, patients with ARF induced by short-distance running, long-distance running and others, the predominance became more definite in the short-distance running group. The first symptoms of the patients are shown in Table 1. It is noteworthy that the first symptoms were loin pain in 35 episodes, abdominal pain in 22 and low-grade fever in seven, which are uncommon in other types of ARF.

In 60 episodes analysed, the rates of symptom onset at 12, 24, 48 and 72 h after exercise were 75.0, 84.6, 98.1 and 100%, respectively.

Distribution of laboratory data

The serum uric acid concentrations during ARF and after recovery, and the maximum serum creatinine concentrations during ARF are shown in Figure 3. The maximum serum uric acid level during the ARF episode was 4.40 ± 2.49 mg/dl (range 0.4–13.3; median 4.30 mg/dl) in 59 episodes of 54 patients. The serum uric acid after recovery was 0.70 ± 0.25 mg/dl (range 0.1–1.4 mg/dl) in 54 patients, while the baseline serum uric acid concentration was ≤1.0 mg/dl in 52 (96.3%) of the 54 patients. The maximum serum creatinine level was 5.45 ± 3.33 mg/dl (range 1.10–17.7; median 4.90 mg/dl) during the ARF episode in 68 episodes of 54 patients.

FENa was described clearly in 41 episodes of 38 patients. FENa ranged from 0.013 to 9.5% (median 2.0%), <1.0% in 9 episodes, 1.0–2.0% in 11 episodes, and >2.0% in 21 episodes.

Number of ARF episodes

Among 54 patients, 41 had one ARF episode, 10 had two episodes, and one each had three, four and six episodes (Figure 1). Thirteen patients (24.1%) experienced recurrent ARF associated with exercise at various intervals. The intervals ranged from 1 month to 11 years (median 20 months). Six episodes occurred at intervals of >5 years.

Histological findings

Histological studies of renal biopsy specimens obtained between 2 days and 46 months (12 specimens within 7 days, 18 within 14 days) after onset of ARF from 28 patients demonstrated acute tubular necrosis in
22 patients and minimal change in six patients. In these two groups, there were no differences in clinical features such as maximum serum creatinine levels and dialysis requirement. No uric acid precipitation in the renal tubules was found in these patients. Chronic renal lesions such as thickening of the tubular basement membrane and interstitial fibrosis were present in one patient. The patient was a 42-year-old male employee of the Self Defence Service, who experienced at least four episodes of exercise-induced ARF (patient no. 9 in Table 2).

**Treatment for ARF episodes**

Treatment modalities depended on the decision of the attending doctor. Treatment conducted at the first episodes included haemodialysis in 12 patients, diuretics without haemodialysis in seven, and fluid control only in 35. In the 11 recurrent episodes, haemodialysis was carried out in only one episode. The maximum serum creatinine level in the first episodes ($5.97 \pm 3.38 \text{ mg/dl, } n=53$) was significantly higher than that in subsequent episodes ($4.19 \pm 2.50 \text{ mg/dl, } n=14$) ($P = 0.045$). The time lag from symptom onset to hospital visit ($3.5 \pm 1.9 \text{ days; median 3 days}$) was significantly longer in the first episodes than in subsequent episodes ($2.0 \pm 0.6 \text{ days; median 2 days}$) ($P = 0.015$).

**Guidance for prevention of ARF**

In terms of doctor’s guidance on prevention of recurrence of ARF episode, 18 patients were instructed to restrict exercise, 12 to restrict use of non-steroidal anti-inflammatory drugs, 16 to ensure adequate fluid

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**Table 2. Clinical characteristics of patients with recurrent episode of exercise-induced acute renal failure**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Recurrence no.</th>
<th>Gender</th>
<th>Age</th>
<th>Defect portion</th>
<th>Serum uric acid (mg/dl)</th>
<th>Daily exercise</th>
<th>Guidance against recurrence</th>
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<tbody>
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<td>Water intake ROE NS Vit E Vit C</td>
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<td>1</td>
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<td>17</td>
<td>PRRD</td>
<td>0.6</td>
<td>?</td>
<td>–</td>
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<tr>
<td>2</td>
<td>1</td>
<td>M</td>
<td>22*</td>
<td>PRRD</td>
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<td>+</td>
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<tr>
<td>3</td>
<td>1</td>
<td>M</td>
<td>21</td>
<td>PRRD</td>
<td>0.7</td>
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<td>–</td>
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<td>4</td>
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<td>M</td>
<td>15</td>
<td>PRRD</td>
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<td>5</td>
<td>5</td>
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<td>PRRD</td>
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<td>6</td>
<td>1</td>
<td>M</td>
<td>33*</td>
<td>ET</td>
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<tr>
<td>7</td>
<td>1</td>
<td>M</td>
<td>17</td>
<td>PRRD</td>
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<td>8</td>
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<td>PRRD</td>
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<td>9</td>
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<td>10</td>
<td>1</td>
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<td>18</td>
<td>PRRD</td>
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<td>11</td>
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<td>PRRD</td>
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PRRD, pre-secretory reabsorption defect; TD, total transport defect; ROE, restriction of exercise; NS, restriction of non-steroidal anti-inflammatory drug administration.

\*Age at first episode unknown.

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*Fig. 3.* Distributions of maximal serum levels of creatinine (Cr) and uric acid (UA) during ARF and minimal uric acid after recovery. Open circles = episodes treated with dialysis; closed circles = episodes treated without dialysis. Mean±1 SD is represented by error bars.
intake during and after exercise, seven to take daily ascorbic acid supplement, and three to take z-tocopherol. Sixteen patients did not receive any guidance. The relationship of each type of guidance to ARF recurrence was analysed by Fisher’s exact probability test. Only exercise restriction was inversely related to ARF recurrence ($P = 0.017$).

**Analysis of risk factors for recurrence**

The clinical characteristics of 13 patients with recurrent ARF episode(s) are shown in Table 2. Female patients never experienced recurrence. We evaluated the relationship between ARF recurrence and various factors using a univariate analysis as shown in Table 3. The small number of female patients in the present series seemed to result in an insignificant relationship for the male factor ($P = 0.15$). The other factors were not significant risk factors of ARF recurrence. A multivariate analysis with a logistic regression model showed similar results (data not shown). The likelihood of recurrent ARF was not related to the type of uric acid handling defect, the baseline level of uric acid, the age at the first episode or daily exercise.

**Discussion**

Hypouricaemia with hyperuricosuria associated with an isolated renal tubular defect is well known to be at risk of urolithiasis and ARF [1,2]. However, the pathogenesis and clinical details of ARF associated with renal hypouricaemia remain unknown. In a recent report [2], we summarized the clinical features of 19 reported cases. Briefly, we found a high prevalence of ARF (17 of 19 patients, 89.5%) among Japanese patients with renal hypouricaemia, and six of 19 patients with recurrent ARF. However, the risk factor of ARF recurrence was not obvious. Therefore, we conducted a questionnaire-based survey in Japan to define the clinical features and risk factor(s) of recurrence with the aim of developing appropriate preventive guidance.

The present study clarified several characteristic features. First, the majority of patients were males, with a male:female ratio of 8:1. Moreover, all cases with recurrent ARF episode(s) were males. The incidence of renal hypouricaemia was reported to be 0.16% of males and 0.23% of females in normal adults [3]. Igarashi [17] reported that three (0.24%) of 1249 males and seven (0.56%) of 1256 females had a serum uric acid concentration <2.0 mg/dl among healthy Japanese children. Therefore, male predominance of exercise-induced ARF is unrelated to the incidence of renal hypouricaemia. Strenuous exercise causes a sequential increase in free radical levels [18–20]. Oxygen free radicals appear to play a crucial role in the pathogenesis of ischaemic ARF [21]. Oxygen free radicals have a vasoconstrictive function, leading to a reduced glomerular filtration rate by directly inactivating cyclooxygenase in the epithelial cells. Ames et al. [22] have suggested that the plasma uric acid serves as a powerful antioxidant and free radical scavenger. Therefore, patients with renal hypouricaemia may be at risk of free radical damage to the kidney during exercise. In addition to free radicals, exercise causes increased levels of endothelin, catecholamines, angiotensin II, arginine vasopressin, endotoxin, cytokines and leukotrienes [20]. These exercise-induced mediators also may facilitate renal ischaemia. Assuming this hypothesis to be true, we may explain the reason for the male predominance of this disease entity from the probability of strenuous exercise. According to Tiidus [23], oestrogen has potent antioxidant properties and may influence the degree of exercise-induced muscle damage and repair processes. This may be one explanation for the gender difference in the incidence of exercise-induced ARF.

Secondly, there was a seasonal/monthly variation in the occurrence of ARF. In this study, ARF episodes were found to occur predominantly in May, September and October, and this trend was especially marked in patients who had ARF episodes induced by short-distance racing. The seasonal/monthly variation seems to coincide with the months in which most athletic meetings are held in Japan. Therefore, ARF in hypouricaemic patients may be associated with specific sports such as short-distance races.

Thirdly, renal biopsies in the present study demonstrated acute tubular necrosis or minimal change without any findings of acute uric acid nephropathy. In contrast, Erley et al. [3] suggested renal tubular obstruction by uric acid crystals. At present, there is no adequate explanation for these disparate data. In a case reported by Erley et al. [3], a renal biopsy showed amorphous uric acid crystals in some of the tubular lumina. However, the histological findings of this patient may be invalid as an outcome of ARF. Furthermore, the short time lag between exercise and symptom onset in the present study also suggests that ARF in hypouricaemic patients is due to a vasoconstriction mechanism rather than cast formation as a result of uric acid nephropathy. Ishikawa et al. [4] reported two cases of hypouricaemia demonstrating patchy wedge-shaped high contrast regions in contrast computed tomography (CT), indicative of patchy renal vasoconstriction. On the other hand, Yuen et al. [9] mentioned that the absence of uric acid precipitation in
patients other than that of Erley et al. was due to late timing of their kidney biopsies. They also claimed that increased renal excretion of uric acid during exercise was responsible for the ARF, based on a preventive effect by allopurinol. However, in their trial, it is possible that allopurinol served the function of free radical scavenger [24]. In our study, there was no finding of acute uric acid nephropathy in the 12 kidney biopsies performed within 1 week after onset of ARF. This finding seems to support the hypothesis that the vasoconstriction mechanism is responsible for the exercise-induced ARF. Renal biopsies can provide some information, but it would still be limited by sampling error because uric acid precipitation tends to occur in the renal medulla and papilla.

Fourthly, the first symptoms were variable and mild. Renal failure improves rapidly when factors including hypovolaemia and/or hypotension are eliminated. If the aetiological factors are not rapidly modified and renal hypoperfusion persists, a gradual and deleterious lesion of the renal parenchyma ensues, leading to a loss of the capacity of the kidney to concentrate and conserve sodium, and the risk of ischaemic tubular necrosis. In our study, the rate of haemodialysis and the maximum serum creatinine levels were clearly higher in the first ARF episodes as compared with the recurrent episodes. Therefore, early recognition and treatment are important to improve the renal outcome. The prognosis of renal hypouricaemia-associated ARF also seems to be favourable because no patient developed chronic renal failure in our study. However, there may be a bias in patient outcome in the present questionnaire survey, because the majority of the patients had only one ARF episode that recovered completely, and it was difficult to accumulate data for long-term follow-up. Alternatively, symptoms mimicking the common cold in this type of ARF might have hindered the detection of an ARF episode. Chronic renal lesions were present in one patient who experienced at least four episodes of exercise-induced ARF. Laboratory findings in this patient showed normal creatinine clearance in spite of the urine concentrating disability. Therefore, the possibility that we underestimated the recurrence of ARF cannot be excluded, and the final outcome in these patients remains unknown.

Finally, the patients were instructed mainly to restrict strenuous exercise and take enough water after exercise. Although restriction of strenuous exercise is likely to prevent recurrence, our data cannot confirm the efficacy of restriction of strenuous exercise to avoid ARF. To date, there is no ideal guidance to prevent ARF recurrence. However, as noted in the paper by Yeun and Hasbargen [9], allopurinol may be useful for the prevention of recurrences.

In conclusion, this study provides data on the typical clinical features of exercise-induced ARF associated with renal hypouricaemia. The reason for the heterogeneity and the pathogenesis, however, cannot be explained and require further studies. The molecular basis for urate handling in the human kidney remains unclear because of the difficulties in understanding diverse urate transport systems and species differences [25]. Recently, Enomoto et al. [26] reported a homozygous point mutation in the SLC22A12 gene that encodes urate anion transporter 1 in patients with renal hypouricaemia. Future development in molecular research may explain the heterogeneity of exercise-induced ARF associated with renal hypouricaemia and contribute to the formation of ideal guidance for individual cases. Also, further studies including the effect of dehydration and exercise on renal functions may contribute to clarifying the pathogenesis of ARF in these patients.

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References


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