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Predictors of rheumatoid arthritis in patients who have monoarthritis in a knee joint

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Abstract To determine the predictive factors for rheumatoid arthritis (RA), 79 patients (11 men, 68 women; average age at onset of symptoms 37.1 years) with fixed joint effusion of one knee joint, of minimum 6 months' duration, were divided into three groups: group I, 11 patients (14%) who progressed to RA; group II, 8 patients (10%) with the correct diagnosis, except that RA became apparent during the subsequent follow-up; group III, 60 patients (76%) whose joint effusion resolved. In group I, the degree of joint effusion and the serological values of interleukin (IL)-1β, IgG-RF, and rheumatoid factor (RF) tended to be higher than those in the other groups at the time of our initial examination. The synovial fluid concentrations of IL-1β and IgG-RF in group I were significantly higher than those in the other groups. Magnetic resonance imaging (MRI)-determined stage and histological assessment of synovial inflammation also tended to be higher in group I than in the other groups. This study revealed that it might be possible to predict the outcome of cases of monoarthritis by examining IL-1β and IgG-RF levels in the synovial fluid, in addition to various elevated inflammation signs in the knee joint.

Key words Interleukin-1 · Rheumatoid factor · Rheumatoid monoarthritis · Synovial fluid

Introduction

Nonspecific monoarthritis is a common form of arthritis that requires only conservative treatment. However, as the onset of rheumatoid arthritis (RA) sometimes occurs in conjunction with monoarthritis,[1] this causes problems for the physician, who must respond to both the patient's immediate concerns regarding therapy, and to concerns regarding the long-term prognosis. Although many physical laboratory investigations, and roentgenological and histological studies have been conducted in order to clarify the clinical conversion from monoarticular synovitis to rheumatoid arthritis,[2–5] almost all of them have failed to show any clear relationship between the two conditions. Therefore, it is important that the early indicators of RA are clarified.

Monoarthritis appears most commonly in the knee joint as a result of monoarticular-type RA, degenerative arthritis, infectious arthritis, pigmented villonodular synovitis, or other diseases.[2,4,5] In this study, we examined the clinical, laboratory, imaging, and pathological features of patients with monoarthritis in the knee joint in order to determine the predictive factors for RA.

Patients and methods

In 1993–1994, a project to check the cytokine levels of serum and joint fluid was conducted by four centers (the Department of Orthopedic Surgery, Sapporo Medical University, the Department of Orthopedic Surgery, Asahikawa Kousei General Hospital, the Sapporo Maruyama Orthopedic Hospital, and the Sapporo Gorinbashi Orthopedic Hospital), and 940 men and women, aged 17–79 years, were enrolled. Among the participants whose blood and synovial fluid concentrations of interleukin 1β (IL-1β), IgG-rheumatoid factor (RF), RF, and biopsy findings were examined, 103 patients who were determined to have nonspecific monoarthritis were retrospectively identified. Nonspecific monoarthritis was defined as the presence of a fixed joint effusion of one knee joint, of minimum 6 months' duration, that remained undiagnosed despite standard examinations. Patients with any of the following symptoms were excluded: (1) any sign of infection, as demonstrated by Gram's stain culture of synovial fluid or biopsy material; (2)

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any history or physical sign of trauma or mechanical derangement; (3) any sign of osteoarthritis. A total of 81 patients met the criteria for inclusion. Findings on physical and laboratory examination, magnetic resonance imaging (MRI) and biopsy at the time of the initial joint effusion were reviewed retrospectively. Follow-up data were obtained during office visits, from telephone interviews, or from written questionnaires. Follow-up was continued until 2000. Follow-up was completed in 79 (96%) of the 82 patients. The mean duration of follow-up was 6.2 years.

Of the 79 patients with completed follow-up, 68 were women and 11 were men. The mean age at onset of symptoms was 37.1 years (range 19–47 years), and the mean duration of symptoms was 7.2 months (range 6–20 months). The study population was divided into three groups according to clinical outcome: group I, 11 patients (14%) who fulfilled the American Rheumatism Association (ARA) 1987 revised criteria[6] during subsequent follow-up; group II, 8 patients (10%) with the correct diagnosis, except that RA became apparent during the subsequent follow-up (5 patients with psoriasis, 2 patients with Behçet's disease, and 1 patient with pustulotic arthroosteitis (PAO)); group III, 60 patients (76%) whose joint effusion had resolved, and who remained undiagnosed (Table 1). At the time of the initial joint effusion, C-reactive protein (CRP) and erythrocyte sedimentation rate in all groups were high. Four patients in group I had anemia (Hb less than 10 g/dl) with positive antinuclear antibody. Two patients with Behçet's disease in group II had high values of IgA (600 and 660 mg/dl). These patients were suspected of having RA, Behçet's disease, and other diseases, but no definite diagnosis was reached.

The following laboratory studies were undertaken following an assessment of the degree of joint effusion performed on admission: blood and synovial fluid concentrations of IL-1β, IgG-RF, and RF. Synovial biopsy was performed under needle arthroscopy after MR imaging of the affected knee joint. Effusion of the knee joint was graded from 0 to 3 (Table 2).[7,8] IL-1β and IgG-RF were measured by radio immunoassay solid-phase methods (sensitivity >10 pg/ml) and enzyme-linked immunosorbent assay. The IgG-RF of the sample examined was expressed as index in comparison with that of a normal sample.

Coronal and sagittal T1-weighted spin–echo images (TR/TE slice thickness = 5 mm) were obtained using a 1.5 Tesla magnetom unit (SIGNA Advantage Ver. 4.8, GE Yokogawa Medical System). After T1-weighted scanning, the patient was kept in the same position in the MR unit, and 0.2 ml/kg body weight (0.1 mmol/kg) of gadolinium-DTPA was injected into a cubital vein. After 5–15 min, the T1-weighted scanning was repeated. The severity of any changes was graded on a scale of 0–V.[9]

After disinfection of the leg and local anesthesia of the skin and joint, a 1.8–2.7-mm needle arthroscope was introduced into the knee joint via the anterolateral approach. Samples were taken from the suprapatellar pouch and the lateral and medial gutters. Biopsy forceps were then inserted through the other portal into the knee joint.[10] Four samples were taken at inflamed sites. Biopsy specimens were stained with hematoxylin and eosin. Synovial inflammatory activity was assessed by averaging the individual grades of the specific parameters (a–i) over four sampling points, as shown in Table 3. The inflammatory activity of each parameter was graded as 0 (none), 1 (mild), 2 (moderate), or 3 (severe), and the average of each set of parameters was calculated as the average grade of the four biopsy samples from each knee. The knees were scored on the basis of the average grade, as follows: knees with an average grade of ≤1 for the given parameters scored 1, the knees with an average grade of 1–2 scored 2, and those with an average grade of <2 scored 3.[11]

Statistical analysis of the data was performed using the Mann–Whitney *U* test.

Table 1. Demographic data on 79 patients with nonspecific monoarthritis, grouped by outcome

Characteristic	All patients	Group I	Group II	Group III
No. of patients	79	11	8	60
Mean age (years)	37.1	31.2	32.2	38.9
Range	19–47	19–45	19–47	20–47
Male/female	11/68	2/9	1/7	8/52
Mean duration of symptoms (months)	7.2	8.1	8.5	6.8
Range	6–20	6–20	6–17	6–11

Table 2. Degree of joint effusion

Score	Degree of joint effusion
3	Considerable effusion, tense joint capsule
2	Moderate effusion with cross fluctuation and patellar ballottement
1	Slight effusion, positive bulge sign
0	No effusion

Results

There were no significant differences between the three groups of patients with regard to age, gender, symptom duration, or types of drug administered. The demographic features for patients in each group are shown in Table 1.

Table 3. Score of pathological findings

Score	Average grade of 4 biopsy samples from each knee	Specific parameters for synovial inflammatory activity grade (0–3)
3	<2, ≤3	(a) Subsynovial infiltration of polymorphonuclear leukocytes (b) Subsynovial infiltration of mononuclear leukocytes (c) Surface fibrin deposition
2	<1, ≤2	(d) Multiplication of the synovial lining (e) Villous hypertrophy of the synovial surface (f) Proliferation of blood vessels
1	≤1	(g) Perivascular edema (h) Formation of granulation tissue (i) Fibrosis

Table 4. Degree of joint effusion at initial examination

	n	Degree of joint effusion score
All patients	79	2.0 ± 0.8
Group I	11	2.5 ± 0.9
Group II	8	2.1 ± 0.6
Group III	60	2.0 ± 0.8

Values are expressed as mean ± standard deviation

Table 5. Serological parameters of IL-1β, IgG-RF, and RF at initial examination

	n	IL-1β (pg/ml)	IgG-RF	RF (IU-ml)
All patients	79	6.8 ± 8.9	0.4 ± 0.9	17 ± 18
Group I	11	15 ± 17	0.9 ± 1.6	29 ± 35
Group II	8	10 ± 8.5	0.4 ± 0.4	17 ± 12
Group III	60	4.9 ± 5.6	0.4 ± 0.8	15 ± 12

Values are expressed as mean ± standard deviation

Degree of joint effusion at initial examination

At the initial investigations, the mean score of all patients was 2.0. The mean score of group-I patients (2.5) tended to be higher than that of group-II (2.1) and group-III (2.0) patients, as shown in Table 4.

Serological parameters of IL-1β, IgG-RF, and RF at initial examination

The mean values of IL-1β, IgG-RF, and RF were 6.8 pg/ml, 0.4, and 17 IU/ml, respectively, in all patients. The mean values in group-I patients again tended to be higher than those in group-II and group-III patients, as shown in Table 5.

Synovial fluid parameters of IL-1β, IgG-RF, and RF at initial examination

The mean values of IL-1β, IgG-RF, and RF were 9.2 pg/ml, 0.5, and 16 IU/ml, respectively, in all patients. The synovial fluid concentrations of IL-1β ($P < 0.05$) and IgG-RF ($P < 0.01$) in group-I patients were significantly higher than those in the other groups, as shown in Table 6.

Synovial fluid concentrations of IL-1β in group-II patients at the time of initial examination were significantly higher than those in group-III patients ($P < 0.0001$). No significance was observed in the secretion patterns of IL-1β, IgG-RF, and RF between patients with psoriatic arthritis and those with arthritis due to Behçet's disease or PAO.

MRI findings at initial examination

At the initial examination, the mean score of all patients was 2.1. The mean score of group-I patients tended to be higher than those of group-II and group-III patients, as shown in Table 7.

Table 6. Synovial fluid parameters of IL-1β, IgG-RF, and RF at initial examination

	n	IL-1β (pg/ml)	IgG-RF	RF (IU-ml)
All patients	79	9.2 ± 11	0.5 ± 0.7	16 ± 15
Group I	11	28 ± 10*	1.7 ± 1.3***	25 ± 28
Group II	8	20 ± 4.6**	0.3 ± 0.3	17 ± 19
Group III	60	4.2 ± 5.6	0.3 ± 0.2	15 ± 11

Values are expressed as mean ± standard deviation
* $P < 0.05$; ** $P < 0.0001$; *** $P < 0.01$

Table 7. MRI findings at initial examination

	n	MRI score
All patients	79	2.1 ± 7.9
Group I	11	2.6 ± 1.1
Group II	8	2.3 ± 0.9
Group III	60	2.0 ± 0.9

Values are expressed as mean ± standard deviation

Table 8. Pathological findings at initial examination

	n	Pathological score
All patients	79	0.7 ± 0.8
Group I	11	1.0 ± 0.7
Group II	8	0.7 ± 1.0
Group III	60	0.6 ± 0.8

Values are expressed as mean ± standard deviation

Pathological findings at initial examination

At the initial examiation, the mean score of all patients was 0.7. The mean score of group-I patients tended to be higher than those of group-II and group-III patients, as shown in Table 8.

Discussion

The prognosis for nonspecific monoarthritis appears to be good in that 60 (76%) of 79 patients showed no symptoms after onset and during subsequent follow-up. However, nonspecific monoarthritis is not a trivial clinical problem. Eleven patients (14%) progressed to RA after a protracted duration of symptoms. The reported proportion of cases of RA developing from nonspecific monoarthritis ranges from 6% to 27%.[12–14] The large discrepancy between these findings is probably due to differences in study design, patient selection, and diagnostic criteria.

In group-I patients, who all developed RA, the degree of joint effusion and the serological values of IL-1β, IgG-RF, and RF tended to be higher than those in the other groups at the time of our initial examination. A notable finding was that the synovial fluid concentrations of IL-1β and IgG-RF in group I were significantly higher than those in the other groups. The synovial fluid concentrations of IL-lβ have

been reported to be higher in patients with RA because rheumatoid patients are genetically programmed to produce higher amounts of IL-lβ.[15,16] It has also been reported that IgG-RF is positive, although RF (IgM-RF) is negative, in the synovial fluid of the monoarthritis of a rheumatoid knee joint, because the number of IgG-producing cells is much greater than that of IgM-producing cells among the rheumatoid synovial cells.[17–19] Thus, the measurement of IL-1β and IgG-RF in synovial fluid is the most important of the overall clinical assessments for the early diagnosis of a case where monoarthritis in a knee joint will progress to RA.

MRI-determined stage and histological assessment of synovial inflammation also tended to be higher in group I than in the other groups. Ostergaard et al.[10] have demonstrated correlations between MRI and histopathologic findings, yet many authors have reported that the synovial histopathologic differences between RA and other diseases are quantitative rather than qualitative.[20–22] The present results clarify the supplementary predictive factor that synovial inflammatory activity is higher in knees which progress to RA than in knees with joint effusion due to other diseases.

Some authors have reported that the joint inflammatory activity in psoriatic arthritis is lower than in rheumatoid arthritis, but higher than in osteoarthritis. A significant increase in synovial fluid IL-1β at disease onset has been reported to be useful in predicting the outcome of such disorders as psoriatic monoarthritis.[16,23] Our study showed the same tendency. The joint inflammatory activity as revealed by symptomatic, laboratory, imaging and pathological findings in group II, which included patients with psoriatic arthritis, was between those of groups I and III. The synovial fluid concentrations of IL-1β in group II at the time of initial examination were significantly higher than those in group III. We also found that the pattern of clinical findings, including synovial fluid examination, failed to reveal any differentiation between patients with psoriatic arthritis and those with arthritis due to Behçet's disease or PAO. Keith et al.[24] have reported that the pattern of cytokine secretion did not allow for differentiation between the new onset synovitis subsets. Thus, the groups of patients diagnosed with different forms of new-onset synovitis, but not RA, suggest that clinically distinct diseases may share a common initiating event or immune response pathway.

Finally, this study revealed that it might be possible to predict the outcome of cases of monoarthritis by examination of IL-1β and IgG-RF levels in the synovial fluid, in addition to various elevated inflammation signs in the knee joint. Furthermore, this study also demonstrated the importance of an examination of those levels as an auxiliary means of diagnosing RA. Careful observation or preliminary treatment for RA should be considered for patients who show the characteristic features described above.

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