Estimated Prevalence and Incidence of Adult Still's Disease: Findings by a Nationwide Epidemiological Survey in Japan

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To estimate prevalence and incidence of adult Still's disease in Japan, and to describe the epidemiological features of the patients, a nationwide epidemiological survey was conducted in 1994. The study consisted of two questionnaires which were distributed to the heads of the relevant departments, randomly sampled, in hospitals throughout Japan. Following major epidemiological findings emerged from the study: (a) The total annual number of patients treated for adult Still's disease was estimated as 1,100 in 1993 in Japan. The estimated crude prevalence among those aged 16 years or older were calculated as 0.73 and 1.47 per 100,000 population for males and females, respectively, with the corresponding crude incidence rate of 0.22 and 0.34. (b) The sex ratio (female to male) of the reported patients was 2.1. This female predominance might be specific to Japan, though additional surveys in other countries will be warranted. The mean age of the patients was 38.1 years, and female patients tended to be older than male ones; 50% of the female patients aged 40 years or older, while so did only 28% of the male patients.
J Epidemiol, 1997; 7 : 221-225.

Still's disease, adult-onset, prevalence, Incidence, Japan

Adult Still's disease is one of the important diseases in the differential diagnosis of fever of unknown origin [1]. Only a few epidemiological studies, however, have been conducted [2-6], and no large-scale survey has been carried out. Therefore, we have only a little information on the prevalence or incidence of the disease [3].

In 1994, Research Committee on Epidemiology of Intractable Diseases and that on Autoimmune Diseases undertook a nationwide epidemiological survey on adult Still's disease in Japan. The survey aimed to estimate the prevalence of the disease, to describe the detailed clinico-epidemiological features, and to provide the information for the appropriate health service planning. In this communication, we report the estimated prevalence and incidence of adult Still's disease, and the distribution of patients by sex and age. The detailed clinico-epidemiological features will be described elsewhere.

MATERIALS AND METHODS

The classification criteria used in the present study were prepared by Research Committee on Adult Still's Disease, Japan [6] (Table 1). In the criteria, patients aged 16 years or older was defined as eligible cases. Classification of adult Still's disease requires five or more criteria including at least two major criteria. Any disease listed under "Exclusions" in the table should

Received January 10, 1997 ; accepted March 21, 1997.
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Table 1. Classification criteria for adult Still's disease.

Major criteria
1. Fever of 39℃ or higher, lasting 1 week or longer
2. Arthralgia lasting 2 weeks or longer
3. Typical rash
4. Leukocytosis (10,000/mm³ or greater) including 80% or more of granulocytes

Minor criteria
1. Sore throat
2. Lymphadenopathy and/or splenomegaly
3. Liver dysfunction
4. Negative RF and negative ANA*

Exclusions
1. Infections (especially, sepsis and infectious mononucleosis)
2. Malignancies (especially, malignant lymphoma)
3. Rheumatic diseases (especially, polyarteritis nodosa and rheumatoid vasculitis with extraarticular features)

*RF : rheumatoid factor, ANA : antinuclear antibody.

be excluded. The departments surveyed were randomly selected through stratified sampling from all the departments of internal medicine in hospitals throughout Japan, since most of the patients with adult Still's disease were treated there in Japan. We stratified the hospitals according to the type (general or university) and the number of beds (Table 2). The sampling was conducted using the registry of all the hospitals in Japan, which was obtained from the Ministry of Health and Welfare by permission. We also selected some departments which are known expectedly to treat many patients, regardless of the above-mentioned strata, to increase the study efficiency. These departments were listed by Research Committee on Autoimmune Diseases, and were included as the additional strata of "selected departments" of internal medicine and allergy/rheumatic diseases (Table 2). Statistically, these strata can be treated just as other groups stratified by the type of hospitals and the number of beds in the hospitals [6].

In this survey, two questionnaires were distributed to the above-mentioned departments, as so were in the previous nationwide surveys for intractable diseases [7,8]. The first questionnaire simply inquired the number of patients with adult Still's disease who satisfied the classification criteria mentioned above. To be eligible in the present survey, a patient had to have visited the department and have been treated in the year 1993. This questionnaire was directly mailed to the heads of 1,561 departments in January 1994, with a sheet of paper which described the classification criteria.

By the second questionnaire, detailed clinico-epidemiological information on individual patient was surveyed. This form covered the major and minor classification criteria of adult Still's disease with exclusions so as to know the proportion of patients who actually satisfy the criteria. The second questionnaire was forwarded to the heads of the departments, which reported the patients with adult Still's disease by the first questionnaire.

A patient reported from more than one hospital or department was treated as a "duplicate" one. We assessed whether a patient met the classification criteria according to the clinical data provided on the second questionnaire. When sufficient information was not available for this judgment, we again asked the relevant attending doctor to provide more detailed information on the patient. Patients who did not satisfy the criteria were excluded from the study as "inappropriate" cases.

An annual number of patients treated for adult Still's disease was estimated, based on the assumption that the response from departments is independent of the number of patients treated there [6,8].

Table 2. Number of the total, surveyed, responded departments and number of the reported patients with adult Still's disease in the first and second survey.

Departments	Strata	First survey						Second survey
		Total No. of departments	No. of surveyed departments	Sampling rate (%)	No. of responded departments	Response rate (%)	No. of reported patients	No. of reported patients
Internal medicine	General hospitals with less than 100 beds	4,462	220	4.9	111	50.5	7	2
	General hospitals with 100-199 beds	2,199	217	9.9	105	48.4	5	1
	General hospitals with 200-299 beds	898	180	20.0	91	50.6	16	4
	General hospitals with 300-399 beds	447	178	39.8	96	53.9	14	5
	General hospitals with 400-499 beds	209	168	80.4	70	41.7	31	11
	General hospitals with 500 or more beds	199	199	100.0	94	47.2	89	17
	University hospitals	267	267	100.0	200	74.9	99	35
	Selected departments	106	106	100.0	53	50.0	118	30
Subtotal		8,787	1,535	17.5	820	53.4	379	105
Allergy/ rheumatic diseases	Selected departments	26	26	100.0	17	65.4	34	20
Total		8,813	1,561	17.7	837	53.6	413	125

The number of patients in stratum k was estimated as

$$\hat{\alpha}_k = \frac{n_k}{N_k} \sum_i i \cdot N_{ki}$$

where n_k, N_k and N_{ki} denote the total number of departments, the number of responded departments, and the number of departments with i patients in stratum k, respectively. The 95% confidence interval of $\hat{\alpha}_k$ was

$$\left(\alpha_k - 1.96 \cdot s_k,\ \alpha_k - 1.96 \cdot s_k\right)$$

$$s_k = \sqrt{\frac{\frac{1}{N_k}\sum_i i^2 \cdot N_{ki} - \left(\frac{1}{N_k}\sum_i i \cdot N_{ki}\right)^2}{n_k - 1} \cdot n_{k3}\left(\frac{1}{N_k} - \frac{1}{n_k}\right)}$$

where s_k is the estimated standard error of $\hat{\alpha}_k$

The total number of patients, $\hat{\alpha}$ was computed as follows:

$$\hat{\alpha} = \sum_k \hat{\alpha}_k$$

and the 95% confidence interval was

$$\left(\hat{\alpha} - 1.96 \cdot s,\ \hat{\alpha} + 1.96 \cdot s\right), \quad s = \sqrt{\sum_k s_k^2}$$

where s is the estimated standard error of $\hat{\alpha}$.

The estimated total annual number of patients was corrected using the proportion of "duplicated" cases (D) and that of "inappropriate" cases (I) among the patients who were reported in the second survey, i.e. the number was multiplied by 1–(D+I). The population of Japan in 1993 was used to calculate the prevalence of the disease. The crude prevalence by sex was estimated as

$$p = \frac{N \cdot A}{P}$$

where N, A and P denote the estimated annual number of patients, the proportion of male/female patients in the second survey, and sex-specific population in Japan (16 years or older) in 1993, respectively. Its 95% confidence interval, however, could not be computed since source of error was not only in the estimated annual number of patients treated for adult Still's disease but also in the proportion of male/female patients in the second survey. Age-specific prevalence was not shown, because patients with adult Still's disease reported in the second survey were too few to show the age-specific figures in detail. To estimate the crude incidence rate by sex, the sex-specific prevalence was multiplied by the corresponding proportion of the patients who newly developed the disease in 1993.

RESULTS

Among 1,561 departments, 837 replied to the first questionnaire; the response rate being 53.6% with 413 patients reported in number (Table 2).

In response to the second questionnaire, 146 cases (35.4% of the patients reported in the first survey) of adult Still's disease were reported. Among them, none was a "duplicate" case. Two patients were excluded from our study, because we could not obtain sufficient information to determine whether they satisfied the classification criteria. Of the remaining 144 patients, 19 (13.2%) were classified as "inappropriate" cases;

Table 3. Sex and age distribution of the patients with adult Still's disease reported on the second questionnaire.

	Males		Females		Total	
Age	N	%	N	%	N	%
16-19	3	7.7	4	4.8	7	5.7
20-24	7	17.9	13	15.5	20	16.3
25-29	3	7.7	12	14.3	15	12.2
30-34	4	10.3	7	8.3	11	8.9
35-39	11	28.2	6	7.1	17	13.8
40-44	3	7.7	7	8.3	10	8.1
45-49	3	7.7	10	11.9	13	10.6
50-54	4	10.3	8	9.5	12	9.8
55-59	0	0.0	10	11.9	10	8.1
60-64	0	0.0	2	2.4	2	1.6
65-69	1	2.6	3	3.6	4	3.3
70-74	0	0.0	0	0.0	0	0.0
75-79	0	0.0	2	2.4	2	1.6
Subtotal	39	100.0	84	100.0	123	100.0
Age unknown	1		1		2	
Total	40		85		125	

13 did not meet the criteria, 5 actually first visited the departments in 1994, and one visited only before 1993. They were also excluded from the study, leaving 125 eligible patients with adult Still's disease. The one patient who visited the department only before 1993 might have been suffering from the disease also in 1993, but we had to exclude this patient because we asked only the number of patients who had visited the departments in 1993 in the first survey. The distribution of the patients identified in the second survey by department, type of the hospital, and number of beds in the hospital was also presented in Table 2. This distribution was quite comparable with that of the patients reported to the first questionnaire ($p = 0.21$ by chi-square test).

Table 3 shows the sex and age distribution of these 125 patients. The sex ratio (female to male) was 2.1. The mean age (±standard deviation) was 38.1±14.3 years, and patients aged 40 years or older was more common in women; such patients accounting for 50.0% in females, whereas only 28.2% in males ($p = 0.023$ by chi-square test).

Taking the proportion of "inappropriate" cases into account, the total annual number of patients with adult Still's disease, who were treated in 1993 throughout Japan, was estimated as 1,100 (95% confidence interval 900-1,400). The estimated crude prevalence among those aged 16 years or older were calculated as 0.73 and 1.47 per 100,000 population in males and females, respectively. According to the second questionnaire survey, 30.0% (12/40) and 22.9% (19/83) of the male and female patients were found as having newly developed the disease in 1993, respectively. These figures yielded the estimated crude incidence rates of 0.22 and 0.34 per 100,000 population, correspondingly.

DISCUSSION

To our knowledge, this is the first nationwide epidemiological survey of adult Still's disease in the world. Because this disease is quite rare, large-scale studies like ours are essentially required in order to elucidate the epidemiological features of this disease.

Several sets of criteria have been proposed for adult Still's disease [8-12]. The criteria used in the present survey have showed excellent sensitivity (96.2%) and specificity (92.1%); indicating better discriminating performance than other sets of criteria [9]. To test the sensitivity and specificity, patients with adult Still's disease and control patients were selected by 11 experts in this disease before defining the criteria [9]. Exclusions were not applied to the control patients. Excellent sensitivity (99.3%) was revealed even when the criteria was applied to non-Japanese cases collected from the literature [13].

One methodological issue in our survey might be that only the patients treated in hospitals (with 20 or more beds) were surveyed, ignoring those treated in clinics (with less than 20 beds or without beds). It would be, however, unlikely in Japan that many patients with adult Still's disease are diagnosed and treated only in clinics, since its diagnosis and treatment will be rather difficult practices for general practitioners.

We estimated an annual number of patients treated throughout Japan under the assumption that the response to the first questionnaire from each department is independent of the number of patients treated there [9]. This assumption should be validated, since our response rate (53.6%) was relatively low. In the present study, we could not obtain any detailed information relevant to the non-responded departments for validating the assumption. Hashimoto et al. [10], however, compared the mean number of the patients with an intractable disease (idiopathic thrombopenic purpura) financially subsidized for treatment among the responded departments with that among the non-responded departments; the ratio of the former to the latter was found to be between 1.0 and 1.1. This figure essentially suggests that the assumption might be sufficiently valid for a nationwide epidemiological survey of such rare disease as adult Still's disease.

In response to the second questionnaire, only 35.4% of the patients identified in the first survey were reported. This would indirectly affect the estimate of annual number of patients, since we used the proportion of "inappropriate" cases among the 146 patients reported in the second survey to estimate the total annual number of patients with adult Still's disease. It would be possible that physicians who are more interested in adult Still's disease were likely to reply, with accurate diagnosis, to the second questionnaire. If this is the case, our proportion of "inappropriate" cases would be underestimated, which might probably result in an overestimation of the annual number of the patients treated. In contrast, if some expert physicians for this disease might tend not to response to the second survey, the proportion of "inappropriate" cases would be overestimated. It would be, therefore, another methodological issue, and efforts to obtain the proportion of "inappropriate" cases with more reasonable estimation are to be required in the future surveys. Nevertheless, the patients reported in the second survey was comparable with those reported to the first questionnaire as for the distributions by department, type of the hospital, and number of beds in the hospital; suggesting that the bias mentioned above was not so large.

No epidemiological survey has been conducted in Japan to estimate the prevalence and incidence of adult Still's disease. This implies that the secular trend in its prevalence/incidence could not be discussed. Magadur-Joly et al. [5] have reported the incidence rate of 0.16 per 100,000 population per year in west France, which was somewhat lower than ours (0.22 and 0.34 per 100,000 population in males and females, respectively). The difference in age distributions between the two study populations, however, should be taken into consideration, when comparing these rates correctly.

A multi-center survey conducted by Research Committee on Adult Still's Disease, Japan [2], has disclosed the sex ratio (female to male) of 2.0, which was quite compatible with the present figure (2.1). In contrast to this, Ohta et al. [13] reported almost identical numbers between the two sexes, when reviewing 228 cases reported from all over the world. This discrepant findings might be due to the different sets of criteria, but Magadur-Joly et al. [3] obtained the sex ratio close to 1.0 in west France, using almost the same criteria as ours. Then, our female predominance may possibly be specific to Japan, though additional surveys in other countries will be warranted. Sex ratio of the prevalence (2.0) was slightly higher than that of the incidence (1.5). This, however, may be by chance, because the proportion of male/female patients or that of newly developed the disease in 1993 was based on relatively small number of patients.

Patients aged 40 years or older were more common among women in the present study. This might be at least partly explained by the finding obtained by the multi-center survey [2] that men were more likely to suffer from the disease at much younger ages.

ACKNOWLEDGMENTS

The authors are grateful to the doctors who replied to the questionnaires and made this study possible. We also thank Ms. Hidemi Hattori for her technical assistance.

This study was supported in part by a Grant-in-Aid from the Ministry of Health and Welfare of Japan for Research Committee on Epidemiology of Intractable Diseases and also for Research Committee on Autoimmune Diseases.

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