Estimated Prevalence of Sjögren's Syndrome in Japan: Findings from a Nationwide Epidemiological Survey

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To estimate the prevalence of Sjögren's syndrome (SS) in Japan, and to describe the clinico-epidemiological features, a nationwide epidemiological survey was conducted in 1994. The study consisted of two questionnaires distributed to the relevant departments of hospitals throughout Japan. The first questionnaire inquired the number of the patients treated in 1993, and the second one detailed clinico-epidemiological information of the patients reported. Following major epidemiological findings emerged from the study: (a) The total number of patients treated for SS in 1993, in Japan, was estimated as 17,000 (95% confidence interval 15,000-20,000). The estimated crude prevalence rates were 1.9 and 25.6 per 100,000 population in males and females, respectively. (b) The ratio of female to male patients was 13.7. The peak of age distribution of SS patients reported was in their fifties. The highest prevalence rate was observed among females with their sixth decade; being 62.2 per 100,000 population. J Epidemiol, 1995; 5: 125-129.

Sjögren's syndrome, prevalence, nationwide survey, epidemiology

Sjögren's syndrome (SS) is one of the common systemic autoimmune diseases¹⁻⁷. The accurate prevalence rate of the disease, however, remains to be clarified, since most previous studies which intended to determine the prevalence rate were based on relatively small population³⁻⁷.

In 1994, the Research Committee on Epidemiology of Intractable Diseases and the Research Committee of Autoimmune Diseases, Ministry of Health and Welfare, undertook a nationwide epidemiological survey on SS in Japan. The survey aimed to estimate the prevalence of the disease, to describe the detailed clinico-epidemiological features, and to provide the administrative information for planning its health services.

MATERIALS AND METHODS

The subjects surveyed were patients with primary/secondary SS. The criteria prepared by the Research Committee of Sjögren's Disease in Japan⁸ were used for clinical diagnosis of SS. Both definite and probable cases were included in the present study. The departments surveyed were those of internal medicine, ophthalmology, and otolaryngology in all hospitals, and those of oral surgery in university hospitals, since these departments were known to cover at least 93% of SS patients in Japan⁹. The departments, to which the questionnaires were sent, were randomly selected through stratified sampling. The sampling was conducted using the list of all the hospitals in Japan, which was obtained from the Ministry of Health and Welfare by
permission. The list includes the information on the hospitals such as names, addresses, numbers of beds, and departments in the hospitals. The sampling rate was about 5%, 10%, 20%, 40%, 80%, 100% and 100%, for the stratum of general hospitals with less than 100 beds, 100-199 beds, 200-299 beds, 300-399 beds, 400-499 beds, 500 or more beds, university hospitals, respectively (Table 1). We also selected some departments expected to treat many patients, regardless of the above-mentioned strata, to increase the study efficiency. These departments were included in one of the additional strata for the “selected departments” of internal medicine, ophthalmology, otolaryngology, oral surgery and allergy/collagen diseases (Table 1).

In this survey, two questionnaires were distributed throughout Japan10,11. The first questionnaire inquired the number of patients with SS, who had visited the department and been treated in the year 1993. This questionnaire was directly sent to 3,144 departments in January 1994, with the criteria above-mentioned. The second questionnaire requested detailed clinico-epidemiological information on individual patients (data to be reported elsewhere). It was forwarded to those departments from which SS patients were reported on the first questionnaire. The epidemiological items surveyed were socio-demographic factors such as gender, date of birth, age, address and job; family history; the time of onset; financial subsidization for treatment; and medical care status.

The same patient reported from more than one hospital or department was treated as a “duplicate” one. Patients who had already died before 1993 or who had first visited the hospitals after 1994 were excluded from the study as “inappropriate cases”.

The number of patients treated in 1993 were estimated, based on the assumption that the response from departments is independent of frequency of patients12. The number of patients in stratum k was estimated as

| Table 1. Number of the total, surveyed, responded departments and number of the reported patients with Sjögren’s syndrome in the first survey. |
|---------------------------------|----------------|----------------|----------------|----------------|
| Strata                          | Total No. of departments | No. of surveyed departments | Sampling rate (%) | No. of responded departments | Response rate (%) | No. of reported patients |
|---------------------------------|----------------|----------------|----------------|----------------|
| Internal medicine               | General hospitals with less than 100 beds | 4,462 | 220 | 4.9 | 111 | 50.5 | 46 |
|                                 | General hospitals with 100-199 beds | 2,199 | 217 | 9.9 | 105 | 48.4 | 26 |
|                                 | General hospitals with 200-299 beds | 898 | 180 | 20.0 | 91 | 50.6 | 92 |
|                                 | General hospitals with 300-399 beds | 447 | 178 | 39.8 | 96 | 53.9 | 88 |
|                                 | General hospitals with 400-499 beds | 209 | 168 | 80.4 | 70 | 41.7 | 269 |
|                                 | General hospitals with 500 or more beds | 199 | 199 | 100.0 | 94 | 47.2 | 695 |
|                                 | University hospitals | 267 | 267 | 100.0 | 200 | 74.9 | 932 |
|                                 | Selected departments | 106 | 106 | 100.0 | 53 | 50.0 | 1,467 |
| Subtotal                        |                 | 8,787 | 1,535 | 17.5 | 820 | 53.4 | 3,615 |
| Ophthalmology                   | General hospitals with less than 100 beds | 388 | 20 | 5.2 | 14 | 70.0 | 20 |
|                                 | General hospitals with 100-199 beds | 509 | 52 | 10.2 | 31 | 59.6 | 31 |
|                                 | General hospitals with 200-299 beds | 475 | 93 | 19.6 | 50 | 53.8 | 59 |
|                                 | General hospitals with 300-399 beds | 337 | 128 | 38.0 | 68 | 53.1 | 92 |
|                                 | General hospitals with 400-499 beds | 186 | 146 | 78.5 | 72 | 49.3 | 162 |
|                                 | General hospitals with 500 or more beds | 198 | 198 | 100.0 | 102 | 51.5 | 393 |
|                                 | University hospitals | 110 | 110 | 100.0 | 73 | 66.4 | 699 |
|                                 | Selected departments | 8 | 8 | 100.0 | 3 | 37.5 | 267 |
| Subtotal                        |                 | 2,211 | 755 | 34.1 | 413 | 54.7 | 1,723 |
| Otolaryngology                  | General hospitals with less than 100 beds | 330 | 16 | 4.8 | 10 | 62.5 | 0 |
|                                 | General hospitals with 100-199 beds | 463 | 44 | 9.5 | 17 | 38.6 | 5 |
|                                 | General hospitals with 200-299 beds | 446 | 90 | 20.2 | 55 | 61.1 | 17 |
|                                 | General hospitals with 300-399 beds | 328 | 133 | 40.5 | 84 | 63.2 | 52 |
|                                 | General hospitals with 400-499 beds | 181 | 144 | 79.6 | 87 | 60.4 | 126 |
|                                 | General hospitals with 500 or more beds | 195 | 195 | 100.0 | 117 | 60.0 | 183 |
|                                 | University hospitals | 115 | 115 | 100.0 | 86 | 74.8 | 606 |
| Subtotal                        |                 | 2,058 | 737 | 35.8 | 456 | 61.9 | 989 |
| Oral surgery                    | University hospitals | 84 | 84 | 100.0 | 66 | 78.6 | 325 |
|                                 | Selected departments | 7 | 7 | 100.0 | 7 | 100.0 | 151 |
| Subtotal                        |                 | 91 | 91 | 100.0 | 73 | 80.2 | 476 |
| Allergy/collagen diseases       | Selected departments | 26 | 26 | 100.0 | 17 | 65.4 | 735 |
| Subtotal                        |                 | 26 | 26 | 100.0 | 17 | 65.4 | 735 |
| Total                           |                 | 13,173 | 3,144 | 23.9 | 1,779 | 56.6 | 7,538 |
\[ \hat{a}_k = \frac{n_k}{N_k} \sum N_{ki} \]

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 \( \hat{a}_k \) was

\[ (\hat{a}_k - 1.96 \cdot s_k, \hat{a}_k + 1.96 \cdot s_k) \]

where \( s_k \) is the estimated standard error of \( \hat{a}_k \). The total number of patients, \( \hat{a} \), was computed as follows:

\[ \hat{a} = \sum \hat{a}_k \]

and the 95% confidence interval was

\[ (\hat{a} - 1.96 \cdot s, \hat{a} + 1.96 \cdot s), s = \sqrt{\sum s_k^2} \]

where \( s \) is the estimated standard error of \( \hat{a} \).

The total number of patients thus computed was corrected using the proportion of “duplicated cases” \((D)\) and that of “inappropriate cases” \((I)\) among the patients 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 rates of the disease. Age- and sex-specific prevalence rates were estimated, using the age distribution of patients by sex which was obtained from the second survey.

**RESULTS**

A total of 1,779 departments replied to the first questionnaire; the response rate being 56.6% (Table 1). Of the 1,779 responded departments, 765 reported at least one patient with SS, and 7,538 patients were identified. About half of the patients were treated in departments of internal medicine, followed by departments of ophthalmology and otolaryngology.

In response to the second questionnaire, 392 (51.2%) of the 765 departments reported 3,231 patients (42.9% of the patients identified by the first questionnaire). Among them, 132 (4.1%) and 84 (2.6%) were found to be “duplicate” and “inappropriate” cases, respectively. These patients were excluded from the study, leaving 3,015 eligible patients with SS.

Table 2 shows the age distribution of the patients by sex, reported on the second questionnaire survey. The ratio of female to male patients was 13.7. The mode of age distribution appeared in the fifties.

Taking the proportion of “duplicate” and “inappropriate” cases into account, the total number of patients with SS, who were treated in 1993 throughout Japan, was estimated as 17,000 (95% confidence interval 15,000-20,000)

by the method described in material and method section. The crude prevalence rates were obtained as 1.9 and 25.6 per 100,000 population in males and females, respectively.

Table 3 summarizes the estimated age-specific prevalence rates by sex. The highest rate was observed among females in their fifties; the rate being 62.2 per 100,000 population.

**DISCUSSION**

The estimated total number of patients with SS had a relatively wide confidence interval. This is ascribable to
the fact that some departments in the stratum for the "selected departments" of ophthalmology reported many patients with SS on the first questionnaire, but the response rate of the stratum was low (37.5%). The proportion of "duplicate" or "inappropriate" cases was comparable with those of recent nationwide surveys in Japan\(^1\) (0.9-7.7% for "duplicate cases" and 1.0-4.8% for "inappropriate cases").

The diagnostic criteria for SS still remain controversial\(^6\). On one hand, a strict set of criteria (the San Diego criteria) has been proposed by Fox et al. since 1986\(^7\). It requires evidence for an autoimmune process associated with destruction of salivary and lacrimal gland tissues. On the other hand, several groups (including the Copenhagen\(^14\) and European Community\(^15\) (EC) study groups) have based their criteria for diagnosis on clinical findings of dry eyes and mouth without absolute requirement for gland biopsy or existence of autoantibodies. The EC study group believes that the San Diego criteria identify only the tip of the iceberg and overlook those patients with milder SS. In the present study, we employed the Japanese criteria, which has been extensively used in Japan since 1977\(^8\). The criteria, like Copenhagen or EC criteria, do not necessarily require abnormal salivary gland biopsy nor presence of autoantibodies for diagnosing SS. Therefore, rather broad spectrum of patients might be included in our study.

We estimated the number of patients under the assumption that the response from departments is independent of frequency of patients\(^12\). This assumption has to be validated since the response rate (56.6%) was relatively low, though comparable with the rates in the six nationwide surveys conducted in 1992\(^13\) (53.0-62.1%). Hashimoto et al.\(^16\) compared the mean numbers of the patients with an intractable disease financially subsidized for treatment among responded departments with those among non-responded departments; the ratio of the former to the latter was found to be between 1.0 and 1.1. This figure suggests that the assumption might be sufficiently valid in the nationwide epidemiological surveys of intractable diseases in Japan.

It might be another issue in our estimation to include only the patients treated in hospitals (with 20 or more beds), ignoring those treated in clinics (with less than 20 beds or without beds). It is through the National One-Day Patient Survey in Japan\(^9\) that about 75% of the patients with SS were estimated to be those treated in hospitals. (The National One-Day Patient Survey is conducted by the Ministry of Health and Welfare of Japan every third year. It survevs all the out-patients and in-patients in hospitals and clinics throughout Japan on the very day of the survey, and collects fundamental data of the patients such as sex, age and clinical diagnosis.) Therefore, 25% underestimation at maximum would be possible for the present estimates. (Some patients may visit both clinics and hospitals during the study period, then the magnitude of underestimation should be smaller than 25%.)

The proportion of "duplicate cases" among the patients reported in the second survey was applied to estimate the total number of SS patients in the present study. This proportion would possibly be lower than that expected among all the patients, and then, would result in an overestimation for the number of SS patients. We could not estimate the proportion of "duplicate cases" among all the patients, because some background factors would be associated with the proportion differently from disease to disease. For example, it must be taken into consideration whether a patient visited two or more departments in one hospital, or so did two or more hospitals. And the locations of the responded and non-responded hospitals might also affect the proportion. It will be an issue in the future surveys to obtain the proportion of "duplicate cases" with more reasonable estimation.

The number of patients with SS in Japan was estimated as 18,000 in 1976\(^17\), using the same diagnostic criteria as the present survey. This estimate is in a good agreement with the present estimate, suggesting that the number of patients treated for SS have remained relatively stable for about 15 years.

### Table 4. Study populations, diagnostic criteria and prevalence rates of Sjögren's syndrome (SS) in the previous surveys.

| Investigators (Year) | Source | Country | Age | No. of males/females | Diagnostic criteria | Prevalence rate (%) |
|----------------------|--------|---------|-----|----------------------|---------------------|--------------------|
| Whaley et al. (1972) | Geriatric inpatients | UK | 81-93 | 36/86 | KCS\(^*\) with xerostomia | 3.3 |
| Strickland et al. (1987) | Elderly female volunteers live in a retirement home | US | 63-92 | 0/103 | At least 2 of the following 3 criteria -(a) KCS, (b) a positive lip biopsy, (c) an autoimmune rheumatic disease (definite SS) | 1.9 |
| Drosos et al. (1988) | Elderly volunteers live in a nursing home | Greece | 67-95 | 32/30 | A positive labial salivary gland biopsy + KCS and/or xerostomia (primary SS) | 4.8 |
| Jacobsson et al. (1989) | A random sample of residents in a city | Sweden | 52-72 | 705 (males+ -females) | Copenhagen criteria (primary SS) | 2.7 |
| Fox et al. (1994) | Patients attending a general medical clinic | US | NA\(^*\) | NA/NA | San Diego criteria (primary SS) | 0.08 |

\(^*\)NA : not available
\(^**\)KCS : keratoconjunctivitis sicca
years. Another estimate was obtainable from the National One-Day Patient Survey in Japan, 1990\(^{10}\); being 21,000 (95% confidence interval 17,000-25,000). This figure is also reasonably comparable with ours, even though the small number of patients with SS could be found in the One-Day Patient Survey.

The prevalence rates of SS reported in the literature range from 0.08% to 4.8%, based on varying diagnostic criteria and study populations\(^3-7\). The study populations, diagnostic criteria and prevalence rates of SS in the previous surveys were summarized in Table 4. The present survey adopted Japanese criteria, which are believed not to be so stringent\(^8\), and we included secondary/probable cases, but the prevalence rates estimated (0.002% for males and 0.026% for females) are much lower than those in the previous studies\(^3-7\). In general, prevalence rate would vary according to sex and age distribution of study population, but the highest rate in our study (0.062% among women in their fifties) is still lower than the figures estimated in other studies\(^3-7\). Our lower prevalence rate might largely be ascribable to exclusion of subclinical cases\(^9\), since only the patients treated for SS were surveyed in the present study. Our estimates should, therefore, be recognized as the prevalence rate based on the patients clinically manifested. It should be noted that population-based survey which includes apparently healthy people will be required to compare the prevalence rates in Japan with those in the previous studies conducted in other countries.

Age and sex distribution of the SS patients observed in the present study was very comparable with the findings in previous reports\(^2,17,19,20\); about 90% or more of the patients were women, and the mode of age appeared in 40-59 years. This particular finding suggests that our series certainly have common demographic features to those in the previous studies, though diagnostic criteria applied were different from study to study.

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