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REVIEW ARTICLE

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Revised Japanese criteria for Sjögren's syndrome (1999): availability and validity

Abstract The Japanese criteria for diagnosing Sjögren's syndrome (SS) were revised in 1999, and consist of four major areas: histopathology, oral examination, ocular examination, and serological examination. A diagnosis of SS can be made when the patient meets at least two of these four criteria. This report describes how the revised Japanese criteria were established. After the publication of the revised Japanese criteria (1999), a research study which focused on evaluating its availability and validity was carried out in 2001 using funds from Grant-in-Aids for Scientific Research supported by the Japan Society for the Promotion of Science. The availability of the revised criteria was investigated by a questionnaire study through the Japanese Medical Society for Sjögren's Syndrome, and the use of the revised criteria for diagnosing SS in these medical facilities was found to be 76%. To evaluate the validity of the revised criteria, the records of 900 patients, including SS patients and non-SS controls, from 54 clinical centers were registered and analyzed to calculate the accuracy of the criteria. The revised Japanese criteria were found to have 96.0% sensitivity, 90.5% specificity, and 94.5% accuracy for diagnosing SS.

Key words Diagnostic criteria · Revised Japanese criteria · Sensitivity · Sjögren's syndrome (SS) · Specificity

Introduction

The Japanese diagnostic criteria for Sjögren's syndrome (SS)[1] were revised in 1999, as shown in Table 1. The previous Japanese criteria had been established in 1977 and published in 1978 in a report entitled *Research Committee on Sjögren's Syndrome of the Japanese Ministry of Health and Welfare*.[2] These old criteria were widely used for 20 years and made a great contribution to the clinical diagnosis of SS in Japan. However, the developments in scientific research and diagnostic technology with regard to SS then led to a revision of the diagnostic criteria. The Research Committee on Autoimmune Diseases of the Japanese Ministry of Health and Welfare requested the cooperation of the Japanese Medical Society for Sjögren's Syndrome in revising the criteria. In 1994, the Society established a board as a working group to revise the criteria. This worked for over 5 years, and reported its progress at every annual meeting of the Society. The final revision was completed at the annual meeting in 1998. The final report was then submitted to the national committee, and published as the revised Japanese criteria for SS in 1999.

After issuing the revised criteria, we planned to assess their availability and validity. This assessment was performed in 2001 using funds from Grant-in-Aids for Scientific Research supported by the Japan Society for the Promotion of Science. This article gives a brief history of how the revised criteria were achieved, and the results of the investigative assessment into their availability and validity.

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Table 1. Revised Japanese Criteria for Sjögren's Syndrome (SS) (1999)

1. Histopathology
   Definition: Positive for at least one of (A) or (B):
   A) Focus score ≧ 1 (periductal lymphoid cell infiltration ≧ 50) in a 4-mm^2 minor salivary gland biopsy
   B) Focus score ≧ 1 (periductal lymphoid cell infiltration ≧ 50) in a 4-mm^2 lacrimal gland biopsy
2. Oral Examination
   Definition: Positive for at least one of (A) or (B):
   A) Abnormal findings in sialography ≧ Stage I (diffuse punctate shadows of less than 1 mm)
   B) Decreased salivary secretion (flow rate ≦ 10 ml/10 min according to the chewing gum test or ≦ 2 g/2 min according to the Saxon test) and decreased salivary function according to salivary gland scintigraphy
3. Ocular Examination
   Definition: Positive for at least one of (A) or (B):
   A) Schirmer's test ≦ 5 mm/5 min and rose bengal test ≧ 3 according to the van Bijsterveld score
   B) Schirmer's test ≦ 5 mm/5 min and positive fluorescein staining test
4. Serological Examinatison
   Definition: Positive for at least one of (A) or (B):
   A) Anti-Ro/SS-A antibody
   B) Anti-La/SS-B antibody

Diagnostic criteria: Diagnosis of SS can be made when the patient meets at least two of the above four criteria

Materials and methods

Before revision

In 1994, the Japanese Medical Society for Sjögren's Syndrome established a board as a working group for the revision of the old criteria. The board consisted of seven members, Takashi Fujibayashi, Susumu Sugai, Nobuyuki Miyasaka, Takeshi Tojo, Shoji Miyawaki, Yukinobu Ichikawa, and Kazuo Tsubota, and each belonged to a different medical clinical center. The subspecialities of the members were internal medicine, especially rheumatology (S.S., N.M., T.T., S.M., and Y.I.), ophthalmology (K.T.), and oral medicine (T.F.). During the first meeting of the board, which was held in Tokyo on September 20, 1994, the general policy and procedures of the revision were discussed. An understanding was reached with regard to the following aims: (1) to make a new revised criteria based on the old Japanese criteria; (2) the results to be judged academically by objective examinations; (3) to be reasonable in consideration of international standards; (4) a subjective feeling of dryness should not always be a necessary prerequisite condition; (5) to make only definite diagnoses and avoid probable cases; (6) to consider new diagnostic techniques such as salivary gland scintigraphy; (7) to consider objective examinations such as serum autoantibodies; (8) to revise the histopathological scale from one focus per lobe of the minor glands, as used under the old Japanese criteria, to one focus per 4 mm^2, as widely used by other countries; (9) to consider whether primary and secondary SS require different rules based on the results of the study. However, after consultation, it was agreed that it was desirable that these could be diagnosed using identical standards. At the second meeting, in November 1994, the survey protocol form used to register each patient's record was discussed, and a form with 42 items, including the necessary examination records for diagnosing SS, was agreed upon. The seven members of the board were asked to register 60 consecutively applicable patients' records from their own files. These were to be grouped as follows: 15 patients with primary SS, 15 with secondary SS, 15 control patients (e.g., with simple dry mouth or dry eye but without SS) as a control for primary SS, and 15 patients with connective tissue diseases (CTD) but without SS as a control for secondary SS. It was agreed that the preliminary selection of patients with or without SS should be made using each board member's clinical judgment. A total of 419 cases had been registered by July 1995. These patients included 129 cases of primary SS, 106 of secondary SS, 108 primary SS controls, and 76 secondary SS controls. The data analysis of these patient's records was carried out at the office of the board (Department of Oral and Maxillofacial Surgery, Dokkyo University School of Medicine, where T. Fujibayashi was then working), and the results were distributed to the board members. Each board member was asked to create and submit at least one draft plan of revised diagnostic criteria. The sensitivity, specificity, and accuracy of every draft plan, as well as those of each examination used in diagnosing SS, were assessed for the 419 cases registered at the office. After several revisions of each draft plan and discussions at several board meetings, three tentative preliminary plans for the revised criteria were submitted to the 5th general meeting of the Japanese Medical Society for Sjögren's Syndrome in Sapporo in September 1995. Preliminary revised criteria were submitted to the national committee in 1996.[3] However, an additional large-scale study was recommended at the 6th general meeting in Nagoya in 1996. At that time, an additional 404 patients' records were registered from 22 clinical centers countrywide, from other members of the society who had agreed to cooperate in this investigation. Each unit was requested to submit 20 consecutively applicable patients' records from their own files, grouped as follows: 5 patients with primary SS, 5 patients with secondary SS, 5 patients as controls for primary SS, and 5 patients with CTD but without SS as controls for secondary SS. In total, 823 cases (419 from the board

members and 404 from the Society members) were registered and analyzed in an additional study in 1997–1998. Continuous discussions about several points in the preliminary plan of the criteria were held during every annual meeting of the Society. A final tentative plan was discussed and decided on as the revised Japanese criteria for SS at the general meeting of the Society in Utsunomiya in September 1998.

After revision

Two years after issuing the revised criteria, an investigation to assess their availability and validity was designed and authorized using funds from a Grant-in-Aids for Scientific Research program supported by the Japan Society for the Promotion of Science. The investigation group consisted of five members: Takashi Fujibayashi, Susumu Sugai, Nobuyuki Miyasaka, Yoshio Hayashi, and Kazuo Tsubota. The assessment investigation had two parts, an availability study and a validity study. For the availability study, a questionnaire form was distributed to clinical centers that belonged to the Japanese Medical Society for Sjögren's Syndrome, after obtaining their agreement. The form consisted of seven questions covering the use of the revised criteria, the use of each examination included in the criteria, including those for minor salivary gland biopsy, lacrimal gland biopsy, sialography, a chewing gum test, the Saxon test, salivary scintigraphy, Schirmer's test, a rose bengal test, a fluorescein staining test, and anti-Ro/SS-A and anti-La/SS-B antibodies. For the validity study, 54 clinical centers responded to the request to cooperate with the assessment investigation and were enrolled. Each center was asked to register 20 consecutively applicable patients' records from their most recent files, grouped as follows: 5 patients with primary SS, 5 patients with secondary SS, 5 control patients (e.g., with simple dry mouth or dry eye but without SS) as the controls for primary SS, and 5 patients with CTD but without SS as the controls for secondary SS. It was agreed that the preliminary selection of patients with or without SS should be made following each center's clinical judgment and not using the new criteria. A total of 900 cases had been registered by March 2002. These patients included 518 cases of SS (269 cases of primary SS, 232 of secondary SS, and 17 of primary–secondary undetermined), and 382 cases of non-SS (170 primary SS controls, 180 secondary SS controls, and 32 primary–secondary undetermined SS controls. The data analysis of the records of the patients who were registered was carried out at the office of the primary investigator (T. Fujibayashi). The frequency of use of the revised criteria for diagnosing SS, and the frequency of use of each individual examination were assayed in the availability study. The sensitivity, specificity, and accuracy of the revised Japanese criteria for diagnosing SS, as well as that of each examination item in the criteria, were calculated in the validity study.

A revised version of the European criteria proposed by the American–European Consensus Group[4] was also tested for sensitivity, specificity, and accuracy by applying these criteria to the 900 Japanese cases registered in the validity study.

Results

Before revision

The values for sensitivity, specificity, and accuracy of each test item for diagnosing SS calculated from the 419 registered cases (235 SS and 184 non-SS) are listed in Tables 2–5. A minor salivary gland (MSG) biopsy was performed on 269 cases (64.2%), but a lacrimal gland (LG) biopsy was performed on only 9.1%. The cutoff values for a positive case were evaluated over the range Grade 2 to Grade 4 using Chisholm and Mason's grading.[5] Grade 3 (equivalent to 1 focus score) for the MSG biopsy showed good sensitivity (88.8%) and high specificity (97.0%) (Table 2). Sialometry with a chewing gum test[6] or with the Saxon test[7], salivary gland scintigraphy, and sialography were evaluated for the oral examination (Table 3). Sialometry alone, with either a chewing gum test or the Saxon test, did not show sufficient accuracy, while salivary gland scintigraphy showed high sensitivity (96.1%). Sialography had been used for 48.2% of the registered cases. Stage I by Rubin and Holt's stage classification[8] as a cutoff value showed a high sensitivity (86.8%) without reducing the high specificity (95.9%). The results of any single test for the ocular examination did not show adequate accuracy, and combining them resulted in little improvement in diagnosing SS (Table 4). In serological examinations, antinuclear antibody showed good purity sensitivity (88.5%) but low specificity (45.6%), while anti-La/SS-B antibody showed high specificity (96.2%) with low sensitivity (18.7%). Anti-Ro/SS-A antibody showed good sensitivity (73.4%) and specificity (77.9%) as a single test (Table 5).

The revised criteria

Each board member created draft plans for the revised diagnostic criteria after considering the results described above for each test.The sensitivity and specificity of every draft plan was calculated immediately at the board office by applying it to 419 registered cases. After intensive discussions at several board meetings and in general meetings of the Japanese Medical Society for Sjögren's Syndrome, and with some revisions and recalculations every time, the final set of revised criteria was agreed and submitted as a report to the national committee. This was published in 1999, as shown in Table 1. The calculated sensitivity, specificity, and accuracy of the revised criteria on the basis of 823 registered cases were 82.8%, 94.6%, and 87.9%, respectively (Table 6). The diagnostic ability of the old Japanese criteria[2] and the European criteria[9] were also tested using the same 823 subjects, and the results are also shown in Table 6. The revised criteria showed a little improvement over the old Japanese criteria and better results than those of the European criteria, especially in terms of sensitivity.

Table 2. Sensitivity, specificity, and accuracy of histopathological examinations of a minor salivary gland (MSG) biopsy and a lacrimal gland (LG) biopsy with various cutoff values calculated for 419 patients, including 235 SS patients and 184 non-SS control patients

Examination item	Cutoff value for positive	Sensitivity (%) TP/(TP+FN)[a]	Specificity (%) TN/(TN+FP)[a]	Accuracy (%) (TP+TN)/(TP+TN+FN+FP)[a]	No. of cases excluded
Minor salivary gland (MSG) biopsy					
(1) MSG	≧Grade 2[b]	162/169 95.9%	68/100 68.0%	230/269 85.5%	150
(2) MSG	≧Grade 3 (focus score ≧ 1)	150/169 88.8%	97/100 97.0%	247/269 91.8%	150
(3) MSG	≧Grade 4 (focus score ≧ 2)	77/169 45.6%	100/100 100%	177/269 68.8%	150
Lacrimal gland (LG) biopsy					
(4) LG	≧Grade 2	25/26 96.2%	4/12 33.3%	29/38 76.3%	381
(5) LG	≧Grade 3 (focus score ≧ 1)	18/26 69.2%	12/12 100%	30/38 78.9%	381
(6) LG	≧Grade 4 (focus score ≧ 2)	7/26 26.9%	12/12 100%	19/38 50.0%	381
(7) (2) or (5)		163/186 87.6%	137/141 97.2%	300/327 91.7%	92

[a] TP, true positive; FN, false negative; TN, true negative; FP, false positive
[b] Histopathological evaluation was expressed using Chisholm and Mason's grading (Grade 2, moderate infiltrate or less than one focus/4 mm^2; Grade 3, one focus/4 mm^2; Grade 4, more than one focus/4 mm^2 of gland tissue)

Table 3. Sensitivity, specificity, and accuracy of each test and combination of tests in oral examinations, with various cutoff values calculated, for 419 patients

Examination item	Cutoff value for positive	Sensitivity (%) TP/(TP+FN)[a]	Specificity (%) TN/(TN+FP)[a]	Accuracy (%) (TP+TN)/(TP+TN+FN+FP)[a]	No. of cases excluded
(1) Chewing gum test	≦10 ml/10 min	134/193 69.4%	76/129 58.9%	210/322 65.2%	97
(2) Saxon test	≦2 g/2 min	65/78 83.3%	18/30 60.0%	83/108 76.9%	108
(3) (1) or (2)		152/203 74.9%	75/134 56.0%	227/337 67.4%	82
(4) SG scintigraphy[b]	hypofunction	99/103 96.1%	52/90 57.8%	151/193 78.2%	226
(5) (3) and (4)		92/146 63.0%	103/123 83.7%	195/269 72.5%	150
(6) Sialography	≧Stage I[c]	112/129 86.8%	70/73 95.9%	182/202 90.1%	217
(7) Sialography	≧Stage II	84/129 65.1%	72/73 98.6%	156/202 77.2%	217
(8) Sialography	≧Stage III	17/129 13.2%	73/73 100%	90/202 44.6%	217
(9) (3) and (6)		70/131 53.4%	112/114 98.2%	182/245 74.3%	174
(10) (6) or (5)		171/198 86.4%	123/144 85.4%	294/342 86.0%	77

[a] TP, true positive; FN, false negative; TN, true negative; FP, false positive
[b] SG scintigraphy, salivary gland scintigraphy
[c] The results for sialography were expressed using Rubin and Holt's stage classification (Stage I, punctate dilatation less than 1 mm; Stage II, globular pattern with 1–2 mm; Stage III, cavitary pattern)

Table 4. Sensitivity, specificity, and accuracy of each test and combination of tests in ocular examinations, with various cutoff values, calculated for 419 patients

Examination item	Cutoff value for positive	Sensitivity (%) TP/(TP+FN)[a]	Specificity (%) TN/(TN+FP)[a]	Accuracy (%) (TP+TN)/(TP+TN+FN+FP)[a]	No. of cases excluded
(1) Schirmer's test	≦5 mm/5 min	120/206 58.3%	86/150 57.3%	206/356 57.9%	63
(2) Schirmer's test	≦10 mm/5 min	178/206 86.4%	40/150 26.7%	218/356 61.2%	63
(3) Rose bengal test	++ (score[a] ≧ 4)	83/182 45.6%	106/122 86.9%	189/304 62.2%	115
(4) Rose bengal test	+ (score[b] 1–3)	146/182 80.2%	57/122 46.7%	203/304 66.8%	115
(5) Fluorescein test	+	110/142 77.5%	51/98 52.0%	161/240 67.1%	179
(6) BUT	≦5 s	46/56 82.1%	10/34 29.4%	56/90 62.2%	329
(7) (1) and (3)		62/196 31.6%	127/134 94.8%	189/330 57.3%	89
(8) (1) and (4)		97/195 49.7%	105/133 78.9%	202/328 61.6%	91
(9) (2) and (3)		78/185 42.2%	113/127 89.0%	191/312 61.2%	107
(10) (2) and (4)		134/184 72.8%	76/126 60.3%	210/310 67.7%	109
(11) (8) or (9)		113/196 57.7%	99/134 73.9%	212/330 64.2%	89
(12) (1) and (5)		71/171 41.5%	104/128 81.3%	174/299 58.5%	120
(13) (2) and (5)		101/147 68.7%	72/112 64.3%	173/259 66.8%	160
(13) (8) or (12)		103/200 51.5%	104/136 76.5%	207/336 61.6%	83

[a]TP, true positive; FN, false negative; TN, true negative; FP, false positive
[b]Score, van Bijsterveld score for the rose bengal test

Table 5. Sensitivity, specificity, and accuracy of serological examinations calculated for 419 patients

Serological test item	Sensitivity (%) TP/(TP+FN)[a]	Specificity (%) TN/(TN+FP)[a]	Accuracy (%) (TP+TN)/(TP+TN+FN+FP)[a]	No. of cases excluded
(1) Rheumatoid factor	151/220 68.6%	114/163 69.9%	265/383 69.2%	36
(2) Antinuclear antibody	201/227 88.5%	77/169 45.6%	278/396 70.2%	23
(3) Anti-Ro/SS-A antibody	163/222 73.4%	127/163 77.9%	290/385 75.3%	34
(4) Anti-La/SS-B antibody	41/219 18.7%	150/156 96.2%	191/375 50.9%	44
(5) Hyper-gammaglobulinemia	128/183 69.9%	94/130 72.3%	223/313 71.2%	106
(6) (3) or (4)	163/222 73.4%	127/163 77.9%	290/385 75.3%	34

[a]TP, true positive; FN, false negative; TN, true negative; FP, false positive

Table 6. Diagnostic ability of various diagnostic criteria for SS applied for 823 registered patients, including 482 SS patients and 341 non-SS control patients, expressed in terms of sensitivity, specificity, and accuracy

Diagnostic criteria for SS	TP/(TP+FN)	Sensitivity (%)	TN/(TN+FP)	Specificity (%)	Accuracy (%)
(1) Revised Japanese criteria (1999)	379/458	82.8%	333/352	94.6%	87.9%
(2) Old Japanese criteria (1978)	380/462	82.3%	329/353	93.2%	87.0%
(3) European criteria (1993)	327/458	71.4%	327/351	93.2%	80.8%

After revision

The frequency of use of the revised criteria in diagnosing SS was assayed in an assessment investigation 2 years after publication. Fifty-four clinical centers were enrolled in the study, and 53 responded to the questionnaire. The revised Japanese criteria had been used at 41 centers (75.9%) for the routine diagnosis of SS. Six centers used the old Japanese criteria (11.1%), one center used the European criteria (1.9%), and two centers used other criteria (3.7%). Three centers had not used any documented criteria (5.6%). The frequency of use of each test during diagnostic examinations for SS is shown in Table 7. Serological tests for anti-Ro/SS-A and anti-La/SS-B, and Schirmer's test for the ocular examination were most commonly used. A lip biopsy (MSG biopsy) was common as a histopathological examination, and was used in 72.2% of the cases examined. A lacrimal gland biopsy was not used in 92.6% of the cases.

The sensitivity, specificity, and accuracy of the revised Japanese criteria for diagnosing SS were 96.0%, 90.5%, and 94.5%, respectively, calculated for 900 registered cases in the validity study (Fig. 1). The ability of the criteria to diagnose primary SS and secondary SS was calculated using their own controls. The sensitivity, specificity, and accuracy in diagnosing SS in patients without CTD were 96.6%, 91.8%, and 95.3%, respectively, and those for patients with CTD were 94.9%, 88.9%, and 93.3%, respectively. These results were close, and no significant difference was found between them (Fig. 1). The utility of each item in the revised criteria for diagnosing SS was also calculated, and is shown in Fig. 2. Histopathology showed the highest value

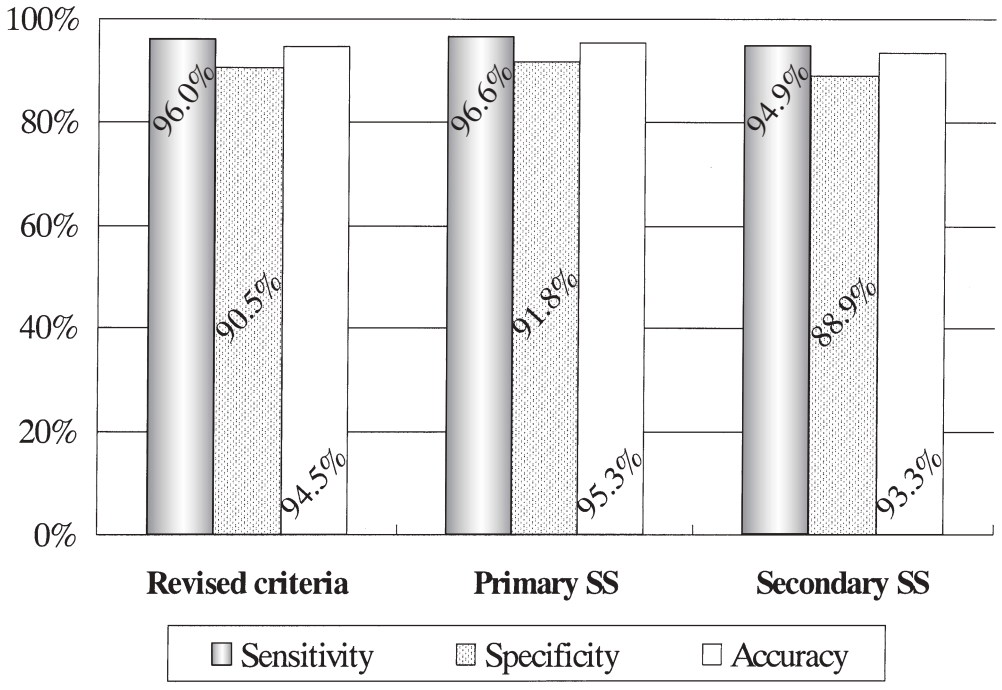

Fig. 1. The sensitivity, specificity, and accuracy of the revised Japanese criteria for diagnosing Sjögren's syndrome (SS) were calculated for 900 registered cases in the validity study. The diagnostic ability of the criteria in diagnosing primary and secondary SS was calculated each using their own control patients

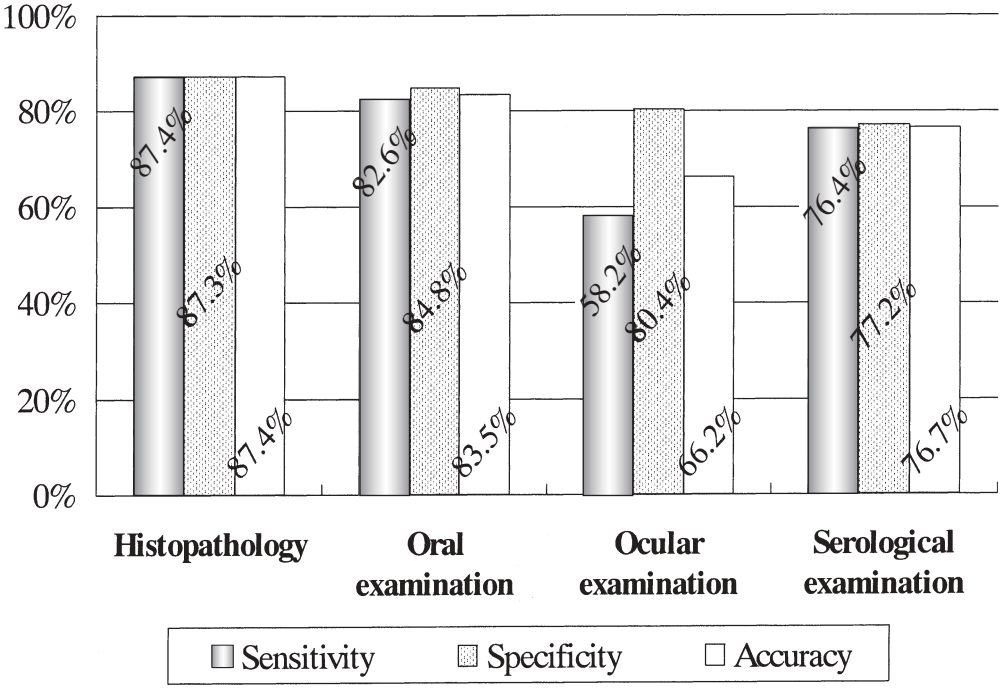

Fig. 2. The ability of each of the four examination items to diagnose SS in the revised criteria was calculated in the validity study. Histopathology showed the greatest accuracy, followed by oral examination, serological examination, and ocular examination

among the four items, followed by oral examination. The sensitivity of the ocular examination was 58.2%. Minor salivary gland (MSG) biopsy or lacrimal gland (LG) biopsy is possible in histopathology. However, the utility of histopathology depends mainly on the results of MSG biopsies because only eight examinations (0.9%) involving LG biopsy were performed without MSG biopsy. The value for the serological examination depends mainly on the results for anti-Ro/SS-A antibody because only four cases (0.4%) of anti-La/SS-B antibody were performed without anti-Ro/SS-A antibody. The sensitivity, specificity, and accuracy of each test involving an oral examination or a combination of such examinations are shown in Fig. 3. Sialography with a cutoff value in stage I showed a high sensitivity (89.1%) and specificity (91.4%). The combination of sialometry (a chewing gum test or the Saxon test) plus salivary gland scintigraphy showed good sensitivity (75.7%) and specificity (78.7%). The results for ocular examinations are

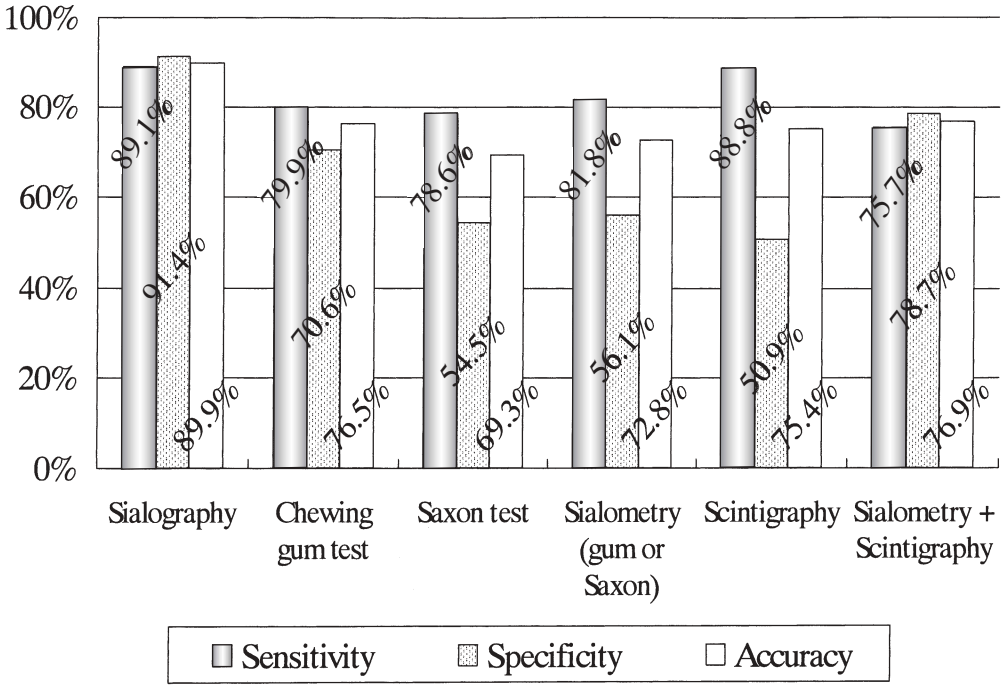

Fig. 3. The sensitivity, specificity, and accuracy of each test involving an oral examination or a combination of such examinations were evaluated in the validity study. Sialography with a cutoff value of stage I showed the greatest accuracy as a single test

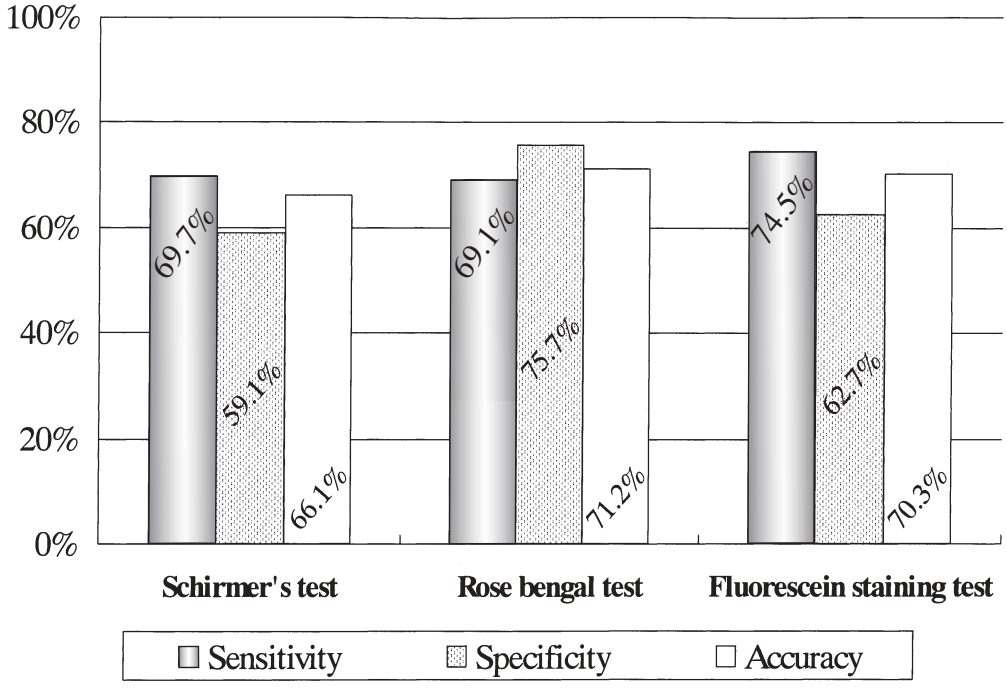

Fig. 4. The ability of three tests that involved an ocular examination to diagnose SS was calculated in the validity study. Schirmer's test with a cutoff value of 5 mm per 5 min did not show satisfactory accuracy as a single test for diagnosing SS

shown in Fig. 4. Schirmer's test with a cutoff value of 5 mm per 5 min did not show sufficient accuracy as a single test for diagnosing SS, although it was one of those used most frequently, as shown in Table 7 of the availability study. A revised version of the European criteria proposed by the American–European Consensus Group (2002) was also applied to the 900 registered cases, and the results are summarized in Table 8.

Discussion

SS is a chronic autoimmune exocrinopathy preferentially associated with dry mouth and dry eye as its major symptoms. As well as these sicca symptoms, it may be accompanied by other CTD such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis

(SSc), polymyositis/dermatomyositis (PM/DM), and mixed connective tissue disease (MCTD) in secondary SS. Some antinuclear antibodies are frequently associated with this condition. Lymphoid cell infiltration in the periductal area of the glandular tissue is a major cause of the pathological mechanism responsible for SS. However, there are no uniformly accepted world-wide criteria for the diagnosis of SS. Since there is no single infallible test to diagnose SS at present, its diagnosis is made by a combination of examinations covering the major characteristics of the disease. The revised Japanese criteria for SS consist of four items: histopathology, oral examination, ocular examination, and serological examination. It was agreed and confirmed with every participant that throughout the study, the primary classification of a patient to be registered either as having SS or as a non-SS control should be made on the basis of the investigator's clinical judgment and not on the basis of any fixed diagnostic criteria. This procedure has been also adopted in other similar investigations.[4,9–11] The revised criteria are recognized as having several differences from the old ones. (1) The revised criteria include only definite cases. (2) The subjective symptom of dry mouth or dry eyes is not indispensable. (3) The revised criteria include one item of serum autoantibody. (4) They also include salivary gland scintigraphy as a new test to evaluate salivary gland function. (5) Several combinations of tests are possible, since SS can be diagnosed when at least two of the four items are positive. As well as these points, the revised criteria contain improvements in each of the tests used for diagnosing SS. The characteristics of the revised criteria are given in Table 9, which compares them with the old Japanese criteria, and with the old European and revised versions of the European criteria (Table 9). In the old Japanese criteria, a positive cutoff value for histopathology was one focus per lobe of salivary or lacrimal gland tissue. However, this was revised to one focus per 4 mm^2, which is also used in the European criteria. The cutoff value for sialography was revised from stage II to stage I because this shift showed a large increase in sensitivity with little reduction in specificity as estimated in the study before the revision (see Table 3). This improvement was also confirmed by the validity study after the revision, which showed a high sensitivity (89.1%) and specificity (91.4%). In 2002, the cutoff value for stage I was also adopted in the revised version of the European criteria. The revised criteria can be used to diagnose primary and secondary SS. The study carried out before revision suggested the reliability of the same criteria for primary and secondary SS, and the validity study after revision confirmed this, as shown in Fig. 1. The validity study revealed that the revised criteria had a high sensitivity (96.0%) for diagnosing SS in 900 cases 2 years after their enforcement. The sensitivity had increased by 13%, but the specificity had decreased by 4% from those assayed in 823 cases before the revision . The accuracy improved by 6.6% after the revision. It is possible that this was caused by a

Table 7. Frequency of use of test items during examinations to diagnose SS by the revised Japanese criteria, summarized from a questionnaire study for 54 clinical centers

Examination tests	Frequency of use		
	Usual	Rare	Never
Minor salivary gland biopsy	72.2%	22.2%	5.6%
Lacrimal gland biopsy	3.7%	3.7%	92.6%
Sialography	37.0%	31.5%	31.5%
Chewing gum test	48.1%	20.4%	31.5%
Saxon test	35.2%	37.0%	25.9%
Salivary gland scintigraphy	40.7%	33.3%	25.9%
Schirmer's test	94.4%	1.9%	3.7%
Rose bengal test	68.5%	16.7%	14.8%
Fluorescein staining test	53.7%	25.9%	20.4%
Anti-Ro/SS-A antibody	96.3%	3.7%	0%
Anti-La/SS-B antibody	94.4%	5.6%	0%

Table 8. Sensitivity and specificity of a revised version of the European criteria proposed by the American–European consensus group applied to 900 registered cases

Items in the criteria	TP/(TP+FN)	Sensitivity (%)	TN/(TN+FP)	Specificity (%)	Accuracy (%)
(1) Revised version of the European criteria (2002)	375/441	85.0%	209/240	87.1%	85.8%
(2) For primary SS					
a. The presence of any four of the six items as long as histopathology or serology is positive	198/225	88.0%	105/111	94.6%	90.2%
b. The presence of any three of the four objective criteria items	187/219	85.4%	113/118	95.8%	89.0%
c. The classification tree procedure	nt		nt		nt
(3) For secondary SS In patients with a potentially associated disease (for instance, another well-defined connective tissue disease (CTD)), the presence of subjective symptoms plus any two from among ocular signs, histopathology, and salivary gland involvement	163/209	78.0%	112/136	82.4%	79.7%

nt, not tested

Table 9. Characteristics of the diagnostic criteria for SS in the revised Japanese version (1999), the old Japanese version (1978), the European version (1993), and the revised European version (2002)

Items, Tests in the criteria	Revised Japanese criteria (1999)[1]	Old Japanese criteria (1978)[2]	European criteria (1993)[9]	Revised version of the European criteria (2002)[4]
(1) Definite and/or probable case	Definite case	Both	Both	Definite case
(2) Subjective symptoms of dryness	Not obligatory	Essential	2 in 6 items Essential for secondary	2 in 6 items Essential for secondary
(3) Histopathology	MSG and/or LG ≧1 focus/4 mm^2	MSG and/or LG ≧1 focus/lobe	MSG ≧1 focus/4 mm^2	MSG ≧1 focus/4 mm^2
(4) Sialography	Optional in an item ≧stage I	Essential in an item ≧stage II	Optional in an item	Optional in an item ≧stage I
(5) Sialometry	Optional in an item Gum or Saxon test	In a probable case Chewing gum test	Optional in an item UWS	Optional in an item UWS
(6) Salivary gland scintigraphy	Optional in an item	Not included	Optional in an item	Optional in an item
(7) Schirmer's test	Essential in an item ≦5 mm/5 min	Optional in an item ≦10 mm/5 min	Optional in an item ≦5 mm/5 min	Optional in an item ≦5 mm/5 min
(8) Rose bengal test	Optional in an item ≧3 Bijsterveld score	Essential in an item ≧++	Optional in an item ≧4 Bijsterveld score	Optional in an item ≧4 Bijsterveld score
(9) Fluorescein staining test	Optional in an item	Optional in an item	Not included	Not included
(10) Serological examination	SS-A and/or SS-B	Not included	At least one of 3 sets	SS-A and/or SS-B
(11) Primary or secondary	Both applicable	Both applicable	Different set of items	Different set of items
(12) Exclusion criteria	Not listed	Not listed	Listed	Listed

decrease in the number of false-negative cases. This suggests that there may be a bias in the registration of patients as either SS or non-SS controls. The primary classification of the patients as SS or non-SS controls was determined using each investigator's clinical judgment. The recent changes in the criteria for the diagnosis of SS might have some effect on this judgment. However, this bias is estimated to be small, because after the revision the 900 registered cases showed similar values to those of 823 cases before revision (see Table 6) when diagnosed using the European criteria (1993). The sensitivity, specificity, and accuracy of the European criteria in these 900 cases were 77.6%, 87.6%, and 81.5%, respectively. The revised version of the European criteria (2002) showed a 7.4% improvement in sensitivity and a slight decrease in specificity over the European criteria (1993) tested using the 900 registered cases. However, the revised version of the European criteria was not the same as the revised Japanese criteria in terms of sensitivity and specificity. The availability study carried out by the questionnaire revealed a high rate of use (76%) of the revised Japanese criteria. This utilization is reasonable considering that it took place only 2 years after the enforcement of the revised criteria. Table 7 shows that the frequency of use of the test items in examinations for diagnosing SS varies. Although lacrimal gland biopsy is seldom used, some ophthalmologists may prefer it to a minor salivary gland biopsy. The flexibility in choosing test items helps to increase the availability of the criteria.

Conclusion

The Japanese criteria for diagnosing SS were revised in 1999. An assessment was carried out in 2001 to evaluate the availability and validity of the revised criteria. The availability of the revised criteria was investigated in 54 clinical centers, and the rate of use of the revised criteria was 76%. The validity of the revised criteria was evaluated using 900 enrolled cases. This evaluation showed 96.0% sensitivity, 90.5% specificity, and 94.5% accuracy in diagnosing SS.

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