A single centre retrospective analysis of AECG classification criteria for primary Sjögren’s syndrome based on 112 minor salivary gland biopsies in a Japanese population

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Abstract

Objective. To assess the usefulness and performance of the American European Consensus Group (AECG) criteria based on minor salivary gland biopsy (MSGB) in Japanese patients with primary SS.

Methods. Among 208 MSGB cases, we retrospectively selected 112 subjects who satisfied the complete set of AECG classification criteria. Of the 112 subjects studied, 63 primary SS patients and 49 non-SS group subjects were classified according to the AECG criteria. The contribution of subjective and objective components was statistically analysed.

Results. Sex, dry eye, Saxon test, Schirmer’s test, anti-SSA/Ro antibody, MSGB grading and sialography statistically contributed to the diagnosis. Multiple logistic regression analysis showed that positive MSGB [odds ratio (OR) 105; 95% CI 13, 849), positive anti-SSA/Ro antibody (OR 96; 95% CI 10, 923), a positive Saxon test (OR 46; 95% CI, 6, 340) and the existence of dry eye (OR 8, 95% CI 2, 43) were associated with the diagnosis of primary SS. Among the components of the AECG criteria, MSGB and anti-SSA/Ro antibody were very strong contributors. Furthermore, the abnormal-finding positive rate in sialography significantly correlated with MSGB grading (P-value for trend = 0.0006), although other subjective and objective components were not associated with MSGB grading.

Conclusion. The usefulness of the AECG criteria for Japanese primary SS patients was confirmed.

Key words: Sjögren’s syndrome, Classification criteria, Minor salivary gland biopsy.
serological positivity is required. On the other hand, the AECG criteria proposed that three of four objective items are indicative of primary SS, even when ocular or oral symptoms were not considered. Among the components of the AECG criteria, the usefulness of minor salivary gland biopsy (MSGB) has been reported by European institutions [6]. In the present study, we evaluated the usefulness and performance of the AECG criteria, focusing on MSGB, for Japanese primary SS patients at a single centre.

Patients and methods

Patients

We performed 208 MSGBs at our institution for suspected SS between 1995 and 2009. Among these cases, we retrospectively selected 112 subjects who had complete sets of the six essential items in the AECG classification criteria. The study was conducted in accordance with the human experimental guidelines of our institution. According to the AECG criteria, the 112 subjects were divided into a primary SS group \((n = 63; \text{male/female: 3/60})\) and a non-SS group \((n = 49; \text{male/female: 9/40})\). The ages and background information of the subjects are summarized in Table 1.

Serological tests and exocrine dysfunction

Antibodies to SSA/Ro and SSB/La antigens were determined by ELISA (Mesacup SSA/Ro test: normal range 10–30; Mesacup SSB/La test: normal range 15–25; Medical and Biological Laboratories Co., Ltd, Nagoya, Japan). To evaluate the secretion of tears and saliva, Schirmer’s test and the Saxon test were employed. Schirmer’s test was considered positive when \(<5 \text{ mm of the strips of filter paper was wet after 5 min. In the original setting in the AECG criteria, unstimulated saliva is shown to be } <1.5 \text{ ml in 15 min. As a modified method for measuring the unstimulated saliva volume, we employed the Saxon test. For the Saxon test, the patients chewed gauze slowly for 2 min; an increase of } <2 \text{ g was defined as a positive outcome. Positivity of sialography was evaluated using the classification determined by Rubin and Holt [7].}

Minor labial salivary gland biopsy and sialography

Minor salivary glands were obtained from the inner surface of the lower lip under local anaesthesia. The grading of mononuclear cell (MNC) infiltration was defined according to Chisholm and Mason [8]. The presence of at least one focus of MNCs in 4 mm² sections was defined as Grade 3 (FS = 1) sialadenitis. MSGB was performed with informed consent from all participants.

Sialography was conducted using a catheter that was inserted into Stensen’s duct [9]. After cannulation, a contrast fluid was slowly injected and then an image was taken.

Statistical analysis

Data were analysed using the Statistical Analysis System Version 9.1.3 (SAS Institute, Cary, NC, USA). Student’s \(t\)-test was used to compare continuous variables. Fisher’s exact test was used for categorical variables. A logistic regression model was used to explore the simultaneous effects of parameters on the diagnosis of primary SS. Starting with a full model including variables in the univariate analysis, the most appropriate model was selected on the basis of Akaike’s information criteria (AIC). The odds ratio (OR) and 95% CI were calculated for each covariate included in the model. The Cochran–Armitage test was used to test for a trend in the prevalence of AECG components according to the grades of MSGB in patients with primary SS.

Results

Contribution of background elements and the AECG components for SS

We initially confirmed the contribution of each of the AECG components as well as the background information in the present study. Positive MSGB grading and the existence of anti-SSA/Ro antibody showed the highest statistical significance among the components (Table 1). Salivary gland involvement, the Saxon test and

Table 1 Background information and contribution of each of the AECG criteria to the diagnosis of primary SS

<table>
<thead>
<tr>
<th></th>
<th>SS ((n = 63))</th>
<th>Non-SS ((n = 49))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>59.4 (12.5)</td>
<td>59.9 (12.7)</td>
<td>0.85</td>
</tr>
<tr>
<td>Sex, male/female, n</td>
<td>3/60</td>
<td>9/40</td>
<td>0.03</td>
</tr>
<tr>
<td>Dry eye</td>
<td>42 (66.7)</td>
<td>19 (38.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>50 (79.4)</td>
<td>34 (69.4)</td>
<td>0.27</td>
</tr>
<tr>
<td>Saxon test</td>
<td>53 (84.1)</td>
<td>25 (51.0)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Schirmer’s test</td>
<td>47 (74.6)</td>
<td>25 (51.0)</td>
<td>0.017</td>
</tr>
<tr>
<td>Anti-SSA Ab</td>
<td>37 (58.7)</td>
<td>7 (14.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anti-SSB Ab</td>
<td>11 (17.5)</td>
<td>4 (8.2)</td>
<td>0.17</td>
</tr>
<tr>
<td>Grades 3 and 4</td>
<td>58 (92.1)</td>
<td>19 (38.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sialography</td>
<td>31 (49.2)</td>
<td>8 (16.3)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Data are shown as means (s.d.) or as numbers and percentages (parentheses). Student’s \(t\)-test was used to compare continuous variables. Fisher’s exact test was used for categorical variables. \(P<0.05\): statistically significant. Ab: antibody.
sialography also demonstrated statistical significance. For lacrimal function, the existence of dry eye and Schirmer’s test showed significance.

Multiple logistic analysis of the AECG components

Multiple logistic regression analysis showed that positive MSGB (OR 105; 95% CI 13, 849), positive anti-SSA/Ro antibody (OR 96; 95% CI 10, 923), a positive Saxon test (OR 46; 95% CI 6, 340) and the existence of dry eye (OR 8; 95% CI 2, 43) were associated with the diagnosis of primary SS (Table 2). Among the six components of the AECG criteria, MSGB was the most significant contributor and anti-SSA/Ro antibody was the second most significant. The ORs of the Saxon test and dry eye were also significant, although their significance was less than that of MSGB grading or anti-SSA/Ro antibody.

Relationship between positive rates of the AECG components according to MSGB grading

Since MSGB positivity was the variable with the greatest significance in the diagnosis of primary SS, we next verified the relationship between MSGB grading and seven items in the AECG classification criteria. As a result, the only relationship shown was between MSGB grading and abnormal sialography findings; the latter significantly increased with MSGB grading (P-value for trend = 0.0006) (Table 3). Other positive items in the logistic analysis including anti-SSA/Ro antibody, the Saxon test and dry eye had no significant relationship with MSGB grading.

Discussion

In the present study, we demonstrated the usefulness of the AECG classification criteria for Japanese subjects. Although the criteria were originally based on data from European subjects, multiple components of the AECG criteria are considered to be reasonably applicable to the Japanese population according to the present analytical result. The revision of the AECG criteria from the preliminary European criteria has improved accuracy of the classification of primary SS.

Among the items in the AECG criteria, MSGB as well as serological examinations made important contributions to the classification of primary SS. Although Schirmer’s test and the Saxon test were also important contributors to the classification, a high specificity of MSGB for SS has been reported in Turkey [10]. In an analysis of 502 MSGB cases among Italian subjects [6], 94.5% of cases met the AECG criteria. Furthermore, Scardina et al. [11] demonstrated that the FS of SS patients remained unchanged in histological sections at three different depths, suggesting that MNC infiltration in a single section has little impact on the results of the classification determined by the AECG criteria. Since reproducibility error that is dependent on the operators should be considered with regard to Schirmer’s or the Saxon test, MSGB may be the most reliable item for detecting the involvement of exocrine glands.

Notably, the radiographic component of the criteria, sialography, also made a major contribution to the classification of primary SS. Originally, it was reported that conventional sialography showed high sensitivity and specificity compared with MSGB in an analysis of 150 subjects [12]. Although sialography was not calculated as a high OR item in our logistic analysis, the severity of MSGB grading correlated well with the rate of abnormality found in sialography, suggesting that sialography effectively represents the histological damage due to SS. We should
note that MSGB grading was adopted in the logistic analysis because the stronger variable was allowed to remain when the relevance of both MSGB grading and sialography was calculated. For future use, less invasive magnetic resonance sialography [13] could be used in place of conventional sialography.

In the application of the AECG criteria, the following points should be considered. One is an exclusion criterion including viral infection or use of anti-cholinergic drugs as revised rules for classification and other, alternative diagnostic tools found in the AECG criteria. Another consideration is that the application of ocular dry scores such as the Rose Bengal score or salivary scintigraphy should also be considered. Although the AECG criteria include the Rose Bengal score or salivary scintigraphy, we did not perform both items. Thus, the bias for the classification of primary SS might occur according to non-usability of these items.

In summary, the present study has shown the usefulness and validity of the AECG criteria for Japanese subjects. Furthermore, the contributions of MSGB, serology, and sialography were shown. As a next step, internationally approved diagnostic criteria should be developed that utilize the advantages of the various diagnostic components. Among the diagnostic items, MSGB could be the most significant component.

**Rheumatology key messages**

- Of the AECG criteria, MSGB made the greatest contribution to diagnosis in the Japanese population.
- The severity of MSGB grading correlated with the rate of abnormality found by sialography.

**Acknowledgements**

*Funding:* This research is supported in part by a grant from The Ministry of Health, Labor and Welfare, Japan.

*Disclosure statement:* The authors have declared no conflicts of interest.

**References**