Lacrimal Gland Function in Autoimmune Pancreatitis

Terumi Kamisawa, Kensuke Takuma, Sawako Kuruma, Junko Fujiwara, Hajime Anjiki, Koichi Koizumi, Naoto Egawa, Naoko Kubota, Noriko Ozaki and Tsuneo Sasaki

Abstract

Objective    Autoimmune pancreatitis (AIP) may be a pancreatic lesion of IgG4-related systemic disease. Lacrimal gland swelling is a rare extrapancreatic lesion of AIP. The aim of the present study was to investigate lacrimal gland function in AIP patients, and to determine changes after steroid therapy.

Patients and Methods    Schirmer’s test and sialochemistry were done prospectively in 11 AIP patients. These tests were also performed after steroid therapy in 7 patients.

Results    Dysfunction of tear secretion was found in at least one eye in 7 (64%) patients. The average lower level in both eyes was 4.3±1.5 mm in the 7 patients with lacrimal gland dysfunction, which was significantly lower than the 8.2±2.4 mm in patients with normal lacrimal gland function (p=0.005). There were no significant differences between the two groups in age at diagnosis of AIP, sex ratio, and the presence of swelling of the lacrimal glands and the salivary glands. Although there was no significant difference, mean serum IgG4 levels and mean salivary Na+ and β2 microglobulin levels were lower in patients with normal lacrimal gland function. After steroid therapy, lacrimal gland function improved in 3 of 5 patients with impaired lacrimal gland function, though the degree of improvement was not marked compared to the improvement of salivary gland function.

Conclusion    Lacrimal gland function was frequently impaired in AIP patients, even when no lacrimal gland swelling was observed clinically. Lacrimal gland function impairment appears to be similar to impairment of salivary gland function in AIP patients.

Key words: IgG4, steroid, Schirmer’s test

(Inter Med 48: 939-943, 2009)  
(DOI: 10.2169/internalmedicine.48.2107)

Introduction

Autoimmune pancreatitis (AIP) is a particular type of pancreatitis that is thought to have an autoimmune etiology. In patients with AIP, serum IgG4 levels are frequently and significantly elevated, and various extrapancreatic lesions are present (1, 2). Based on histological and immunohistochemical examinations of various organs of AIP patients, we have found dense infiltration of IgG4-positive plasma cells and CD4- or CD8-positive T lymphocytes, as well as fibrosis in the peripancreatic retroperitoneal tissue, bile duct wall, gallbladder wall, periportal area of the liver, and salivary glands, as well as in the pancreas. Furthermore, all of the extrapancreatic lesions associated with AIP, such as sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis, show abundant infiltration of IgG4-positive plasma cells and fibrosis. Both the pancreatic and extrapancreatic lesions of AIP respond well to steroid therapy. Therefore, we proposed the existence of a novel clinicopathological entity, IgG4-related sclerosing disease. We also suggested that AIP is a pancreatic lesion of this systemic disease, and that the extrapancreatic lesions of AIP are lesions of organs involved in this disease (3, 4).

Mikulicz’s disease is a unique condition that involves enlargement of the lacrimal and salivary glands associated with prominent mononuclear infiltration (5). AIP patients sometimes show enlargement of bilateral salivary glands and lac-
Salivary glands (1, 2).

Some cases of AIP associated with Sjogren’s syndrome have been reported (6, 7). However, recent studies have indicated that the salivary gland lesion associated with AIP is sclerosing sialadenitis, which has been recognized as Mikulicz’s disease and it differs from Sjogren’s syndrome with respect to the following points: 1) serum IgG4 elevation and infiltration of abundant IgG4-positive plasma cells in the salivary and lacrimal glands are characteristic findings in Mikulicz’s disease, but are absent in Sjogren’s syndrome; 2) autoantibodies, such as anti-SSA and anti-SSB antibodies are usually negative in Mikulicz’s disease; 3) Mikulicz’s disease is more responsive to steroid therapy than Sjogren’s syndrome (8).

We have demonstrated that salivary gland function was frequently impaired in AIP patients (9, 10). However, there have been no reports dealing with lacrimal gland function in AIP patients. In the present study, lacrimal gland function of AIP patients was examined before and after steroid therapy.

Patients and Methods

Patients

The subjects consisted of 11 AIP patients (7 men and 4 women; age range 44-70 years, mean age 62.8 years). AIP was diagnosed according to the 2006 Japanese clinical diagnostic criteria (11). All patients had pancreatic enlargement [diffuse (n=7) and segmental (n=4)] and irregular narrowing of the main pancreatic duct. Serum IgG4 levels were elevated (>135 mg/dL) in all patients. Anti-SSA and anti-SSB antibodies were negative in all patients. On histological examination of the pancreas in 3 patients, fibrosis with dense infiltration of IgG4-positive plasma cells and lymphocytes was found. Seven patients received steroid therapy, which was effective in all of them. Prednisolone was given at an initial dose of 30 mg/day, and then tapered by 5 to 2.5 mg every 1 to 2 weeks, depending on serological and radiological changes. Maintenance steroid therapy (prednisolone, 5 or 2.5 mg/day, from 2 months to 8 years) was necessary to control the serological and radiological abnormalities in 6 patients. Swelling of bilateral salivary glands was detected in 5 patients, and 1 of them also showed bilateral lacrimal gland swelling. Two patients had dry mouth (mild and moderate), but no patient complained of dry eyes. Swelling of the salivary and lacrimal glands improved after steroid therapy.

Schirmer’s test

To examine tear production as a measure of lacrimal gland function, Schirmer’s test was performed prospectively in the 11 AIP patients before steroid therapy. Schirmer’s test was also performed after steroid therapy in 7 patients (2, 4, 6, 12, 48, 96, and 120 months after the start of steroid therapy). Schirmer’s test involves measuring the amount of wetness of a special filter paper, which is 5-mm wide and 35-mm long. First, the filter paper is folded 5 mm from one end and inserted between the middle and outer third of the lower lid. The patient is then asked to keep his eyes open and to blink as necessary. After 5 minutes, the filter strip is removed, and the length of wetness on the fold is measured. A normal eye will wet between 10 mm and 25 mm during that period. Measurements between 5 mm and 10 mm are considered borderline, and values of less than 5 mm are indicative of impaired secretion (12). A participant with one or both eyes yielding abnormal test results was defined as having tear secretion dysfunction. The lower level of the test for the right and left lacrimal glands was analyzed.

Sialochemistry

Sialochemistry was performed in the 11 patients within a week of when Schirmer’s test was performed. Sialochemistry was also performed after steroid therapy in the 7 patients who received steroid therapy. Saliva was collected from all patients without stimulation. The patients allowed the saliva to drain continuously from the lower lip or spit it for 30 minutes in the morning. Salivary Na+ and β2 microglobulin levels were investigated.

Statistical analysis

The data of patients with normal lacrimal gland function were compared to those of patients with impaired lacrimal gland function. For the statistical analyses, the Mann-Whitney U test and Fisher’s exact test were used. p<0.05 was considered to be statistically significant.

Results

Schirmer’s test showed that 7 (64%) patients had tear secretion dysfunction in at least one eye. The average lower level in both eyes was 4.3±1.5 mm in the 7 patients with lacrimal gland dysfunction, which was significantly less than the 8.2±2.4 mm in patients with normal lacrimal gland function (p=0.005). There were no significant differences between the two groups in age at diagnosis of AIP, sex ratio, and the presence of swelling of the lacrimal glands and the salivary glands. Although there was no significant difference, mean serum IgG4 levels and mean salivary Na+ and β2 microglobulin levels were lower in patients with normal lacrimal gland function (Table 1).

After steroid therapy, lacrimal gland function improved in 3 of 5 patients with impaired lacrimal gland function (Cases 1, 2, 3, 6, and 7), though the degree of improvement was not marked (Table 2). After steroid therapy, salivary Na+ levels tended to decrease (p=0.063), and salivary β2 microglobulin levels decreased significantly (p=0.035) (Table 3).

Discussion

AIP is frequently associated with various extrapancreatic lesions. Salivary gland swelling is a common extrapancreatic lesion of AIP (1, 2). It was present in 24% of our 50 AIP
patients. Recent studies have indicated that the salivary gland lesion associated with AIP is sclerosing sialadenitis, which has been recognized as Mikulicz’s disease (8).

Lacrimal gland swelling is a rare extrapancreatic lesion of AIP. Lacrimal gland swelling was detected in 2% of our 50 cases. It involved bilateral swelling, was associated with bilateral salivary gland swelling, and improved after steroid therapy. Hamano et al (13) reported that lacrimal gland swelling was detected in 8 (12.5%) of 64 AIP patients, and 6 of them also had salivary gland swelling. Recently, it was reported that serum IgG4 levels were elevated, and abundant infiltration of IgG4-positive plasma cells with fibrosis was detected in the lacrimal glands in patients with Mikulicz’s disease (8, 14), and the entity of IgG4-related chronic sclerosing dacryoadenitis was proposed (14). Sjogren’s syndrome is a chronic inflammatory autoimmune disease characterized by the presence of typical symptoms of dry mouth and dry eye. Dry eye is induced by decreased tear secretion due to inflammation. In 111 patients with Sjogren’s syndrome, median Schirmer test level was 5.0 mm (15), which was similar to the levels in this study. Histopathology of the lacrimal gland of Sjogren’s syndrome is marked infiltration of lymphocytes destroying exocrine gland tissue, including acinar cells, ductal cells, and nerves (15, 16). However,

Table 1. Clinical Differences between Autoimmune Pancreatitis Patients with Normal and Impaired Lacrimal Gland Function

<table>
<thead>
<tr>
<th></th>
<th>Normal lacrimal gland function (n=4)</th>
<th>Lacrimal gland dysfunction (n=7)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schirmer’s test* (mm)</td>
<td>8.2±2.4</td>
<td>4.3±1.5</td>
<td>.005</td>
</tr>
<tr>
<td>Age* (years)</td>
<td>64.2±6.5</td>
<td>61.8±9.4</td>
<td>.749</td>
</tr>
<tr>
<td>Male/Female</td>
<td>2/2</td>
<td>5/2</td>
<td>.575</td>
</tr>
<tr>
<td>Swelling of lacrimal glands +</td>
<td>1 (25%)</td>
<td>0 (0%)</td>
<td>.363</td>
</tr>
<tr>
<td>Serum IgG4* (mg/dL)</td>
<td>368.8±356.4</td>
<td>899.1±730.7</td>
<td>.185</td>
</tr>
<tr>
<td>Na+ in saliva* (mEq/L)</td>
<td>19.4±8.4</td>
<td>24.2±18.5</td>
<td>.334</td>
</tr>
<tr>
<td>β 2 microglobulin in saliva* (mg/L)</td>
<td>1.6±0.8</td>
<td>2.8±1.4</td>
<td>.161</td>
</tr>
</tbody>
</table>

*: mean±SD

Table 2. Changes in Lacrimal Gland Function on Schirmer’s Test after Steroid Therapy

<table>
<thead>
<tr>
<th></th>
<th>Right lacrimal gland (mm) Before</th>
<th>After</th>
<th>Left lacrimal gland (mm) Before</th>
<th>After</th>
<th>Interval between the tests (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>6</td>
<td>5*</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>2*</td>
<td>4</td>
<td>1*</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>4*</td>
<td>6</td>
<td>7</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>7</td>
<td>11</td>
<td>8</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>5*</td>
<td>5</td>
<td>6</td>
<td>8</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>3</td>
<td>5*</td>
<td>3</td>
<td>120</td>
</tr>
</tbody>
</table>

*: impaired lacrimal gland function

Table 3. Changes in Sialochemistry after Steroid Therapy

<table>
<thead>
<tr>
<th></th>
<th>Before steroid</th>
<th>After steroid</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na+ in saliva* (mEq/L)</td>
<td>31.2±14.8</td>
<td>22.5±5.6</td>
<td>.063</td>
</tr>
<tr>
<td>β 2 microglobulin in saliva* (mg/L)</td>
<td>3.1±1.1</td>
<td>1.6±1.1</td>
<td>.035</td>
</tr>
</tbody>
</table>

*: mean±SD
abundant infiltration of IgG4-positive plasma cells is not observed in the lacrimal glands of Sjögren’s syndrome. Anti-SSA and anti-SSB antibodies are sometimes diagnostic of the disease. From these findings, pathophysiology of Sjögren’s syndrome appears to be different from dacryoadenitis associated with AIP.

We previously examined salivary gland function using sialochemistry and salivary gland scintigraphy (9, 10). The salivary Na+ levels are increased in patients with Sjögren’s syndrome, due to altered resorption caused by the periductal lymphocytic infiltration (17). Salivary β2 microglobulin levels show a high specificity for salivary gland inflammation, and they are increased in patients with Sjögren’s syndrome (18). Both Na+ and β2 microglobulin levels were higher in AIP patients than in controls (9). On salivary gland scintigraphy, the ratio of cumulative peak count to injected radionuclide and the washout ratio were significantly lower in most AIP patients than in controls (9, 10). Furthermore, salivary gland function was more impaired in AIP patients with high serum IgG4 levels than in those with low serum IgG4 levels (10). In our previous study, abdominal lymphadenopathy was detected more frequently, and the number of IgG4-positive plasma cells infiltrating abdominal lymph nodes, the bile duct wall, and the gastric mucosa was greater in AIP patients with high serum IgG4 levels than in AIP patients with low serum IgG4 levels. Thus, IgG4-related phenomena in various organs seem to occur less frequently in AIP patients with low serum IgG4 levels (19).

If AIP is a systemic disease, the lacrimal glands may be involved in the same manner as salivary glands, even in cases without clinical manifestations of lacrimal gland involvement. Therefore, in the present study, lacrimal and salivary gland functions were prospectively examined in AIP patients before and after steroid therapy.

Lacrimal gland function was impaired in 64% of AIP patients, even when no lacrimal gland swelling was observed clinically. Although all patients enrolled in the study had elevated serum IgG4 levels, the mean serum IgG4 levels were higher in patients with impaired lacrimal gland function. This finding seems to be similar to the relationship between salivary gland function and serum IgG4 levels. Although there was no statistically significant difference, mean salivary Na+ and β2 microglobulin levels were lower in patients with normal lacrimal gland function. Lacrimal function seems to be impaired in a similar manner to salivary gland function in AIP patients.

After steroid therapy, lacrimal gland function improved in 3 of 5 patients with impaired lacrimal gland function. However, the degree of improvement was not marked, compared with the degree of improvement of sialochemistry. Lacrimal gland function did not improve or worsened in 3 patients after steroid therapy. In these patients, irreversible change appeared to occur in the lacrimal glands during follow-up.

Both lacrimal and salivary gland functions were impaired in most AIP patients with or without related clinical symptoms. Improvement of lacrimal gland function after steroid therapy was observed in half of the patients but it was less than that of salivary gland function. Although this is the first report dealing with lacrimal gland function of AIP patients, a limitation of this study is that the number of patients was limited. To further clarify lacrimal gland function in AIP patients, a larger series is needed.

In conclusion, lacrimal gland function was impaired in 64% of AIP patients, even when no lacrimal gland swelling was observed clinically. Lacrimal gland function appears to be impaired in a similar manner to salivary gland function in AIP patients.

Acknowledgement
This study was supported by Research for Intractable Disease of the Pancreas, Ministry of Health, Labour and Welfare of Japan.

References