The Relationship of Salivary Gland Function to Elevated Serum IgG4 in Autoimmune Pancreatitis

Terumi Kamisawa 1, Yuyang Tu 1, Ryoko Sasaki 1, Naoto Egawa 1, Noriko Kamata 2 and Tsuneo Sasaki 3

Abstract

Objective To compare salivary gland function in autoimmune pancreatitis (AIP) patients with and without an elevated serum IgG4 concentration.

Patients and Methods We allocated 14 AIP patients into 2 groups: one group had high (>135 mg/dL) serum IgG4 and the other low serum IgG4. Sialochemistry and submandibular and parotid gland scintigraphy were done in these patients.

Results Serum IgG4 levels were elevated in 10 patients. Bilateral submandibular gland swelling was present in 5 patients with a high serum IgG4; there was no swelling in patients with a low serum IgG4. The salivary Na+ concentration was increased significantly in both patient groups (p<0.01) compared to controls. The β2-microglobulin concentration was significantly higher in patients with a high serum IgG4 than in those with a low serum IgG4 (p<0.05) and controls (p<0.01). On submandibular and parotid gland scintigraphy, both the ratio of the cumulative peak count to the injected radionuclide (PCR) and the washout ratio (WR) were significantly lower in the high serum IgG4 group than in controls (p<0.01). In the low serum IgG4 group, the PCR on submandibular gland scintigraphy, and the PCR and WR on parotid gland scintigraphy were significantly lower than in controls (p<0.05, p<0.01 and p<0.05, respectively). On submandibular gland scintigraphy, the PCR was significantly lower in the high serum IgG4 group than in the low serum IgG4 group (p<0.05).

Conclusions Salivary gland function was impaired in all AIP patients, but it was more impaired in patients with a high serum IgG4 than in those with a low serum IgG4.

Key words: autoimmune pancreatitis, IgG4, salivary gland

(DOI: 10.2169/internalmedicine.46.6222)

Introduction

Autoimmune pancreatitis (AIP) is a recently described type of pancreatitis that has a presumed autoimmune etiology. It is characterized morphologically, by enlargement of the pancreas and irregular narrowing of the main pancreatic duct; serologically, by elevated serum IgG or the presence of autoantibodies; histologically, by lymphoplasmacytic infiltration and fibrosis in the pancreas; and clinically, by a favorable response to steroid therapy (1-5). Another characteristic feature of AIP is that the serum IgG4 levels are elevated in many patients; however, the exact role of IgG4 in the pathogenesis of AIP remains unknown (6, 7). In addition, patients with AIP sometimes have extrapancreatic lesions with histopathological findings that are similar to those in the pancreas, including sclerosing cholangitis, retroperitoneal fibrosis, and sclerosing sialadenitis (8).

The salivary glands and pancreas have many histological and functional similarities. A recent report revealed that carbonic anhydrase I and II were distributed both in the ductal and the acinar cells of salivary glands, as well as in the pancreatic ductal cells (9, 10). Salivary gland involvement in patients with chronic pancreatitis has been studied (11-13). We have previously reported that, in patients with AIP, salivary gland function was frequently impaired, and it im-

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Received for publication September 4, 2006; Accepted for publication December 15, 2006

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proved after steroid therapy (14). We have also examined the clinicopathological differences between AIP patients with and without elevated serum IgG4 levels (15). In this study, we examined whether there were differences in salivary gland function between AIP patients with a high serum IgG4 level and those with a low serum IgG4 level.

**Patients**

Between 1990 and 2005, we measured serum IgG4 levels (single radial immunodiffusion kits; The Binding Site, Birmingham, United Kingdom) in 14 patients with AIP (10 males and 4 females; age range, 29-83 years; average age, 63.3 years) before steroid therapy was started or surgical resection was done. AIP was diagnosed based on: characteristic radiological findings of irregular narrowing of the main pancreatic duct (n=14) and enlargement of the pancreas (n=13); elevation of serum IgG (n=6), presence of autoantibodies, including anti-nuclear antigen and rheumatoid factor (n=7); and confirmed by histology (n=2). In all patients, steroid therapy was given and was effective. Prednisolone was given at an initial dose of 30 mg/day, and then tapered by 5 mg every 1 to 2 weeks, depending on serological and radiological changes. In 2 patients, treatment was discontinued, since their cholangiopancreatographic findings normal radiological changes. In 2 patients, treatment was discontinued. In 2 patients, treatment was discontinued.

**Patients and Methods**

**Statistical analysis**

The data for both groups were compared to each other and to the control group. For the statistical analyses, first the Kruskall-Wallis test and then the Mann-Whitney U test were used. Correlation between serum IgG4 levels and data of salivary gland function was examined using single regression analysis. A value of p<0.05 was considered significant.

**Results**

Serum IgG4 concentrations were elevated (150-1240 mg/dL) in 10 patients (8 males and 2 females; age range, 52-77 years; average age, 65.6 years); serum IgG4 concentrations ranged from 11 to 50 mg/dL in the other 4 patients (2 males and 2 females; age range, 29-83 years; average age, 57.5 years).

Bilateral submandibular gland swelling was detected in 5 AIP patients with a high serum IgG4; 2 of these patients also showed swelling of the right parotid gland. Swelling of the cervical or mediastinal lymph nodes was also detected in the 5 AIP patients with a high serum IgG4. However, swelling of the submandibular or parotid glands was not detected in AIP patients with a low serum IgG4. Only 1 patient with a high serum IgG4 had symptoms of oral sicca. Stenosis of the extrapancreatic bile duct and retroperitoneal fibrosis were associated in 1 and 3 patients with a high serum IgG4 (Table 1).

An adequate volume of saliva (2 mL) could be collected in all patients and controls during the 30 min collection. The salivary Na+ concentration increased significantly in both AIP patient groups (p<0.01) compared to controls. The β2-microglobulin concentration was significantly higher in AIP patients with high serum IgG4 than in AIP patients with low serum IgG4 (p<0.05) and controls (p<0.01) (Table 2).

On submandibular and parotid gland scintigraphy, both the PCR and the WR in the high serum IgG4 group were significantly lower than in controls (p<0.01). In the low serum IgG4 group, the PCR on submandibular gland scintigraphy and the PCR and WR on parotid gland scintigraphy were significantly lower than in controls (p<0.05, p<0.01, and p<0.05, respectively). On submandibular gland scintigraphy, the PCR was significantly lower in the high serum IgG4 group than in the low serum IgG4 group (p<0.05) (Tables 3, 4).

A significant correlation between serum IgG4 levels and data of salivary gland function was detected in PCR on submandibular gland scintigraphy (p<0.01) and on parotid gland scintigraphy (p<0.05). Salivary gland function im-
Table 1. Cases with High and Low Serum IgG4 Concentration and Associated Extrapancreatic Lesions

<table>
<thead>
<tr>
<th>Case</th>
<th>Serum IgG4 (mg/dL)</th>
<th>Swelling of salivary gland</th>
<th>Swelling of lymph nodes*</th>
<th>Stenosis of bile duct**</th>
<th>Retroperitoneal fibrosis</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1240</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1170</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
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<td>1140</td>
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<td>-</td>
</tr>
<tr>
<td>4</td>
<td>1030</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
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<td>5</td>
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<td>-</td>
<td>-</td>
<td>+</td>
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<td>341</td>
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<td>-</td>
<td>-</td>
<td>+</td>
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<td>7</td>
<td>298</td>
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<td>8</td>
<td>240</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>206</td>
<td>-</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>12</td>
<td>39</td>
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</tr>
<tr>
<td>13</td>
<td>31</td>
<td>-</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>11</td>
<td>-</td>
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</tr>
</tbody>
</table>

*: cervical or mediastinal lymph nodes

**: extrapancreatic bile duct

Table 2. Concentrations of Na+ and β2-microglobulin in Saliva

<table>
<thead>
<tr>
<th></th>
<th>No. of cases</th>
<th>Na+ (mEq/L)</th>
<th>β2-microglobulin (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune pancreatitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>high serum IgG4</td>
<td>10</td>
<td>27.2±11.2 **</td>
<td>2.8±1.4 ** #</td>
</tr>
<tr>
<td>low serum IgG4</td>
<td>4</td>
<td>21.7±6.6 **</td>
<td>1.1±0.8</td>
</tr>
<tr>
<td>Controls</td>
<td>30</td>
<td>13.7±8.2</td>
<td>1.0±0.6</td>
</tr>
</tbody>
</table>

**: p<0.01 compared with controls

#: p=0.05 compared with low serum IgG4

proved in all 6 patients who underwent steroid therapy.

Discussion

Hamano et al. (6) reported that serum IgG4 levels are significantly and specifically elevated in AIP patients. The characteristic histological finding of AIP is dense lymphoplasmacytic infiltration with fibrosis in the pancreas. This atypical finding is also observed in the peripancreatic retroperitoneum, biliary tract, and salivary glands. AIP patients sometimes have extrapancreatic lesions, including sclerosing cholangitis, retroperitoneal fibrosis, and sclerosing sialadenitis; the histopathological findings of these extrapancreatic lesions are similar to those seen in the pancreas. Immunohistochemically, abundant infiltration of IgG4-positive plasma cells associated with CD4+ or CD8-positive T lymphocytes has been detected in various organs, including the pancreas, retroperitoneum, biliary tract, and salivary glands of AIP patients, but it has not been detected in organs of patients with chronic alcoholic pancreatitis or Sjogren’s syndrome. Given these findings, we previously suggested the existence of a new clinicopathological entity, IgG4-related sclerosing disease, and suggested that AIP is a pancreatic lesion seen with this systemic disease (17-19). Furthermore, sclerosing sialadenitis, which is sometimes associated with AIP, seems to be a salivary gland manifestation of this systemic disease (19, 20).

Recently, the incidence of serum IgG4 level elevation in AIP patients has been reported to be 65% (2)-68% (21). We have previously examined the clinicopathological differences between AIP patients with and without elevated serum IgG4 levels (15). In the present study, there were no differences between the 2 groups with respect to age, gender, or the frequency of pancreatic enlargement or biliary stenosis. However, abdominal lymphadenopathy was detected more frequently, and the number of IgG4-positive plasma cells infiltrating abdominal lymph nodes, bile duct wall, and gastric mucosa was greater in AIP patients with a high serum IgG4 than in AIP patients with a low serum IgG4. Thus, IgG4-related phenomena in various organs seem to occur less frequently in AIP patients with a low serum IgG4.

Salivary fluid is normally isotonic with plasma; Na+ and
Cl- are extensively resorbed via the ductal system to produce a hypotonic secreted fluid (22). Sjogren’s syndrome causes lymphocytic infiltration in affected salivary glands. The salivary Na⁺ concentration is increased in patients with Sjogren’s syndrome, due to altered resorption caused by the periductal lymphocytic infiltration (23). On the other hand, salivary β2-microglobulin levels show a high specificity for salivary gland inflammation, and salivary β2-microglobulin levels increase in Sjogren’s syndrome (24, 25). Salivary gland scintigraphy is used to quantitatively assess salivary gland function. Since ⁹⁹mTc pertechnetate is trapped and secreted in the ductal epithelium and is excreted in the saliva, salivary gland scintigraphy is correlated with salivary gland flow rates (26, 27). The PCR and WR are used as functional parameters; the WR gives a relative expression of the excretion response and is calculated based on the decrease in gland activity after stimulation (16). In Sjogren’s syndrome, both the PCR and the WR were significantly lower than in controls.

To investigate whether there are differences in salivary gland function between AIP patients with a high serum IgG4 level and those with a low serum IgG4 level, we examined salivary gland function using sialochemistry and salivary gland scintigraphy.

Both submandibular and parotid gland function impaired in all AIP patients, independently of serum IgG4 level. In AIP patients, even if swelling of the salivary glands or symptoms of sicca are not apparent, the salivary glands are frequently involved, probably due to the presence of an aggressive immune mechanism directed against the salivary ducts, which is the same mechanism that is directed against the pancreatic ducts. However, swelling of the salivary gland or symptoms of oral sicca was detected in only patients with a high serum IgG4, and submandibular gland function more impaired in patients with a high serum IgG4 than in those with a low serum IgG4. Other extrapancreatic lesions were also detected in only patients with a high serum IgG4. Salivary gland function is more impaired similar to other organs in AIP patients with a high serum IgG4, although the role of IgG4 in the development of sialadenitis and pancreatitis is unknown.

In conclusion, salivary gland function was impaired in all AIP patients, but it was more impaired in patients with a high serum IgG4 than in those with a low serum IgG4.

### References


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**Table 3.** Submandibular Gland Function Examined by Scintigraphy

<table>
<thead>
<tr>
<th></th>
<th>No. of cases</th>
<th>PCR (%)</th>
<th>WR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune pancreatitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>high serum IgG4</td>
<td>10</td>
<td>10.4±8.0 ** #</td>
<td>45.6±27.7 **</td>
</tr>
<tr>
<td>low serum IgG4</td>
<td>4</td>
<td>23.3±8.5 *</td>
<td>56.4±28.4</td>
</tr>
<tr>
<td>Controls</td>
<td>14</td>
<td>35.1±8.2</td>
<td>87.6±9.0</td>
</tr>
</tbody>
</table>

PCR: Ratio of cumulative peak count

WR: Ratio of washout

**#: p<0.01 compared with controls

*: p<0.05 compared with controls

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**Table 4.** Parotid Gland Function Examined by Scintigraphy

<table>
<thead>
<tr>
<th></th>
<th>No. of cases</th>
<th>PCR (%)</th>
<th>WR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune pancreatitis</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>high serum IgG4</td>
<td>10</td>
<td>17.8±7.1 **</td>
<td>54.5±23.7 **</td>
</tr>
<tr>
<td>low serum IgG4</td>
<td>4</td>
<td>18.4±4.3 **</td>
<td>59.2±12.1 *</td>
</tr>
<tr>
<td>Controls</td>
<td>14</td>
<td>43.4±6.6</td>
<td>78.1±10.5</td>
</tr>
</tbody>
</table>

PCR: Ratio of cumulative peak count

WR: Ratio of washout

**#: p<0.01 compared with controls

+: p<0.05 compared with controls


