Concise report

Identification of relapse predictors in IgG4-related disease using multivariate analysis of clinical data at the first visit and initial treatment

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Abstract

Objectives. Inducing clinical remission by glucocorticoid treatment is relatively easy in IgG4-related disease (IgG4-RD), but relapse also occurs easily with tapering of the steroid dose. The present study tried to analyse the cases to extract predictors of relapse present at the diagnosis of IgG4-RD.

Methods. Subjects comprised 79 patients with IgG4-related dacryoadenitis and sialadenitis, known as Mikulicz’s disease, who were diagnosed between April 1997 and October 2013 and followed-up for >2 years from the initial induction treatment. They were applied to Cox proportional hazard modelling, based on the outcome of interval to relapse. We performed multivariate analysis for the clinical factors of these cases and identified predictors of relapse.

Results. Identified factors were male sex and younger onset in cases without organ involvement at diagnosis and low levels of serum IgG4 in cases with organ dysfunction at diagnosis. Complication with autoimmune pancreatitis and low steroid dose at initial treatment also tended to be associated with recurrence.

Conclusion. Follow-up is important in cases with recognized risk factors for relapse, including male sex and younger onset in cases without organ damage.

Key words: autoimmune pancreatitis, IgG4-related disease, Mikulicz’s disease, multivariate analysis, relapse.

Introduction

IgG4-related disease (IgG4-RD) can cause irreversible damage to various organs through type 2 T helper (Th2) inflammation and progressive fibrosis [1, 2]. Induction of clinical remission is easily achieved using glucocorticoid treatment [3], but relapse also readily occurs when the steroid dose is tapered [4]. The annual rate of recurrence in 2012 was 19.0% in our facility, and half of relapsed cases reportedly present with new organ lesions [5]. On the other hand, many cases can continue in clinical remission with low-dose glucocorticoid, and steroid can even be discontinued in some cases. Because no markers can reflect disease activity and predict relapse in IgG4-RD, rheumatologists often encounter difficulties in clinical practice. Thus the present study tried to analyse cases followed for >2 years after initiating therapy to extract predictors of relapse present at the diagnosis of IgG4-RD.

Methods

Subjects comprised 79 patients with IgG4-related dacryoadenitis and sialadenitis, known as Mikulicz’s...
disease, who were diagnosed between April 1997 and October 2013 and followed up for >2 years from the initial induction treatment. Cases were diagnosed with bilateral and continuous enlargement of the lacrimal and salivary glands, elevated levels of serum IgG4 and abundant infiltration of IgG4-bearing plasmacytes into involved organs. We analysed the following clinical factors: sex; age at onset; disease duration; eosinophil count; serum levels of IgG, IgG4 and IgE at diagnosis; presence of hypocomplementaemia and ANA and levels of RF at diagnosis; presence of organ involvement other than the lacrimal and salivary glands; numbers of organ lesions other than those of the lacrimal and salivary glands; complication with autoimmune pancreatitis, IgG4-related kidney disease or retroperitoneal fibrosis and the initial dose of steroid. Disease duration was defined as the interval between the appearance of subjective symptoms and the start of treatment. Autoimmune pancreatitis, IgG4-related kidney disease and retroperitoneal fibrosis were diagnosed based on imaging findings. As our treatment protocol, starting prednisolone at a dose of 0.6 mg/kg/day was appropriate with only lacrimal and salivary gland involvement, increasing to 1.0 mg/kg/day with multiple organ lesions. The initial dose of prednisolone was continued for 2–4 weeks, tapering the dose by 10% every 2 weeks. If the patient was >80 years of age or had existing complications, the amount of prednisolone was decreased up to 30% of the predetermined amount. Relapse was defined as re-enlargement of the lacrimal and/or salivary glands or appearance of other organ involvement.

First, all 79 cases were applied to Cox proportional hazard modelling, based on the outcome of interval to relapse. We performed uni- and multivariate analysis for each clinical factor and identified predictors of relapse. On multivariate analysis, we used the backward elimination method (Wald method, excluding factors presenting with $P > 0.1$) and extracted the factors offering high predictive power. The existence of organ involvement was considered to represent a strong risk factor for relapse. We stratified patients into groups with and without organ lesions at diagnosis and performed uni- and multivariate analysis for each group. In multivariate analysis, we applied those variables that showed $P < 0.2$ in univariate analysis and used the backward elimination method (Wald method, excluding factors presenting with $P > 0.1$). $P$-values $<0.05$ were considered statistically significant. All statistical analyses were performed using SPSS Statistics version 20.0.0 software (IBM, Armonk, NY, USA).

Written consent to use the information from these cases was obtained from all patients in accordance with the Declaration of Helsinki. This study proceeded under the approval of the Sapporo Medical University Hospital Institutional Review Board (SMU 22-57, 24-155).

Results

Table 1 shows the profiles of the patients. For the 79 cases, age at onset, presence of organ involvement and complication of autoimmune pancreatitis at diagnosis in univariate analysis and age at onset, levels of serum IgG and RF and presence of organ involvement at diagnosis in multivariate analysis were extracted.

The results from analyses by group with and without organ involvement, which was considered a strong predictor of relapse, showed that sex, age at onset and disease duration were significant on univariate analysis and sex and age at onset were extracted from multivariate analysis for the group without organ lesions at diagnosis. On the other hand, levels of serum IgG and IgG4 at diagnosis were significant on univariate analysis and the level of serum IgG at diagnosis was extracted by multivariate analysis for the group with organ dysfunction (Table 2).

### Table 1 Characteristics of the patients

<table>
<thead>
<tr>
<th>Organ involvement at the first visit</th>
<th>Presence</th>
<th>Absence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No relapse during follow-up n = 28</td>
<td>Relapse during follow-up n = 5</td>
</tr>
<tr>
<td>Male:female, mean (s.d.)</td>
<td>8:20 (1:2.5)</td>
<td>3:2 (1:0.7)</td>
</tr>
<tr>
<td>Age at onset, mean (s.d.), years</td>
<td>62.6 (10.8)</td>
<td>45.8 (18.0)</td>
</tr>
<tr>
<td>Period of illness, mean (s.d.), years</td>
<td>1.39 (1.69)</td>
<td>4.00 (3.39)</td>
</tr>
<tr>
<td>Eosinophils, mean (s.d.), per ml</td>
<td>220.7 (252.8)</td>
<td>106.0 (60.7)</td>
</tr>
<tr>
<td>Serum IgG, mean (s.d.), mg/dl</td>
<td>2035.0 (1027.0)</td>
<td>1479.6 (160.2)</td>
</tr>
<tr>
<td>Serum IgG4, mean (s.d.), mg/dl</td>
<td>556.5 (393.2)</td>
<td>221.8 (181.1)</td>
</tr>
<tr>
<td>Serum IgE, mean (s.d.), IU/ml</td>
<td>314.1 (439.4)</td>
<td>412.4 (395.5)</td>
</tr>
<tr>
<td>Hypocomplementaemia, %</td>
<td>14.3</td>
<td>20.0</td>
</tr>
<tr>
<td>ANA positive, %</td>
<td>17.9</td>
<td>40.0</td>
</tr>
<tr>
<td>RF positive, %</td>
<td>14.3</td>
<td>60.0</td>
</tr>
</tbody>
</table>
Male sex and younger onset in cases without organ involvement and a low level of serum IgG at diagnosis in cases with organ dysfunction were identified as predictors of relapse.

Discussion
The results of this analysis showed that extracted predictors of relapse differed between cases with
and without organ dysfunction at diagnosis in IgG4-related dacrooyadenitis and sialadenitis. This might provide an opportunity to reconsider initial treatment in IgG4-RD.

First, we discuss cases without organ lesions other than of the lacrimal and salivary glands in IgG4-related dacrooyadenitis and sialadenitis. Male sex and younger onset were predictors of relapse. IgG4-RD is a disorder based on Th2 inflammation [1]. With regard to the relationship between Th1/Th2 cytokine balance and sex hormones, oestrogen is known to promote the Th1 response [6], while progesterone promotes Th2 inflammation [7]. For this reason we have sometimes found that symptoms worsen when a female patient with IgG4-RD becomes pregnant. In addition, Th1 response is gradually suppressed in menopause due to the reduction in the production of oestrogen. In other words, Th2 immune response tends to be dominant in women after menopause. On the other hand, dihydrotestosterone, an active androgen, inhibits both Th1 and Th2 immune responses [8]. Th2 response is less likely to arise in males and younger patients due to the sex hormone environment. The occurrence of IgG4-RD in males and younger patients may thus suggest high disease activity. These results could also be confirmed using the SMART (Sapporo Medical University and related institutes database for investigation and best treatments of IgG4-RD) cohort database. We analysed 110 cases treated with maintenance therapy and overlapped them with the 79 subjects in the main analysis. The annual relapse rate in the male cases without organ involvement was 9.09% and in the female cases it was 3.85%. The amount of prednisolone at the maintenance treatment was 5.27 mg/day (s.d. 2.72) in males without organ involvement and 3.96 mg/day (s.d. 2.82) in females. Furthermore, there was no relapse in patients who were ≥70 years of age.

On the other hand, the low levels of serum IgG before treatment in cases with organ dysfunction are difficult to interpret. It was previously reported that expression levels of IL-6 mRNA at diagnosis of IgG4-RD were not significantly low [9]. The interpretation of this result is very difficult at present. In our analysis, complication with autoimmune pancreatitis and the use of low-dose glucocorticoid at initial induction therapy were not significant factors, but tended to be associated with relapse in cases with organ involvement. These factors might be identified as significant with increased numbers of cases for analysis.

The rate of complication with autoimmune pancreatitis was approximately 20% in these patients. Although this study could not suggest a precise interpretation, there was also a high rate of relapse in younger cases with autoimmune pancreatitis. This subject was not included in the cases with only autoimmune pancreatitis, and so was not statistically examined, but younger and male might be predictive risk factors in IgG4-RD.

There is currently no guideline on treatment in IgG4-RD as a whole. Japanese pancreatologists have developed a treatment guideline only for autoimmune pancreatitis. It recommends that the indication for steroid treatment is only symptomatic, starting at 0.6 mg/kg/day of prednisolone as initial dose [10]. This strategy can lead to clinical remission, but relapse often occurs. It is possible that the initial dose, which is required for the pathogenesis, is insufficient. Our analysis showed that the rate of recurrence was high in cases where we could not prescribe the predetermined amount and cases with multiple organ involvement.

We also have to follow up those cases with recognized risk factors for relapse, namely male sex and younger onset in the absence of organ damage. A sufficient dose of steroid at the initial induction treatment may inhibit recurrence in cases complicated with autoimmune pancreatitis.

### Rheumatology key message

- Relapse predictors in IgG4-related disease without organ involvement at diagnosis were male sex and younger onset.

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###Disclosure statement

The authors have declared no conflicts of interest.

###References


