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ORIGINAL ARTICLE

Characterization and Comparison of Patient Subgroups Suspicious for IgG4-Related Disease and Malignant Lymphoma in Patients Followed-up for Sjögren's Syndrome

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Abstract Differential diagnosis of patients with Sjögren's syndrome (SS), IgG4-related disease (IgG4-RD) and SS patients having high risk for lymphoma (LHR) can be challenging. Some patients with IgG4-RD might be misdiagnosed as having SS. There are special symptoms of SS that raise the possibility of IgG4-RD whereas other symptoms identify patients as having LHR. The purpose of this study was to characterize and compare patients with SS, possible IgG4-RD and SS patients with LHR. Sixty-five SS patients were divided into 4 subgroups according to having possible IgG4-RD (n = 15), LHR (n = 16), eligible for both aforementioned groups (n = 20) and not eligible for either group (n = 14), respectively. Four patients fulfilled the diagnostic criteria for IgG4-RD. The serum levels of IgG4 were significantly higher in patients suspicious for IgG4-RD compared to that of LHR patients (0.46 g/l vs. 0.12 g/l, p = 0.032). Shared features of the patient groups (salivary gland swelling (SGS) and lymphadenopathy), were separately analysed: SGS patients had higher IgG4/IgG ratio (p = 0.036), lymphadenopathic patients had higher IgG4 levels (p = 0.042). Some patients may be "hidden" under the diagnosis of SS. Although patients with LHR and patients with possible IgG4-RD share some symptoms, they differ significantly regarding IgG4 levels and IgG4/IgG ratio.

Keywords IgG4-related disease · Malignant lymphoma · Sjögren's syndrome

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Introduction

IgG4-related disease (IgG4-RD) has been discovered recently as a heterogeneous group of diseases [1]. Clinical diagnostic criteria for the disease were established in 2009, where Sjögren's syndrome (SS) appears as one of the exclusion criteria [2]. In 2011, comprehensive diagnostic criteria were developed for practical use where "definite", "probable" and "possible" categories were defined, and differentiation from similar diseases including Sjögren's syndrome was also highlighted [3]. Mikulicz's disease is a special condition which can be misdiagnosed as SS since the 2002 American-European Consensus Criteria [4] allows it (e.g. salivary gland swelling, negative testing for anti-Ro/SS-A, anti-La/SS-B, lympocytic/lymphoplasmocytic sialadenitis upon histology, decreased glandular functions). Therefore, some of the IgG4-RD patients might nowadays be misdiagnosed as SS.

Among patients diagnosed as having SS, male gender, negative serology for anti-Ro/SS-A and anti-La/SS-B, co-existence of autoimmune hepatitis, sclerosing cholangitis, Riedel's thyroiditis, persisting salivary gland enlargement and lymphadenopathy raise the possibility of having IgG4-RD [5]. The latter two, together with low C4 complement levels, neutropenia, polyneuropathy, gammopathy and vasculitis (palpable purpura, cryoglobulinemia) identify patients as having high risk for developing malignant lymphoma [6]. Based on the aforementioned features and their shared clinical symptoms - namely:

Table 1 Inclusion criteria for the different patient groups (eligible if at least one criterion is present)

Criteria for IgG4-RDsusp group	Criteria for LHR group
Male gender	Persisting leukopenia
Negative serology for anti-Ro/SS-A and anti-La/SS-B	Low complement levels
Autoimmune pancreatitis	Polyneuropathy
Autoimmune hepatitis	Vasculitis
Sclerotizing cholangitis	Gammopathy
Riedel's thyroiditis	Cryoglobulinemia
*Persisting salivary gland swelling	
*Lymphadenopathy	

IgG4-RD: IgG4-related disease

IgG4-RDsusp: patients suspicious for IgG4-RD

Lymphoma high risk (LHR): patients with high risk for malignant lymphoma

*shared features of the two patient groups

persisting salivary gland swelling and lymphadenopathy - we aimed to compare patients with high lymphoma risk to patients with possible IgG4-RD. Our purpose was to unravel whether the measurement of serum IgG4 levels is able to help classifying patients with the shared symptoms into the different subgroups mentioned above.

Patients and Methods

Study Patients

Data of 65 patients with primary SS (57 female and 8 male) were involved in this study. All patients were Caucasian, followed-up at the Outpatient Clinic of the University of Debrecen, Medical Faculty, Division of Clinical Immunology. Each patient fulfilled the American European Consensus Group criteria for primary SS [4]. Patients were divided into 4 subgroups according to the criteria shown in Table 1.:

- Patients suspicious for IgG4-RD (IgG4-RDsusp): patients with at least one criterion from column "IgG4-RDsusp".
- Lymphoma high risk (LHR): patients with at least one criterion from column "LHR".
- IgG4-RDsusp + LHR: patients eligible for both IgG4-RDsusp and LHR groups.
- Control: patients with SS who are not eligible for any of the aforementioned groups.

Patients were further sub-divided according to the presence or absence of extraglandular symptoms (EGS) which were defined as non-sicca symptoms caused by immune complex deposition or mononuclear cell infiltration: polyarthritis, vasculitis, interstitial pneumonia, interstitial nephritis, Raynaud's phenomenon or lymphadenopathy (persistent enlargement of certain lymph nodes).

Informed consent was obtained from each patient. The study was approved by the Institutional Ethics Committee of the University of Debrecen and conducted in accordance with the Declaration of Helsinki.

Patients' age, clinical course, complement levels, total IgG and IgG4 levels, as well as IgG4/IgG ratios were compared. EULAR Sjögren's syndrome disease activity index (ESSDAI) [7] was calculated for each patient at the time of the laboratory examinations.

Table 2 Age and complement levels of the different patient groups

	IgG4-RDsusp	LHR	IgG4-RDsusp + LHR	Controls	p
age (years ± SD)	59.1 ± 14.1	47.6 ± 15.7 (*)	57.3 ± 12.6	62.3 ± 9.7	* $p = 0.02$
C3 (mg/ml)	1.26 ± 0.28	1.25 ± 0.29	1.30 ± 0.28	1.23 ± 0.25	ns
C4 (mg/ml)	0.252 ± 0.113	0.188 ± 0.064	0.219 ± 0.064	0.239 ± 0.072	ns
CH50	62 ± 13	60 ± 19	65 ± 10	66 ± 14	ns

IgG4-RD: IgG4-related disease

IgG4-RDsusp: patients suspicious for IgG4-RD

LHR: patients with high risk for malignant lymphoma

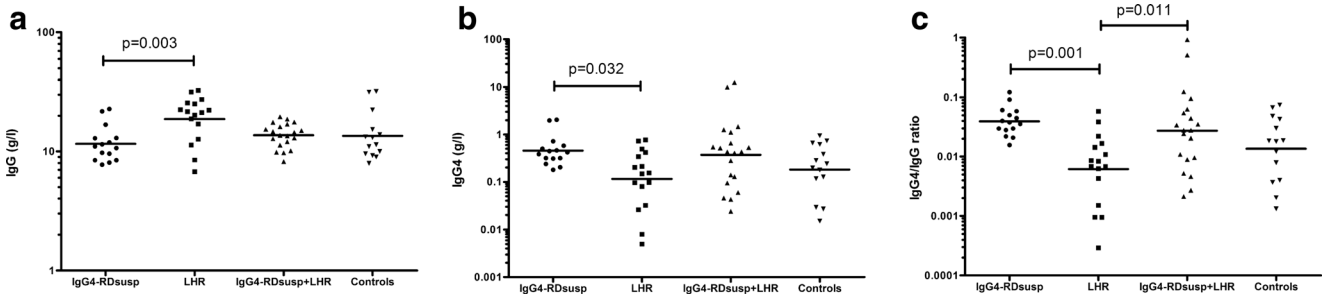

Fig. 1 **a** IgG levels in the different patient subgroups. **b** IgG4 levels of the different patient subgroups. **c** IgG4/IgG ratio of the different patient groups. IgG4-RD: IgG4-related disease, IgG4-RDsusp: patients suspicious for IgG4-RD, LHR: patients with high risk for malignant lymphoma

Immunoserology

Serum Immunoglobulin G (IgG) was analyzed by turbidimetric method (Dialab GmbH, Wiener Neudorf, Austria,). IgG4, complement C3 and C4 concentrations were measured by nephelometry (Siemens AG, Munich, Germany) on a Siemens Dade Behring BN II nephelometer. Calibrator values were traceable to ERM-DA470k (IgG) and WHO IRP67/97 (IgG4), respectively. Total complement activity (CH50) was analysed with hemolytic method. Anti-Ro/SS-A and anti-La/SS-B antibody levels were determined by a commercially available ELISA kit, according to the manufacturer's instructions (HYCOR Biomedical Inc., Indianapolis, IN, USA).

Statistical Analysis

Statistical analyses were performed with SPSS 19.0 software. Normal distribution of data was verified with Shapiro Wilk test. Normally distributed data were compared with ANOVA or two-sample t-tests, otherwise Kruskal-Wallis or Mann-Whitney non-parametric tests were used. Data of IgG, IgG4 and IgG4/IgG ratio were normally distributed after logarithmic transformation. Logistic regression model was used to analyse binary clinical outcome. $P < 0.05$ was considered statistically significant.

Results

Fifteen patients were selected for the IgG4-RDsusp group, 16 for the LHR group, 20 for the IgG4-RDsusp + LHR group and 14 served as controls.

Demographic Data of Patients and Immunological Analysis of the Subsets

Mean age of patients with high risk for malignant lymphoma was significantly lower compared to the others (Table 2). Complement levels did not differ significantly among the four patient subsets.

The total IgG level of LHR patients was significantly higher than that of the IgG4-RDsusp patients (geometric mean: 18.7 g/l vs. 11.6 g/l, $p = 0.0033$, Fig. 1a). IgG4 levels differed among the four groups ($p = 0.022$). IgG4 concentrations were significantly higher in the IgG4-RDsusp patients than in the LHR group (geometric mean: 0.46 g/l vs. 0.12 g/l, $p = 0.032$) (Fig. 1b).

IgG4/IgG ratio was calculated in each patient. IgG4/IgG ratio was significantly higher both in the IgG4-susp and in the IgG4-susp + LHR group compared to the LHR group (Fig. 1c).

Table 3 Patients with elevated IgG4 levels

Patient	Age	Gender	IgG (g/l)	IgG4 (g/l)	IgG4/IgG (%)	anti-Ro/SS-A	anti-La/SS-B	Organs involved	Fulfilled clinical criteria [2]
1	71	M	19.64	9.99	50.87	−	−	P, SG, LN	1,2,3/a-b.
2	59	F	14.1	12.5	88.66	−	−	P, SG, LN	1,2,3/a-b.
3	64	F	14.3	1.46	10.2	+	+	SG	1,2
4	38	F	16.8	2.04	12.14	+	−	SG	1
5	67	F	22.2	1.97	8.87	−	−	SG	1,2,3/a-b.

F female

M male

P pancreas

SG salivary gland

LN lymph nodes

Patients with Elevated IgG4 Levels

Elevated serum IgG4 levels were found in 5 patients. All of them belonged to the IgG4-RDsusp group. Among them, 4 patients fulfilled the diagnostic criteria for IgG4-RD (Table 3). In 3 of the 4 patients, the diagnosis was confirmed with histology, as well. Patient 3 refused biopsy sampling from the affected salivary gland; therefore, although the patient met the clinical diagnostic criteria for IgG4-RD, it was not confirmed with histology. The fifth patient (Patient 4) was a 38-year-old female patient with slightly elevated serum IgG4 level. She had severe allergic rhinitis due to pollen allergy although did not develop bronchial asthma. Detailed clinical data of these patients have been described before [8].

Analysis of Patients with and Without Salivary Gland Swelling and Lymphadenopathy

Since there are two common features among the selection criteria for the IgG4-RDsusp and the LHR group, these were analysed separately, as well.

Among patients with salivary gland swelling (n = 35), the IgG4/IgG ratio was significantly higher compared to patients without that symptom. Neither total IgG, nor IgG4 levels differed significantly (Table 4). Patients with lymphadenopathy (n = 10) had significantly higher IgG4 levels compared to patients without this phenomenon (p = 0.042, Table 4).

Impact of Extraglandular Symptoms and Disease Activity on IgG and IgG4 Levels

Patients with extraglandular symptoms (EGS) had significantly higher IgG and lower IgG4 levels, thus lower IgG4/IgG ratio than those without EGS (geometric means, Table 5, Fig. 2a-c).

ESSDAI values did not directly correlate with IgG4 serum levels. However, ESSDAI median was higher in those cases where IgG4 concentrations were higher than 1.35 g/l (2 vs. 6, p = 0.026) and also ESSDAI mean was, though not significantly, higher in the IgG4susp group (3.3 vs 2.2, p = ns). The average ESSDAI score was elevated in the LHR group (4.0 vs. 1.3, p = <0.001).

Table 5 Comparison of IgG, IgG4 serum levels and IgG4/IgG ratio in patients with and without extraglandular manifestations

	Without EGS	With EGS	p
IgG (g/l)	12.6	15.9	**0.02**
IgG4 (g/l)	0.37	0.17	**0.035**
IgG4/IgG ratio	0.029	0.011	**0.005**

Bold entries indicate statistically significant p values.

EGS extraglandular manifestations

Prediction of IgG4-RD Based on the Number of Characteristic Symptoms

Logistic regression model was used to determine the probability of IgG4-RD based on the number of the characteristic symptoms present in a certain patient. A significant correlation was found between increasing numbers of symptoms and the likelihood of IgG4-RD even when laboratory features (negative testing to anti-Ro/SS-A and anti-La/SS-B) were not considered (Fig. 3).

Discussion

It is not necessarily accurate to consider SS as an exclusion criterion for IgG4-RD until the diagnostic conditions of IgG4-RD are not widely ensured (principally regarding Europe). Namely, some IgG4-RD patients can be misdiagnosed as SS if their IgG4 serum levels were not measured, or the minor salivary gland biopsy specimens were not assessed for IgG4 with immunohistochemistry. According to the latest, comprehensive diagnostic criteria [3], patients 1, 2 and 5 have "definite IgG4-RD", Patient 3 can be categorized as "possible IgG4-RD" but Patient 4 is unlikely to have the disease. These results further support the hypothesis that some patients may be "hidden" under the diagnosis of SS, unless their serum IgG4 level is measured. Therefore, we recommend that in SS patients who are suspicious for IgG4-RD, the aforementioned investigations should be performed. However, elevated IgG4 levels alone do not confirm the diagnosis of IgG4-RD since there are various conditions (e.g. chronic rhinosinusitis as experienced by our Patient 4) in which IgG4 can be elevated coincidentally [9].

Table 4 IgG, IgG4 levels and ratio of patients with (+) and without (−) persisting salivary gland swelling and lymphadenopathy

	SGS+	SGS-	p	L+	L-	p
IgG (g/l)	13.3	15.3	ns	16.2	13.8	ns
IgG4 (g/l)	0.33	0.18	ns	0.59	0.21	**0.042**
IgG4/IgG	0.025	0.012	**0.036**	0.036	0.016	ns

Bold entries indicate statistically significant p values.

SGS salivary gland swelling

L lymphadenopathy

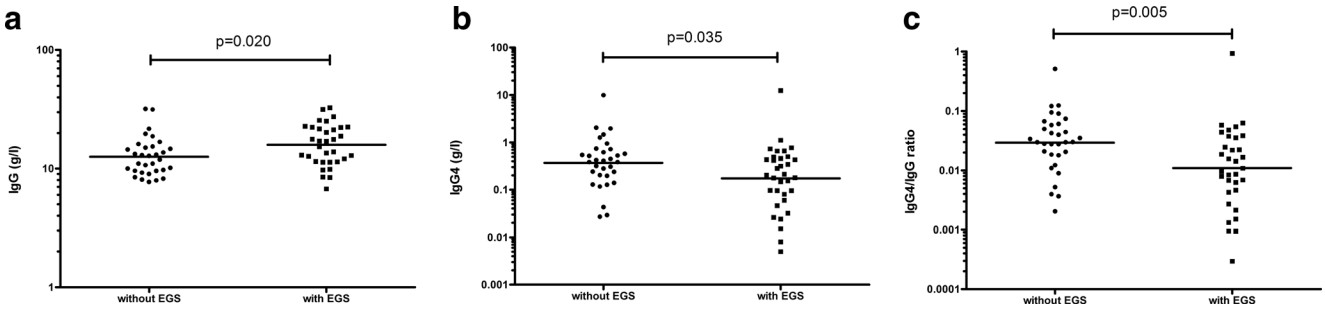

Fig. 2 **a** Comparison of IgG levels between patients with and without extraglandular symptoms. **b** Comparison of IgG4 levels between patients with and without extraglandular symptoms. **c**. Comparison of IgG4/IgG ratios between patients with and without extraglandular symptoms. EGS: extraglandular symptoms

Moriyama et al. compared clinical characteristics of patients with SS and patients with Mikulicz's disease [10]. According to their results, although Mikulicz's disease and SS affect similar organs, they differ regarding clinical and histological characteristics. No significant difference was found between the ratio of patients with elevated IgG levels in the two disease subsets, and IgG4 serum levels were not measured in SS patients. Antinuclear factor was positive in a considerable ratio of patients with Mikulicz' disease (26.3 %) and in each patient with SS. Anti-Ro/SS-A and anti-La/SS-B were negative in the Mikulicz's disease group and positive in 88.90 and 50 % in SS, respectively [9]. Our patient with possible IgG4-RD (Patient 3) was positive for anti-Ro/SS-A and anti-La/SS-B, and so was the patient with elevated IgG4 serum level who was unlikely to have IgG4-RD (Patient 4). However, positive results for anti-Ro/SS-A and anti-La/SS-B are currently not exclusion criteria. Moriyama et al. experienced improvement of the salivary gland function after the administration of corticosteroid treatment in patients with Mikulicz's disease. Since the increasing ratio of salivary function negatively correlated with disease duration, early diagnosis and treatment of Mikulicz's disease was highlighted [10].

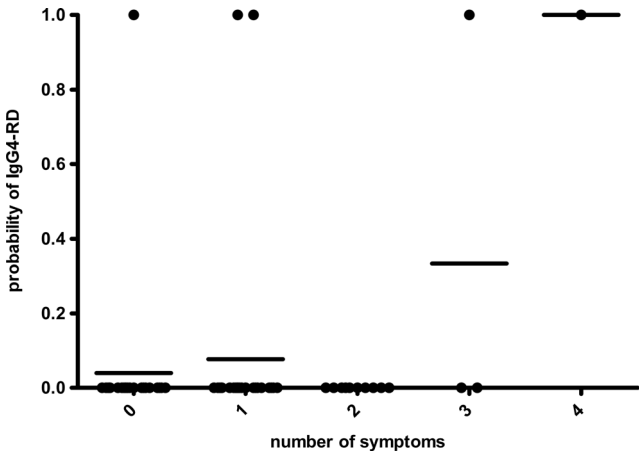

Fig. 3 Logistic regression model to predict the likelihood of IgG4-related disease based on the number of clinical symptoms of patients. IgG4-RD: IgG4-related disease, OR: Odds ratio, OR: 2.49 (95 % CI:1.03–6.00)

Two of our patients with IgG4-RD had multiple organ involvement, two of them had only salivary gland manifestation. This corresponds with the fact that some patients (10–20 %) have solitary organ involvement while the majority of the patients have multi-organ lesions synchronously or metachronously [11].

The accurate diagnosis of IgG4-related lymphadenopathy is of high importance in order to avoid misdiagnosing lymphoma [12]. Based on our findings, although patients with high risk of malignant lymphoma and patients with possible IgG4-RD share some clinical symptoms (namely lymphadenopathy and persisting salivary gland swelling), they differ significantly regarding their IgG and IgG4 levels as well as IgG4/IgG ratio. Considerably, according to the recent data of Quartuccio et al., among SS patients with persistent salivary gland swelling, only those positive for at least 2 of the following biomarkers have an increased risk for lymphoma: cryoglobulinaemia, low c4 complement levels, anti-La/SS-B positivity and leukopenia [13]. However, SS patients are required to be evaluated for lymphoma risk upon diagnosis and re-evaluated regularly during follow-up: the aforementioned tests should be performed and the clinical symptoms indicating lymphoma risk and mentioned in the Introduction section are recommended to be assessed.

We defined the IgG4-RDsusp group instead of using only the data of patients with an accurately diagnosed, definitive IgG4-RD. Since glucocorticoid treatment results in significant decrease of the serum IgG4 levels and the clinical symptoms [9], we could not exclude the possibility that in fact, even more of our patients would fulfil the diagnostic criteria for IgG4-RD. Namely, some of the patients might have already been treated with glucocorticoids at the time of the serum IgG4 measurement, therefore both the clinical and the serological characteristics could be affected and limited by this. Our results, especially the IgG4/IgG ratio, support this hypothesis. Moreover, 40 % of IgG4-RD patients have no elevated IgG4 levels, so normal circulating IgG4 does not rule out the disease [14]. Biopsy from the affected organs would have helped us identify further cases. However, re-biopsy of patients with normal IgG4 serum levels and under corticosteroid treatment would raise

ethical concerns. Therefore, available minor salivary gland histological samples of 6 more patients were revised in our Institute of Pathology. They were taken between 1999 and 2011. All were negative for IgG4 with immunohistochemistry, and the indirect histological signs for IgG4-RD were missing, as well. Unlike us, another clinicopathological study could retrospectively identify 6 cases of IgG4-related submandibular gland disease, which suggests that histopathological diagnosis can be revised even years after sampling if necessary [15, 16]. Once suspected, IgG4-RD is recommended to be proven by biopsy in order to exclude malignancy, SS or similar disorders. Moreover, patients diagnosed as SS but having also IgG4-RD-compatible manifestations should be thoroughly evaluated for IgG4-RD. Incisional biopsy of the submandibular gland seems to be more useful and appropriate for the definitive diagnosis of IgG4-RD than biopsy of the labial salivary glands [17].

Not only accuracy, but also timing of the establishment of the diagnosis plays a pivotal role in the disease course and prognosis of the patients with IgG4-RD. Recently, Shimizu et al. have highlighted the importance of early diagnosis and treatment since the improvement obtained in salivary secretion decreases with the histological changes due to the delay in therapeutic intervention [18]. Therefore, in patients in whom the possibility of IgG4-RD can be raised, we recommend the serological and histological analysis before the introduction of any immunosuppressive treatment, as was also highlighted previously [8].

Based on the results of our logistic regression model performed in this study, it can be decided from the clinical appearance whether it is beneficial to test a patient for serum IgG4 level. In conclusion, we highly recommend the measurement of serum IgG4 level if at least 2 of the following criteria are present: male gender, negative serology for anti-Ro/SS-A and anti-La/SS-B, co-existence of autoimmune pancreatitis, autoimmune hepatitis or sclerotizing cholangitis, Riedel's thyroiditis, persisting salivary gland swelling and lymphadenopathy.

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Compliance with Ethical Standards

Conflict of Interest None.

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