Differences in Immune Indicators and Prognosis Between IgG4-Positive and Negative Lacrimal Gland Benign Lymphoepithelial Lesion

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Abstract

Purpose: The differences in immune indicators and prognosis between IgG4-positive and negative lacrimal gland benign lymphoepithelial lesion (LGBLEL) were analyzed.

Methods: This was a single-center retrospective clinical study. Clinical data of 146 patients with LGBLEL were collected from June 2011 to June 2019.

Results: The age, preoperative glucocorticoid history, and serum C3, C4, IgG, IgG2, IgG4 had statistical difference between the IgG4-positive and negative groups (P<0.05). The expression levels of IgG and IgG4 in the IgG-positive group with preoperative glucocorticoid therapy were lower than those in the IgG4-negative group without preoperative glucocorticoid therapy (P=0.021 and P=0.013). The 5-year recurrence-free cumulative percentages of IgG4-positive group was 81.85%, and 83.46% in the IgG-negative group, which had no statistical difference (P=0.216). The history of preoperative glucocorticoid therapy, serum C4, IgG1 and IgG2 were the factors affecting IgG4-positive LGBLEL' recurrence, while the history of preoperative glucocorticoid therapy, serum C4, and IgG1 were the factors affecting LGBLEL' recurrence (P<0.05).

Conclusion: Serum C3, C4, IgG, IgG2, IgG4 had statistical difference between the IgG4-positive and negative LGBLEL. The history of preoperative glucocorticoid therapy, serum C4 and IgG1 were the factors affecting LGBLEL' recurrence, while the expression level of IgG4 was not the factor affecting LGBLEL' recurrence.

Introduction

Lacrimal gland benign lymphoepithelial lesion (LGBLEL) is a kind of benign lesion with diffuse infiltration of lymphocytes into lacrimal gland, leading to atrophy of gland parenchyma and proliferation of myoepithelial basal cells[1–2]. The main manifestations of the disease are painless eyelid swelling and lacrimal gland swelling. Current studies have shown that the occurrence of LGBLEL may be related to the increase of IgG4 level and the disorder of estrogen level[3–4]. IgG4-related disease (IgG4-RD) is an immune-mediated systemic disease characterized by diffuse infiltration of plasma cells expressing positive IgG4, which results in swelling of the diseased tissue accompanied by a significant increase in serum IgG4[5]. IgG4-ROD is a subtype of IgG4-RD, IgG4-related ocular disease (IgG4-ROD) can involve all orbital tissues, the most common of which is the lacrimal gland[6]. The incidence of IgG4-ROD accounts for 4–34% of IgG4-RD and 25% of all instances of orbital lymphoproliferative disease[7–8].

The diagnostic criteria for IgG4-ROD: (1) Imaging findings show enlargement of lacrimal gland, trigeminal nerve or extraocular muscle as well as masses, enlargement or hypertrophic lesions in various ophthalmic tissues;(2) Histopathological examination shows marked lymphocyte and plasmacyte infiltration, and sometimes fibrosis. histopathological findings > 10 IgG4 + plasma cells per high power field (HPF, ×400) and an IgG4+/IgG + cell ratio > 40%;(3) Serum IgG4 was elevated (≥ 135 mg/dl)[9].

LGBLEL is the bilateral, painless, and symmetrical swelling of the lacrimal glands. Part of LGBLEL has elevated serum IgG4 levels and infiltration of numerous IgG4-expressing plasma cells, defined as IgG4-positive LGBLEL and considered to be part of IgG4-ROD[10–11]. While some LGBLEL without elevated serum IgG4 levels and infiltration of numerous IgG4-expressing plasma cells is defined as IgG4-negative LGBLEL. Therefore, this study comparatively analyzed the clinical characteristics, laboratory indicators, prognosis, and prognostic influencing factors of IgG4-positive and negative LGBLEL to identify the clinical indicators with differential diagnostic and prognostic significance.

Methods

Patients

This was a single-center retrospective clinical study. The medical records of 146 LGBLEL confirmed by pathology from June 2011 to June 2019 were collected from the medical records database of the Department of Ophthalmology, Beijing Tongren Hospital, Capital Medical University, by professional ophthalmologists. The number of IgG4 positive expression was counted and confirmed by two professional pathologists. 105 cases were IgG4-positive LGBLEL and 41 cases were IgG4-negative LGBLEL. Inclusion criteria for IgG4-positve group were as follows: (1) lacrimal gland enlargement, histopathological manifestations of extensive infiltration of lymphocytes and plasma cells, and hyperplasia of fibrous connective tissue; (2) histopathological findings > 10 IgG4+ plasma cells per high power field (HPF) and an IgG4+/IgG+ cell ratio >40%; and (3) a serum IgG4 concentration >135 mg/dl. Inclusion criteria for patients with IgG4-negative group were (1) lacrimal gland enlargement, histopathological manifestations of extensive infiltration of lymphocytes and plasma cells, and hyperplasia of fibrous connective tissue; (2) histopathological findings ≤ 10 IgG4+ plasma cells per high power field and an IgG4+/IgG+ cell ratio ≤40%; and (3) a serum IgG4 concentration ≤135 mg/dl. Exclusion criteria were as follows: (1) serum and staining data for IgG4 were unavailable; or (2) other lacrimal gland diseases and tumors, such as Wegener granuloma. Participants with LGBLEL were required to satisfy the first two or more inclusion criteria. Written informed consent was obtained from all patients, and the study was approved by the Institutional Review Board of Beijing Tongren Hospital and conducted according to the tenets of the Declaration of Helsinki.

Clinical data collection

The clinical data of the IgG4-positive and negative LGBLEL were collected, including age, gender, affected eye, past medical history (postoperative glucocorticoid history, operation history, sinusitis, asthma, lymph node swelling, and other immune system diseases), clinical manifestations (including main symptoms and simultaneous symptoms), imaging characteristics, disease course, and immunohistochemical indicators. All patients had complete medical history, and the imaging examination included magnetic resonance imaging (MRI) or computed tomography (CT). The affected locations (including the lacrimal gland, orbital fat, extraocular muscle, optic nerve, eyelid, and conjunctiva) were recorded. Course of disease referred to the duration of clinical symptoms.

Laboratory data collection

Peripheral venous blood samples of IgG4-positive and negative LGBLEL were collected using the enzyme-linked immunosorbent method (ELISA) to test for related indicators, including complement C3, C4, and rheumatoid factor (RF), c-reactive protein (CRP), anti-streptolysin O (ASO), immunoglobulin A (IgA), IgM, and IgG and its subtypes (IgG1, IgG2, IgG3, and IgG4). The laboratory indicators of the two groups were compared and analyzed.

Treatment and prognosis

All patients were treated with partial surgical excision and glucocorticoid therapy. According to the volume of the lesion, either a subarcuate skin incision or a double eyelid skin incision on the anterior orbital temporal eyebrow was selected for the surgical approach. The subcutaneous tissue was separated to reach the orbital margin, and the orbital partition was cut into the orbit. The lesion was removed and histopathological examination was conducted. The patients were given glucocorticoids 80–120 mg/d for 3 days after the operation, which was then changed to methylprednisolone tablets 24–28 mg/d. The dosage was reduced by 1 tablet for 1–2 weeks until the withdrawal of the drug. The course of treatment was 1.5–3 months.

The effective follow-up time was from the definitive diagnosis of the first biopsy to the death of the patient or June 2020. The following observation indicators were collected during follow-up. (1) General conditions: vision, eyelid swelling, proptosis, and others. (2) Imaging findings: in order to objectively evaluate the therapeutic effect and observe recurrence, preoperative and postoperative MRI examination was necessary. The specific time points were pre-operation, half a year after operation, 1–3 years after operation, and 5 years after operation. The criteria for recurrence include eyelid swelling and an MRI showing lacrimal gland enlargement. If the patient had contraindications to MRI, CT can be used instead.

Statistical analysis

Graphpad Prism 8.0 and SPSS 25.0 software were used for analysis. Measurement data were tested by One-sample Kolmogorov-Smirnov test. Mean± standard deviation and independent sample t test were used to test the data of two groups consistent with normal distribution. Median and non-parametric rank sum test were used for data that did not conform to normal distribution. The chi-square test or Fisher's exact test were used for counting data. Survival curves for recurrence were created using the Kaplan–Meier method and compared between groups using log-rank tests. The influencing factors were analyzed by binary logistic regression analysis. A P value <0.05 was considered statistically significant.

Results

Higher expressed of age and more preoperative glucocorticoid therapy cases in the IgG4-positive group than IgG4-negative group

A total of 146 patients with biopsy-proven LGBLEL were ultimately enrolled in the study, and 105 (71.9%) patients were placed in the IgG4-positive group on the basis of pathological analysis. The results (Table 1) showed that the male-female ratio of the IgG4-positive group was 1:2.8, the ratio in the IgG4-negative group was 1:4.9, and there was no significant difference between the two groups ($P = 0.283$). The mean age of IgG4-positive group was 50.10 ± 14.23 years old, and that of the IgG4-negative group was 44.76 ± 11.43 years old, which was statistically significant ($P = 0.033$). There were 14 cases of right eye lesions, 24 cases of left eye lesions, and 67 cases of binocular lesions in the IgG4-positive group, and 11 cases of right eye lesions, 12 cases of left eye lesions, and 18 cases of binocular lesions in the IgG4-negative group, with no statistically significant difference between the two groups ($P = 0.059$). 24 cases of preoperative glucocorticoid therapy, 3 cases of operation history, 3 cases of asthma, 27 cases of sinusitis, 4 cases of history of lymph node enlargement, and 3 cases of other immune system diseases in the IgG4-positive group. 5 cases of sinusitis in the IgG4-negative group. There were statistically significant differences in preoperative glucocorticoid therapy between two groups ($P = 0.000$).

The main clinical manifestations of the IgG4-positive group were eyelid swelling in 96 cases, proptosis in 2 cases, and eyelid mass in 7 cases. The main clinical manifestations of the IgG4-negative group were eyelid swelling in 33 cases, eyelid mass in 2 cases, and proptosis in 6 cases. Eyelid swelling was the main clinical manifestation in both groups. The simultaneous symptoms of the IgG4-positive and negative group included tearing, pain, dry eyes, and decreased vision. There were no statistical differences in main and simultaneous symptoms between the two groups ($P > 0.05$). Both two groups showed signs of lacrimal gland enlargement and eyelid swelling. IgG4-positive group mainly manifested as sinus mucosa thickening (25.7%), extraocular muscle thickening (15.2%), and nerve thickening (3.8%), while IgG4-negative group mainly manifested as sinus mucosa thickening (12.2%), and extraocular muscle thickening (14.6%). There were no statistically significant differences in imaging findings between the two groups ($P > 0.05$). The mean course of disease was 18.70 ± 19.16 months in the IgG4-positive group and 21.22 ± 25.87 months in the IgG4-negative group, with no statistical difference ($P > 0.05$).

Table 1
Analysis results of clinical characteristics of IgG4-positive and negative LGBLEL.

Data	IgG4+ (n = 105)	IgG4- (n = 41)	Test value	P
Gender				
Male	28	7	1.489	0.283#
Female	77	34		
Age (years)	50.10 ± 14.23	44.76 ± 11.43	2.149	**0.033&**
Laterality				
Right	14	11	5.635	0.059#
Left	24	12		
Bilateral	67	18		
Previous history				
Glucocorticoid	24	0	-	**0.000***
Operation	3	0	-	0.559*
Asthma	4	0	-	0.577*
Sinusitis	27	5	3.149	0.118#
Lymph node enlargement	4	0	-	0.577*
Other immune system disease	3	0	-	0.559*
Clinical manifestations				
Eyelid swelling	96	33	3.431	0.084#
Proptosis	2	2	-	0.314*
Eyelid mass	7	6	2.308	0.192#
Simultaneous symptoms				
Decreased vision	3	1	-	1.000*
Dry eyes	4	2	-	0.673*
Tearing	8	0	-	0.106*

Note: "#" represents chi-square test, "&" represents *t* test, "^" represents non-parametric rank sum test and "*" represents Fisher's exact test. $P < 0.05$ is considered to indicate statistical significance. NA: Not Applicable.

Data	IgG4+ (n = 105)	IgG4- (n = 41)	Test value	P
Pain	8	4	-	0.740#
Imaging findings				
Lacrimal gland enlargement	105	41	NA	NA
Sinus mucosa thickening	27	5	3.149	0.118#
Extraocular muscle thickening	16	6	0.008	1.000#
Nerve thickening	4	0	-	0.577*
Course (months)	18.70 ± 19.16	21.22 ± 25.87	-0.565	0.574&
Laboratory indicators (mg/dl)				
C3 (900–1800)	1002.00	1164.72 ± 245.20	-2.791	**0.005^**
C4 (100–400)	204.50	241.60	-3.042	**0.002^**
RF (0–20)	7.30	8.30	-1.034	0.301^
ASO (0–200)	48.50	45.00	-0.142	0.887^
CRP (0–5)	1.35	1.31	-0.388	0.698^
IgA (0.7–4)	2.01	2.25 ± 0.84	-0.727	0.467^
IgM (0.4–2.3)	0.94	1.20 ± 0.61	-1.509	0.131^
IgG (751–1560)	1480.00	1219.76 ± 262.15	-4.614	**0.000^**
IgG1 (382–930)	674.00	676.12 ± 204.36	-0.712	0.476^
IgG2 (242–700)	534.00	466.58 ± 179.81	-2.639	**0.008^**
IgG3 (22–176)	53.50	39.60	-0.764	0.445^
IgG4 (4–87)	155.00	22.90	-7.681	**0.000^**
Treatment				
Surgery + glucocorticoid therapy	105	41	NA	NA
Follow-up (years)	4.10 ± 1.91	5.09 ± 2.45	-2.304	**0.025&**
Prognosis				
Lost to follow-up	6	3	4.131	0.226*

Note: "#" represents chi-square test, "&" represents *t* test, "^" represents non-parametric rank sum test and "*" represents Fisher's exact test. $P < 0.05$ is considered to indicate statistical significance. NA: Not Applicable.

Data	IgG4+ (n = 105)	IgG4- (n = 41)	Test value	P
Recurrence	21	3		
No recurrence	77	35		
Natural death	1	0		

Note: "#" represents chi-square test, "&" represents *t* test, "^" represents non-parametric rank sum test and "*" represents Fisher's exact test. *P* < 0.05 is considered to indicate statistical significance. NA: Not Applicable.

Compared with the IgG4-negative group, the expression levels of C3 and C4 were lower, while IgG, IgG2 and IgG4 were higher in the IgG4-related group

The twelve indicators of C3, C4, RF, ASO, CRP, IgA, IgM, IgG, IgG1, IgG2, IgG3, and IgG4 were analyzed via the ELISA method (Table 1). According to statistical analysis, C3, C4, IgA, IgM, RF, ASO, CRP, IgG, IgG1, IgG2, IgG3 and IgG4 were not normal distribution. There was no significant statistical difference in laboratory indicators between the two groups, including RF, IgM, ASO, CRP, IgA and IgG3 (P > 0.05). And the expression of serum C3 and C4 was lower in IgG4-positive group than IgG4-negative group (P = 0.005, P = 0.002), while the expression of serum IgG, IgG2 and IgG4 was higher in IgG4-positive related group than IgG4-negative group (P = 0.000, P = 0.008, P = 0.000).

The expression levels of IgG and IgG4 in the IgG4-positive LGBLEL group with preoperative glucocorticoid therapy history were lower than those in the group without preoperative glucocorticoid therapy history

As was shown in Table 2, compared with IgG4-positive LGBLEL group without preoperative glucocorticoid therapy history, the expression levels of IgG and IgG4 in IgG4-positive LGBLEL group with preoperative glucocorticoid therapy history were lower (P = 0.021 and P = 0.013), while the expression levels of C3, C4, IgA, IgM, RF, ASO, CRP, IgG1, IgG2 and IgG3 had no difference (P > 0.05).

Table 2
Analysis results of immune indicators in IgG4-positive LGBLEL between preoperative glucocorticoid therapy history and no preoperative glucocorticoid therapy history

Data	G+ (n = 24)	G- (n = 81)	Test value	P
Laboratory indicators (mg/dl)				
C3 (900–1800)	1052.37 ± 243.62	1027.28	-0.580	0.562^
C4 (100–400)	217.35	201.18 ± 79.70	-1.278	0.201^
RF (0–20)	5.45	7.50	-0.927	0.354^
ASO (0–200)	61.70	48.40	-1.652	0.098^
CRP (0–5)	1.34	1.35	-0.351	0.726^
IgA (0.7–4)	2.09 ± 0.80	2.01	-0.290	0.772^
IgM (0.4–2.3)	0.92	0.94	-0.149	0.882^
IgG (751–1560)	1320.00	1530.00	-2.301	**0.021^**
IgG1 (382–930)	638.50	680.00	-0.775	0.439^
IgG2 (242–700)	523.50 ± 184.31	549.00	-1.206	0.228^
IgG3 (22–176)	46.05	56.00	-0.435	0.664^
IgG4 (4–87)	119.80	155.00	-2.487	**0.013^**
Note: "^" represents non-parametric rank sum test.				

The prognosis between IgG4-positive and IgG4-negative LGBLEL had no significant difference

146 patients all underwent surgical resection combined with glucocorticoid therapy. The results are shown in Table 1. The average follow-up time of the IgG4-positive group was 4.10 ± 1.91 years, and 77 cases had no recurrence, 21 cases had recurrence, 6 cases were lost to follow-up, and 1 patient died naturally. The average follow-up time of the IgG4-negative group was 5.09 ± 2.45 years, and 35 cases had no recurrence, 3 cases had recurrence and 3 cases were lost to follow-up. After eliminating the loss to follow-up and natural death cases, we contrastively analyzed the recurrence-free survival curve between IgG4-positive and negative LGBLEL. The results showed that the recurrence-free cumulative percentages at 5 years were about 81.85% and 83.46%, respectively, which had no statistical difference in recurrence-free cumulative percentage between the two groups ($P = 0.216$) (Fig. 1).

The preoperative glucocorticoid therapy history, serum C4, and IgG1 may be factors influencing the recurrence of LGBLEL

The cases of loss to follow-up and natural death were excluded. Binary logistic regression analysis was performed on 136 patients with LGBLEL. Group (IgG4-positive and negative), gender, age, laterality, preoperative glucocorticoid therapy history, operation history, asthma, sinusitis, lymph node enlargement, other immune system disease history, nerve thickening, extraocular muscle thickening and laboratory indicators were analyzed in Table 3. The results showed that preoperative glucocorticoid therapy history, serum C4, and IgG1 may be factors influencing the recurrence of LGBLEL ($P = 0.003$, $P = 0.003$, $P = 0.017$, respectively).

Binary logistic regression analysis was performed on 98 patients with IgG4-positive LGBLEL. The results showed that preoperative glucocorticoid therapy history, serum C4, IgG1 and IgG2 may be factors influencing the recurrence of LGBLEL (P = 0.002, P = 0.008, P = 0.046, P = 0.009, respectively) (Table 4).

Table 3
Analysis of influencing factors in 136 patients with LGBLEL.

Factors	Wald	P	Odds Radio (OR)	95% confidence interval	
				Lower limit	Upper limit
Group	2.811	0.094	6.345	0.732	55.025
Gender	0.075	0.784	1.236	0.272	5.627
Age	3.605	0.058	0.931	0.865	1.002
Laterality	2.361	0.307	-	-	-
Preoperative glucocorticoid therapy history	8.780	**0.003***	19.713	2.744	141.644
Operation history	0.005	0.943	0.876	0.024	32.218
Asthma	1.830	0.176	18.513	0.270	1270.796
Sinusitis	3.126	0.077	3.746	0.866	16.193
Lymph node enlargement	0.247	0.619	2.122	0.109	41.160
Other immune system disease	0.000	0.999	0.000	0.000	-
Nerve thickening	0.471	0.493	0.244	0.004	5.932
Extraocular muscle thickening	0.315	0.575	0.489	0.040	5.932
C3	1.496	0.221	1.002	0.999	1.006
C4	9.066	**0.003***	1.025	1.009	1.041
RF	1.621	0.203	1.020	0.990	1.051
ASO	0.589	0.443	1.005	0.993	1.017
CRP	0.558	0.455	0.947	0.820	1.093
IgA	0.045	0.832	0.924	0.447	1.912
IgM	0.011	0.918	1.080	0.250	4.654
IgG	2.641	0.104	0.999	0.997	1.000
IgG1	5.725	**0.017***	1.005	1.001	1.009
IgG2	3.176	0.075	0.997	0.993	1.000
IgG3	1.248	0.264	1.012	0.991	1.033

Note: "*" represents statistical significance.

Factors	Wald	P	Odds Radio (OR)	95% confidence interval	
				Lower limit	Upper limit
IgG4	0.779	0.377	0.998	0.995	1.002
Note: "*" represents statistical significance.					

Table 4
Analysis of influencing factors in 98 patients with IgG4-positive LGBLEL.

Factors	Wald	P	Odds Radio (OR)	95% confidence interval	
				Lower limit	Upper limit
Gender	0.835	0.361	2.458	0.357	16.905
Age	0.726	0.394	1.035	0.956	1.122
Laterality	2.277	0.320	-	-	-
Preoperative glucocorticoid therapy history	9.288	**0.002***	0.020	0.002	0.248
Operation history	0.122	0.727	2.004	0.040	99.370
Asthma	1.453	0.228	0.045	0.000	6.976
Sinusitis	2.953	0.086	0.213	0.036	1.243
Lymph node enlargement	0.082	0.775	1.798	0.032	100.467
Other immune system disease	0.000	0.999	0.000	0.000	-
Nerve thickening	1.373	0.241	12.138	0.187	789.754
Extraocular muscle thickening	0.001	0.980	1.039	0.055	19.634
C3	2.518	0.113	0.996	0.992	1.001
C4	6.935	**0.008***	0.972	0.951	0.993
RF	2.719	0.099	0.974	0.944	1.005
ASO	1.110	0.292	0.990	0.973	1.008
CRP	1.009	0.315	1.091	0.921	1.292
IgA	0.313	0.576	0.769	0.306	1.932
IgM	0.310	0.577	0.564	0.075	4.233
IgG	0.450	0.502	1.001	0.999	1.002
IgG1	3.986	**0.046***	0.995	0.990	1.000
IgG2	6.824	**0.009***	1.007	1.002	1.012
IgG3	1.131	0.287	0.987	0.962	1.011
IgG4	2.018	0.155	1.003	0.999	1.008

Note: "*" represents statistical significance.

Discussion

In recent years, the prevalence of IgG4-ROD has been increasing gradually, which has attracted extensive attention from ophthalmologists. According to a study in China, the incidence of IgG4-ROD accounted for 60% of idiopathic orbital inflammatory disease. A study in Japan showed that the incidence of IgG4-ROD is about 61.5%, with 52.4% incidence in the United States, and 45.8% incidence in South Korea[12–15]. LGBLEL with IgG4 positive expression was classified as IgG4-ROD. The results of this study showed that LGBLEL was more common in female, both in IgG4-positive and negative groups. The lacrimal gland inflammation could be influenced by the expression level of estrogen. Jiang et al.[16] found that estrogen and its receptor might inhibit the inflammatory response in rat colon tissues, suggesting that a decrease in estrogen may be one of the relevant factors leading to the occurrence of inflammation. In addition, there was a significantly difference in age between the two groups, and the mean age of IgG4-positive LGBLEL was older. This may indicate that levels of estrogen in female patients gradually decline with age, increasing the incidence of IgG4-positive LGBLEL.

IgG4-ROD may be associated with immune system diseases, such as allergic rhinitis, asthma, lymph node enlargement, and Sjogren's syndrome [17–18]. In our study, LGBLEL had a history of immune system disease, among which allergic rhinitis, sinusitis, and lymph node enlargement were common. The imaging findings were primarily lacrimal gland enlargement, accompanied by sinus mucosa, extraocular muscle, and ocular nerve thickening. In this study, about 15.2% of patients in IgG-positive group presented with extraocular muscle thickening and 3.8% of patients presented with ocular nerve thickening, while 14.6% of IgG4-negative group presented with ocular muscle thickening and no case presented with ocular nerve thickening, which showed no significant difference between the two groups. These results may suggest that extraocular muscle and ocular nerve thickening are not specific indicators to differentiate IgG4-positive and negative LGBLEL.

Immunoglobulin has the functions of activating complement, absorbing cells, and extracellular killing. Compliment is a type of protein that mediates autoimmune and inflammatory responses. Studies have found that IgG can activate complement C3 through the classical pathway and IgG4 can activate complement C3 through the bypass pathway to play an immunomodulation role, while the complement system can play an anti-infection role, regulate inflammatory response and maintain immune homeostasis through the massive consumption of C3 and C4[19–21]. Some studies had found that the expressions of serum C3, C4, IgG1, IgG2, IgG3, IgE, and CRP, were significant for the diagnosis of IgG4-ROD[22–23]. Chen[12] et al. found that compared with other orbital idiopathic inflammatory disease, serum C3 of IgG4-ROD were significantly decreased. In our study, relevant immune indicators were systematically analyzed, and the results showed that C3, C4, IgG, IgG2, and IgG4 were of great significance for the differentiation between IgG4-positive and negative LGBLEL, while there was no significant difference in the expressions of RF, ASO, CRP, IgA, IgM, IgG1 and IgG3. Compared with IgG4-negative LGBLEL, the expression levels of complement C3 and C4 were decreased, while those of IgG,

IgG2, and IgG4 were increased in the IgG4-positive group, which had differential significance. And preoperative glucocorticoid therapy could reduce IgG and IgG4 expression in IgG4-positive LGBLEL.

At present, partial surgical resection combined with glucocorticoid therapy is the main treatment for LGBLEL, and more patients still relapse after treatment. Chen[12] et al. reported that the recurrence rates of IgG4-positive and IgG4-negative idiopathic orbital inflammatory disease were 32.2% and 19.1%, respectively. A French study showed that about 2/3 of IgG4-ROD cases relapsed, and Suimon et al. found that the recurrence rate was about 33.3%[22, 24]. Owing to differences in race, sample size, follow-up time, and sensitivity to glucocorticoids, the recurrence rate of IgG4-ROD differed across some research centers, but mostly ranged from 18–58%[25–27]. In our study, the recurrence rate of 5-year in IgG4-positive and negative LGBLEL patients was 18.15% and 16.54%, respectively. There was significant difference in recurrence rates between the two groups.

All patients were treated via the partial surgical resection combined with glucocorticoid therapy. The prognostic factors of LGBLEL were statistically analyzed, and lost to follow-up and natural death cases were excluded. The results showed that preoperative glucocorticoid therapy history, serum C4, and IgG2 were the factors affecting the recurrence of LGBLEL. Studies have found that C3 and C4 levels are significantly decreased during active inflammation, while IgG and its subtypes are increased[12,22–24]. In patients with active IgG4-ROD, a large number of immune complexes will be produced, leading to elevated levels of IgG and its subtypes, thus activating the complement system. However, complement C3 and C4 can be consumed through classical and bypass pathways to eliminate immune complexes, leading to a decreased level of C3 and C4. Therefore, patients with increased C4 expression and decreased IgG2 expression may have a lower risk of recurrence.

Kubota[28] et al. found that extraocular muscle and trigeminal nerve thickening could affect the therapeutic effect of glucocorticoids and the prognosis of IgG4-ROD. Previous studies had shown that serum IgG4, RF, and male gender were risk factors for recurrence of IgG4-ROD treated with glucocorticoid therapy[29–31]. Our study showed that gender, extraocular muscle thickening, nerve thickening, sinusitis, IgG4 and RF were not risk factors for recurrence of LGBLEL. And the preoperative glucocorticoid therapy history, serum C4, IgG1 and IgG2 were the factors affecting the recurrence of IgG4-positive LGBLEL.

There were some shortcomings in this study. First, this was a retrospective study, which presented difficulties to the complete collection of research data. Second, there were no standardized criteria for treatment, and the dose of glucocorticoid depended on the disease condition, which had an impact on the prognosis of LGBLEL. In addition, the follow-up time also influenced prognosis of LGBLEL. Some LGBLEL with IgG4 positive expression were treated with glucocorticoid before operation, which had a certain effect on the expression of immunological indexes.

In summary, this study analyzed the clinical characteristics, immune indicators, and prognosis of IgG4-positive and negative LGBLEL. The expression of C3 and C4 was decreased, while the expression of IgG, IgG2, and IgG4 was increased, which had significance for distinguishing between IgG4-positive and

negative LGBLEL. Preoperative glucocorticoid therapy, serum C4, IgG1 and IgG2 could influence the recurrence of LGBLEL, and the expression of IgG4 was not a major prognostic factor.

Abbreviations

LGBLEL
lacrimal gland benign lymphoepithelial lesion
IgG4-RD
IgG4-related disease
IgG4-ROD
IgG4-related ocular disease
ELISA
enzyme-linked immunosorbent method
HPF
high power field
MRI
magnetic resonance imaging
CT
computed tomography
RF
rheumatoid factor
CRP
c-reactive protein
ASO
hemolysin against streptococcus
OR
odds radio

Declarations

Ethics approval and consent to participate

This article does not include the patients' name, portrait and other private information. Written informed consent was obtained from all patients, and the study was approved by the Institutional Review Board of Beijing Tongren Hospital and conducted according to the tenets of the Declaration of Helsinki.

Consent for publication

All authors read and approved the final manuscript to public.

Availability of data and materials

Not applicable

Conflict of Interest Statement

Rui L, None; Nan W, None; Jinjin W, None; Jing L, None; Xin G, None; Jingxue Z, None; Jianmin M, None.

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Authors' contributions

Rui L analyzed and wrote the manuscript; Nan W, Jinjin W and Jing L helped collect data; Jianmin M, Xin G and Jingxue Z read and criticized the manuscript. All authors critically read and edited the manuscript. All authors read and approved the final manuscript.

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References

1. Ma JM, Cui YX, Ge X, Li J, Li JR, Wang XN. Association of TCR-signaling pathway with the development of lacrimal gland benign lymphoepithelial lesions[J]. International Journal of Ophthalmology, 2015, 8(4):685–689.
2. Jianmin Ma, Jing Li, Xin Ge, Ming Li. Jinru Li, Xiaona Wang. Clinical research on benign lymphoepithelial lesions of lacrimal gland(s) in 20 cases of Chinese patients[J]. CMJ.2015,128(4): 493–498.
3. Yamamoto M, Harada S, Ohara M, Suzuki C, Naishiro Y, Yamamoto H, Takahashi H, Imai K. Clinical and pathological differences between Mikulicz's disease and Sjögren's syndrome[J]. Rheumatology (Oxford), 2005;44(2):227–234.
4. Xiao-Na Wang, Xin Ge, Jing Li, et al. B cell receptor signaling pathway involved in benign lymphoepithelial lesions of the lacrimal gland. Int J Ophthalmol, 2017,10(5):665–669.
5. Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease[J]. Lancet. 2015;385(9976): 1460–71.
6. Cheuk W, Yuen HK, Chan AC, et al. Ocular adnexal lymphoma associated with IgG4 + chronic sclerosing dacryoadenitis: a previously undescribed complication of IgG4-related sclerosing disease[J]. Am J Surg Pathol, 2008, 32(8): 1159–1167.
7. Soussan JB, Deschamp R, Sadik JC, et al. Infraorbital nerve involvement on magnetic resonance imaging in European patients with IgG4-related ophthalmic disease: a specific sign[J]. Eur Radiol, 2017;27:1335–1343.
8. Japanese Study Group of IgG4-related Ophthalmic Disease. A prevalence study of IgG4-related ophthalmic disease in Japan[J]. Jpn J Ophthalmol, 2013, 57(6): 573–579.

9. Goto H, Takahira M, Takahira M, et al. Diagnostic criteria for IgG4-related ophthalmic disease[J]. Jpn J Ophthalmol, 2015, 59(1):1–7.
10. Wang M, Zhang P, Lin W, et al. Differences and similarities between IgG4-related disease with and without dacryoadenitis and sialoadenitis: clinical manifestations and treatment efficacy[J]. Arthritis Res Ther, 2019, 21(1):44.
11. Maehara T, Mattoo H, Ohta M, et al. Lesional CD4 + IFN-γ + cytotoxic T lymphocytes in IgG4-related dacryoadenitis and sialoadenitis[J]. Ann Rheum Dis, 2017, 76(2):377–385.
12. Chen J, Zhang P, Ye H, et al. Clinical features and outcomes of IgG4-related idiopathic orbital inflammatory disease: from a large southern China-based cohort[J]. Eye (Lond). 2020. doi: 10.1038/s41433-020-1083-x.
13. Takahira M, Ozawa Y, Kawano M, Zen Y, Hamaoka S, Yamada K, et al. Clinical aspects of IgG4-related orbital inflammation in a case series of ocular adnexal lymphoproliferative disorders[J]. Int J Rheumatol. 2012;2012: 635473.
14. Plaza JA, Garrity JA, Dogan A, Ananthamurthy A, Witzig TE, Salomao DR. Orbital inflammation with IgG4-positive plasma cells: manifestation of IgG4 systemic disease[J]. Arch Ophthalmol. 2011;129(4):421–8.
15. Sa HS, Lee JH, Woo KI, Kim YD. IgG4-related disease in idiopathic sclerosing orbital inflammation[J]. Br J Ophthalmol. 2015;99(11):1493–7.
16. Jiang Q, Li WX, Sun JR, Zhu TT, Fan J, Yu LH, Burnstock G, Yang H, Ma B. Inhibitory effect of estrogen receptor beta on P2X3 receptors during inflammation in rats[J]. Purinergic Signal. 2017;13(1):105–117.
17. UmeharaH, OkazakiK, MasakiY, et al. A novel clinical entity, IgG4-related disease(IgG4-RD): general concept and details[J]. Mod Rheumatol, 2012;22:1–14.
18. Chidambaram VA, Anita CSY, Robert C, Garry C. IgG4 related orbit disease - An unusual cause of an orbital mass[J]. Med J Malaysia. 2018;73(6):415–417.
19. Divatia M, Kim SA, Ro JY. IgG4-related sclerosing disease, an emerging entity: a review of a multi-system disease[J]. Yonsei Med J, 2012, 53 (1): 15–34.
20. Ricklin D, Hajishengallis G, Yang K, Lambris JD. Complement: a key system for immune surveillance and homeostasis[J]. Nat Immunol, 2010, 11 (9): 785–797.
21. Ricklin D, Lambris JD. Complement in immune and inflammatory disorders: pathophysiological mechanisms[J]. Joumal of Immunology, 2013, 190 (8): 3831–3838.
22. Ebbo M, Patient M, Grados A,et al. Ophthalmic manifestations in IgG4-related disease: Clinical presentation and response to treatment in a French case series[J]. Medicine(Baltimore), 2017;96(10): e6205.
23. Kawashiri Sy, Origuchi T, Umeda M, et al. Association of serum levels of fibrosis-related biomarkers with disease activity in patients with IgG4-related disease[J]. Arthritis Res Ther, 2018;20:277.

24. Suimon Y, Kase S, Ishijima K, Kanno-Okada H, Ishida S. A clinicopathological study on IgG4-related ophthalmic disease[J]. Int J Ophthalmol. 2018;11(9):1539–1544.
25. Min HK, Lee YS, Yang SW, Lee J, Kwok SK, Ju JH, Kim WU, Park SH. Clinical outcomes and pathological characteristics of immunoglobulin G4-related ophthalmic disease versus orbital inflammatory pseudotumor[J]. Korean J Intern Med. 2019;34(1):220–226.
26. Park J, Lee MJ, Kim N, Kim JE, Park SW, Choung HK, Khwarg SI. Risk factors for extraophthalmic involvement and treatment outcomes in patients with IgG4-related ophthalmic disease[J]. Br J Ophthalmol. 2017;102(6):736–741.
27. Kubota T, Katayama M, Moritani S, Yoshino T. Serologic factors in early relapse of IgG4-related orbital inflammation after steroid treatment[J]. Am J Ophthalmol. 2013;155(2):373–379.
28. Kubota T, Katayama M, Nishimura R, Moritani S. Long-term outcomes of ocular adnexal lesions in IgG4-related ophthalmic disease[J]. Br J Ophthalmol. 2020;104(3):345–349.
29. Hong JW, Kang S, Song MK, et al. Clinic serological factors associated with response to steroid treatment and recurrence in patients with IgG4-related ophthalmic disease. Br J Ophthalmol 2018;102: 1591–5.
30. Yamamoto M, Nojima M, Takahashi H, et al. Identification of relapse predictors in IgG4-related disease using multivariate analysis of clinical data at the first visit and initial treatment. Rheumatology 2015;54: 45–9.
31. Sasaki T, Akiyama M, Kaneko Y, et al. Risk factors of relapse following glucocorticoid tapering in IgG4-related disease [J]. Clin Exp Rheumatol, 2018, 36 (Suppl 112): 186–189.

Figures

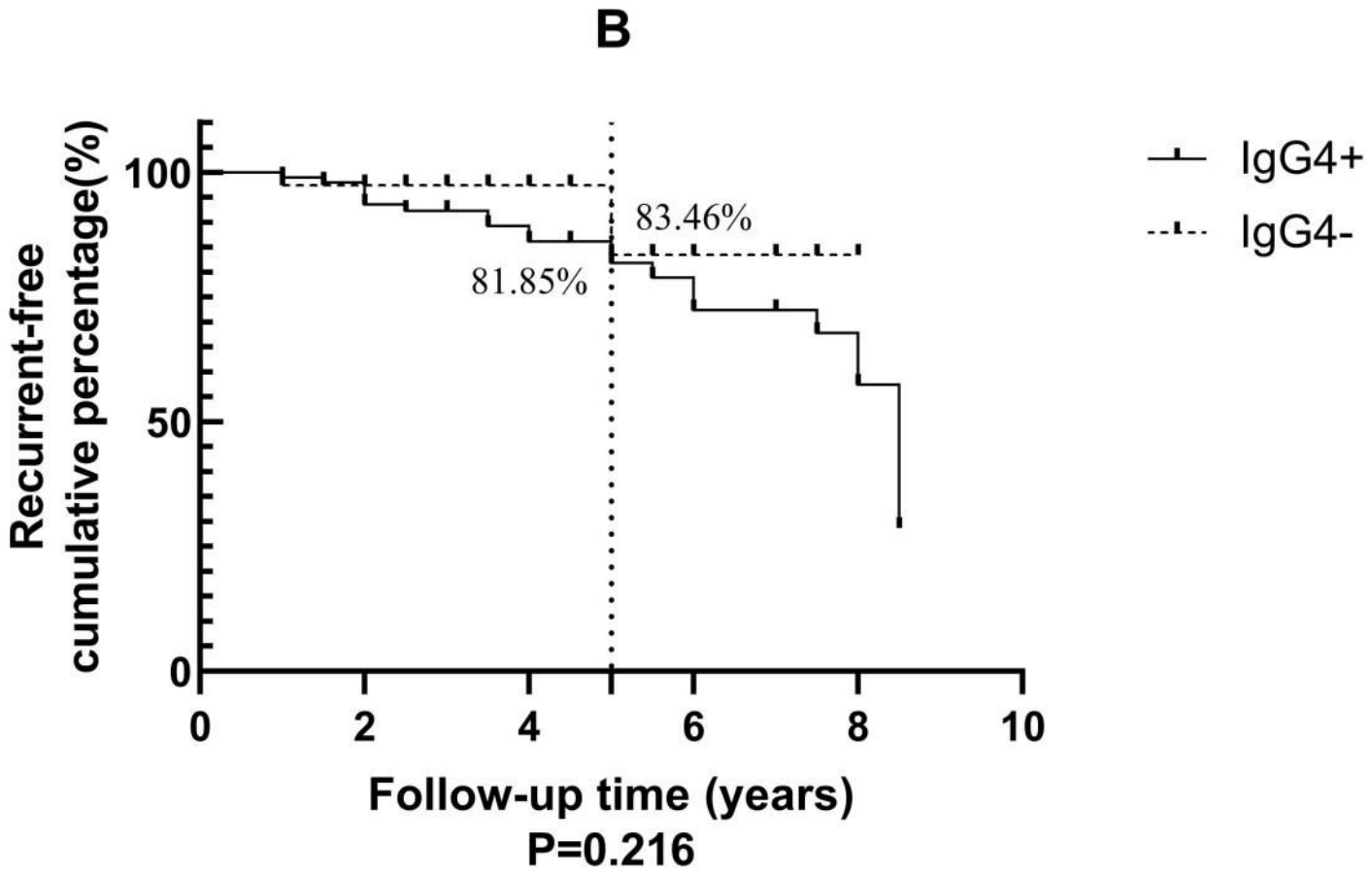

Figure 1

Comparative analysis of prognosis between IgG4 positive and IgG4 negative LGBLEL. The recurrence-free cumulative percentages at 5 years in IgG4 positive and IgG4 negative dacryoadenitis was 81.85% and 83.46%, respectively (P=0.216).