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Does IgG4 level at the time of diagnosis correlate with disease outcome in IgG4-Related disease?

Tsang K.F. Patrick, Oppong W. Kofi, Leeds S. John, Bekkali L.H. Noor, Nayar K. Manu*

HPB Unit, Freeman Hospital, Freeman Road, Newcastle Upon Tyne, NE7 7DN, UK

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ABSTRACT

Background/Objectives: Serum IgG4 level is used as a diagnostic criterion for immunoglobulin G4-related disease (IgG4-RD) but whether it predicts disease progression is unclear. Aim of the study was to investigate if serum IgG4 level at the time of diagnosis correlates with disease outcome.

Methods: Patients with a definitive diagnosis of IgG4-RD were included in this study. They were divided into two groups – Group 1: Elevated serum IgG4 at diagnosis and Group 2: Normal serum IgG4 at diagnosis. Outcome parameters including multiple organ involvement, exocrine and endocrine dysfunction, relapse and mortality were compared. Data was subanalysed for outcomes on 2 levels of serum IgG4 cut-off – A: The upper limit of normal (ULN) and B: Twice the ULN.

Results: Of 47 patients, 31 (66%) patients had elevated serum IgG4 at diagnosis. There was no statistically significant difference between the two groups in any of the outcome parameters. Data analysed with the serum IgG4 levels > ULN showed no difference between the 2 groups for any of the outcome parameters. However, when the serum IgG4 cut-off was set to twice the ULN, there was a significantly higher rate of disease relapse (42.9% vs 11.5%, $p = 0.02$) and pancreatic exocrine insufficiency (PEI) (76.2% vs 42.3%, $p = 0.041$).

Conclusion: Raised serum IgG4 greater than two times the ULN was significantly associated with disease relapse and PEI in patients with IgG4-RD. Larger multicentre studies with longer follow-up are required to corroborate these findings and define the role and cut-off value of serum IgG4 in outcomes of IgG4-RD.

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a systemic disease involving multiple organ systems, with characteristic imaging and histological findings which include an abundance of IgG4-positive plasma cell infiltrate in the involved organs and a predictable response to steroid therapy [1,2] The diagnosis of the disease is commonly based on a consensus diagnostic criteria i.e. International Consensus Diagnostic Criteria (ICDC) [3] Probable or definitive diagnosis is defined according to the level of evidence i.e. radiological, histological, serology, extrapancreatic manifestation and response to steroid therapy.

IgG4 is a serum biomarker which is frequently elevated in 43–90% of patients with IgG4-RD [2,4–6] Although a raised serum IgG4 is a well-established diagnostic criterion in the ICDC, whether elevated IgG4 and the level of elevation has prognostic significance is largely unknown. Most studies have applied multiple diagnostic criteria and recruited patients with both probable and definite diagnosis [2,4].

Follow-up periods were also insufficient for assessment of outcomes such as relapse or end organ damage thus providing inconsistent results [2,5].

The aim of the study was to investigate the role of serum IgG4 level at the time of diagnosis on the outcomes in patients with definitive diagnosis of IgG4-RD.

Methods

Patients from a prospectively maintained database in our unit from January 2005 to December 2016 were included in this study. Patients with suspected IgG4-RD referred to the Freeman Hospital were investigated, treated and followed up in the medical pancreatology clinic. Information collected on the database include the demographic data, clinical symptoms, serum markers including

* Corresponding author. Consultant Pancreaticobiliary Physician, HPB Unit, Freeman Hospital, Newcastle Upon Tyne, NE7 7DN, UK.
E-mail address: Manu.Nayar@nuth.nhs.uk (K.M. Nayar).

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serum total IgG & IgG4 subclass levels at the time of diagnosis, imaging findings, histology, fasting glucose and faecal elastase levels. Inclusion criteria were:

1) A definite diagnosis of IgG4-RD using the ICDC
2) Minimum follow up of 12 months.

The diagnosis of definite IgG4-RD was made if tissue biopsy or resection specimen, typical imaging findings and/or response to steroids. Histology demonstrated two of three major histopathological features of the disease (lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis) and immunostaining confirmed IgG4 and IgG staining as per the Boston Consensus Histopathological Criteria (typically >10 IgG4+ plasma cells per high power field on biopsy or >50 IgG4+ plasma cells per high-power field on resection, with a ratio of IgG4/IgG of >40%) in an appropriate clinical context. The diagnosis of probable IgG4-RD was made with typical organ involvement, characteristic radiographic appearance of those affected organs and radiological response to corticosteroid therapy [3].

Patient groups

Patients were divided into two groups based on serum IgG4 levels at the time of diagnosis– Group 1: Elevated serum IgG4 and Group 2: Normal serum IgG4. Outcome parameters were compared between the 2 groups. With reference to the ICDC (3) & based on recently published data by Culver EC et al. [2], we sub analysed the data based on 2 levels of IgG4 cut-off – A: The upper limit of normal (ULN) and B: Twice the ULN.

Serum IgG4 measurements assays

Serum IgG4 level was measured using assay 'Siemens BNII Analyser' (Siemens Heathineers, U.K.) and 'The Binding Site' (The Binding Site Group Ltd, Birmingham, U.K.) before and after November 2013 respectively at the Blood Science Laboratory, Freeman Hospital, Newcastle Upon Tyne, UK. The normal ranges for the 2 assays used in this study were:

Siemens BNII Analyser = 0.0–2.4 G/l.

The Binding Site = 0.04–0.86 G/l.

Other organ involvement was defined according to ICDC.(3) Either histological or radiological evidence of extra-pancreatic organs was considered. Based on the definition in previous studies (5,6) proximal bile duct was defined as involvement of either intrahepatic bile ducts or the extrahepatic common bile duct proximal to the head of pancreas. Single organ involvement was defined as involvement of one organ system only, while multiple organ involvement was defined as involvement of more than one organ system histologically or radiologically [2]. Lesions at the head of pancreas (either a focal mass or diffuse pancreatic enlargement) and a distal common bile duct stricture was regarded as one organ involvement [2,3].

Treatment and follow up

The goals of treatment with corticosteroid therapy are not well defined in IgG4-RD. Treatment response was defined as a reduction in absolute values in liver function tests, reduction in serum IgG4 level, reduction in size and/or resolution of abnormal changes on imaging, reduction and/or resolution of stricture and biliary stent removal at endoscopic retrograde cholangiopancreatography [2].

Pancreatic organ damage was assessed by exocrine insufficiency and endocrine dysfunction (diabetes mellitus). Exocrine pancreatic dysfunction was defined as faecal elastase less than 200 μg/g faeces. Endocrine dysfunction (diabetes mellitus) was defined as fasting blood glucose greater than 7.0 mmol/L, random blood glucose greater than 11.1 mmol/L, or HbA1c level more than 48 mmol/mol (6.5%) according to WHO definition [7]. Extra-pancreatic end organ damage was defined as biochemical or radiological evidence of end organ damage other than pancreas.

Disease relapse was defined as deterioration of disease on imaging or biochemical parameters such as liver function tests after partial or complete remission. We closely monitored the disease progress in our outpatient clinic after steroid therapy. In order to allow sufficient time for relapse, there were at least 12 months of follow-up for every patient. Malignancy, overall and disease specific mortality were also recorded.

Statistical analyses

Data are presented as median ± standard deviation or percentage frequencies. Chi-square test or Fisher's exact test was used to analyse categorical variables and Student's *t*-test was used to analyse continuous variables. For all analyses, a *P* value less than 0.05 was considered as statistically significant. Statistical analyses were performed using MedCalc version 11.2.1.0 software (MedCalc Software bvba). In addition the area under the receiver operating curve (AUROC) was calculated for the two cut off levels for serum IgG4.

Ethical approval from an institutional review body was not required for this study. Data collection was performed as part of ongoing clinical audit of the quality of our service. Normal NHS Clinical Audit Practice was observed. All aspects of the study were conducted in accordance with the Declaration of Helsinki 1964, as revised in Tokyo 2004.

Results

53 patients were referred and managed in the pancreatology clinic (MN, KO & JL) during the study period. A total of 47 patients with definite diagnosis of IgG4-RD formed the study group (Fig. 1).

There were 35 males (74.5%) and 12 females (25.5%). The median age was 64 years (range = 33–83). Majority of the patients 42/47 (89.3%) had pancreas as the primary organ involved. The remaining 5 patients who did not have pancreas involvement were – 2 patients with retroperitoneal fibrosis, 2 patients had isolated biliary stricture and 1 patient with breast involvement. Thirty two (68.1%) patients had histology either by biopsy or resection specimen. Twenty three (48.9%) patients had multiple organ involvement (proximal bile duct, pericardium, renal, gall bladder, pleura, lymph nodes and salivary glands).

Median follow-up was 41 months (range 15–145 months) with a relapse rate of 12/47 (25.5%). 5/12 (41.7%) patients had relapse whilst tapering of steroid therapy and 7 (58.3%) patients after completion of steroid therapy. When relapse occurred, eight (66.7%) patients were treated with steroid and immunosuppressants including azathioprine or mycophenolate. One patient was treated with rituximab while 3 patients were treated with maintenance steroid alone.

The overall rate of pancreatic exocrine and endocrine dysfunction in patients with pancreatic involvement was 57.4% and 42.6% respectively. In patients with pancreatic exocrine dysfunction, 92.9% were diagnosed within 12 months of diagnosis of IgG4-RD (range = 1 month–47 months), compared to a much lower proportion (53.8%) within the first year (range 1–85 months) among patients who developed pancreatic endocrine dysfunction. Two patients developed malignancy in the follow up period – breast cancer (1) and squamous cell carcinoma of skin (2).

Five patients died during follow up. One patient developed end

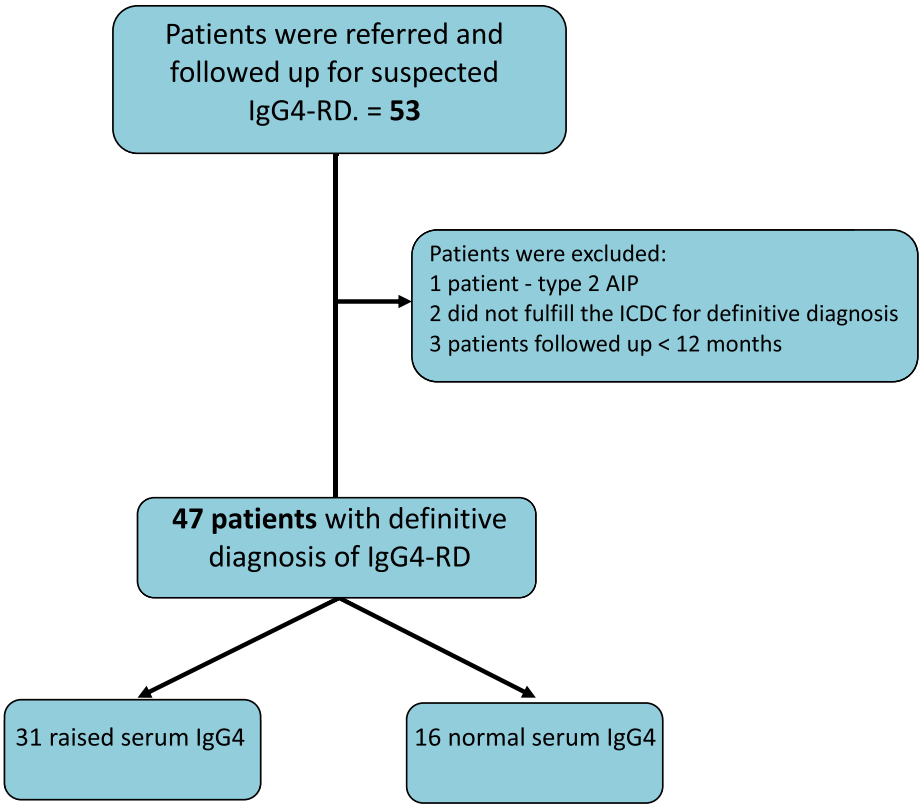

Fig. 1. Flow Chart of study patients.

stage decompensated liver disease as a result of secondary biliary cirrhosis due to IgG4 RD which was refractory to treatment. The remaining patients died of ruptured abdominal aortic aneurysm (n = 1), pneumonia (n = 2) or sepsis (n = 1).

Outcome data based on raised serum IgG4 levels

Patients were divided into two groups – Group 1: patients with elevated serum IgG4 at diagnosis and Group 2: normal serum IgG4 level at diagnosis. Patient characteristics of the two groups are shown in Table 1. 31/47 (66.0%) patients had elevated serum IgG4 and 16/47 (34.0%) patients had normal serum IgG4 at diagnosis. In addition, treatment modalities i.e. steroid therapy, use of maintenance therapy and follow-up were not significantly different between the two groups.

The outcome data when analysed with the serum IgG4 cut-off at the upper limit of normal (ULN), showed no statistically significant difference between the two groups with regard to multiple organ involvement, requirement of biliary stenting, response to steroid therapy, pancreatic and extra-pancreatic end organ damage, exocrine/endocrine insufficiency, rate of relapse, malignancy and mortality (Table 2).

However, if the serum IgG4 cut-off was set to twice the ULN, there was significantly higher prevalence of disease relapse (42.9% vs 11.5%, $p = 0.020$) and pancreatic exocrine insufficiency (76.2% vs 42.3%, $p = 0.041$). There was no statistically significant difference for other parameters (Table 3).

Receiver operating curve (ROC) analysis for serum IgG4 level cut-off at the ULN with respect to relapse and PEI showed an area under the curve (AUROC) of 0.617 (95% CI 0.463–0.755) p = 0.096 and 0.602 (95% CI 0.449–0.742) p = 0.172 respectively. When recalculated for a cut-off at twice the ULN the AUROC was 0.704 (95% CI 0.553–0.828) p = 0.008 and 0.712 (95% CI 0.561–0.834) p = 0.001 respectively.

Discussion

This study has evaluated serum IgG4 subclass levels in the outcome of patients in a large tertiary referral centre for the management of IgG4-RD. Over the past decade, various studies have investigated the role of serum IgG4 in the short and long term outcomes of the disease [2,5,6,8]. However; follow-up periods were insufficient (5) for assessment of sequelae such as end organ damage and disease relapse [2,4–6,8,16]. The present study identified patients from a prospectively maintained database that were followed up for a minimum period of 12 months (median = 41 months). When the ULN was used as the cut-off level of serum IgG4, no statistical significance was seen in any outcome parameter. However, if the cut-off value of serum IgG4 was doubled to two times the ULN, significantly more patients with raised serum IgG4 had disease relapse and PEI.

High serum IgG4 levels may reflect the disease activity and predict the outcomes of IgG4-RD. The role of serum IgG4 in the diagnosis of IgG4-RD was well described in many diagnostic criteria introduced over the past decade [3,9,10]. However, its role in the disease mechanism and prognosis is not fully understood. In addition, the cut-off value of serum IgG4 for prediction of outcomes has not been investigated until recently. The cut-off value of serum IgG4 also varies depending on the assay used among different centres. (6) Culver et al. [2] showed that if the cut-off value of serum IgG4 was doubled, its specificity was increased from 84.7% to 96.2% and predicted long term sequelae including relapse and multiple organ involvement. This high specificity may indicate an important role of a high serum IgG4 in the disease mechanism, which

Table 1
Characteristics of patients with elevated and normal IgG4 serology.

	High serum IgG4 (n = 31) Count (%)	Normal Serum IgG4 (n = 16) Count (%)	*P* value[a]
Age (years)	66.0 ± 10.7	63.5 ± 12.3	0.243[c]
Gender			
Male	25 (80.6)	10 (62.5)	0.318
Female	6 (19.4)	6 (37.5)	
Inflammatory bowel disease	1 (3.2)	1 (6.3)	1.000[b]
Other bowel diseases	3 (9.7)	1 (6.3)	1.000[b]
Chronic liver disease	1 (3.2)	0 (0.0)	1.000[b]
Chronic renal disease	2 (6.5)	1 (6.3)	1.000[b]
Cardiovascular disease	3 (9.7)	2 (12.5)	1.000[b]
Hypertension	11 (35.5)	4 (25.0)	0.527[b]
Chronic lung disease	4 (12.9)	1 (6.3)	0.648[b]
Autoimmune disease	7 (22.6)	5 (31.3)	0.770
Previous pancreaticobiliary or bowel surgery	5 (16.1)	4 (25.0)	0.466[b]
Serum albumin (g/L)	41.0 ± 4.9	41.0 ± 4.1	0.712[c]
Serum bilirubin (umol/L)	15.0 ± 73.6	8.0 ± 98.0	0.869[c]
Alkaline phosphate (unit/L)	337.0 ± 347.8	199.0 ± 291.3	0.127[c]
Creatinine (umol/L)	89.0 ± 30.1	80.0 ± 32.6	0.547[c]
Initial treatment			
Steroid therapy	26 (83.9)	11 (68.8)	0.410
Surgery for suspected malignancy	0 (0.0)	1 (6.3)	0.340[b]
Conservative	5 (16.1)	4 (25.0)	0.466[b]
Steroid/immunosuppressant maintenance therapy	11 (35.5)	5 (31.3)	0.972
Follow-up duration (months)	34.0 ± 27.9 (12–100)	41.5 ± 35.1 (14–140)	0.345[c]

[a] *P* value derived from Chi-square test.
[b] *P* value derived from Fisher's exact test.
[c] *P* value derived from Student's *t*-test.

Table 2
Outcomes of IgG4-RD with elevated (>ULN) and normal serum IgG4.

Outcomes	Serum IgG4 >ULN (n = 31) Count (%)	Normal Serum IgG4 (n = 16) Count (%)	*P* value[a]
Multiple organs involvement	17 (54.8)	6 (37.5)	0.413
Biliary stenting	6 (19.4)	5 (31.3)	0.583
Response to steroid therapy[c]	25 (96.2)	10 (90.9)	0.512[b]
End organ damage			
Pancreatic			
Exocrine	20 (64.5)	7 (43.8)	0.292
Endocrine	14 (45.2)	6 (37.5)	0.848
Extra-pancreatic	1 (3.2)	0 (0.0)	1.000[b]
Relapse	10 (32.3)	2 (12.5)	0.176[b]
Malignancy	2 (6.5)	1 (6.3)	1.000[b]
IgG4-RD associated mortality	1 (3.2)	0 (0.0)	1.000[b]

[a] *P* value derived from Chi-square test.
[b] *P* value derived from Fisher's exact test.
[c] The denominator differs because not all patients were treated with steroid therapy as shown in table.

Table 3
Outcomes of IgG4-RD with elevated (>2xULN) and normal serum IgG4.

Outcomes	Serum IgG4 >2xULN (n = 21) Count (%)	Normal Serum IgG4 (n = 26) Count (%)	*P* value[a]
Multiple organs involvement	12 (57.1)	11 (42.3)	0.473
Biliary stenting	4 (19.0)	7 (26.9)	0.731[b]
Response to steroid therapy[c]	16 (94.1)	19 (95.0)	1.000[b]
End organ damage			
Pancreatic			
Exocrine	16 (76.2)	11 (42.3)	**0.041**
Endocrine	9 (42.9)	11 (42.3)	0.796
Extra-pancreatic	1 (4.8)	0 (0.0)	0.447[b]
Relapse	9 (42.9)	3 (11.5)	**0.020**[b]
Malignancy	1 (4.8)	2 (7.7)	1.000[b]
IgG4-RD associated mortality	1 (4.8)	0 (0.0)	0.447[b]

[a] *P* value derived from Chi-square test.
[b] *P* value derived from Fisher's exact test.
[c] The denominator differs because not all patients were treated with steroid therapy as shown in table.

reflected a higher degree of inflammation of the organs involved and thus more prone to end organ damage and disease relapse in IgG4-RD [11].

The role of IgG4 in the pathophysiology of IgG4-RD may explain the association between high serum IgG4 and negative disease outcomes [11–13]. Overproduction of IgG4 antibodies may behave

as tissue-destructive immunoglobulins [11]. On the other hand; the excess of IgG4 may simply be an overexpression of these antibodies in response to an unknown primary inflammatory stimulus. Regardless of the mechanism, presence of IgG4 implies an active destructive inflammation in the disease process. Therefore, its high level may reflect increased disease activity and may predict poor outcomes in IgG4-RD [14,15].

The overall incidence of exocrine insufficiency and endocrine insufficiency in this study were 57.4% and 42.6% respectively. These figures were lower than the study by Buijs et al. [4] (exocrine insufficiency 82%, endocrine insufficiency 57%) but similar to that by Huggett MT et al. [16] in which exocrine and endocrine insufficiencies were present in 53% and 37% of patients respectively. However, the actual incidence may be higher because faecal elastase has limited sensitivity for mild exocrine dysfunction [17].

The present study revealed a significant difference in pancreatic exocrine insufficiency but not endocrine dysfunction. If data is extrapolated from studies on chronic pancreatitis, endocrine insufficiency due to loss of pancreatic islet cells is a late manifestation of chronic pancreatitis [18,19]. We were unable to differentiate type 3c diabetes mellitus from other types [20,21], resulting in dilution of the effect of high serum IgG4 on predicting type 3c DM. Therefore, longer minimum follow-up periods and tests to differentiate type 3c DM from other types may be required for full assessment of pancreatic endocrine dysfunction in IgG4 disease.

Twelve patients (25.5%) encountered at least one relapse in our study. This was similar to other studies [2,5,6,16], in which relapse rates of 27–60% were reported.

The strengths of this study are the long median follow-up of 41 months and inclusion of patients with a definitive diagnosis of IgG4-RD based on ICDC only. This methodology is associated with the highest diagnostic ability [22].

Nonetheless, there are a few limitations to this study. Firstly, the relatively small sample size in this retrospective study made it difficult to draw robust conclusions. However, this is a disease with a low prevalence in the general population and the present study represents one of the largest cohorts reported from a single tertiary centre. Secondly, in comparison to the study by Culver EC et al. [2]; cases selected in this study were patients with suspected IgG4-RD in whom the serum IgG4 levels were measured rather than all serum IgG4 subclass concentrations in a larger cohort of patients. The group investigated the diagnostic utility of IgG4 in differentiating patients with IgG4-RD from other disease conditions and the role of IgG4 serology in a prospective cohort of IgG4-RD patients. IgG4-RD diagnostic criteria were met in only 5.1% (58/1140) of patients who had serum IgG4 measured for the purpose of discriminating IgG4-RD from other disease conditions. However the aim of our study was to corroborate the findings by Culver EC et al. in patients with a definite diagnosis of IgG4-RD. Thirdly, the diagnosis of pancreatic exocrine dysfunction and diabetes mellitus are based on faecal elastase levels and blood glucose level respectively both of which have low sensitivities and are likely to underestimate the prevalence. However, the available alternatives are not practical in routine practice.

In conclusion, IgG4 serology could be applied in both diagnosis and prognosis of IgG4-RD. This study showed that a raised serum IgG4 greater than 2 times the ULN was significantly associated with disease relapse and PEI in patients with IgG4-RD. IgG4-RD is a rare disease and therefore larger multicentre studies with longer follow-up are required to corroborate these findings and define the role and cut-off value of serum IgG4 in outcomes of IgG4-RD.

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