Serum immunoglobulin G4 in giant cell arteritis and polymyalgia rheumatica

M. Burkel[1], F. Arndt[1], J.H. Schirmer[1,2], F. Moosig[1,3], J.U. Holle[1,3]

[1]*Department of Rheumatology and Immunology, Klinikum Bad Bramstedt, Bad Bramstedt, Germany.*
[2]*Department of Internal Medicine I, University Hospital Schleswig-Holstein, Campus Kiel and Christian-Albrechts-University of Kiel, Kiel, Germany;*
[3]*Rheumazentrum Schleswig-Holstein Mitte, Neumünster, Germany.*

Mara Burkel
Fabian Arndt, MD
Jan Henrik Schirmer, MD
Frank Moosig, Prof.
Julia U. Holle, MD

Please address correspondence to:
Dr Mara Burkel,
Rheumazentrum
Schleswig-Holstein Mitte,
Kuhberg 5A,
24534 Neumünster, Germany.
E-mail: mara.burkel@gmx.de

Received on March 13, 2016; accepted in revised form on July 11, 2016.

Clin Exp Rheumatol 2017; 35 (Suppl. 103): S94-S97.

Key words: IgG4, eosinophilia, biomarker, giant cell arteritis, polymyalgia rheumatica

Funding: This work was supported by Orgentec (ORGENTEC Diagnostika GmbH; Mainz; Germany).
Ethics approval: Ethics Committee University of Lübeck (13-228A).
Competing interests: none declared.

ABSTRACT

Objective. *To date, no specific serum marker for giant cell arteritis and polymyalgia rheumatica has been established in routine practice. Therefore, the aim of this study was to examine whether immunoglobulin G4 serum concentrations could be a potential biomarker for the differentiation of both diseases.*

Methods. *Serum immunoglobulin G4 (IgG4) concentrations were measured in patients with giant cell arteritis (n=41) and polymyalgia rheumatica (n=27) by an in-house enzyme-linked immunosorbent assay.*

In the subgroup of untreated patients with disease activity (polymyalgia rheumatica n=27, giant cell arteritis n=19) additional parameters of T-helper 2 cell inflammatory responses were analysed.

Results. *IgG4-values above the prior determined cut-off value of 1400 µg/ml in giant cell arteritis were rare and also significantly less frequent in giant cell arteritis than in polymyalgia rheumatica patients (7.3% vs. 44.4%; p<0.001). The relative risk that patients with clinical features of PMR, presenting without elevated IgG4 levels, have simultaneously GCA was 5.8 compared to those patients with elevated IgG4 levels.*

In untreated patients absolute counts of eosinophilic leukocytes were lower in giant cell arteritis than in polymyalgia rheumatica (p=0.002) and the cytokines interleukin-4 (p=0.013) and interleukin-10 (p=0.033) were less frequently detectable in giant cell arteritis than in polymyalgia rheumatica.

Conclusion. *In giant cell arteritis serum levels of IgG4 usually are within the normal range. In polymyalgia rheumatica however, increased IgG4 serum levels are frequently found. Normal IgG4 serum levels in polymyalgia rheumatica may have predictive value in identifying patients with additional, clinically non-apparent giant cell arteritis.*

Introduction

Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are closely related conditions often occurring in the same patient. Approximately 50% of patients with GCA show symptoms of PMR before, at the time of or after the diagnosis of large-vessel arteritis (1, 2). Clinical studies showed, that approximately 5–30% of patients with clinical PMR display large-vessel arteritis in positron emission tomography (PET) imaging or in the temporal artery biopsy, even though other typical symptoms of large-vessel vasculitis are absent (3-5). While unspecific markers of inflammation, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are usually elevated two- to tenfold in both conditions, there are currently no established specific serum markers for the diagnosis or distinction of PMR and GCA in routine practice (6). Thus, the diagnosis of GCA is based on clinical symptoms, histological examinations and imaging techniques (7). Using PET-CT or magnetic resonance angiography (MRA) it occasionally can be difficult to distinguish between GCA and other inflammatory large-vessel diseases, such as idiopathic aortitis and chronic periaortitis (CP) (8). In this situation the measurement of IgG4 serum concentrations could be helpful for the serological differentiation of GCA and CP, as it has been shown that in 50% of the cases CP is associated with IgG4-related disease (IgG4-RD) (9). However, to our knowledge, the frequency of elevated IgG4 serum levels in GCA has not been assessed so far.

This raises the question of whether, GCA is associated with elevated IgG4 serum levels, and if the IgG4 serum concentration can be used as a marker to distinguish between GCA and isolated PMR. Values of eosinophilic leukocytes, interleukin-(IL)-4, IL-10 and eo-

Table I. Epidemiological data and serological parameters of GCA and PMR patients.

NS	GCA treated and untreated (n=41)	PMR untreated (n=27)	*p*-value
Mean age in years at initial diagnosis (95 % CI)	67.9 (65.57-70.19)	68.5 (64.93-72.10)	*p*=0.543
Gender (m:w)	11:30	6:21	*p*=0.779
Gender (m:w) in %	27:73	22:78	*p*=0.779
Number of untreated patients at initial diagnosis	19 (46.34 %)	27 (100 %)	*p*=<0.0001
NS	GCA untreated (n=19)	PMR untreated (n=27)	*p*-value
Mean concentration of CRP in mg/dl at initial diagnosis (95% CI)	14.00 (0.09-27.95)	8.95 (1.22-16.69)	*p*=0.088
Mean concentration of ESR in mm/h at initial diagnosis (95% CI)	78.53 (67.84-89.21)	68.35 (58.11-78.58)	*p*=0.235
Mean concentration of leukocytes in thousand/µl at initial diagnosis (95% CI)	8.81 (7.66-9.96)	9.50 (8.50-10.50)	*p*=0.547
Mean concentration of haemoglobin in g/dl at initial diagnosis (95% CI)	11.20 (10.22-12.18)	11.96 (11.47-12.45)	*p*=0.137
Mean concentration of ferritin in µg/l at initial diagnosis (95% CI)	561.40 (174.00-948.90)	265.20 (149.90-380.50)	*p*=0.019

CI: confidence interval.

sinophil cationic protein (ECP) serum levels have also been described to be associated with the induction of IgG4-production and IgG4-RD (10).

Methods

Patients

A chart review was done for all patients suffering from GCA and PMR, who were referred to our centre between 2005 and 2013. Patients with the diagnosis of GCA were only included, if they fulfilled the American Collegue of Rheumatology (ACR)-criteria (11) and furthermore had a positive temporal artery biopsy or detection of large-vessel arteritis at PET/CT or magnetic resonance angiography (MRA). PMR patients were included, if they fulfilled at least 4 of 7 Bird criteria (12), had no evidence of another rheumatic disease and had not received any treatment before referral. Exclusion of vasculitis by PET and/or MRA was not required. PMR patients were excluded if diagnosed as rheumatoid arthritis according to the 2010 ACR/ European League Against Rheumatism (EULAR)-criteria (13).

Analysis of laboratory results and clinical presentation

Epidemiological data, clinical symptoms, results from histological examinations and imaging techniques (PET-CT, MRA) and serological parameters at disease onset (CRP, ESR, absolute number of eosinophilic leukocytes) were collected retrospectively by reviewing the patients' medical history (Table I).

Measurement of IgG4, IL-4, IL-10 and ECP

Serum specimens were obtained from our biobank, where the samples had been preserved since the patients' first visit at our department. IgG4 serum levels were examined via an in-house enzyme-linked immunosorbent assay (ELISA), which is currently not commercially available. The IgG4-ELISA was developed in cooperation with Orgentec (ORGENTEC Diagnostika GmbH; Mainz; Germany). There were IgG4 positive and negative samples available to use as benchmark. In addition we measured IgG4 serum concentrations in serum samples of fifteen healthy controls.

MikroWin (v. 5.15; Mikrotek Laborsysteme GmbH; Overath; Germany) was used to evaluate the measurement. IgG4 serum concentration of 1400 µg/ml was determined by receiver operating characteristic (ROC)-analysis and defined as cut-off value. On the basis of extinction mean values and concentrations of the standard series, a standard curve was created, which was used to calibrate the extinctions measured.

Concentrations of IL-4 and IL-10 were measured using commercially available ELISA according to the manufacturers recommendations (R&D Systems, Inc.; Minneapolis, USA).

Statistical analysis

Data are shown as mean value with 95% confidence interval (95% CI). The statistical calculations were performed with Graph Pad Prism (Prism 5 for Windows; v. 5.0; GraphPad Software), using Mann-Whitney U-test, Chi-square test and Fisher's exact test. *p*-values <0.05 were considered statistically significant.

Ethics approval

The study was approved by the ethics committee of the University of Lübeck (13-228A).

Results

41 GCA and 27 PMR patients were included in this study. 19 GCA and all 27 PMR patients had not received glucocorticoid treatment before referral. There were no major differences concerning the baseline characteristics between PMR and GCA patients. CRP and ESR were not significantly different in untreated patients (CRP: *p*=0.088; ESR: *p*=0.235). Significantly more PMR than GCA patients had IgG4 values above the prior determined cut-off value of 1400 µg/ml (PMR all: 12 of 27; 44% *vs*. GCA all: 3 of 41; 7%; *p*<0.001); (PMR untreated: 12 of 27; 44% *vs*. GCA untreated: 2 of 19; 11%; *p*=0.020). In two of three GCA patients

with elevated IgG4 serum levels the values almost reached a two-fold increase above the upper normal range. In all three patients the diagnosis was based on imaging techniques. Vice versa, all nine GCA patients with biopsy proven GCA had normal IgG4 serum levels.

Thirteen of the 41 GCA patients (4 of the 19 untreated GCA patients) had typical PMR symptoms. In these GCA patients with associated PMR symptoms the IgG4 values were significantly lower than in the 27 PMR patients without evidence of GCA (581.3 μg IgG4/ml (95% CI: 393.1-769.5) *vs*. 1300 μg IgG4/ml (95% CI: 874.3-1725.0)) (p=0.0496) and only one treated GCA patient with associated PMR had IgG4 concentrations above 1400 μg/ml, whereas all of 7 PMR patients having no sign of GCA by MRA or PET-CT had serum IgG4 values above 1400 μg/ml (p=0.030). The relative risk that patients with clinical features of PMR, presenting without elevated IgG4 levels, have simultaneously GCA was 5.8 compared to those patients with elevated IgG4 levels.

Further analyses in untreated patients showed that in GCA (n=19) significantly lower absolute eosinophil counts were documented on initial presentation compared to PMR (n=23) (GCA: 75.1/μl (95% CI: 38.8-111.3); PMR: 160.1/μl (95% CI: 122.4-197.8)) (p=0.002). Regarding the additional cytokine measurements, we found that in GCA the detection rate of IL-4 (4 of 18; 22%) and IL-10 (4 of 19; 21%) was significantly lower compared to PMR (IL-4: 58%; p=0.030 and IL-10: 54%; p=0.040). In accordance with that the quantitative results showed lower IL-4 (p=0.013) and IL-10 (p=0.033) concentrations in GCA than in PMR serum samples.

Discussion

In this study we measured IgG4 serum levels in patients suffering from GCA and PMR. We found that increased IgG4 serum levels in GCA are not only rare but also significantly less frequent than in PMR, even though in both conditions systemic inflammation is common.

CRP and ESR were not significantly different in GCA and PMR patients of our study. We rarely detected increased IL-4 and IL-10 levels in the sera of GCA patients. Furthermore, absolute eosinophil counts were low, even in untreated GCA patients. Thus, all indicators of the activation of the Th2-pathway examined in this study (eosinophilic leukocytes, IL-4, IL-10), were significantly lower in GCA compared to PMR. Since IgG4 production is primarily controlled and induced by Th2-responses (9) these findings are in agreement with low IgG4 serum levels in most GCA patients. An exception to this general finding were two GCA patients in whom IgG4 serum levels were outstandingly high and almost two-fold increased above the upper normal range. In these two patients the diagnosis of GCA was based on imaging techniques. It was recently reported, that IgG4 serum levels >2700 μg/ml had a positive predictive value of 43% for the diagnosis of IgG4-RD in Chinese patients (14). IgG4 related large-vessel vasculitis or periaortitis fulfilling the classification criteria of GCA cannot be excluded due to the retrospective design of our study. In general we would recommend to screen those patients for clinical manifestations of IgG4-RD and to attempt a temporal artery biopsy to confirm GCA histologically.

In PMR, however, 44% of the patients showed elevated IgG4 serum levels. This frequency was unexpectedly high. Yet, we found detectable amounts of IL-4 an IL-10 in an equal amount of patients and these cytokines are related to the production of IgG4. It was recently shown that elevated IgG4 serum levels are frequently found in systemic rheumatic diseases (15).

All nine patients with biopsy proven GCA had normal IgG4 serum levels. We examined too limited patient numbers to draw conclusions from this, but it is mentionable, that we found differences in IgG4 serum concentrations between biopsy proven patients and patients diagnosed by cross sectional imaging techniques. This could be a hint, that temporal arteritis and aortitis may not underlie identical pathomechanisms. More research is required to clarify this question.

Conclusively, our data suggest that in PMR patients IgG4 serum levels within the normal range might be a predictor for additional GCA. Thus, IgG4 measurement bears the potential to facilitate the diagnostic procedure in PMR patients, which warrants further examination to assess this issue.

Acknowledgements

We thank Monika Backes for her assistance with the experimental work and Claudia Möck for her assistance with methodology.

We would also like to show our gratitude to Orgentec for the provision of microtitre plates and reagents.

References

1. PAULLEY JW, HUGHES JP: Giant-cell arteritis, or arteritis of the aged. *Br Med J* 1960; 2: 1562–7.
2. WILSKE KR, HEALEY LA: Polymyalgia rheumatica. A manifestation of systemic giant-cell arteritis. *Ann Intern Med* 1967; 66: 77-86.
3. SALVARANI C, GABRIEL SE, O'FALLON WM, HUNDER GG: The incidence of giant cell arteritis in Olmsted County, Minnesota: apparent fluctuations in a cyclic pattern. *Ann Intern Med* 1995; 123: 192-4.
4. MOOSIG F, CZECH N, MEHL C *et al*.: Correlation between 18-fluorodeoxyglucose accumulation in large vessels and serological markers of inflammation in polymyalgia rheumatica: a quantitative PET study. *Ann Rheum Dis* 2004; 63: 870-3.
5. BLOCKMANS D, De CEUNINCK L, VANDERSCHUEREN S, KNOCKAERT D, MORTELMANS L, BOBBAERS H: Repetitive 18-fluorodeoxyglucose positron emission tomography in isolated polymyalgia rheumatica: a prospective study in 35 patients. *Rheumatology* 2007; 46: 672-7.
6. HAYREH SS, PODHAJSKY PA, RAMAN R, ZIMMERMAN B: Giant cell arteritis: validity and reliability of various diagnostic criteria. *Am J Ophthalmol* 1997; 123: 285-96.
7. ELEFANTE E, TRIPOLI A, FERRO F, BALDINI C: One year in review: systemic vasculitis. *Clin Exp Rheumatol* 2016; 34 (Suppl. 97): S1-6.
8. MITCHINSON MJ: The pathology of idiopathic retroperitoneal fibrosis. *J Clin Pathol* 1970; 23: 681-9.
9. HAMANO H, KAWA S, OCHI Y *et al*.: Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. *Lancet* 2002; 359: 1403-4.
10. STONE JH, ZEN Y, DESHPANDE V: IgG4-related disease. *N Engl J Med* 2012; 366: 539-51.
11. HUNDER GG, BLOCH DA, MICHEL BA *et al*.: The American College of Rheumatology 1990 criteria for the classification of gi-

ant cell arteritis. *Arthritis Rheum* 1990; 33: 1122-8.
12. BIRD HA, ESSELINCKX W, DIXON AS, MOWAT AG, WOOD PH: An evaluation of criteria for polymyalgia rheumatica. *Ann Rheum Dis* 1979; 38: 434-9.
13. ALETAHA D, NEOGI T, SILMAN AJ *et al*.: 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010; 62: 2569-81.
14. YU KH, CHAN TM, TSAI PH, CHEN CH, CHANG PY: Diagnostic performance of serum IgG4 levels in patients with IgG4-related disease. *Medicine* (Baltimore) 2015; 94: e1707.
15. SOLIOTIS F, MAVRAGANI CP, PLASTIRAS SC, RONTOGIANNI D, SKOPOULI FN, MOUTSOPOULOS HM: IgG4-related disease: a rheumatologist's perspective. *Clin Exp Rheumatol* 2014; 32: 724-7.