

## IMMUNE SYSTEM DISORDERS IN PATIENTS WITH SCLERITIS

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**Summary.** *A large number of abnormalities is present in the immune system of the patients suffering from scleritis of unknown etiology as well as from scleritis associated with other systemic diseases. The aim of the present work was to investigate the level immune parameters in serum patients (immunoglobulin IgG, IgA, IgM, complement-C3, circulating immune complexes - CIC, rheumatoid factor - RF, antinuclear antibodies - ANA) with scleritis and/or associated systemic mediate disease. The first group included 30 patients with scleritis of unknown etiology, the second group included 30 patients with systemic diseases without ocular changes and the third one consisted of 30 patients with scleritis associated with other systemic diseases of connective tissue. Increased IgG was found in 33.3% of the patients in group I and in 66.7% of the patients in groups II and III, with  $p < 0.05$ . Increased IgM values were found in 13.3% of the patients in group I, 33.3% of the patients in group II and in 53.3% of the patients in group III, showing again statistically significant difference in relation to the control group. Increased serum CIC values were found in 26.7% of the patients in group I, in 46.7% of the patients in group II and in 60% of the total number of subjects in group III; there is statistically significant difference in favour of group with scleritis with associated diseases. Statistically significant negative correlation between serum CIC levels and complement C3 component in the investigated groups was found in the work. No significant difference between CIC levels and RF presence was found in group I, while statistically significant correlation between CIC levels and RF presence was found in group III of the subjects.*

**Key words:** *Scleritis, circulating immune complexes, complement, rheumatoid factor, antinuclear antibody*

### Introduction

Scleritis is an inflammation of deep layers of sclera. It can occur as isolated (independent) or associated with systemic diseases of connective tissue (1,2,3). (Rheumatoid arthritis- RA, Systemic lupus erythematosus-SLE, Wegener's granulomatosis, Polyarteritis nodosa-PAN). Scleritis is considered to develop as a result of vasculitis of small blood vessels of sclera, having in its base type III hypersensitive reaction, in which tissue lesion begins with antigen-antibody complex (4,5). Antigens can be of endogenous (nucleus, tumor) or exogenous (viruses, bacteria, parasites, fungi) origin. The antibody acting in type III hypersensitive reaction are IgG, IgM (fix a complement in a conventional way) and IgA (fixes a complement in an alternative way). Rheumatoid arthritis is the most frequent systemic disease of connective tissue associated with scleritis. For this reason, determination of serum RF in patients is essential in the evaluation of the seriousness of disease (6,7). The rheumatoid factors are anti-immunoglobulin antibodies directed to Fc fragments of IgG. High RF titre was noticed in serum of the patients with serious forms of disease, in which extra-articular manifestations, including ocular changes, were present. The presence of CIC in serum, synovia, skin and kidney of the patients suffering from RA and SLE was also significant. Most

of the studies indicated positive correlation between CIC levels and activity of the disease. Patients with extra-articular manifestations have higher CIC levels, which suggest their pathogenic role (8).

The objective of the work was to compare immune parameters of the patients suffering from scleritis of unknown etiology with immune parameters of the patients suffering from scleritis associated with systemic diseases of connective tissue.

### Patients and Methods

Four groups of patients were subjected to the prospective study: I - first group - thirty patients with scleritis of unknown etiology - (SC); thirty patients with systemic diseases only - group II (RA and SD). Thirty patients with scleritis associated with systemic diseases - group III (SC+RA and SD); thirty healthy patients - group IV. The immune parameters observed included: IgG, IgM, IgA, C3, CIC, RF, ANA.

We reviewed the records of 60 patients with non-infectious anterior scleritis. The diagnosis of scleritis was based on the edema of sclera and episclera which displaces the edges of the thin slit-lamp beam forward as the beam makes an excursion across the surface of the sclera with associated congestion of the superficial and

deep episcleral vessels; congestion of the deep episcleral vessels remains after the application of 10% phenylephrine. Ocular symptoms included ocular pain and tenderness to palpitation.

All patients with rheumatoid arthritis had a definitive diagnosis, satisfying revised criteria outlined by the American Rheumatism Association in 1988. Systemic immune-mediated diseases other than rheumatoid arthritis associated with scleritis included connective tissue diseases and other inflammatory conditions (systemic lupus erythemathodes, ankylospoding spondylitis, polyarthritis nodosa, Wegner's granulomatosis, giant cell artheritis). Diagnosis criteria for these systemic immune mediated diseases have been published elsewhere. The investigations were carried out in Niska Banja Institute for Prevention, Treatment and Rehabilitation of Rheumatological and Heart Diseases.

Control group consisted of the patients hospitalized in the Eye Clinic because of cataracta operation but not because they suffered from any other disease as confirmed in the detailed patient's history and clinical examination. They gave their written consent for clinical and laboratory examination which included immunological analysis.

Level of serum immunoglobulin (IgG, IgA, IgM): investigated in the Immunology Laboratory of the Haematology Clinics of the Niš Clinics Centre (KC Niš). C3 component, as a level of circulating immune complexes CIC, using PEG method of precipitation, was investigated in the Child Internal Clinics of KC Niš

IgM RF determination was done by the method of Latex agglutination; the patients with 1:40 and higher titre were considered to be positive. Anti-nuclear antibodies ANA were determined by the method of indirect immunofluorescence (patients with 1:40 and higher titre) were considered to be ANA positive. The investigations were carried out in the Niš Health Institute.

Statistical tests were used:

- Student's test
- Pearson's-  $\chi^2$  test
- Fisher exact probability test
- Rank sum test (Mann-Whitney U-test).

For statistical processing of the obtained results of investigation statistical packages SPSS (ver. 6.0) and Statistical Calculator within EPI Info 6.0 Programme were used.

## Results

The results of serum IgG concentrations are shown in Table 1.

Ten persons or 33.3% of the total number of subjects in the group of the patients with scleritis had increased IgG values. Increased IgG values were recorded in 20 patients (66.7%) in the group of the patients affected with rheumatoid arthritis and other systemic diseases of connective tissue and in the group of the patients affected with scleritis associated with other systemic diseases (Table 1). Increased IgG values were present in statistically more significant percentage in the patients suffering from scleritis than in the control group (Fichers's exact probability test;  $p = 0.042$ ,  $p < 0.05$ ). In relation to the control group. IgG increased values are statistically more significantly present in the subjects with systemic diseases of connective tissue and in the patients with both scleritis and systemic diseases ( $\chi^2 = 12.5$ ,  $p < 0.001$ ). No statistically significant difference in increased IgG values was found between other groups.

Average IgG value in the group of the subjects with scleritis was 15.48 g/L and in the group of the patients suffering from systemic diseases besides eye diseases it was 17.74 g/L. This difference is statistically significant ( $t = 2.23$ ;  $p = 0.037$ ;  $p < 0.05$ ).

Average IgG values in all other groups were statistically significantly greater than the average in the control group ( $p < 0.01$ ).

Statistically significant difference of the average IgG level ( $p > 0.05$ ) between other groups was not found.

The finding of total serum IgA of the subjects is shown in Table 2. It is obvious from the table that the structure of normal and increased IgA in the group of the patients with scleritis is identical to that in the group of the said diseases associated with systemic diseases of connective tissue (4 persons or 13.3% with increased

Table 1. The level of total IgG (g/l) in patients serum

IgG	Scleritis		Only systemic disease		Scleritis and systemic disease		Control group	
	N	%	N	%	N	%	N	%
Normal value (8 - 18 g/L)	20	66.7	10	33.3	10	33.3	30	100.0
High value (> 18 g/L)	10	33.3	20	66.7	20	66.7	0	0
Total	30	100.0	30	100.0	30	100.0	30	100.0
$\bar{x} \pm SD$	15.48 $\pm$ 3.48		17.10 $\pm$ 2.76		17.74 $\pm$ 1.77		10.47 $\pm$ 3.44	

Table 2. The level of total IgA (g/l) in patients serum

IgA	Scleritis		Only systemic disease		Scleritis and systemic disease		Control group	
	N	%	N	%	N	%	N	%
Normal value (0.9 - 4.5 g/L)	26	86.7	30	100.0	26	86.7	30	100.0
High value (> 4.5 g/L)	4	13.3	0	0	4	13.3	0	0
Total	30	100.0	30	100.0	30	100.0	30	100.0
$\bar{x} \pm SD$	2.57 $\pm$ 1.02		1.88 $\pm$ 0.57		2.37 $\pm$ 1.68		1.73 $\pm$ 0.52	

values). All the subjects in the remaining two groups had normal IgA values. No statistically significant difference in the increased IgA values between the investigated groups and in the average values ( $p < 0.05$ ) was found.

The finding of total serum IgM is shown in Table 3. Increased IgM values were found in 13.3% patients in the group with scleritis. This percentage is higher (10 or 33.3%) in the group with systemic diseases and it increases further if these diseases are associated with scleritis (46.3%).

The presence of increased IgM values in the group of the patients affected with scleritis associated with systemic diseases of connective tissue is by 33.3% higher than in the subjects with idiopathic scleritis, and the difference is statistically significant ( $\chi^2 = 4.89$ ;  $p = 0.027$ ;  $p < 0.05$ ).

A similar distribution of normal and decreased values of complement 3 component in the investigated groups was observed, which is shown in Table 4. Sixteen patients (53.3%) with idiopathic scleritis, 12 subjects (40.0%) suffering from systemic diseases of connective tissue and 16 patients (53.3%) with associated eye and systemic diseases had values below 0.87 g/L. As there were no decreased values of complement C3 component in the control group, the structure of normal and decreased values ( $p < 0.05$ ) of the other three groups of subjects was statistically significantly different in relation to it.

Average value of C3 complement component is in the range between 0.93g/L in the group of subjects with connective tissue systemic diseases and 1.09g/L for patients with idiopathic episcleritis and scleritis. Control

group had the highest average C3 value – 1.31g/L, which was within the limits of reference values. Statistically significant difference in C3 complement component values between the control group and other groups ( $p < 0.05$ ) was found. Difference of the average values between the investigated groups with particular diseases were in the range from 0.01 to 0.03 and it was not statistically significant ( $p > 0.05$ ).

In the group affected with scleritis, 8 persons (26.7%) had increased CIC values. CIC values above 116 mg/L in the group of the subjects with systemic diseases of connective tissue were present in 14 (46.7%) of the the diseased. The largest number of the patients with increased CIC values was in the group with scleritis associated with systemic diseases (18 or 60%), as given in Table 5.

The difference in CIC values rank in the three groups of the patients with certain diseases shows, in relation to the control group, statistically significant difference ( $p < 0.01$ ). Comparison between the values of the investigated groups did not give statistical significance ( $p > 0.05$ ).

Statistically significant difference in the structure of normal and higher CIC values between the control group and those suffering from connective tissue systemic diseases (Fisher's exact probability test:  $p = 0.0063$ ;  $p < 0.01$ ) was proven. Statistically significant difference in the occurrence of higher CIC values between the control group of the subjects and patients with associated systemic diseases and episcleritis and scleritis (Fisher's exact probability test:  $p = 0.000699$ ;  $p < 0.001$ ) was also present.

Table 3. The level of total IgM (g/l) in patients serum

IgM	Scleritis		Only systemic disease		Scleritis and systemic disease		Control group	
	N	%	N	%	N	%	N	%
Normal value (0.6 - 2.8 g/L)	26	86.7	20	66.7	16	46.3	30	100.0
High value (> 2.8 g/L)	4	13.3	10	33.3	14	53.7	0	0
Total	30	100.0	30	100.0	30	100.0	30	100.0
$\bar{x} \pm SD$	2.17 $\pm$ 0.97		2.48 $\pm$ 1.09		2.81 $\pm$ 1.08		2.32 $\pm$ 0.51	

Table 4. The level C<sub>3</sub> (g/l) component of complement in patients serum

C <sub>3</sub>	Scleritis		Only systemic disease		Scleritis and systemic disease		Control group	
	N	%	N	%	N	%	N	%
Normal value (0.87 – 2.8 g/L)	14	46.7	18	60.0	14	46.7	30	100.0
Lower value (< 0.87 g/L)	16	53.3	12	40.0	16	53.3	0	0
Total	30	100.0	30	100.0	30	100.0	30	100.0
$\bar{x} \pm SD$	1.09 $\pm$ 0.29		0.93 $\pm$ 0.25		0.94 $\pm$ 0.37		1.31 $\pm$ 0.25	

Table 5. The level of CIC (mg%) in patients serum

CIC	Scleritis		Only systemic disease		Scleritis and systemic disease		Control group	
	N	%	N	%	N	%	N	%
Normal value (24 - 116 mg%)	22	73.3	16	53.3	12	40.0	30	100.0
High value (> 116 mg%)	8	26.7	14	46.7	18	60.0	0	0
Total	30	100.0	30	100.0	30	100.0	30	100.0
$\bar{x} \pm SD$	77.33 $\pm$ 44.78		108.93 $\pm$ 64.49		115.0 $\pm$ 71.77		34.53 $\pm$ 28.32	

CIC values show statistically significant negative correlation with the level of serum complement C3 component in the subjects of both SC group with associated systemic diseases and of the group with systemic diseases only ( $p < 0.05$ ); in SC group of unknown etiology there is negative correlation of statistically marginal significance. Our results and the results of other authors, together with complement changes, suggest probable CIC pathogenic role in the occurrence of scleritis, especially in SC group with associated diseases. Similar results can be found in literature. Akpek E. M. points out that CIC increased values in the patients with vasculitis diseases, suffering also from scleritis, may lead to hypoplementemia and drop of complement C3 component.

RF and ANA presence in the investigated groups is shown in Tables 6 and 7. In the group of patients with systemic diseases of connective tissue, RF was proven to be present in 14 subjects (46.7%), while in the group of patients affected with scleritis, rheumatoid factor was proven to be present in 18 subjects (60.0%). In the group of patients with scleritis, 4 subjects (13.3%) were found to be RF positive. In the control group there were no RF positive findings, Table 6. Anti-nuclear antibodies were found in total 14 patients: 8 (26.7%) in the group of patients with systemic diseases of connective tissue and 6 (20.0%) in the group of subjects with scleritis associated with systemic diseases. ANA were not proven in other groups, which is shown in Table 7.

Table 6. The presence of RF in patients serum.

RF	Scleritis		Only systemic disease		Scleritis and systemic disease		Control group	
	N	%	N	%	N	%	N	%
+	4	13.3	14	46.7	18	60.0	0	0
-	26	86.7	16	53.3	12	40.0	30	100.0
Total	30	100.0	30	100.0	30	100.0	30	100.0

Table 7. The presence of ANA in patients serum

ANA	Scleritis		Only systemic disease		Scleritis and systemic disease		Control group	
	N	%	N	%	N	%	N	%
+	0	0	8	26.7	6	20.0	0	0
-	30	100.0	22	73.3	24	80.0	30	100.0
Total	30	100.0	30	100.0	30	100.0	30	100.0

No statistically significant difference between CIC serum levels and RF presence in the group of scleritis of unknown etiology was found in the study, though there is statistically significant difference between CIC levels and RF presence in the group of scleritis with associated systemic diseases. Westard and Sar indicate that RF positive patients had significantly higher CIC levels (Table 8).

### Discussion

The real pathogenesis of scleritis is not sufficiently known yet, but type III hypersensitivity is considered to have an important role, i.e. the presence of mucroangiopathy in most of the samples points out to the associated immunocomplex reaction the vascular lesion of which is the result of antibody-antigen complex inside and outside blood vesels walls and surrounding tissues (3, 9,10,11).

There are few data in the available literature about the values of serum immunoglobulin in the patients with scleritis. Dinning (4) gives first data about the increased IgM values in the serum of the patients with scleritis. Other authors also offer various results (12,13).

While Akpek E.M. (14) finds out abnormal values of serum C3 component in 53.3% patients with scleritis of unknown etiology and even in 40% of the cases in the group of patients with scleritis and associated diseases, other authors find wide scale of serum C3 complement component of the patients with scleritis.

Different complement values may result from the effect of a number of factors: adjustment of the time of investigation, managing the therapy or presence of associated diseases. The result of this investigation in the patients with lower values of C3 components indicates an increased consumption and participation in immunocomplex diseases.

In patients with connective tissue systemic diseases, including vasculitis diseases, higher circulating immune complexes may persist in the serum for prolonged time. An increase of serum CIC is significant in both RA patients and patients with other connective tissue disease.

CIC values show statistically significant negative correlation with C3 complement component level in the serum of subjects both in the group of SC with associated systemic diseases and in the group of the subjects with systemic disease only ( $p < 0.05$ ), while negative correlation on the verge of statistical significance was present in the group with SC of unknown etiology.

Table 8. The presence of RF and the level CIC in patients serum

CIC	Only systemic disease				Scleritis and systemic disease			
	RF (+)		RF (-)		RF (+)		RF (-)	
	N	%	N	%	N	%	N	%
Normal value (24 - 116 mg%)	6	42.9	10	62.5	10	55.5	2	16.7
High value (> 116 mg%)	8	57.1	6	37.5	8	44.5	10	83.3
Total	14	100.0	16	100.0	18	100.0	12	100.0
Fisher's test	$p > 0.05$				$p > 0.05$			

The most similar results can be found in literature. Akpek E.M. indicates that in the patients with vasculitis diseases having also scleritis, higher CIC values lead to hypocomplementemia and decrease of the level of C3 complement component.

Jans (2) et al. point out that patients with extra-articular manifestations, including eye changes, have higher CIC levels, which suggests their pathogenic role. Higher values are greatest in patients with nodes, eye changes, vasculitis and other extra-articular changes.

Our results and the results of other authors, as well as complement changes, suggest that CIC probably have pathogenic role in the development of scleritis, especially in the SC group with associated systemic diseases.

Jans (2) et al. indicate that the patients with extra-articular manifestations, including ocular changes, have higher CIC levels, which suggest their pathogenic role.

It may be concluded on the basis of immune investigations that this microangiopathy, induced by the deposits of immune complexes and found out by immunohistochemical investigation of scleral biopsies, supported by fluorescence angiography and good response to corticosteroids and immunosuppressives, advocates auto-immune nature of scleritis. Some authors indicate that this inflammatory scleral microangiopathy, as well as systemic vasculitis, can develop in genetically predisposed persons, exposed to the environment factors (viruses, bacteria, trauma) which are still unclear (10,14).

Rheumatoid factors are antibodies directed not only to Fc fragment but to other IgG fragments, too. High titer is found in the serum of the patients with serious type of disease and with present extra-articular manifestations (3).

Our study did not show statistical significance in relation to higher serum CIC and positive RF of patients. This may be explained by the fact that the groups of subjects were small, relatively inhomogeneous groups.

Gupta and Mocha (15) pointed out that RF positive patients have significantly high CIC levels.

Melsom et al. (16) indicate that patients with systemic manifestations (nodules, cutaneous vasculitis, eye changes and KVS changes) have significantly higher CIC values in relation to the patients without systemic changes.

Westedt et al. (17) point out that RF positive patients had significantly higher CIC; the results were comparable and support the fact that significant part of CIC in RA patients are formed by complexes of IgG RF-IgG composition (important for joint process activity), IgG RF-IgG (more frequent in patients with systemic manifestations). It can be seen that SC patients with associated systemic diseases had results closer to the patients having only systemic diseases without eye manifestations than to patients with SC of unknown etiology. Statistically significant difference between these groups and control group also points out to this. The results of the investigation allow the following results: the presence of RF in the group with systemic diseases without eye manifestations and in SC group with associated systemic diseases are the consequence of inflammatory systemic disease, not of eye manifestation. It may be obvious from this that there is pathogenic connection of patients with scleritis and associated systemic diseases and those having systemic diseases only.

## Conclusion

The level of circulating immune complexes-CIC is significantly increased in the group of scleritis of unknown etiology and in the group of scleritis associated with other systemic diseases, thus it may be concluded that their role is pathogenic.

The results of this investigation allow the following conclusion: RF presence in the group of systemic diseases without ocular manifestations and in SC group with associated diseases is a consequence of a systemic inflammatory disease not of an ocular manifestation. It might result that there is pathogenic connection between the patients with scleritis and associated diseases and the patients affected with systemic diseases only. No statistically significant difference between CIC serum levels and RF presence in the group of scleritis of unknown etiology was found in the study, though there is statistically significant difference between CIC levels and RF presence in the group of scleritis with associated systemic diseases.

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## POREMEĆAJ IMUNSKOG SISTEMA KOD SKLERITISA

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Kratak sadržaj: *U imunskom sistemu bolesnika sa skleritisom kako nepoznate etiologije, tako i sa pridruženim sistemskim bolestima prisutne su brojne abnormalnosti. Cilj rada je bio da ispitamo nivo imunskih parametara u serumu bolesnika (imunoglobulini klase IgG, IgM, IgA, komplementa-C3, cirkulišući imuni kompleksi - CIC, reumatoidni faktor-RF i antinuklearna antitela-ANA) koji su imali skleritis sa ili bez pridruženog sistemskog oboljenja. Prva grupa je imala 30 bolesnika sa skleritisom nepoznate etiologije, II grupa je imala 30 bolesnika sa sistemskim bolestima bez promena na očima, III- grupu su činili 30 bolesnika koji su imali skleritis udružen sa sistemskim bolestima vezivnog tkiva. U I grupi povišene vrednosti IgG imalo je 33,3% bolesnika, dok je u II i III grupi 66,7% bolesnika i ovde je  $p < 0,05$ . Povišene vrednosti IgM je u I grupi imalo 13,3% bolesnika u II grupi 33,3%, dok je u III grupi 53,3% bolesnika: i ovde postoji statistički značajna razlika u odnosu na kontrolnu grupu. Povišene vrednosti CIC u serumu je u I grupi imalo 26,7% ispitanika, u II grupi 46,7%, dok je u III grupi njih 60% od ukupnog broja ispitanika; postoji statistički značajna razlika u korist grupe sa skleritisom sa pridruženim bolestima. U našem radu smo pronašli statistički značajnu negativnu korelaciju između nivoa CIC u serumu i C3 komponente komplementa u ispitanim grupama. U I grupi nema značajne razlike između nivoa CIC i prisustva RF, dok u III grupi ispitanika postoji statistička značajna povezanost između nivoa CIC i prisustva RF.*

*Ključne reči: skleritis, cirkulišući imuni kompleksi, komplement, reumatoidni faktor, antinuklearna antitela*