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C_3 COMPLEMENT LEVEL IN THE BLOOD OF MULTIPLE SCLEROSIS PATIENTS

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C_3 (β_1C) complement was followed in the blood of 68 patients, clinically definitive cases of multiple sclerosis. Control groups included 16 healthy persons and 22 patients affected by other neurological noninflammatory diseases. Hypocomplementaemia (C_3 values below 0.95 g/l) was found in 14 patients (20.6%), but only 9 of them had a persistent hypocomplementaemia. Conversely to data in the literature, the authors were unable to find any relationship between hypocomplementaemia and the incidence of B 18 specificity of the major histocompatibility complex. Significantly lower complement values were found in groups of patients suffering from serious infections and having multiple sclerosis longer than 10 years. It is interesting that patients with a higher disability score had a significantly higher level of the complement. The arthors' results do not support the view about hypocomplementaemic multiple sclerosis as a specific form of disease.

The etiology of multiple sclerosis is still unclear. Considerable evidence accumulated in the recent period points to the importance of the genetic component and environmental factors[1,2]. Furthermore, both parts of immune response, cellular and humoral immunity, are involved in the pathogenesis and clinical course of multiple sclerosis. The most profound immunological changes are found in the cerebrospinal fluid of multiple sclerosis patients, such as the rise of immunoglobulins G and A and the appearance of oligoclonal immunoglobulins. There are changes of humoral immunity effectors in the blood also, with the elevation of IgM and antiviral antibodies[3]. The changes of cell-mediated immunity are not so profound, but they are present[4].

Complement, a complex of eleven plasma proteins, represents a major element in the system of humoral immunity and plays an important role as a mediator of many immune reactions. There are conflicting data on the role of complement and of its changes in the clinic-

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al course of disease. Cook et al.[3] found a significantly elevated levels of C_4 when compared to normal controls. On the basis of these results they concluded that C_3 is rearely abnormal in multiple sclerosis patients. Trouillas and coworkers[5] found that about 30% of multiple sclerosis patients had a persistent or fluctuating C_3 hypocomplementaemia. Furthermore, Trouillas and Betuel[6], on the basis of familial studies, showed that the low C_3 is associated with some HLA haplotypes, especially with those containing B-18. They postulated a »complement abnormality susceptibility« gene.

The aim of this work was to analyse the level of the C_3 component of the complement in the blood of multiple sclerosis patients in various conditions depending on the stage and duration of disease, therapy, complications and/or infections etc. In our opinion a serious analysis of complement components, including C_3 as well, may be of considerable value in assessing the activity and progression of the disease.

MATERIAL AND METHODS

C_3 complement was determined in the blood sera of 68 patients, clinically definitive cases of multiple sclerosis. Multiple sclerosis was diagnosed according to the criteria described by Schumacher et al.[7] Thirty-one patients were treated with vitamins only; 16 patients with ACTH, and 10 patients with azathioprin (Imuran). The treatment with ACTH started with i.v. injections of 50 I. U. daily for a 4-week period and was followed by the Synacthen depot, one injection every 15 days. Azathioprin was given in a dose of 2.5 mg/kg daily. Blood samples for the determination of C_3 complement were taken at least once, but regularly several times C_3 complement was determined by the method of single radial immunodiffusion by using commercial plates (Meloy, Springfield). Precipitation rings were measured after 48 hours. The results obtained were statistically analyzed by the variance analyses and the testing of differences between two independent means[8]. The control group consisted of 16 healthy persons. In the neurological control there were 22 patients affected by other neurological noninflammatory diseases. All controls were age matched with the group of patients.

RESULTS

Individual results in the group of healthy persons (age-matched control) ranged from 0.95 to 1.88 g/l (Table 1). There is no result for C_3 complement below 0.95 g/l in the group of patients with other neurological diseases. However, in the group of multiple sclerosis patients 14 out of 68 (20.6%) patients had C_3 complement values below the lowest value in the control group. Nine of them (13.2%) had persistent hypocomplementaemia confirmed by repeated testing, but values of the complement in five patients showed considerable variations (fluctuating hypocomplementaemia). C_3 complement in the persistent hypocomplementaemia group (group 5) is significantly different ($p<0.001$) compar-

ed with other groups. When all hypocomplementaemic patients were separated from the multiple sclerosis group (group 4) C_3 complement reached the level of the neurological control. A statistically significant difference was found when multiple sclerosis patients were divided into subgroups according to the disease duration, disability score, and infections (Table 2). There is a significantly lower level of C_3 complement in patients with the longer duration of the disease and serious infections, but a higher C_3 in patients with a higher disability score. We could not find any difference in C_3 complement comparing patients in the active or the stable phase of the disease. There is a slight suppression of C_3 complement in patients treated with ACTH and a significant decrease in the Azathioprin treated group, when compared with multiple sclerosis patients using vitamins only (Table 3). Blood sera samples were analyzed one month after the last injection of the drug.

Table 1

C_3 complement values (g/l) in the blood of multiple sclerosis patients and controls

Group	No. of patients	$\overline{X} \pm SD^*$	Range
1. Health control	16	1.61 ± 0.075	0.95 — 1.88
2. Neurological control	22	1.42 ± 0.07	1.00 — 2.20
3. Multiple sclerosis[a]	68	1.24 ± 0.25	0.68 — 1.96
4. Multiple sclerosis[b]	54	1.43 ± 0.056	0.95 — 1.96
5. Hypocomplementaemic multiple sclerosis	9	0.80 ± 0.08	0.68 — 0.90

*=Mean ± standard deviation
a=all multiple sclerosis patients
b=multiple sclerosis group without patients with persistent or fluctuating hypocomplementaemia
Levels of significance (p): 1) All groups vs. hypocomplementaemic multiple sclerosis $<0{,}001$
2) group 1 : group 3 $<0{,}001$
3) group 2 : group 3 $<0{,}01$

Table 2

Clinical characteristics and C_3 complement

		No. of patients	$\overline{X} \pm SD^*$	Difference (p)
Disease duration (years)	0 — 9	33	1.31 ± 0.046	< 0.02
	> 10	28	1.15 ± 0.045	
Disability score (after Kurtzke)	0 — 4	36	1.19 ± 0.04	< 0.001
	5 — 9	25	1.30 ± 0.056	
Serious infections	No	50	1.26 ± 0.036	< 0.001
	Yes	11	1.15 ± 0.071	

X=Mean ± standard deviation (g/l)

Table 3.

C_3 complement (g/l) in the blood of immunosupressed patients

Group	Treatment	Number	$\overline{X} \pm SD$*
1. Neurological control	∅	22	1.42 ± 0.07
2. Multiple sclerosis	vitamins	31	1.27 ± 0.028
3. Multiple sclerosis	ACTH	16	1.16 ± 0.058
4. Multiple sclerosis	Azathioprin	10	1.06 ± 0.077

*=Mean ± standard deviation

Levels of significance: 1 : (2, 3, 4) $p < 0.001$

2 : 4 $p < 0.02$

DISCUSSION

As emphasized in the introduction, there are a great many conflicting data relating to the level of complement components in the blood as well as in the cerebrospinal fluid of multiple sclerosis patients. It seems to us that these differences could be explained by the fact that the group of multiple sclerosis patients is not a homogeneous one but consists of patients with various characteristics of the disease. In the recent literature, particular interest was focussed on the fact that some multiple sclerosis patients are hypocomplementaemic. Trouillas and others[5,9] reported that about 30% of all multiple sclerosis patients have either persistant or fluctuating hypocomplementaemia. Zibeti et al[10] found a similar percentage of hypocomplementaemic multiple sclerosis patients. It was suggested that hypocomplementaemic multiple sclerosis is a specific form of the disease having many specificities in the clinical course and immunological tests. Furthermore, it is interesting that hypocomplementaemia proved associated with the higher incidence of B 18 specificity of the major histocompatibility complex[6]. As already presented in Table 1, we had about 13% of patients showing C_3 complement lower than the lowest level in the control group. All patients from this group showed hypocomplementaemia at the first examination when multiple sclerosis was diagnosed, before the introduction of specific treatment. Tests were repeated but C_3 hypocomplementaemia was always observed. Furthermore, we followed histocompatibility antigens of A and B series in all multiple sclerosis (to be published) but were unable to connect B 18 specificity with hypocomplementaemia. Namely, there is no B 18 specificity at all among our hypocomplementaemic patients, which may reflect the lower frequency of this antigen in our population as well. This difference could be explained by the fact that the frequency of some haplotypes in multiple sclerosis patients depends on the geographic region with serious differences between regions[11]. Trouillas and Batuel[6] concluded that in their group of seventy-five patients normocomplementaemia was significantly associated with B 7. It is interesting that the B 7 frequency was almost the same in our group of multiple sclerosis patients as well (to be published).

Geraud et al.[12] found the C_3 level to be lower than in controls in the acute phase of the disease in non-infected multiple sclerosis patients. They stressed the importance of infection as a stimulatory mechanism for complement synthesis. However, it is hard to accept this suggestion in the light of our results, because the level of C_3 complement was significantly lower in the group of patients with serious infections compared with noninfected patients.

It is interesting that the levels of C_3 complement are lower in the group of patients with a longer duration of the disease, but higher in the case of a higher disability score (Table 2). To explain this apparent discrepancy, the preexisting immunopathological status should be analyzed, i.e. the patients' immunological status before the onset of multiple sclerosis symptoms. According to Trouillas and Betuel[6], hypocomplementaemic multiple sclerosis is a specific form of the disease having, among other characteristics a fairly benign prognosis. Conversely, normocomplementaemic multiple sclerosis is associated with a late onset and poor prognosis. The analysis of clinical characteristics of the disease in our group of hypocomplementaemic patients has shown that they are approximately equally found in groups with the benign and the malign course of the disease, respectively with benign and poor prognosis[13]. Taking into account this facts as well as other data discussed above, it could be concluded that our results do not support the view of hypocomplementaemic multiple sclerosis as a specific form of disease.

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SAŽETAK

KRETANJE C_3 KOMPLEMENTA U KRVI BOLESNIKA S MULTIPLOM SKLEROZOM

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Pratili smo kretanje C_3 komponente komplementa u grupi od 68 bolesnika s klinički potvrđenom dijagnozom multiple skleroze. Kontrolne skupine sačinjavalo je 16 zdravih osoba i 22 bolesnika oboljela od drugih neupalnih neuroloških bolesti. Bolesnici s multiplom sklerozom imali su niže vrijednosti C_3 komplementa nego zdrave osobe i bolesnici oboljeli od drugih neuroloških bolesti. Hipokomplementemiju (vrijednosti C_3 ispod 0,95 g/l) imalo je 14 bolesnika (20,6%), a od toga 9 perzistentnu hipokomplementemiju. Za razliku od podataka u literaturi, u našoj populaciji nismo našli nikakvu povezanost između hipokomplementemije i B 18 specifičnosti HLA sustava. Značajno niže vrijednosti komplementa imali su bolesnici s teškim infekcijama i trajanjem bolesti dužim od 10 godina. Interesantno je da su bolesnici s većim stupnjem invalidnosti (prema Kurtzkeu) imali i značajno više vrijednosti komplementa. Naši rezultati ne podupiru mišljenja o hipokomplementemičnoj multiploj sklerozi kao benignijoj formi bolesti.