

## INVESTIGATION ON THE ROLE OF VIRAL ANTIBODIES IN THE PATHOGENESIS OF MULTIPLE SCLEROSIS

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*Summary.* — An attempt was made to elucidate the role of antibodies to measles, rubella and mumps viruses in the pathogenesis of multiple sclerosis by correlating their levels in the blood of patients with clinical manifestations of the disease. Antibody titres to measles and rubella viruses were higher during exacerbations of the process and decreased during remissions. No correlation was found between the level of viral antibodies and the duration of the disease, features of its course (rapidly or slowly progressing), or the phase of the disease. The rise of viral antibody titres in multiple sclerosis appears to be a secondary process not associated with the disease aetiologically and playing no role in its pathogenesis.

*Key words:* multiple sclerosis; measles antibody; rubella antibody; mumps antibody

### Introduction

In many patients with multiple sclerosis (MS), measles antibody in the blood serum is found in higher titres than in convalescents after measles (Brody *et al.*, 1972; Panelius *et al.*, 1973; Cendrowski and Niedzielska, 1974; Pille *et al.*, 1977; and others). The level of these antibodies in the patients varies, increasing during the exacerbation of the process and declining in the periods of remissions (Pille *et al.*, 1976). In some cases, MS patients were found to have higher than normal levels of antibodies to rubella, chickenpox, and other viruses. It was also demonstrated that, in MS patients, viral antibodies could be produced directly in the central nervous system (CNS) (Norrby *et al.*, 1974).

The most plausible explanation of these phenomena seems to be an activation of persisting viruses or parts of their genomes in MS patients. The existence of active virus infection is indicated by the detection in some patients of IgM immunoglobulins reacting with measles, mumps (Miller *et*

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*al.*, 1971) or rubella (Pille *et al.*, 1977) viruses. It remains obscure, however, whether these viruses play any role in the aetiology of MS or, on the contrary, whether the development of this disease leads to activation of a latent virus infection, a rise in viral antibody levels only reflecting this secondary process. There is no common opinion on the significance of viral antibodies in the pathogenesis of MS. Some workers believe that antibodies play a protective role and this led to attempts of using measles immunoglobulin for treatment of the patients (Cajal *et al.*, 1973). According to another opinion, synthesis of virus-specific immunoglobulins in the brain tissue causes a destructive process in the CNS. The use of immunosuppressing drugs for treatment of the patients did not elucidate the problem: some workers observed a positive effect (Lance *et al.*, 1975), whereas others found no effect of the immunosuppressants on the course of the disease (Tourtellotte *et al.*, 1976).

We tried to elucidate the role of viral antibodies in the pathogenesis of MS by correlating their levels with the clinical picture of the process.

### Materials and Methods

*The study population.* The observations included 130 MS patients (55 men and 75 women) aged from 14 to 52 years with a duration of the disease from several months to 34 years. Blood was taken from the patients once or 2–4 times at various intervals. The control group consisted of 94 persons aged from 17 to 50 years: 49 healthy donors and 45 patients with different diseases of the nervous system (osteochondrosis in the period of regression of the pain syndrome, vegetative vascular dystonia, neurasthenia, degenerative diseases of the nervous system). Since antibody levels in the donors and patients were practically the same, the values obtained were summarized.

*Viral antibody levels* were determined by the haemagglutination-inhibition (HI) test as described (Pille *et al.*, 1977). IgM and IgG to measles, rubella and mumps viruses were detected by the HI test after fractionation of the sera by ultracentrifugation in sucrose gradient (Pille *et al.*, 1977). The results were treated statistically by the t-test.

### Results

Table 1 presents the results of determinations of antibodies to measles, rubella and mumps viruses in 130 patients. No significant sex differences in the intensity of immunological response were found, with the exception of slightly higher titres of antibodies to mumps virus in women than in men.

Table 1. Antibody levels in sera from MS patients in different phases of the disease

Antibody to virus	MS patients						Controls			
	remission phase			exacerbation phase			M	F	Total	
	M	F	Total	M	F	Total				
Measles	I	20	34	54	44	64	108	54	40	94
	II	5.20	4.90	5.01	6.38	6.20	6.27	4.94	4.02	4.55
Rubella	I	18	34	52	43	61	104	54	39	93
	II	4.11	4.51	4.40	4.67	4.34	4.48	3.67	3.05	3.40
Mumps	I	20	35	55	42	64	106	53	39	92
	II	4.00	4.68	4.47	5.54	6.64	6.20	2.98	2.53	2.78

I — No. of sera; II — geometric mean antibody titre ( $\log_2$  values).

M — men; F — women.

Table 2. Antibody levels in sera from MS patients with different course of the disease

Antibody to virus	Patients in the exacerbation phase						Patients in the remission phase		
	Rapidly progressing disease			Slowly progressing disease			Rapidly progressing disease	Slowly progressing disease	
	M	F	Total	M	F	Total			
Measles	I	9	19	28	29	29	58	5	34
	II	7.00	6.58	6.71	6.37	5.93	6.15	4.60	5.08
Rubella	I	7	16	23	28	29	57	4	33
	II	5.29	3.87	4.30	4.57	4.62	4.59	2.75	4.60
Mumps	II	8	19	27	27	28	55	5	35
	II	5.13	6.21	5.89	5.51	6.25	5.89	4.60	4.25

Patients in the early stage of the disease, when the type of the course was not yet clear, were not included.

For explanations see Table 1.

A comparison of antibody titres in MS patients in different phases of the disease demonstrated a rise of antibody levels to measles (5.01 and 6.27  $\log_2$ ;  $t = 3.5$ ) and mumps (4.47 and 6.2  $\log_2$ ;  $t = 4.9$ ) viruses in the period of exacerbation. No significant differences were found with rubella antibody.

Previously we had demonstrated that in many MS patients the titre of measles antibody increased during the exacerbation of the disease and declined during remissions (Pille *et al.*, 1976). This was confirmed by subsequent studies. For example, the patient Zh. had during 2 years two episodes of exacerbation of the disease accompanied by a marked rise in measles antibody titres (up to 9 and 11  $\log_2$ ); in remissions the titre declined to 5  $\log_2$ . Such correlation of measles antibody titres and the clinical picture was not regularly observed. Sixteen patients were examined both during remissions and in exacerbations. In 11 of them the antibody titre was higher in exacerbation period than during remission, in 3 it was lower and in 2 it remained at the same level.

Table 3. Antibody levels in sera from MS patients with different duration of the disease

Antibody to virus	Patients in the remission phase				Patients in the exacerbation phase			
	Duration of the disease (years)							
	<1	2-5	6	<1	1	2-5	6	
Measles	I	6	20	13	21	17	18	35
	II	5.33	5.20	4.61	7.28	5.94	6.05	6.54
Rubella	I	5	20	12	16	14	16	31
	II	3.20	4.00	4.58	3.62	4.28	4.37	4.93
Mumps	I	6	20	13	20	17	19	33
	II	4.50	4.75	3.92	6.55	5.24	5.36	6.18

For explanations see Table 1.

Table 4. Antibody levels in sera from MS patients at different stages of the disease

Antibody to virus		Stage I		Stage II		Stage III
		exacerbation	remission	exacerbation	remission	
Measles	I	33	15	69	28	8
	II	5.87	5.73	6.44	4.71	5.37
Rubella	I	32	15	60	25	8
	II	4.09	4.13	4.68	4.44	4.37
Mumps	I	32	16	66	28	8
	II	5.78	3.62	6.33	4.89	5.50

Several patients who at the time of the examination developed exacerbation of the process, and in whom the stage of the disease thus could not be determined accurately, were not included. For explanations see Table 1.

When comparing antibody titres in MS patients during exacerbations and in control persons, there was a significant difference with antibody to all the 3 viruses: 6.27 and 4.55  $\log_2$  for measles ( $t = 5.4$ ), 4.48 and 3.4  $\log_2$  for rubella ( $t = 3.9$ ), and 6.2 and 2.78  $\log_2$  for mumps ( $t = 11.7$ ). Titres in the sera collected from the patients during the remission period differed less from those in the controls, but even here the patients had higher antibody levels.

To establish an active virus infection in the patients, some sera were examined for the presence of the respective IgM and IgG. In exacerbations of the process, IgM to measles and mumps viruses were found more frequently (11 out of 19 and 5 out of 6 cases, respectively) than in the stage of remission (2 out of 12 and 1 out of 5 cases, respectively). In 2 patients measles IgM was found during exacerbation but not during remission. IgM to rubella virus was found in 10 out of 18 patients examined, showing no correlation with the phase of the process.

The activity of immunological responsiveness of the patients was not age-dependent: no significant differences in antibody titres were found in patients aged 14–20, 21–30 years or more.

Table 2 presents the results of examinations of sera from patients with different severity of the disease: rapidly progressing severe disease when invalidism developed in the first 2 years of the disease, and slowly progressing, comparatively mild MS when the patients retained their working capacity for 2 or more years. No manifest correlation between antibody titres and the severity of the disease was demonstrated. There was only a very slight difference in the levels of measles antibodies: slightly higher titres in the severe disease than in slowly progressing process (the difference was statistically insignificant).

We attempted to reveal changes in viral antibody levels in relation to the duration of the disease, but found no regularity (Table 3). Certain differences between individual groups were most likely due to small numbers of patients in some of them.

We furthermore compared antibody levels in patients in relation to the stage of the disease (Table 4). Stage I was the initial period of the disease when after an exacerbation the disturbed functions were restored completely

or nearly completely. In stage II after an exacerbation there was an improvement without complete recovery of the functions; the working capacity of the patients decreased. Stage III corresponded to the decompensation period: the patients had severe irreversible organic symptoms for several years, lost their working capacity and required care of another persons. No marked remissions or exacerbations were observed in stage III.

In stage I of the disease antibody titres were higher than in controls, but the difference between remission and exacerbation periods was demonstrable for mumps antibody only. In stage II antibody titres were higher; a significant difference was observed between their values during exacerbations and remissions ( $t = 4.1$  for measles and  $3.48$  for mumps antibodies). In stage III antibody titres decreased slightly. On the whole, differences in antibody levels at different stages of MS were small and statistically insignificant.

### *Discussion*

Many MS patients have antibodies to some viruse in higher titres than normal persons, most frequently to measles virus, less frequently to rubella, herpes simplex mumps and other viruses, sometimes simultaneously to several viruses. This fact as well as demonstration of IgM to different viruses appear to indicate the presence of an active infectious process due to these viruses. We attempted to elucidate the role of viral antibodies in the pathogenesis of MS by determining their levels in patients with different severity of the process, with different courses of the disease, at various intervals after the onset. If viral antibodies were indicative of MS-specific immune response, the process could be expected to run a milder course at a high antibody level than at a lower one. Of adhering to the opinion of the determining role in the MS pathogenesis of immunopathological reactions in which antibodies take part in the development of destructive processes in the brain tissue, it could be assumed that antibody levels would correlate with the intensity of the pathological process.

An increase in viral antibody titres during exacerbations of the process appears to be in favour of the latter point of view; but these data may also be interpreted as indicating that exacerbation of the process induces enhanced antibody production favouring the next remission.

The present data on viral antibody levels in MS processes running different courses confirmed neither the former nor the latter point of view of the importance of antibodies in the pathogenesis of MS. Antibody titres in patients with severe rapidly progressive disease were the same as in those with comparatively mild slowly progressive disease.

Nor was a correlation established between the antibody level and the stage of the disease. Since in stage I there was a complete recovery of the disturbed functions and subsequently only partial compensation (stage II) or its complete lack (stage III), a corresponding rise or fall in viral antibody titres could be expected. No such relationship was observed.

Our studies revealed no relationship between the clinical picture of MS and the level of virus antibodies in the blood serum. We suggest that if a rise in viral antibody levels were due to the activation of viruses persisting in the host, this process is a secondary one in relation to MS, not associated with it aetiologically and playing no role in its pathogenesis.

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