ANTIBODIES AGAINST DNA IN MYASTHENIA

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UDC 616.74-009.54-008.939.332-097.5

The titer of antibodies against DNA is higher in the blood serum of patients with myasthenia than in healthy persons. Antibodies against DNA are found in all cases where myasthenia is associated with a thymus tumor. Their titer does not correlate with the severity of the disease and is unaffected by procedures directed toward the thymus.

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The question of polyautoimmune disturbances in the pathogenesis of myasthenia has been extensively discussed in the recent literature [6-8, 17-19]. As well as clinical observations, many immunologic and experimental data have been obtained indicating the importance of autoimmune changes in this disease. Auto antibodies against components of the muscle fiber [6, 7, 19], antithyroid antibodies [6], antibodies against various components of the nucleus – antinuclear factor [6, 16, 19], and antibodies against denatured DNA [18] have been found in the sera of patients with myasthenia.

In the present investigation the presence of various types of antibodies against DNA was determined in the serum of patients with myasthenia.

EXPERIMENTAL METHOD

Antibodies against DNA were detected by the passive hemagglutination (PHR) and antibody neutralization (ANR) reactions, performed as fully described previously [1]. Formalinized sheep's erythrocytes loaded with single-stranded DNA were used for the reactions. DNA from calf thymus and DNA obtained from Escherichia coli and Bacillus lysodeikticus were used in the ANR.

Nucleic acids were isolated from calf thymus by Kay's method [10] and bacterial nucleic acids by Marmur's method [13]. The nucleic acid preparations contained not more than 2% protein. Denatured DNA was obtained by boiling for 10 min. In addition, DNA heated to 100° in the presence of a 1.2% formaldehyde solution was used. According to Grossman [9], spiralized segments are virtually absent from such DNA.

Antibodies were divided into three types depending on their ability to react in the ANR with various DNA preparations [3]: type 1 – antibodies capable of reacting only with single-stranded DNA; type 2 – antibodies reacting with single-stranded and denatured DNA (60% of the nucleotides of which are in a spiralized state); type 3 – antibodies reacting with both single-stranded and negative DNA.

EXPERIMENTAL RESULTS

Altogether 95 patients with myasthenia of different forms and varied severity and having had various procedures directed towards the thymus were investigated. The blood sera of 112 healthy persons aged from 18-30 years were investigated as controls. As Table 1 shows, antibodies against DNA were discovered in 82% of cases in the blood serum of patients with myasthenia. In clinically healthy persons they were discovered in 58% of cases. Antibody titers in patients with myasthenia were higher than in healthy persons. The view has been held for a long time that the appearance of antibodies against DNA is pathognomonic of systemic lupus erythematosus [14].

It was on this basis that Burnet connects the genesis of formation of antibodies against DNA with the appearance of prohibited clones. It was soon discovered, however, that antibodies against DNA are found not

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TABLE 1. Titer of Antibodies Against DNA in Serum of Patients with Myasthenia and Healthy Persons

Group of subjects	Number of persons investigated (in %) by titers of antibodies against DNA	Total number investigated	Distribution of sera (in %) by titers of antibodies against DNA			Antibodies of type 1	Antibodies of type 2
			1:20	1:80	1:80		
Patients with myasthenia	82	95	15	55	30	64	36
Healthy persons	58	112	24.5	65	10.5	95.5	4.5

TABLE 2. Titer of Antibodies Against DNA in Patients with Myasthenia Depending on Character of Disease

	Number of patients	Detection of antibodies against DNA				No antibodies detected	
		type 1		type 2			
		number of patients					
		abs.	%	abs.	%	abs.	%
Myasthenia	95	50	53	28	29	17	18
Without thymoma	85	43	51	25	29	17	20
With thymoma	10	7	70	3	30	0	0
Mild form	8	4	50	3	38	1	12
Moderately severe form	57	32	56	15	26	10	18
Severe form	30	14	47	10	33	6	20
History of frequent remissions	34	17	50	9	27	8	23
No remissions	61	33	54	19	31	9	15
Duration of disease							
Under 5 years	68	35	52	19	28	14	20
Over 5 years	27	15	56	9	33	3	11

only in systemic lupus erythematosus [2], but also in diseases such as tuberculosis, leprosy, rheumatic fever, and so on, and also in completely healthy persons. The facts relating to experimental production of antibodies against DNA [5, 11, 15] invalidate Burnet's hypothesis of the role of prohibited clones in causing their appearance. Since antibodies against DNA have been determined in diseases accompanied to some extent by degeneration of cell nuclei (tuberculosis), the suggestion has been made that degenerative processes play a role in the induction of antibodies against DNA.

The experiments showed that antibodies of type 2 are found in 36% of patients with myasthenia, but in only 4% of healthy persons (Table 1). Induction of antibodies of type 2 in experimental animals has been shown to take place much less intensively than induction of type 1 antibodies, which are formed readily and in high titer. Type 2 antibodies are more commonly found in elderly persons [4]. The possible mechanism of these phenomena could be chronic degeneration of cell nuclei (with a probable disturbance of DNA homeostasis). It is interesting to note that degenerative processes develop in the thymus in experimental myasthenia, as a result of which it has been suggested that a humoral substance producing a neuromuscular block enters the blood stream [8].

In this connection the data given in Table 2 are interesting. They show that the titer of antibodies against DNA in the blood serum correlates with neither the severity nor the character of the disease. It is about equal in mild forms accompanied by frequent remissions and in a rapidly progressive, malignant type of myasthenia. Very slight differences were detected in patients with differences in the duration of the disease. However, antibodies against DNA were detected in all patients with myasthenia in which the disease was associated with the presence of a thymoma. A high frequency of detection of autoantibodies against other tissue components has also been reported in the serum of patients with thymomas by other authors [7, 17],

who likewise found no correlation between the clinical and immunologic indices. It may accordingly be postulated that pathological changes in the thymus play a role in the genesis of antibody production against DNA in myasthenia. This hypothesis is to some extent contradicted by the results of investigation of antibodies against DNA in patients undergoing various procedures on the thymus. They indicate stability of the titer of antibodies against DNA before and after procedures on the thymus. Mackay found no changes in the titer of antinuclear factor in the blood serum of patients with systemic lupus erythematosus before and after thymectomy for 3 years [12].

The results of this investigation thus showed that the titer of antibodies against DNA is higher in the blood serum of patients with myasthenia than in healthy persons. Antibodies against DNA were found in every case in the serum of patients with myasthenia accompanied by a tumor of the thymus. Antibodies of type 2, hardly ever found in clinically healthy persons but typical of systemic lupus erythematosus, were detected in 36% of patients with myasthenia. No correlation was found between the titer of antibodies against DNA and clinical indices of the course of the myasthenia. Operations and other procedures on the thymus do not affect the titer of antibodies against DNA in the blood serum.

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