

Virus Antibody Levels In Systemic Lupus Erythematosus

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Antibody titers to a group of viral antigens have been determined in sera from patients with systemic lupus erythematosus (SLE), control groups with inflammatory diseases and normals. Mean titers in SLE sera for all viruses tested were significantly greater than in four control groups, but not greater than in active tuberculosis, both by the complement-fixation (CF) and hemagglutination-inhibition (HI) methods. By the CF method, only measles virus showed significantly higher titers in SLE than in all control groups; by the HI method, measles antibody titers were higher in SLE than in all groups but tuberculosis. There was no correlation between antibody titers and gammaglobulin levels. The results indicated a moderate though variable overall hypereactivity in SLE to the viral antigens tested.

Interest has grown recently in the possibility that the etiology of SLE is viral in nature. One reason for this interest has been the observation of cytoplasmic myxovirus-like tubular structures in the tissues of patients with SLE. These have been most commonly reported (1-5) in kidney biopsies of patients with lupus nephritis. The cytoplasmic structures described are simi-

lar in appearance to those seen in the brain tissue of patients with subacute sclerosing panencephalitis (6-9). In this condition, elevated measles antibody titers have been consistently demonstrated (8, 10-12), and measles virus, a myxovirus, has been isolated from brain tissue of patients with this disease (13-16).

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Because of the morphologic similarities of the tubular structures seen in SLE to those of the myxoviruses (17-19), it seemed appropriate to measure virus antibody levels in patients with SLE, with particular emphasis on the myxovirus group. Recent studies (20-22) have reported elevated antibody levels to several viral antigens. In a preliminary study in this laboratory (23) of viral antibody titers in patients with lupus nephritis and matched normal controls, complement fixing antibody titers were significantly elevated to a number of myxoviruses, coronavirus OC 43 and herpes simplex virus. By the HI technic, significant elevations were observed in parainfluenza 1 and measles viruses, both myxoviruses. The overall trend of antibody titers in the SLE group as compared

with normal controls was highly significant both by the CF and HI tests. In the present study, antibody titers have been studied by the same technics in patients with SLE and normal

individuals. In addition, control studies have been carried out in groups of patients with a variety of chronic inflammatory diseases.

Table 1. Age and Sex Distribution of SLE and Control Groups

| Group | No. of patients | Mean age (yr) | Age range | Ratio Male:female |
|------------------|-----------------|---------------|-----------|-------------------|
| SLE | 20 | 34 | 17-51 | 0:20 |
| Tuberculosis | 20 | 33 | 17-53 | 0:20 |
| RA | 28 | 53 | 24-74 | 0:28 |
| Bronchial asthma | 13 | 42 | 16-79 | 0:13 |
| Miscellaneous | 11 | 57 | 19-75 | 2:9 |
| Normal | 14 | 33 | 16-50 | 0:14 |

MATERIALS AND METHODS

Sera were collected from 20 patients who had well-documented histories of SLE with nephritis and who were being followed in the Parkland Memorial Hospital Arthritis Clinic. The average age of the patients with SLE was 34 years (17 to 57). All had active disease. Seventeen were receiving prednisolone; the average daily dosage in the 20 patients was 14.8 mg (0 to 60 mg). All patients were ambulatory. Seventeen were black and 3 white. Control sera were obtained from: a) 20 age- and sex-matched hospitalized patients with far-advanced tuberculosis; all were receiving INH, 11 were black (B), 8 white (W) and 1 Latin American (LA); antinuclear fluorescence tests were negative in all; b) 28 patients with rheumatoid arthritis (RA) (10 B, 16 W, 2 LA); c) 13 patients with bronchial asthma (12 B, 1 W); d) 11 patients with miscellaneous diseases, including 5 with degenerative joint disease, 2 with polymyositis, 2 with chronic alcoholism, 1 with gout and 1 with psoriasis (5 B, 5 W, 1 LA); and e) 14 normal individuals (4 B, 10 W).

Antibody titers were determined in the laboratories of the Virology Section of the Center for Disease Control, US Public Health Service, Atlanta, Ga. The complement-fixation microtiter technic (24) was used to determine antibody titers to the following myxovirus antigens: purified ribonucleoprotein (soluble antigen) of mumps virus and influenza virus Types A and B; and unpurified whole-virus preparations of influenza virus Type C, parainfluenza virus Types 1, 2 and 3, mumps virus, measles and respiratory syncytial virus. Complement fixation tests were also performed with an RNA coronavirus (Infectious Bronchitis virus-like virus strain OC 43) and adeno and herpes simplex viruses, both DNA viruses. Antibody titers were also determined by the HI technic (25) to the following an-

tigens: parainfluenza virus Types 1, 2 and 3, mumps virus, measles virus and coronavirus OC 43.

All patients with SLE had positive antinuclear fluorescence (ANF) and LE cell tests. Twenty-two of the RA patients had positive sensitized sheep cell agglutination (SSCA) tests (range, 0 to 1:896). Three of the patients with SLE and 2 of the tuberculosis group also had positive SSCA tests.

Statistical Analysis

The patients in each group were tested for individual viruses, two groups at a time using the following tests: a) to compare patients with SLE to those with tuberculosis subjects were matched according to age, and the observed differences for each pair were analyzed using the Wilcoxon Signed-Rank Test (26); b) for comparison of other groups, the Wilcoxon Rank-Sum Test (26) was also used, except the subjects were not matched. In cases where sample values were "tied,"—ie, appeared more than once, a test of equal binomial proportions (26) or Fisher's exact probability test (26) was applied.

Correlations between γ -globulin level and individual virus titers were computed. When the sample size N exceeded 10, these were tested against the Null permutation distribution (27). Spearman's ρ was tested when N was ≤ 10 .

Since the discrete nature of the data rendered methods based on normally distributed variables inappropriate, only distribution-free tests were applied.

RESULTS

Geometric mean viral antibody titers measured by the CF test are shown in Table 2.

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Table 2. Geometric Mean Viral Antibody Titers by the CF Test

| | Diagnosis | | | | | |
|--|-----------|-------------------|-----|---------------------|--------------------|--------|
| | SLE | Tubercu- losis | RA | Bronchial asthma | Miscel- laneous | Normal |
| No. of patients | 20 | 20 | 28 | 13 | 11 | 14 |
| A Sol* | 2.9 | 3.4 | 2.5 | 2.7 | 3.0 | 2.6 |
| B Sol* | 2.3 | 2.3 | 2.1 | 2.3 | 2.5 | 2.8 |
| C Influenzavirus Parainfluenzavirus | 3.7 | 3.8 | 2.5 | 3.2 | 3.0 | 3.9 |
| 1 | 2.6 | 2.4 | 2.1 | 2.3 | 2.4 | 2.1 |
| 2 | 2.9 | 2.4 | 2.0 | 2.8 | 2.8 | 2.5 |
| 3 | 4.1 | 3.8 | 2.9 | 3.3 | 3.7 | 3.5 |
| Mumps Sol* | 2.8 | 2.4 | 2.3 | 2.3 | 2.1 | 2.1 |
| Viral | 2.9 | 3.2 | 2.3 | 2.4 | 2.4 | 2.8 |
| Measles | 5.2 | 4.1 | 2.9 | 3.1 | 3.5 | 3.8 |
| Herpes | 5.1 | 4.9 | 4.6 | 4.5 | 5.1 | 4.5 |
| Adenovirus | 3.1 | 2.6 | 2.2 | 2.5 | 2.4 | 3.0 |
| RSV† | 3.3 | 3.1 | 2.3 | 2.4 | 2.8 | 2.5 |
| Average‡ | 3.4 | 3.2 | 2.6 | 2.8 | 3.0 | 3.0 |

*Soluble antigen (A Sol = A soluble influenza; B Sol = B soluble influenza)

†Respiratory Syncytial Virus

‡Average overall geometric mean antibody titer

The average titer for each group is also shown. Similar titers measured by the HI test are shown in Table 3. By the CF test (Table 4), only measles virus showed significantly higher titers in SLE than in all the 5 control groups. Respiratory syncytial virus showed elevated titers with respect to 3 of the 5 control groups and in the case of the other viruses the eleva-

tions were scattered. When compared with the normal group, patients with SLE were higher for parainfluenza 1, measles, herpes simplex and respiratory syncytial viruses.

By the HI test (Table 5), none of the six viruses studied showed a significantly higher antibody titer in SLE than in all the control groups examined. In the case of four of the vi-

Table 3. Geometric Mean Viral Antibody Titers by the HI Test

| Diagnosis | No. of patients | Parainfluenzavirus | | | Mumps | Measles | OC43* | Average† |
|---------------------|--------------------|--------------------|-----|-----|-------|---------|-------|----------|
| | | 1 | 2 | 3 | | | | |
| SLE | 20 | 2.6 | 4.5 | 6.4 | 3.2 | 8.6 | 5.8 | 5.2 |
| Tuberculosis | 20 | 2.9 | 3.6 | 5.2 | 3.4 | 7.9 | 5.0 | 4.7 |
| RA | 28 | 2.5 | 3.5 | 5.4 | 2.6 | 6.6 | 4.4 | 4.2 |
| Bronchial asthma | 13 | 2.3 | 3.7 | 5.3 | 2.8 | 5.3 | 5.2 | 4.1 |
| Miscellaneous | 11 | 2.3 | 3.0 | 6.8 | 2.3 | 7.1 | 4.5 | 4.3 |
| Normal | 14 | 2.3 | 3.1 | 4.7 | 2.7 | 6.5 | 4.7 | 4.0 |

*Coronavirus OC43

†Average overall geometric mean antibody titer

Table 4. Significance of Antibody Titers to Viral Antigens by CF Test-Comparison with SLE Group

| ρ values* | Diagnosis | | | | |
|-----------------------|-------------------|-----|---------------------|--------------------|--------|
| | Tubercu- losis | RA | Bronchial asthma | Miscel- laneous | Normal |
| Influenzavirus | | | | | |
| A Sol† | — | — | — | — | — |
| B Sol† | — | — | — | — | — |
| C | — | .01 | — | — | — |
| Parainfluenzavirus | | | | | |
| 1 | — | .01 | — | — | .05 |
| 2 | — | .01 | — | — | — |
| 3 | — | .01 | — | — | — |
| Mumps | | | | | |
| Soluble | — | — | — | — | — |
| Viral | — | .01 | .05 | — | — |
| Measles | .04 | .01 | .01 | .05 | .04 |
| Herpes simplex | — | — | — | — | .006 |
| Adenovirus | — | .01 | — | — | — |
| Respiratory syncytial | — | .01 | .01 | — | .02 |

* ρ values represent level of significance of elevation of titers in the SLE group in comparison with the corresponding group

†Soluble antigen

ruses, however,—ie, parainfluenza 2 and 3, measles and coronavirus OC 43, the titers were elevated with respect to 4 of the 5 control groups studied. With respect to the normal group, patients with SLE were higher for parainfluenza 2 and 3, measles and coronavirus OC43 viruses.

When the geometric mean titers in SLE were

averaged for all viruses tested and compared with those of the control groups (Table 6), it was found that the titers in patients with SLE were significantly greater than in all control groups but tuberculosis, both by the CF and HI tests.

Gammaglobulin levels were determined by serum electrophoresis. Only rarely were there

Table 5. Significance of Antibody Titers to Viral Antigens by HI Test—Comparison with SLE Group

| Diagnosis | ρ values* | | | | | |
|---------------------|--------------------|-----|-----|-------|---------|------|
| | Parainfluenzavirus | | | Mumps | Measles | OC43 |
| | 1 | 2 | 3 | | | |
| Tuberculosis | — | .01 | .02 | — | — | .05 |
| RA | — | .01 | .01 | .01 | .01 | .01 |
| Bronchial asthma | — | — | .02 | — | .01 | — |
| Miscellaneous | — | .01 | — | .01 | .05 | .05 |
| Normal | — | .01 | .01 | — | .01 | .05 |

* ρ values indicate level of significance of elevation of titers of the SLE group with respect to the corresponding group

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Table 6. Significance Levels for Overall Viral Antibody Titers-Comparison of SLE and Control Groups

| SLE greater than | CF | HI |
|------------------|------|------|
| Tuberculosis | ns | ns |
| RA | <.01 | <.01 |
| Miscellaneous | <.01 | <.01 |
| Bronchial asthma | <.01 | <.01 |
| Normal | <.05 | <.01 |

statistically significant correlations between these levels and viral antibody titers. When gammaglobulin level in the 6 patient groups was correlated with antibody titers for each of the 12 viruses tested by the CF method, only four of the 72 possible correlations of antibody titer with gammaglobulin level were significant at the .05 level. Among the 36 possible correlations by the HI method, only one was significant at the .05 level. No instance of a significant correlation between gammaglobulin level and antibody titer occurred in the SLE group.

DISCUSSION

In the present study, an attempt has been made to compare viral antibody titers in SLE with those of control groups with inflammatory diseases as well as normal individuals. The data obtained demonstrate that patients with SLE have elevated antibody titers to a number of viruses when compared with certain control groups. However, with the exception of measles virus, there was no predilection for increased antibody response in this disease to any one specific virus among those tested. Of all 12 viral antigens tested by the CF test, only measles antibody levels were significantly higher in SLE than in all of the control groups. However, by the HI method, the measles antibody titer was not significantly higher than in the tuberculosis group though it was elevated with respect to the 4 other control groups.

When geometric mean titers of all viruses tested were averaged for each patient group, the overall mean titer was higher in the SLE group than in 4 of the 5 control groups by both the CF and HI methods. However, it was not significantly higher in the tuberculosis group by either test. Except for the comparison with the tuberculosis group, it would appear that there is an overall hyperreactivity to viral antigens in the patients with SLE when compared with 3 control groups with inflammatory disease and with normal individuals.

It was of considerable interest that patients with far-advanced tuberculosis formed the only group with respect to which the patients with SLE did not have an overall increase in viral antibody response. A high frequency of autoantibodies, particularly antinuclear antibodies and rheumatoid factor, has recently been reported by Lindquist, Coleman and Osterland in patients with chronic pulmonary tuberculosis (28). These authors suggested that factors such as chronicity of inflammation, tissue breakdown and the adjuvant effect of mycobacteria may play a role in the production of these autoantibodies. Injection of Freund's complete adjuvant (29) has, in fact, been shown to hasten the development of Coombs positive hemolytic anemia in NZB mice. Thus, the relatively high viral antibody titers seen in tuberculosis could be secondary to an adjuvant effect of the mycobacterial infection. It is unlikely that INH, which all of these patients were receiving, contributed to the antibody response since antinuclear antibody tests were negative in all of the patients in this group.

The relatively elevated viral antibody titers observed in tuberculosis raises the question of the role of an adjuvant effect in the response of patients with SLE to viral antigens. There is some evidence that patients with SLE may have defective cellular immunity (30-32). Several lines of evidence for the presence of diminished cellular immunity have also been described in NZB and NZB-NZW F₁ hybrid mice. More-

over, the development of autoantibodies in mice has been correlated with a deficient thymus-dependent cellular immune system (33, 34). Diminished cellular immunity could facilitate chronic infection with a passenger virus, which might in turn exert an adjuvant effect on viral antibody formation. Viral infections have, in fact, been shown to enhance the formation of autoantibodies (35-39).

A variety of antibodies to polynucleotides (native DNA, single-stranded DNA and single and double-stranded RNA) have been found in sera from patients with SLE (40, 41). This has led to the speculation that these antibodies may have originated in response to viral infections (41). The possibility that a genetically determined modification of the immune response to viral antigens can lead to increased viral antibody formation in SLE has been raised by the studies of Grumet and co-workers (42), demonstrating the selective occurrence of certain histocompatibility antigens in patients with SLE. In this respect, they may resemble NZB/NZW F₁ hybrid mice which have shown a hyperreactive response to viral (35) and polynucleotide antigens (43, 44) which Cerottini, Lambert and Dixon (45) have suggested may be genetically determined.

It should be pointed out that the viral antibody titers of the patients with RA measured in the present studies by the CF test might be falsely low because serum rheumatoid factor may exert an inhibitory effect on CF (46). This possibility cannot be ruled out. However, similarly decreased antibody titers were also obtained by the HI method, which is not dependent on the complement system.

The present study, using conventional sero-diagnostic tests and common viral antigens, does not elucidate the nature of the cytoplasmic myxovirus-like tubular structures in the tissues of patients with SLE. However, it is possible that the tubular structures are evidence of chronic infection in SLE with a passenger virus of a type which might act as an adjuvant for the

overall elevation in viral antibody titer observed.

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