The Influence of Serum Immunoglobulin Concentration on Measles Antibody Level[1] (36670)

P. E. PHILLIPS AND C. L. CHRISTIAN

Departments of Medicine, Cornell University Medical College and Rheumatic Disease, The Hospital for Special Surgery, New York, New York 10021

Increased measles antibody levels have been found in patients with systemic lupus erythematosus (SLE) (1, 2), but whether this was a result of chronic measles infection has not been clear. This report describes a direct relationship between measles antibody level and gamma globulin (GG) or IgG levels in serums from patients with SLE and with other diseases.

Materials and Methods. Single serums were obtained from patients with SLE, other connective tissue diseases, and other unrelated diseases during the course of routine diagnosis and treatment. Measles hemagglutination-inhibition (HI) antibody was measured by a standard micromethod using commercial reagents as described previously (1), recently modified by treatment of the measles antigen with Tween-80 and ether prior to use (3). Antibody titers were expressed as the $\log_2$ of the reciprocal of the highest serum dilution showing HI. Appropriate controls and reference serums were included in each test (1). GG levels were determined by cellulose acetate electrophoresis using Beckman Microzone equipment in the hospital laboratory. Correlation between levels of measles antibody and GG was calculated using the estimating equation for the regression line, the correlation coefficient r and the t test to determine if r differed significantly from zero (4).

Sequential serums were tested for measles antibody in duplicate; all specimens from a subject were done in the same test to assure comparability. To minimize variability due to technical factors, the test was repeated and the mean titer for each specimen was calculated. IgG concentration was measured in duplicate by radial immunodiffusion (5) using a purified anti-human IgG globulin prepared in a goat and made mono-specific by absorption with IgM paraprotein. Again all specimens from an individual were done in the same test, and the test was repeated for the reasons stated above.

Results. Measles antibody levels showed a highly significant direct correlation with GG levels in single serums from subjects both with SLE and with other diseases, as well as in the combined group (Table I). Figure 1 shows the individual measles antibody and GG levels for each group and the regression line for the combined group. The regression lines calculated for each group separately had similar slopes, nor was the line, r or p value for the other diseases group significantly altered by exclusion of the 3 subjects with the most extreme GG values, suggesting the data are statistically homogenous (4). The relationship of measles antibody titer to age, sex, race, corticosteroid treatment and several laboratory parameters was also examined. No significant independent relationships were found.

Figure 2 shows the levels of IgG and measles antibody in a 20-yr-old woman with SLE who was followed for 2 yr. The maximum variations in IgG and measles antibody were quantitatively similar: 7- and 6-fold, respectively. There was also close qualitative correspondence between changes in each parameter through most of the 2 yr period. Figure 3 shows another SLE patient, a 13-yr-old girl, whose IgG fell to half its initial level

[1] This work was presented in part at the interim meeting of The American Rheumatism Association, Washington, DC Jan. 8–9, 1971. (Arthritis Rheum. 14, 180 (1971) Abstr.). Hospital for Special Surgery Research Publication No. 419.

TABLE I. Correlation Between Measles Antibody and Gamma Globulin Levels.

Group	Subjects (no.)	Geometric mean measles antibody titer (log_2)	Mean gamma globulin (g/100 ml)	Correlation	
				r	p
SLE[a]	52	6.27	2.00	0.36	<.01
Non-SLE[b]	84	4.52	1.71	0.48	<.001
Total	136	5.19	1.82	0.46	<.001

[a] Systemic lupus erythematosus.
[b] Diseases other than SLE.

and then rose again over a 2 yr period. Qualitatively similar changes occurred in her measles antibody level, with the final increase being more than 5-fold. Adenovirus group complement-fixation antibody was also measured in this patient and showed changes similar to those in IgG, with a final 8-fold increase. The third subject, a normal 30-yr-old man, showed much smaller variations in both IgG and measles antibody (maximum variation 781 to 1072 mg/100 ml and 1:384 to 1:640, respectively) in 6 serums over 3.5 yr, but the changes again corresponded closely.

Discussion. This study indicates that the level of GG or, more specifically, of IgG is an important determinant of the level of residual measles antibody, *i.e.*, antibody measured years after primary measles infection, as was done here. The majority of GG is IgG (6) and residual measles antibody is exclusively IgG (7). Thus it is logical that a diffuse

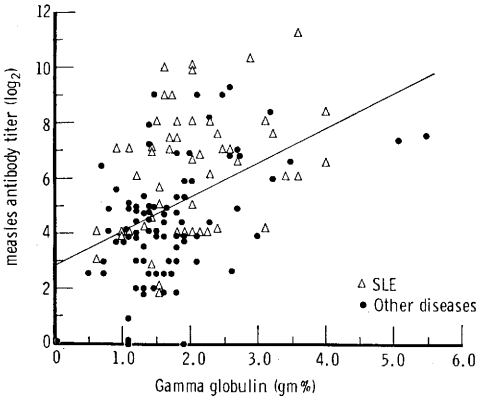

FIG. 1. Scatter plot of measles antibody and GG levels in patients with SLE (△) and other diseases (●). Regression line: $y = 2.916 + 1.248x$.

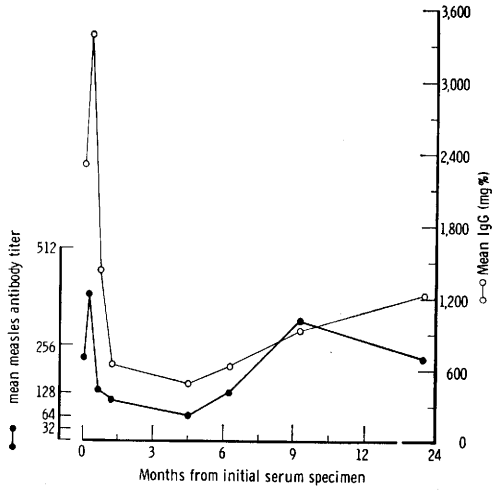

FIG. 2. Sequential IgG and measles antibody levels in a patient with SLE.

(polyclonal) change in IgG (or GG) level would result in a similar change in residual measles antibody, as was shown in this study. However IgG is clearly not the only determinant of measles antibody since, as shown in Fig. 1, the correlation did not allow prediction of the measles antibody level of a subject from his GG level. Likewise, the sequential studies showed quantitatively comparable changes in IgG and measles antibody in the first subject, but not in the second. Other possible determinants of measles antibody level include age, sex and race, which are considered important variables in epidemiologic studies. Residual measles antibody does decline gradually with increasing age (and remoteness of primary infection (8), but our study suggests this may in part reflect the gradual decline of IgG from the third to the seventh decades shown by others (9). Since IgG levels also vary according to sex and

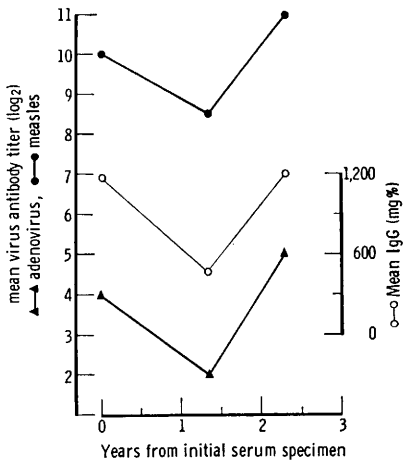

FIG. 3. Sequential measles antibody, IgG and adenovirus antibody levels in a patient with SLE.

race (9), IgG may be a common factor in the importance of these variables as well. What factors other than reinfection influence residual measles antibody levels are unknown.

When sequential serums from an individual are tested for a virus antibody at the same time, as was done here, 4-fold or greater changes are usually interpreted as "significant," indicating recent primary infection or reinfection with that virus (3). This is an unlikely reason for the "significant" changes in measles antibody in our subjects because they had the disease in early childhood and had not been vaccinated with measles since, and because reinfection occurs very rarely in the presence of moderate to large amounts of antibody such as they had (3, 10). Furthermore 2 reinfections within a year would be necessary to account for the changes observed in our first patient (Fig. 2). While "significant" changes in a virus antibody level may be found after infection with another antigenically related virus, no viruses related to measles are known to infect man (11). The measles HI antibody test is specific for measles antibody and we and the others have shown that antinuclear and other autoantibodies do not affect the test (2).

There are two practical applications of this study: first, "significant" changes in measles antibody level in an individual can result from changes in IgG, without measles reinfection. Although adenovirus reinfection cannot be excluded as the cause of the changes in adenovirus antibody shown in Fig. 3, the parallelism with IgG suggests that "significant" changes without infection may be seen here, and perhaps with other virus antibodies, as well.

Second, populations with increased polyclonal IgG levels may have increased measles antibody levels. Thus this appears to be the proximate cause of the elevated measles antibody levels found in SLE by us and others (1, 2), and perhaps of the increases in other virus antibodies in SLE also (1, 2, 12). This may also be the reason for increased measles antibody in other diseases with polyclonal hypergammaglobulinemia, *e.g.*, multiple sclerosis (13, 14). Although IgG level may be a common variable behind the importance of matching for age, sex and race in epidemiologic studies, as discussed earlier, this study indicates that matching for IgG levels is clearly important in such studies of measles antibody and perhaps of other virus antibodies. Otherwise a statistically significant difference between antibody levels of disease and control groups may be interpreted incorrectly as implicating the virus in the pathogenesis of that disease.

Summary. Measles antibody level correlated directly with gamma globulin level in single serums from 136 subjects. Changes in measles antibody and IgG levels corresponded in sequential serums from 3 subjects. In a population increased immunoglobulins may cause elevated measles antibody, while in individuals changes in IgG may cause similar changes in measles antibody levels.

We thank J. Benson, R. Hargrave and J. Brindisi for technical assistance and Mrs. Covolo for sera and GG determinations. Supported by grants from U.S. Public Health Service and Hartford Foundation.

1. Phillips, P. E., and Christian, C. L., Science 168, 982 (1970).

2. Hollinger, F. B., Sharp, J. T., Lidsky, M. D., and Rawls, W. E., Arthritis Rheum. 14, 1 (1971).

3. Katz, S. L., and Enders, J. F., *in* "Diagnostic Procedures for Viral and Rickettsial Infections" (E. H. Lennette and N. J. Schmidt, eds.), p. 504. Amer. Pub. Health Ass. New York (1969).

4. Croxton, F. E., "Elementary Statistics with Applications in Medicine and the Biological Sciences," pp. 112, 312, Dover, New York (1959).

5. Mancini, G., Carbonara, A. O., and Heremans, J. F., Immunochemistry **2**, 235 (1965).

6. Merler, E., and Rosen, F. S., N. Engl. J. Med. **275**, 536 (1966).

7. Schleuderberg, A., Nature (London) **205**, 1232 (1965).

8. Enders-Ruckle, G., Arch. Gesamte Virusforsch. **16**, 182 (1965).

9. Buckley, C. E., and Dorsey, F. C., Ann. Intern. Med. **75**, 673 (1971).

10. Stokes, J., Reilly, C. M., Buynak, E. B., and Hilleman, M. R., Amer. J. Hyg. **74**, 293 (1961).

11. Imagawa, D. T., *in* "Progress in Medical Virology," (J. L. Melnick, ed.), Vol. 10, p. 160. Karger, New York (1968).

12. Evans, A. S., Rothfield, N. F., and Niederman, J. C., Lancet **1**, 167 (1971).

13. Pette, E., Neurology **18**, 168 (1968).

14. Kolar, O. J., Ross, A. T., and Herman, J. T., Neurology **20**, 1052 (1970).

Received Apr. 21, 1972. P.S.E.B.M., 1972, Vol. 140.