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The humoral immunity status of measles patients

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Children with uncomplicated measles were examined for IgG, IgM and IgA serum levels as well as for titres of diphtheria antitoxin, antistreptolysin O, isohaemagglutinins and bacterial agglutinins (*B. pertussis*, *E. coli* O55, *E. coli* O111, *Sh. flexneri* 2a, *Sh. sonnei*). Sera taken during the disease and 1 to 2 months after recovery were assayed.

Neither immunoglobulin determinations nor antibody titrations revealed any changes in humoral immunity that could account for the increased susceptibility of measles patients to other infections.

IgG and IgM levels were found lower after recovery than during the disease. To account for these changes, it is assumed that measles infection elicits an overproduction of immunoglobulins and the levels return to normal after recovery.

Susceptibility of the organism to unrelated infections is well-known to increase during an attack of measles. Observations so far have proved the suppressive effect of measles mainly on cellular immunity. Preisich [18] and Pirquet [17] were the first to notice a transient depression of tuberculin positivity in measles patients. Further investigations have shown that measles infection as well as immunization with live measles vaccine may suppress delayed hypersensitivity also to other antigens [4, 7, 8, 12, 13, 14, 22]. According to Burnet [6], measles is a generalized delayed hypersensitivity reaction brought about by the interaction of sensitized lymphocytes and by virus antigen bearing cells. This interaction leads to the exhaustion of immunocompetent cells and, consequently, to the extinction of other delayed hypersensitivity reactions together with the decrease of anti-infectious resistance.

The influence of measles on humoral immunity is less clear. Lorenz and Rossipal [10] found that the serum γ-globulin and γ_1A-globulin levels decreased during the first days of the disease and returned to normal by the 8th day. No decrease was observed in the γM level. Osváth et al. [16] reported decreased serum properdin levels in the prodromal period and at the time of the appearance of the rash. Bondarenko and Chelysheva [2] observed that the serum diphtheria antitoxin titres decreased and the preexisting negative Schick reactions turned into positive in 10%

of measles vaccinated subjects. On the other hand, FIREMAN et al. [7] found no change in diphtheria and poliovirus antibody titres or in the immunoglobulin concentrations after measles vaccination.

In the present study an attempt has been made to decide whether humoral immunity changes could account for the decrease of anti-infectious resistance during measles. Measles patients were examined for the concentration of serum immunoglobulins and of various humoral antibodies at different points of time during the disease and after recovery.

MATERIALS AND METHODS

Patients. Thirty-six children with uncomplicated, serologically confirmed measles were investigated. Their age ranged from 2 to 14 years with a mean of 7.5 years. Blood was taken 1 day after admission to the hospital and on the day before discharge, i.e. 1 to 4 and 7 to 12 days after the appearance of the rash. From 18 children a third sample was also taken 1 to 2 months (34 to 63 days) after the onset of the disease. Sera were assayed for IgG, IgM and IgA concentrations and for measles, diphtheria, pertussis, *E. coli*, shigella, streptolysin-O antibody and isohaemagglutinin titres.

Serological tests. Immunoglobulins were quantitated by the radial gel-diffusion method as described by MANCINI et al. [11]. We used monospecific anti-IgG, anti-IgM and anti-IgA sera (Human, Budapest) and a preparation of pooled human sera which was calibrated to the International Standard for Human Serum Immunoglobulins in the Immunobiological and Vaccine Research Department of the National Institute of Public Health, Budapest. Immunoglobulin concentration was expressed as IU/ml serum.

Measles haemagglutination inhibition (HAI) antibody titres were determined by ROSEN's technique [20].

Diphtheria antitoxin was titrated by passive haemagglutination [23].

Pertussis antibodies were measured by tube agglutination test, using *Bordetella pertussis* phase I bacterium suspension (Human, Budapest).

Antibodies to *E. coli* O55, *E. coli* O111, *Sh. flexneri* 2a, and *Sh. sonnei* were titrated by passive HA method. Sheep red cells were sensitized by the Boivin extract of the corresponding bacteria [19].

Antistreptolysin-O was quantitated as described by BÖSZÖRMÉNYI [3].

Isohaemagglutinins were titrated by slide agglutination test.

The majority of the samples was assayed for all the antibodies listed above. In some cases, however, when the amount of the serum was low, one or more determinations had to be omitted.

RESULTS

Table I shows the IgG, IgM and IgA content of sera taken 1 to 4 and 7 to 12 days after the onset of the rash. As can be seen, no difference was found between the first and the second samples.

In Table II, the immunoglobulin levels in the first days of the disease are compared with the levels found 1 to 2 months later. IgA values remained unchanged, IgG and IgM concentrations, however, were lower after recovery than on the first days of the disease. By Student's t-test, the difference proved significant only in the case of IgG. If we compare the data of Table I with those of Table II, it can be noticed that SD values for both IgG and IgM were higher in the first days of measles

TABLE I

Serum immunoglobulin levels in 36 measles patients 1 to 4 and 7 to 12 days after the onset of the rash

Immunoglobulin		Immunoglobulin levels (IU/ml) on days	
		1 to 4	7 to 12
IgG	mean	188	181
	SD	±58	±56
	range	98—305	72—305
IgM	mean	135	142
	SD	±39	±37
	range	56—182	68—237
IgA	mean	67	69
	SD	±36	±36
	range	26—182	24—175

TABLE II

Serum immunoglobulin levels in 18 measles patients during the acute phase of the disease and after recovery

Immunoglobulin		Immunoglobulin levels	
		1 to 4	34 to 63
		days after onset of the rash	
IgG	mean	177	136*
	SD	±74	±24
	range	97—262	93—188
IgM	mean	132	118**
	SD	±31	±18
	range	86—185	88—148
IgA	mean	67	69
	SD	±26	±19
	range	28—154	40—147

* $t = 5.135$, $p < 0.001$
** $t = 1.93$ $p = 0.10—0.05$

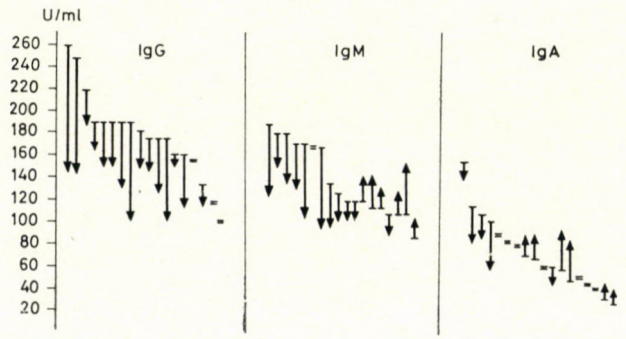

FIG. 1. Individual serum immunoglobulin levels of measles patients. The butt ends of the arrow indicate values obtained 1 to 4 days, and the heads of the arrows, 34 to 63 days, after the onset of rash. Symbol = indicates unchanged levels

than after recovery. Moreover, the lowest individual IgG and IgM levels observed during the disease and after recovery were practically the same, while the peak values were strikingly different.

In Fig. 1, the trend and the extent of the changes in the individual immunoglobulin levels are presented. IgG concentration decreased in 15 patients. Decreases were more pronounced in the cases where initial

TABLE III

Changes in antibody titres during measles

Antibody	Blood sample*	No. of sera tested	No. of sera without detectable antibody	Geometrical mean of titres	No. of cases with more than fourfold	
					increase	decrease
					in titre	
Measles	I	36	4	1/60.6		
HAI	II	36	0	1/343.0	33	0
Diphtheria	I	36	0	2.71 IU/ml		
antitoxin	II	36	0	2.58 IU/ml	0	0
	III	18	0	2.58 IU/ml	0	0
	I	29	10	1/8.9		
B. pertussis	II	36	15	1/12.2	2	1
	III	18	4	1/10.7	0	0
E. coli	I	36	21	1/7.3		
O111	II	36	23	1/5.5	1	1
	III	18	12	1/5.6	0	1
E. coli	I	36	13	1/7.3		
O55	II	36	13	1/5.7	2	0
	III	18	8	1/13.1	0	1
Shigella	I	36	18	1/5.6		
sonnei	II	36	14	1/5.3	4	2
	III	18	9	1/5.6	0	2
Shigella	I	36	8	1/8.5		
flexneri 2a	II	36	8	1/10.7	2	6
	III	18	4	1/10.7	1	1
Antistreptolysin O	I	18	0	160.1 U/ml		
	II	22	0	140.6 U/ml	0	0
	III	17	0	149.8 U/ml	0	0
Isohaemagglutinin	I	12		1/23.9		
anti-A	II	12		1/26.2	0	0
	III	7		1/21.4	0	0
Isohaemagglutinin	I	8		1/22.6		
anti-B	II	8		1/25.9	0	0
	III	6		1/16.0	0	0

* Blood sample I was taken 1 to 4; II, 7 to 12; and III, 34 to 63 days after the onset of the rash.

values were relatively high. In 3 patients the IgG level remained unchanged. IgM concentration decreased in 11 patients, increased in 6, and remained unchanged in 1. IgA changes were less pronounced.

In Table III, antibody titres in the sera taken 1 to 4 days, 7 to 12 days and 1 to 2 months after the onset of rash are presented. A significant rise in titre was observed only for measles HAI antibody. In most of the cases, the concentration of other antibodies remained constant. At times, more than fourfold differences in agglutinin titres against *B. pertussis* and against enteric bacteria were observed. There was, however, a similar number of cases showing a rise and a decrease in titre.

Discussion

The present data indicate that immunoglobulin concentrations are stable during measles. One to two months after recovery, the IgG level was however significantly lower than the initial one. Besides, a remarkable, although statistically not significant, decrease in IgM levels was observed particularly in patients with high initial values. Thus, our results do not agree with those of Lorenz and Rossipal [10] who reported decreased serum immunoglobulin concentrations in the course of the first days of measles. The contradiction of the observations is probably due to methodological differences.

Two different explanations may be advanced to account for the immunoglobulin changes observed in our study. The first explanation is that measles infection brings about a late suppression of immunoglobulin synthesis, hence the values found after recovery are to be considered subnormal. A second possible explanation is that measles infection elicits an overproduction of IgG and IgM during the incubation period. Accordingly, the values observed during the disease are to be regarded as elevated and those after recovery as normal. Which of the explanations offered is the proper one could be decided only if the observed values were compared with the preinfection ones. We are, however, unaware of the normal immunoglobulin levels of our patients since, obviously, examinations were not feasible before the onset of the disease. For several reasons, "normal values" reported by others are not suitable for comparison. Owing to technical difficulties [4, 21], normal values have been set up differently by various authors [9]. On the other hand, in children the immunoglobulin concentrations increase with age [1, 4], therefore the mean values calculated from the individual immunoglobulin levels of our patients aged 2 to 14 years cannot be compared with any mean value that has been set up for a given age group. The following observations, however, tend to support the concept that IgG and IgM levels during measles are elevated and return to normal after recovery. In the acute-phase sera, the SD for the IgG and

IgM levels was higher than in the sera taken after recovery. Furthermore, unusually high initial concentrations decreased considerably by the time of recovery, while relatively low concentrations remained unchanged. Both observations speak for the stimulation of immunoglobulin production in the first days of the disease. The elevated IgG and IgM levels do not seem to be connected with the production of specific antibody. As has been shown earlier [15] as well as in the present study, measles patients develop significant HAI titres by the time of the appearance of the rash. Nevertheless, HAI titres remain high after recovery while immunoglobulin levels decrease by that time.

It must be stressed that no extremely low immunoglobulin level has been found in the present study. Thus, the increased susceptibility of measles patients to other infections cannot be due to a shortage in immunoglobulins. Neither did a follow-up of a variety of antibodies reveal any impairment of the humoral immune status in measles patients. Diphtheria antitoxin, antistreptolysin-O and isohaemagglutinins remained at constant levels during the observation period. The same was true for pertussis, *E. coli* and Shigella agglutinins in the majority of cases. Occasionally, paired sera with more than fourfold differences in agglutinin titre were observed. However, no trend in these changes was noticeable, therefore they can be regarded as technical shortcomings or as the consequences of inapparent infections.

Thus, we may conclude that changes in immunoglobulin concentrations or in various antibody titres cannot account for the decrease in the antiinfectious resistance of measles patients.

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