Serum Immunoglobulins in Kwashiorkor

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Infection and protein calorie malnutrition frequently coexist (Smythe, 1958; Brown, 1965; Phillips and Wharton, 1968), and though it is apparent that infection may affect nutrition adversely, it is difficult to prove that malnutrition is a factor in poor response to infection.

In 1965 the World Health Organization Expert Committee on nutrition stated: 'The concept that malnutrition could make man more susceptible to infectious disease and also alter the course and outcome of the resulting illness has long been current in the history of medicine and public health. Circumstantial evidence is plentiful, principally based on clinical experience. Well-controlled observations have been few, and hence clear proof in support of the concept has been slow to accumulate. It has been much easier to demonstrate that infection is often directly responsible for lowering the state of nutrition.'

In a few diseases, however, there is proof that with coexistent protein calorie malnutrition the mortality rate is higher than expected, e.g. measles (Hendrickse, 1967) and herpes simplex infection (Becker, Kipps, and McKenzie, 1968). Yellow fever vaccination antibody response was found much impaired in children deficient in protein (Brown and Katz, 1966a, b).

If it is assumed that protein calorie malnutrition can be held responsible for proneness and poor response to infection, the mechanism for the susceptibility to infection is still to be clarified. One mechanism for host resistance to infection is the production of immunoglobulins.

Anderson and Altmann (1951) found that the total γ -globulin fraction of the serum proteins tended to be high in kwashiorkor, whereas Brown and Katz (1965) reported a significant reduction ($p < 0.05$) in the serum IgG concentrations of 20 kwashiorkor patients compared with 5 controls, with no difference between IgA and IgM levels in the two groups.

The present study was undertaken to compare

quantitatively the serum immunoglobulin fractions IgG, IgA, and IgM in children suffering from kwashiorkor and infection with those of children from a similar environment suffering from infection alone, to see whether there was a deficiency of one or more of the immunoglobulins in the kwashiorkor patients.

Materials and Methods

The case material consisted of 11 Cape Coloured children suffering from obvious kwashiorkor (Cases 1-11). In 10 children the body weights after rehydration were below the 3rd Boston centile even though they were oedematous. The uncorrected weight of one grossly oedematous child was within the normal range (Case 2). All cases showed skin lesions compatible with kwashiorkor.

All these children showed evidence of a variety of infections, e.g. conjunctivitis, otorrhoea, respiratory tract infection, urinary infection, gastro-enteritis, or candidiasis. Case 9 developed measles.

A control series consisted of 11 apparently well-fed Cape Coloured children suffering from similar infections (Cases 12-22). Some of these children were slightly underweight, but none of them showed skin lesions or oedema.

Venous blood samples were obtained from all these children during the same season. The total serum protein was estimated by the biuret method. Fractionation of serum proteins was done by zone electrophoresis using a Beckman model R100 microzone system. The rest of the serum was kept frozen and flown to Aberdeen, Scotland, where the specimens arrived in a frozen state. The concentrations of immunoglobulins G, A, and M were obtained as the means of duplicate determinations as described by Thom, McKay, and Gray (1967) but using 'Behringwerke Standard Human Serum Stabilized' at a number of dilutions to provide the reference standard line. Values which fell either above or below the range of standard dilution values were re-estimated, using different serum dilutions.

Results

The serum protein concentrations are given in Tables I and II. Total serum protein concentrations were low in all the malnourished children but above 6 g./100 ml. in the controls. Similarly,

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TABLE I
Kwashiorkor Cases

Case No.	Age (mth.)	Weight (kg.)	Serum Protein Concentrations				
			Total Protein (g./100 ml.)	Albumin (g./100 ml.)	IgG (mg./100 ml.)	IgA (mg./100 ml.)	IgM (mg./100 ml.)
1	9	6.75	4.1	1.78	995	149	170
2	12	11.23	4.5	1.61	1850	250	195
3	13	7.71	4.6	—	1730	104	355
4	14	7.63	4.4	2.04	1075	129	162
5	18	8.28	3.5	1.42	1345	265	210
6	19	7.71	4.7	1.68	1590	108	135
7	21	6.89	2.7	1.41	875	275	130
8	29	7.63	3.1	—	1225	91	145
9	30	10.24	4.0	1.45	1205	101	143
10	30	10.38	4.1	1.37	1625	127	75
11	34	8.39	4.3	1.34	1550	218	93
Means	20.8	8.44	3.9*	1.55*	1335*	152*	152*

* The means of all the serum protein concentrations have been calculated from the logarithms of the actual concentrations.

TABLE II
Clinically Well-fed Cases

Case No.	Age (mth.)	Weight (kg.)	Serum Protein Concentrations				
			Total Protein (g./100 ml.)	Albumin (g./100 ml.)	IgG (mg./100 ml.)	IgA (mg./100 ml.)	IgM (mg./100 ml.)
12	7	6.86	6.5	2.65	1635	150	315
13	9	7.37	8.7	4.22	1260	64	93
14	9	6.27	6.3	3.35	1075	69	170
15	12	10.77	7.6	4.13	1525	70	130
16	12	9.02	6.5	3.10	920	59	104
17	13	9.55	—	—	890	85	142
18	15	9.53	6.4	3.66	1270	56	123
19	18	9.64	6.8	4.35	1125	52	179
20	30	13.15	6.0	3.05	915	87	153
21	33	12.98	7.1	3.39	1675	83	189
22	34	12.02	7.2	4.15	1365	50	143
Means	17.5	9.74	6.9*	3.56*	1212*	71*	150*

* The means of all the serum protein concentrations have been calculated from the logarithms of the actual concentrations.

the albumin concentrations of the kwashiorkor cases were very low compared with those of the control group.

The mean $\pm$ 2SD range for the serum IgG concentrations of the kwashiorkor cases (from the logarithms of the actual values) was 819–2173 mg./100 ml., with a mean value of 1335 mg./100 ml., while that of the well-fed cases was 763–1925 mg./100 ml., with a mean value of 1212 mg./100 ml. There was no significant difference between these two groups of log values ($t = 0.95$; $0.4 > p > 0.3$).

The serum IgM values of the two groups were very similar. The mean and $\pm$ 2SD range (from logs) for the kwashiorkor cases was 152 mg./100 ml.,

range 67–346 mg./100 ml., and for the control group was 150 mg./100 ml., range 78–290 mg./100 ml.

The serum IgA values, however, were much higher in the kwashiorkor group. Of these 11 children, only 1 had a serum IgA concentration less than 100 mg./100 ml., whereas, of the 11 clinically well-fed cases, only 1 had a serum IgA concentration greater than 100 mg./100 ml., and this was the youngest child of the group who had also an unusually high IgM concentration.

The mean $\pm$ 2SD range (from logs) for the serum IgA of the kwashiorkor cases was 65–354 mg./100 ml., with a mean value of 152 mg./100 ml., while

the range for the well-fed cases was 38–134 mg./100 ml., with a mean value of 71 mg./100 ml. The difference between the two sets of logarithmic values was significant ($t = 4.76$ $p < 0.001$).

Though the ages of the children ranged from 7 to 34 months, there was no obvious increase with age in the serum levels of IgA or IgM in either group.

Two children (Cases 1 and 8) died; neither of them showed a deficiency of serum IgG, IgA, or IgM.

Discussion

In this small series no deficiency of IgG, IgA, or IgM was found in children suffering from kwashiorkor and infection. On the contrary, the serum levels of IgG and IgM in both malnourished and control children were higher than those reported in normal children of similar ages in the U.S.A. (Stiehm and Fudenberg, 1966) and Sweden (Johansson and Berg, 1967), while the IgA levels of the control children were similar to those reported. It is interesting to note that Johansson, Mellbin, and Vahlquist (1968) found significantly raised levels of serum IgG, IgD, and IgE in Ethiopian children as compared to Swedish children, but IgA and IgM levels showed less marked increases. In Gambian adults, mean levels of IgG, IgA, and IgM were two to three times higher than those of a European control group (Rowe *et al.*, 1968).

In the present series, the serum concentrations of IgG and IgA in the kwashiorkor cases were similar to those reported by Brown and Katz (1965), while the IgM values were somewhat higher. The serum IgG values of the control children were lower than those of Brown and Katz (1965), and no significant difference was found between the IgG values of the kwashiorkor and the control children.

The high IgA values found in the kwashiorkor cases need confirmation and explanation. Though the mean age of the kwashiorkor cases in this series is higher than that of the control group, it seems unlikely that this factor alone can be held responsible for the higher IgA levels.

IgA is known to be involved in antibody response to salmonella organisms (Turner and Rowe, 1964), and much of the neutralizing activity of nasal secretion against rhinoviruses and polioviruses is carried on the IgA antibody (Bellanti, Artenstein, and Buescher, 1965). In this connexion it is interesting to note that Smythe (1958) described septicaemia caused by Gram-negative organisms in several of his cases of kwashiorkor. Unfortu-

nately, blood cultures are not available in this series.

Tomasi *et al.* (1965) showed that the predominant immunoglobulin of the external secretions is IgA. However, this secretory IgA is a more complex molecule than serum IgA and contains an additional fragment, termed 'transport piece' by South *et al.* (1966), which is probably synthesized by the mucosal lining cells and may be involved in the selective transport of IgA to the mucosal surfaces. In kwashiorkor the jejunal mucosa is abnormal (Stanfield, Hutt, and Tunncliffe, 1965), and it would be interesting to determine the levels of IgA in the mucosal secretions in cases of kwashiorkor, particularly those suffering from concomitant measles or herpes simplex infection.

Hobbs and Hepner (1968) have reported raised serum IgA levels in some patients with coeliac disease, and quote H. Poen *et al.* (unpublished) as finding this quite commonly in patients with gastrointestinal diseases.

Summary

Concentrations of IgG, IgM, and IgA were determined in the sera of 11 children suffering from kwashiorkor and a variety of infections, and 11 well-fed children suffering from similar infections. There were no differences between the IgG and IgM values of the two groups, most of the results being high compared with those reported for normal children. The IgA values of the kwashiorkor cases were much higher than those of the controls and normal children.

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