Dysgammaglobulinaemia in Tropical Sprue

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Summary : Study of immunoglobulin levels in 16 Indian control subjects showed that, compared with a Danish control series, they had a significantly higher mean level of IgG, but not of IgA or IgM. By contrast, the IgG levels in eight patients with tropical sprue were decreased or low normal in six cases and raised in only one case. Two patients with tropical sprue had agamma-A-globulinaemia.

Turnover studies with ^{125}I-labelled IgG showed a high rate of synthesis in three Indian controls and an appreciably reduced or low rate in seven of the eight cases of tropical sprue.

Introduction

The aetiology of tropical sprue is unknown. Dietary factors, malnutrition, and infections have been incriminated, and it may well be that the cause of the disease is complex (Klipstein, 1968). Infection seems to play a significant part, since remission is regularly induced by oral treatment with antibiotics, but often the improvement is only temporary.

Immunoglobulin deficiency is now a well-established cause of malabsorption syndromes in Western countries (Bull and Tomasi, 1968). Data on immunoglobulins in tropical sprue are sparse, and, theoretically, dysgammaglobulinaemia should be included as one of the possible causes of the syndrome. In the present study we report data on the serum level of the major fractions of immunoglobulins (IgG, IgA, IgM) in a series of Indian patients with tropical sprue. Turnover studies with radioiodine-labelled IgG were also made.

Patients and Controls

Patients with Tropical Sprue.—Eight patients with tropical sprue were studied. They were aged 18 to 55 years ; 4 were women and 4 men (Table I). All suffered from chronic diarrhoea and had various other dyspeptic complaints. They were underweight (28–50 kg.), their haemoglobin was from 11.2 to 14.4 g./100 ml., and all had malabsorption, since at least two of the following four absorption tests were abnormal: faecal fat, D-xylose test, Schilling's test, and folic acid absorption (Jeejeebhoy, Desai, Noronha, Antia, and Parekh, 1966). All but one of the patients had steatorrhoea. In addition all had malabsorption of the D-xylose and partial villous atrophy of the jejunal mucosa, ascertained by peroral biopsy. None of them received any treatment before or during the time of the study.

Indian Controls.—Sixteen subjects without gastrointestinal disease or diseases known to affect the immunoglobulins served as controls There were 10 males and 6 females. Their ages ranged from 25 to 67 (mean 41) years, and their body weight from 34 to 65 (mean 49) kg. Nine were attending the outpatient clinic for simple goitre. The rest were "normal" controls without complaints at the time of the study. Immunoglobulin levels were determined in all cases and IgG turnover in three.

Danish Controls.—A previously published normal series comprising 98 subjects (Jensen, 1967) was used for comparison of immunoglobulin levels because the method applied was essentially the same. IgG turnover measured in another Danish control series consisted of 21 subjects aged 24–70 (mean 48) years and body weight 48–94 (mean 69) kg. (Andersen, 1964).

Methods

Serum levels of immunoglobulins (IgG, IgA, and IgM) were determined immunochemically after the radial diffusion method (Mancini, Carbonara, and Heremans, 1965). Prefabricated plates with antibody-containing agar were applied (Partigen, Behringwerke, Marburg, Lahn, Germany).

IgG turnover was determined with ^{125}I-labelled IgG. IgG was isolated from normal Danish serum by diethylaminoethyl-Sephadex chromatography and was immunologically and metabolically pure (Andersen, 1964). The labelling procedure, preparation control, and details of the procedure used in studies of patients have been reported elsewhere (Andersen, Jarnum, Jensen, and Rossing, 1968). Intravenous injections of 10–15 μCi were given and blood samples withdrawn 10 to 15 minutes after the injection and at daily intervals for 10 to 20 days. Twenty-four-hour urine collections were made. Calculation of turnover data was made after Pearson, Veall, and Vetter (1958).

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TABLE I.—*Immunoglobulins in Eight Cases of Tropical Sprue*

Case No.	Sex	Age (Years)	Weight (kg.)	Total Serum Protein (g./100 ml.)	Albumin (g./100 ml.)	Gamma-globulin (g./100 ml.)	IgG (mg./ml.)	IgA (mg./ml.)	IgM (mg./ml.)
1	F	18	28	5·7	3·3	0·62	3·8	0	0·4
2	M	30	44	6·1	3·8	0·77	8·8	1·0	0·7
3	M	55	40	7·0	4·0	1·15	8·8	1·9	0·8
4	M	24	37	5·8	3·7	1·15	9·5	2·3	1·6
5	F	36	41	6·7	3·5	1·60	9·6	0	0·9
6	F	28	43	7·3	4·3	1·45	11·6	1·4	1·9
7	M	35	50	6·5	4·0	1·37	14·9	2·4	2·4
8	F	34	30	7·6	4·1	1·74	23·2	4·3	2·1
Normal Indian values (n = 16): Mean				6·75	4·23	1·23	15·4	2·0	0·95
Range (mean ± 2 S.D.)				5·3–8·2	3·7–4·8	0·3–2·3	9·4–21·4	0·6–3·4	0–2·12
Normal Danish values* (n = 98): Mean							10·8	1·86	0·67
Range (mean ± 2 S.D.)							7·4–14·2	0·37–3·35	0·11–1·23

* Jensen (1967).

Results

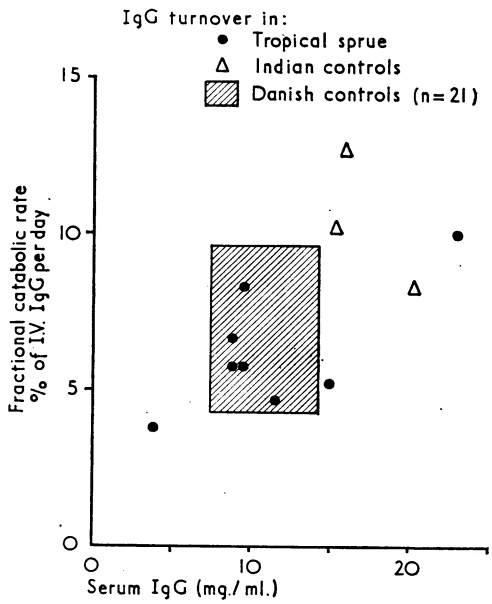
Serum levels of IgG, IgA, and IgM are shown in Table I. When the Indian and Danish controls were compared a highly significant difference was found between the IgG levels ($P<0.001$), the Indian mean being 15.4 mg./ml. and the Danish only 10.8 mg./ml. IgA and IgM levels were similar.

In the sprue patients the most conspicuous finding was that two (Cases 1 and 5) had agamma-A-globulinaemia. One of these (Case 1) had a decreased IgG level and the other a low normal IgG. Among the remaining six patients four had a low normal or subnormal IgG level and only one (Case 8) had a raised IgG compared with the Indian controls. IgA was raised in one patient; IgM was slightly raised in two patients, but otherwise was normal.

TABLE II.—*IgG Turnover in Eight Cases of Tropical Sprue*

Case No.	Diagnosis	Fractional Catabolic Rate % of Intravascular Pool per Day	Synthetic Rate	
			g./day	mg./kg./day
1	Tropical sprue	3·7	0·21	7
2	Tropical sprue	5·7	0·95	22
3	Tropical sprue	6·6	1·1	28
4	Tropical sprue	5·7	0·88	24
5	Tropical sprue	8·3	1·5	36
6	Tropical sprue	4·6	1·0	24
7	Tropical sprue	5·2	1·7	33
8	Tropical sprue	9·9	3·7	124
9	Indian control	10·1	3·5	60
10	Indian control	12·8	5·5	123
11	Indian control	8·3	5·4	101
Danish controls* (n=21): Mean		6·9	2·5	36
Range (mean ± 2 S.D.)		4·2–9·6	1·1–3·9	18–54

* Andersen (1964).



IgG turnover data are listed in Table II. One patient (Case 1) with agamma-A-globulinaemia had a decreased fractional catabolic rate, 3.7% of the intravascular pool of IgG/day, and in one (Case 8) it was slightly increased (9.9%/day) as compared with the Danish control material though comparable to the three Indian controls. In five of the remaining six patients the fractional catabolic rate was low normal. There was a tendency to a linear relation between the serum IgG level and the fractional catabolic rate (see Chart), but the limited number of patients does not justify a statistical treatment of the data.

The synthetic rate of IgG was decreased or low normal in most of the patients, compared with both the normal Danish values and the three Indian controls, of whom two had a synthetic rate of more than twice the normal Danish average value.

Discussion

In non-tropical sprue an isolated IgM deficiency is a common finding. It has been reported in more than half of the untreated patients (Hobbs and Hepner, 1968). In the present series of untreated patients with tropical sprue the IgM level in serum was normal or slightly increased. However, it turned out that IgA was missing in two patients (Cases 1 and 5). One (Case 1) had a reduced IgG concentration (3.8 mg./ml.), and would represent a case of dysgammaglobulinaemia type I (Bull and Tomasi, 1968) if IgM had been present in increased concentration; but it was not. The other (Case 5) had a low normal IgG level. In the remaining patients IgA and IgM were normal or slightly raised compared with the Indian controls. In contrast, IgG was decreased in two patients (Cases 2 and 3), at the lower normal limit in two, and increased in only one (Case 8).

In all except Case 8 the fractional catabolic rate of ^{125}I–IgG was low and the synthetic rate markedly decreased (see Chart) as compared with three Indian controls, and in all but three patients the absolute synthetic rate was low or decreased even compared with Danish controls. These findings make it highly improbable that intestinal protein loss accounts for the low IgG levels. Furthermore, in most of the patients serum albumin was normal or only slightly decreased, which shows that no important loss of protein took place.

One may object that Danish and not Indian IgG was used for turnover studies, and that Danish IgG may have a different (lower) catabolic rate than Indian IgG. Though not investigated it is improbable, since a similar high degradation rate of labelled IgG has been found in untreated Gambians with malaria whether they were studied with European or adult Gambian IgG (Cohen, McGregor, and Carrington, 1961).

Thus the low or low normal serum IgG level found in six out of eight cases of tropical sprue reflects a low synthetic rate of this immunoglobulin. It may reflect a partial immunological deficiency state which may contribute to the cause of tropical sprue.

The demonstration that two patients in this series had agamma-A-globulinaemia leaves open the question whether this condition occurs with high incidence among Indian patients with tropical sprue. Only in one of them (Case 5) was an isolated IgA deficiency present (Hobbs's (1968) type IV B). In the other (Case 1) serum IgG was markedly decreased. IgM was normal in both. Studies on a larger scale would clarify the relation between tropical sprue and immunoglobulin deficiency.

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