Transient paraproteinaemia in a patient with coeliac disease

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SUMMARY A case is reported of a 43 year old man who suffered from a grass pollen allergy and a malabsorption syndrome and in whom a paraproteinaemia was found. The grass pollen hypersensitivity was abolished by desensitization. The malabsorption syndrome was found to be due to coeliac disease—that is, a 'flat' mucosa of the jejunum with an almost normal ileal mucosa—followed by clinical recovery and morphological improvement on a gluten-free diet. A short period of gluten reintroduction caused deterioration of the jejunum. The monoclonal immunoglobulin (Ig G- λ) diminished and disappeared in the course of three years. Although it has not been possible to demonstrate that this paraprotein had anti-gliadin activity, it is suggested that the constant stimulation of the gut reticuloendothelial system by gluten might bear some relation to the appearance of the paraproteinaemia.

Dameshek and Schwartz (1959) suggested that chronic stimulation of the reticuloendothelial system might influence the appearance of plasma cell dyscrasia. Aleutian disease of mink, which is characterised by a diffuse proliferation of plasma cells, terminates in some mink as a paraproteinaemia, together with the appearance of Bence Jones proteinuria (Porter *et al.*, 1965). In man, it has been stressed that chronic inflammatory processes can be associated with paraproteinaemia (Combined Staff Clinic, 1968), thus giving support to the suggestion of Dameshek and Schwartz (1959).

In adult coeliac disease there is evidence of lymphoreticular dysfunction (McCarthy *et al.*, 1966; Hobbs and Hepner, 1968; Blecher *et al.*, 1969) and there are data supporting an increased incidence of lymphoma and reticulosis (Gough *et al.*, 1962; Harris *et al.*, 1967).

Transient paraproteins have been found in association with a variety of conditions (Young, 1969). Although their significance is not entirely clear, in some case they may represent an antibody response (Seligmann *et al.*, 1971).

We wish to report the case of a transient monoclonal IgG of the lambda type in a patient with adult coeliac disease.

Case history

B.M.B., a male, was born in Indonesia (on 30 October 1926). His father was Dutch and his mother Indonesian. The patient emigrated to The Netherlands when he was 20 years of age. Before this he had suffered from malaria, dysentery, and pleuritis. He remained well till 1965 when he had several episodes of hay fever and allergic rhinitis. In May 1969 he visited the Allergy Clinic at our hospital and it was found that he was highly sensitive to grass pollen and to a minor extent to cat and dog hair. There was also a delayed skin reaction to *Haemophilus influenzae* and streptococcus. He was advised to follow a cure of desensitization with grass pollen and was vaccinated against *H. influenzae*.

He followed this treatment from 1969 to 1971 by which time all his allergic symptoms disappeared. In 1969 he was seen for the first time at our department of gastroenterology. He had a 24 year history of vague abdominal symptoms but in the last few months he had diarrhoea almost every day with colicky abdominal pain.

Laboratory investigations in 1969 showed an ESR of 20 mm in the first hour, a mild macrocytic anaemia: Hb 11.7 g/dl; erythrocytes 2.9×10^6 per mm³, leucopenia 900 to 1400 with neutropenia, low folic acid 0.6 mg/ml. Vitamin B₁₂ in blood was

normal. Schilling test was normal as well (29.3%).

SERUM IMMUNOGLOBULINS

IgA and IgM were measured by radial immunodiffusion using the Tri-Partigen plates (Behring).

	Date					Normal range (mg/100 ml)
	19.1.70	6.10.72	13.12.72	10.2.75	1.5.75	
IgA	175	150	226	269	268	90-450
IgM	38	280	68	88	100	60-250

IMMUNOLOGICAL STUDIES

Agar electrophoresis showed a definite homogeneous band in the gamma region (Fig. 1). Immunoelectrophoresis and immunoselection (Rádl, 1972) showed an IgG paraprotein of the lambda type.

Immunofluorescence of the bone marrow (1969) revealed an increased number of plasma cells which were mainly positive for IgG. Seven per cent of the positive cells were IgA, 5% IgM, 2% IgD, and 86% IgG; 90% of the IgG positive cells were of the lambda type.

Fig. 1 Agarose gel electrophoresis of serum. 1 and 6 normal human serum, 2, 3, 4, and 5 serum from the patient in 1970, 1971, 1972, and 1973 respectively. Arrows indicate M component.

Immunofluorescence investigation of jejunal biopsy specimen (1969) showed numerous IgA positive cells, many IgM, and several IgG. There was no indication of preponderance of IgG-positive cells.

Immunofluorescence of the bone marrow (1975) showed IgA pos. 41.6%, IgM pos. 8.0%, IgG pos. 54.4%, IgD pos. 1.0%, IgE pos. 0%. Ratio K/ λ light chains = 63.1/36.9 (normal).

IMMUNOABSORPTION

In order to study possible antigliadin activity of this paraprotein, immunoabsorption was tried in a column of sepharose to which gliadin was coupled. To prove the proper functioning of this column, serum of rabbit immunised with gliadin was applied first.

As can be seen in Fig. 3 one of the precipitation bands is retained by the column. This has been further eluted with a glycine-HCl buffer pH 2.3; the eluate showed a precipitation line against gliadin (well 4 of Fig. 3). The same experiment was repeated with the patient's serum. Neither this immunodiffusion nor the immunoelectrophoresis of the same fractions of the patient's serum against rabbit-anti-human immunoglobulins (Fig. 2) gave evidence of any anti-gliadin component.

Fig. 2 Immunoelectrophoresis of serum against rabbit antihuman immunoglobulins. 1. Serum of the patient. 2. Serum of the patient after passing a Sepharose B4 column. 3. Serum of the patient after passing a Sepharose B4 column coupled to gliadin. 4. Eluate of the second column with glycine-HCl buffer, pH 2.3. 5. Normal human serum.

Fig. 3 Ouchterlony plate. In the central well of gliadin (5 mg/ml) 1. Rabbit serum (15.3-74) 2. Rabbit serum passed through column of sepharose B4 coupled to gliadin. 3. Gliadin (0.5 mg/ml). 4. Eluate obtained with glycine-HCl buffer, pH 2.3 after passage of rabbit's serum. 5. Free well. 6. Gliadin (0.5 mg/ml).

STUDIES OF SMALL INTESTINE

The glucose tolerance test was normal (maximum rise 25 mg%), a lactose tolerance test was flat (maximum rise 4.5 mg), and a xylose test was also abnormal (13.8% were excreted in five hours' urine after 5 g d-xylose; a normal level being more than 27%). A jejunal biopsy specimen showed a hyperplastic type of mucosal atrophy with an increased number of interepithelial lymphocytes and an increased number of plasma cells in the lamina propria. The ileum biopsy specimen showed a mild partial villous atrophy. A fat balance showed a mild steatorrhoea (6.8 g/24 h).

TREATMENT AND COURSE

The patient was treated with folic acid, iron tablets, and a gluten-free diet with a good clinical response and normalization of biochemical parameters. Repeated small intestinal biopsies showed improvement of the villous architecture with diminution of the mononuclear cell infiltrate. Three years later he was challenged with 3.5 g gliadin and there was an immediate deterioration of the small intestinal mucosa.

The effect of gliadin on the intestinal mucosa was assessed in two ways: (1) enzymatically, by estimating disaccharidase activity, and (2) by quantitative histological examination, using the method of Dunnill and Whitehead (1972). Biopsy specimens were taken under fluoroscopic control

20 cm beyond the duodenojejunal flexure using a hydraulic multiple biopsy instrument. Biopsy specimens were taken before and three and 24 hours after instilling 3.5 g gliadin dissolved in water (pH 6.8) via a tube which was located fluoroscopically 10 cm above the site of biopsy.

DISACCHARIDASE ESTIMATIONS

These were performed using the method of Dahlqvist (1970). Results are expressed in units per g protein.

	Before challenge	After challenge (h)	
		3	24
Lactase	3	2	2
Sucrase	17	9	9
Maltase	81	44	39

QUANTITATIVE HISTOLOGICAL EXAMINATION

The method of Dunnill and Whitehead (1972) was followed. A template of 15 lines of equal length was drawn according to the specifications of Weibel (1963) on an eye-piece graticule prepared for us by Graticules Ltd. The objective and ocular combination of the microscope yielded a magnification of $\times 100$. At this magnification the length of each line east on the section was 1.8×10^{-2} cm.

The index c:lh, which is related to the surface-to-volume ratio, was calculated. The mean number of hits per microscopic field ($\bar{h}$) was also determined. It is proportional to the mucosal volume.

	Before challenge	After challenge (h)	
		3	24
C:lh	15.2	14.3	10.9
$\bar{h}$	20.9 ± 3.5	13.2 ± 1.98	$13.7 \pm 1.85 (\mu \pm SD)$

Both the disaccharidases assay and the morphological study showed a response to the gliadin instillation thus confirming the patient's sensitivity to gluten.

Discussion

Transient paraproteins—that is, homogeneous immunoglobulins which suddenly appear in the serum and disappear within weeks or months—are not very common. Young reviewed the literature in 1969 and, with his five cases, the total amounted to 36 cases.

On the other hand, there is clinical and experimental evidence (for review, see Rádl, 1975) that paraproteins appear often in immunodeficiency diseases. In a longitudinal study of three patients

with the Wiskott-Aldrich syndrome made by Rádl *et al.*, it was found that they all produced temporarily one or more populations of paraproteins. Studies made in experimental models (Rádl, 1975) showed that the absence or delay in maturation of the T-cells could contribute to a high frequency of transient paraproteins.

Weetman *et al.* (1974) have studied the distribution and faecal loss of peripherally harvested lymphocytes labelled with 51-Cr and reinjected into human subjects and have shown that the five-day faecal loss of untreated patients with coeliac disease was as great as that of patients with lymphangiectasia.

Ferguson (1974) has suggested that thymus-dependent lymphocytes may be involved in the pathogenesis of the jejunal lesion and recently O'Donoghue *et al.* (1975) have measured circulating T-cells in the blood of coeliac patients and controls. They have shown that the relative and absolute number of T-cells were decreased in untreated coeliac patients compared with controls.

It might be, then, that there is a link between coeliac disease and the production of this transient paraproteinaemia in our patient. In favour of an immunodeficiency state were his leucopenia and low IgM. Both recovered to normal levels when a gluten-free diet was instituted.

It might be that the paraproteinaemia represents another example of altered immunity in coeliac disease. Although we have not been able to find another report of a transient paraprotein in coeliac disease, Cooke (1969) has reported three cases of steatorrhoea associated with an IgG paraproteinaemia. Presumably they were cases of coeliac disease. No further details are given in the text. Other examples of disordered immunity in coeliac disease are dysgammaglobulinaemia (Hobbs *et al.*, 1969) and the occurrence of mixed cryoglobulinaemia in four patients with coeliac disease (Doe *et al.*, 1972).

Two cases of transient paraproteinaemia have been reported in association with low-folic acid (Roman and Coles, 1966). They disappeared as soon as folic acid was given. Although our patient had a low folic acid at the time of diagnosis, the paraprotein disappeared three years later when this deficiency and his anaemia had been corrected for a long period of time.

It has been suggested that transient paraproteins are antibodies (Seligman *et al.*, 1971; Rádl, 1975). The paraprotein in our patient had no detectable anti-gliadin activity. Whether it represented an antibody against one of the multiple vaccines he received is a possibility, although unlikely. Penny and Hughes (1970) were not able to find any para-

protein in 30 cases who had been fully treated by desensitization.

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