

Dietary manipulation for idiopathic nephrotic syndrome

A new approach to therapy

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To evaluate the role of food antigens in idiopathic nephrotic syndromes, we used dietary manipulations in 26 cases in whom steroid therapy had failed. In the six reported, restricted diets according to clinical and biological data were followed by complete remissions, suggesting that food can be responsible for idiopathic nephrotic syndrome in selected cases, and leading to a new therapeutic approach. The mechanism by which such antigens can be implicated in the pathogenesis of this glomerular disease is discussed.

Key words: allergy; foods limited diet; idiopathic nephrotic syndrome.

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Ten years ago, Sandberg et al. (20) demonstrated the responsibility of food allergy in the idiopathic nephrotic syndrome (INS) (4, 5). Five of the six reported cases had eczema and/or asthma. Although classic manifestations of food hypersensitivity were lacking, milk sensitization was revealed by positive skin testing. Dietary manipulations, first by an elemental diet then by specific dairy avoidance induced complete remission.

Since this initial report, a few cases of INS with food allergy have been reported with (18) or without (7, 11) simultaneous allergic manifestations, that could lead to considering such cases as exceptional. However, in recent years we have systematically searched for any food allergy in INS, also when there was sensitivity to respiratory allergens.

MATERIAL AND METHODS

Food allergy has been systematically investigated in 26 INS patients, (12 male, 14 female;

mean age 32 years, range 7 to 72 years). The previous duration of INS was from 3 months to 20 years.

Allergy investigations included anamnesis with emphasis on personal history, for example gastro-intestinal disturbances, such as food intolerance during childhood or at present and obvious symptoms of asthma, eczema or hay fever. It was also attempted to fully define the possible allergic features of upper respiratory disturbances.

Intradermal tests were performed with commonly ingested food extracts, as well as routine tests with inhalant allergens (Stallergens Laboratory, Pasteur Institute) including dust, mite, feather, mold, pollen, and animal epithelia.

Serum IgE levels were measured by RIST. Specific IgE were investigated by radio-allergosorbent test (RAST): the allergens were chosen according to anamnesis data, skin test results, and products available from Pharmacia. Histamine release basophil test (HRBT)

Table 1
Idiopathic nephrotic syndrome and food hypersensitivity. Literature reports

	<i>n</i>	Method	Responsible foods
Sandberg (8)	6	elemental diet	cow's milk (5 cases) gluten (2) unknown (1)
Richards (5)	1	specific avoidance	cow's milk egg white
Howanietz (6)	1	specific avoidance	pork
Genova (7)	6	specific avoidance	unknown
Laurent (in press)	5	specific avoidance	gluten (1) cow's milk (1) egg, milk (1) pork-beef gluten (1)
Laurent (10)	9	oligo-antigenic diet	unknown

was performed with food allergens, as previously reported (1, 9, 11).

If the data demonstrated any sensitization, we made a systematic search for the food responsible by long-term limited avoidance(s) and specific reintroduction in the diet. With sensitization to inhalant allergens, these were also avoided if possible. Steroids were subsequently reduced or not given during limitation diet in an attempt to reduce the threshold of steroid dependence. According to their effect, dietary avoidance was extended to cross-reacting antigens or other food allergens.

RESULTS

In most cases, i.e. 20 of the 26 INS patients, specific avoidance was not able to prevent relapses and we had to use immunosuppressive drugs, alkylating agents or, more recently, cyclosporin (8). However, in six cases specific avoidance was helpful, and this prompted us to present this report and to propose continuing such systematic investigations in INS. The six reported patients have INS with normal renal function and blood pressure. They have minimal changes nephropathy (Cases 1, 5, 6), focal and segmental glomerulo-sclerosis (Case 2) and

previous corticosteroid sensitive INS (Cases 3, 4). Clinical data are given in Table 1 and case reports presented. None of the six INS patients had a personal history of food allergy but one had allergic rhinitis (Case 2). They had no gastro-intestinal symptoms, but patients 3 and 6 had disliked milk since childhood but not other dairy products. The results of intradermal testing with various inhalant or food allergens, serum IgE levels, RAST and HBDT are summarized in Table 1. According to these data the patients followed specific avoidance(s). Avoidance of house dust mite was realized in patients 1, 5 and 6 by use of acaricide spray.

CASE REPORTS

Case 1

B. Jean-Yves (born in 1965). The nephrotic syndrome appeared in 1966 and was steroid-sensitive with multiple relapse. Renal biopsy showed minimal changes and absence of deposits by immunofluorescence study. The multiple relapses were treated with chlorambucil which induced a stable remission for 4 years. In 1972, just after poliomyelitis vaccine, a relapse occurred

and long-term treatment with prednisolone (P) was introduced: steroid dependence was observed, up to 1982 with a threshold of 20 mg P and permanent proteinuria of approx. 3 g/day.

A first period of cow's milk and egg avoidance led to a reduction in proteinuria of 50% of the initial value in 15 days. Challenge with egg was followed by a two-fold increase of proteinuria. Thus, since March 1983, we decided on a long-term avoidance of egg, chicken, cow milk and dairy products according to HRBT data. Within a few weeks the proteinuria disappeared and steroids could be discontinued in January 1984. Proteinuria, recurred once in October 1985 after overeating. One month after a return to strict diet there was complete remission and, up to now (Dec. 1987), steroids have not been required.

Case 2

R. Jeanne (born in 1921 and working in a bakery). NS appeared in 1962. A renal biopsy in 1963 showed minimal nephropathy changes. This INS patient was steroid-sensitive, but steroid-dependent with a threshold of 10 mg/day of P from 1962 to 1980. Subsequent biopsies showed focal glomerulo-sclerosis in 1969 and an increase of the sclerosis lesions in 1974.

Steroid reduction under 10 mg/day always resulted in the reappearance of proteinuria.

Four injections with wheat flour extract were followed by significantly increased proteinuria. A first avoidance of wheat flour was followed by decreased proteinuria, but complete remission was only obtained when the avoidance was extended to all foods containing gluten. In June 1982, steroids could be withdrawn and, until now (Dec. 1988), there has been no relapse of proteinuria.

Case 3

H. Manuel (born in 1969). A steroid-sensitive NS occurred in 1981. However, as cortico-dependence was observed at 20 mg/day, with NS relapse, the use of alkylating agents was discussed when investigating dietary hypersensitivity (1983). Avoidance of cow's milk and dairy products was begun in October 1982. Steroids could be reduced then withdrawn in September 1984 with no relapse up to the present (Dec. 1988).

Case 4

G. Grégoire (born in 1980). A cortico-sensitive NS occurred in 1981. Nevertheless, NS relapsed

Table 2

Clinical and biological data for the six INS patients. Effects of long-term dietary avoidance

Age (years)	Previous history (years)	Steroid threshold efficacy	IgE KUL/l	Precipitator	Results
20	18	10 mg/d	3590	milk, chicken, egg white	complete remission, steroids withdrawn (4 y)
62	20	15 mg/d	20	gluten	complete remission, steroids withdrawn (5 y)
15	3	15 mg/d	1800	milk	complete remission, steroids withdrawn (1 y)
7	5	5 mg/d	960	gluten, pork, milk	complete remission, steroids withdrawn (1 y)
25	4	no steroid	640	wheat flour	complete remission (3 y), without steroid withdrawal
26	3	10 mg/d	16	beef, pork, egg white	complete remission, steroids withdrawn (3 g)

when P was reduced under 10 mg/day. Four relapses were subsequently observed, which suggested the use of alkylating agents when investigating for food allergy (1984).

Avoidance of pork and cow's milk did not prevent a relapse, thus avoidance was extended to gluten since January 1985. A reduced steroid-sensitivity threshold was demonstrated in December 1985 and steroids could be withdrawn in March 1986. In October 1986, overeating was followed by proteinuria lasting 3 weeks but a return to strict avoidance produced complete remission without use of steroids. Later, in 1988, a relapse occurred, in spite of maintenance of the same limited diet. Steroids had to be reintroduced.

Case 5

M. J. Luc (born in June 1958). An acute membranoproliferative glomerulonephritis was diagnosed in 1965 with complete remission in 1966 after steroid and chlorambucil treatment. Proteinuria remained absent until October 1983, when a NS occurred with normal renal function; the new renal biopsy showed minimal change on light microscopy and absence of deposits by immunofluorescence.

Complete and durable remission occurring 1 month after gluten avoidance was associated with disodium cromoglycate *per os*. Thus steroids were not used in this patient.

Case 6

H. Didier (born in 1959). NS appeared in October 1982. Renal biopsy showed minimal changes. Steroids were given 1 mg/kg/day but remission was not obtained until after the 4th month of treatment, when steroid-dependence occurred with a threshold dose of 15 mg P/day. The use of alkylating agents was discussed when conducting allergy investigations (1983).

Two treatments with disodium cromoglycate during steroid therapy (20 mg of P/day) cured the proteinuria. Since December 1983 the avoidance of beef and pork has reduced the steroid-dependence threshold, but a relapse prompted us to

include eggs in the avoidance diet according to the new results of HRBT. Complete remission was observed for 15 months and steroids were withdrawn in July 1985.

DISCUSSION

These reported cases clearly demonstrate that long-term specific food avoidances can be helpful in selected INS patients. Our patients had no obvious gastro-intestinal symptoms, nor patient reactions to food allergens. Food allergy, as a contributory factor in proteinuria or steroid-dependence, was only detected because we, as Sandberg et al. (20), deliberately suspected it when giving the elemental diet in INS children. Sensitization was sought by means of skin tests as in their reported cases; we used also RAST and HRBT, the latter appearing to be the most sensitive (9). Thus various food sensitizations were documented in these patients after skin or laboratory tests. In spite of a weak correlation between these tests, specific avoidance(s) was realized in the aim to detect a latent food hypersensitivity responsible for INS. As in the six reported cases, limited diets were followed by complete remission, these tests appear helpful when choosing the foods to be eliminated.

We have previously reported cases in which house dust was incriminated (14). Obviously, acaricides were used in three of the reported cases at the beginning of food avoidance. Pollens (3, 6, 10, 17, 19) or molds (22) were also responsible in the early reports. Some inhalant allergens can cross-react with foods as observed by us in an isolated case (13). However, food products appear to be more frequently implicated as attested by the effect of oligoantigenic diet in unselected INS patients (15). Of 26 patients only six benefited from this specific avoidance strategy. In five other cases, encouraging data were observed but a complete remission with steroid withdrawal has not yet been obtained. Thus, over 25 % of INS cases could be improved by food avoidance(s). This is a new etiology for INS. Because of these data, an allergy survey should be conducted in every INS patient. We suggest performing skin test, RAST and HRBT without delaying steroid therapy for the first bout of INS, in order to begin

dietary manipulation in the case of multiple relapses, steroid dependence or steroid resistance.

The implicated foods in this report were cow's milk, gluten, eggs, chicken, beef and pork. Their responsibility was demonstrated in an open study, because in the long-term a limited diet cannot be carried out in a double-blind study. However, improvement of the disease is demonstrated by significant proteinuria variations according to dietary changes. The attainment of complete remission without steroids or after withdrawal of steroids in steroid-dependent patients, is a strong argument in favour of the reality of this effect.

The mechanism by which a food allergen can induce proteinuria remains unknown. A modification of the electric changes the capillary wall is probably responsible for the INS (2). An immune process related to IgE could explain the capillary permeability leakage by the action of various released mediators (23). Vascular permeability factor, produced by stimulated lymphocytes (12) can also be implicated, and house dust was able to induce its release (16); we are now investigating whether food allergens could also be responsible for vascular permeability factor production by lymphocytes.

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