

CHAPTER 2

IgG and IgA antibodies to dietary antigens in food allergy and intolerance

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In studies of antibodies to dietary antigens the experimental approach has been based, almost without exception, on detection by the enzyme-linked immunosorbent assay (ELISA) which is well-suited to antibody testing of multiple serum samples, for determination of antibody isotypes (IgG, IgG subclasses and IgA) and which has high sensitivity for antibody binding [1,2]. Nonetheless, the conventional enzyme-linked immunosorbent assay (ELISA) technique does not discriminate between high and low affinity antibodies and an important caveat is that techniques capable of detecting only high affinity antibody binding, i.e. fast on-rates, have yet to be exploited in this area of investigation [3]. A further consideration is the lack of assay standardization, e.g. using reference sera containing high levels of well-defined antibody (IgG or IgA) to specific food antigens, makes quantitative evaluation of different studies difficult. Early studies based on the determination of IgG, and especially IgG4 antibodies to food proteins highlighted their occurrence in healthy individuals and, more significantly, these data emphasized that immunological sensitization and production of IgG antibody is part of the normal immune response to dietary antigen exposure [4-7]. Furthermore, studies in healthy children have demonstrated high levels of IgG antibody to milk and egg in the early years of life which gradually diminish with increasing age; interestingly, the reverse appears to be the case for antibodies to inhalant antigens, e.g. house dust mite [8,9]. It is clear, therefore, that the inclusion (or otherwise) of appropriate control subjects, particularly age-matched healthy children, is crucial to the interpretation of much published data.

Following the observation that patients with atopic eczema (AE) have high total serum IgG4 levels [10], there has been much interest in the IgG subclass distribution of antibodies to food antigens in this condition. These IgG antibodies have been detected in some, but not all, studies of adult AE patients and, when present, these antibodies are distributed between the IgG1 and IgG4

subclasses [7,10-14]. Recent studies in AE children and healthy age-matched controls have demonstrated that IgG antibodies to egg and milk antigens are common in both groups between the ages of 1-5 years, with a similar IgG subclass profile [8,9]. These IgG (and IgE) antibodies appeared to persist only in AE children, however, which may be related to the defect in immunoregulation underlying AE which modulates the synthesis of IgE but also of IgG4 [15-17]. The interplay between cytokines and TH subsets is relevant to an understanding of the aetiopathogenesis of atopic diseases and possible routes of intervention [17,18].

Against this background it is pertinent to examine recent reports on the relevance of IgG and IgG subclass antibodies in food-allergic patients documented by double-blind challenge. With the exception of one study which lacked control data on IgG4 antibody levels [19], these have demonstrated that determination of IgG, and especially IgG4, antibody levels had no predictive value for dietary manipulation or management of patients with classical food allergy [20-22], consistent with the view that production of IgG antibodies to dietary antigens reflects a normal immune response [22,23].

In gluten-sensitive enteropathy (GSE) both IgG and IgA antibodies to gliadin, as well as other dietary antigens, have been well documented in relation to both coeliac disease and dermatitis herpetiformis [24-26]. In contrast to IgG antibody, however, serum IgA anti-gliadin antibody has been shown to correlate far better with overt or covert GSE [27,28] and these findings have been complimented by studies of antibodies in intestinal secretions of these patients [29,30]. Further support for the determination of serum IgA anti-gliadin antibody as a diagnostic procedure in GSE has been provided by a recent large prospective study [31]. It is also of interest that following the original observation of increased levels of IgG and IgA, antibodies to the yeast *Saccharomyces cerevisiae* in Crohn's disease [32], IgA anti-*Saccharomyces* antibody has been shown to discriminate between Crohn's disease and ulcerative colitis [33]. Production of these antibodies, which are unlikely to be of aetiological relevance, may be secondary to the

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marked activation of mucosal T cells characteristic of Crohn's disease [34].

IgG antibodies to bovine milk proteins have also been described in association with cow's milk intolerance [35,36] but, in carefully controlled studies in infants and children, it has been clearly shown that IgG, and particularly IgA, antibody levels were no different between patients and controls and, hence, of limited diagnostic potential [37–39].

Taken together the sero-epidemiological studies reviewed here, however, have provided little clarification of immunopathogenic mechanisms, or of the basis of food protein breakdown and presentation of antigenic peptides to the systemic or mucosal immune systems.

In conclusion, IgG antibodies to common dietary antigens can be detected both in health and disease, but there is no good evidence at this time to support their application for investigation of suspected food allergy and intolerance. In contrast, determination of IgA antibody to selected dietary antigens can provide clinically relevant information.

References

- Kemeny DM. Immunoglobulin and antibody assays. In: *Allergy: An International Textbook*. Lessof MH, Lee TH, Kemeny DM, eds. London, Wiley 1987: 319–35.
- Björkstén B. In vitro methods in the evaluation of food hypersensitivity. In: *Food Allergy: Adverse reactions to Food and Food Additives*. Metcalfe, Sampson HA, Simon RA. Oxford, Blackwell Scientific Publications, 1991: 67–80.
- Karjalainen J, Saukkonen T, Savilahti E, Dosch H-M. Disease-associated bovine serum albumin antibodies in type 1 (insulin-dependent) diabetes mellitus are detected by particle concentration fluoroimmunoassay, and not by enzyme-linked immunoassay. *Diabetologia* 1992; 35:985–990.
- Merrett J, Burr ML, Merrett TG. A community survey of IgG4 antibodies *Clin Allergy* 1983; 13:397–407.
- Barnes RMR, Barton PG, Doig JE et al. Distribution of serum antibodies to wheat gliadin and bovine milk non-atopic healthy adults. *J Clin Lab Immunol* 1993; 12:175–8.
- Husby S, Oxelius V-A, Teisner B, Jensenius JC, Svehag S-E. Humoral immunity to dietary antigens in healthy adults. *Int Archs Allergy Appl Immunol* 1985; 77:416–22.
- Barnes RMR, Harvey MM, Blears J, Finn R, Johnson PM. IgG subclass human serum antibodies reactive with dietary proteins. *Int Archs Allergy Appl Immunol* 1986; 81:141–7.
- Okahata H, Nishi Y, Mizoguchi N et al. Deve serum *Dermatophagoides farinae*, ovalbumin- and lactalbumin-specific IgG1, IgG4, IgA and IgM in children with bronchial asthma/allergy atopic dermatitis. *Clin Exp Allergy* 1990; 20:39–44.
- Barnes RMR, Lewis-Jones MS, Allan S, Dixon TA, Vickers CFH. Deve and isotype diversity of antibodies to inhalant and dietary antigens in childhood atopic eczema. *Clin Exp Dermatol* 1993; 18:211–6.
- Merrett J, Barnetson R StC, Butt ML, Merrett TG. Total and specific IgG4 antibody levels in atopic eczema. *Clin Exp Immunol* 1984; 56:645–52.
- Shakib F, Brown HM, Stanworth DR. Relevance of milk- and egg-specific IgG4 in atopic eczema. *Int Archs Allergy Appl Immunol* 1984; 75:107–12.
- Kemeny DM, Urbanek R, Amlot PL, Ciclitira PJ, Richards D, Lessof MH. Subclass of IgG in allergic disease I. IgG sub-class antibodies in immediate and non-immediate food allergy. *Clin Allergy* 1986; 16:571–81.
- Rowntree S, Platts-Mills TAE, Cogswell JJ, Mitchell EB. A subclass-specific antigen-binding radioimmunoassay (RIA): comparison between IgG4 antibodies to food and inhalant antigens in adult atopic dermatitis after desensitization treatment and during development of antibody responses in children. *J Allergy Clin Immunol* 1987; 80:622–30.
- Husby S, Schultz Larsen F, Svehag S-E. IgG subclass antibodies to dietary antigens in atopic dermatitis. *Acta Derm Venereol* 1989; Suppl 144:88–92.
- Romagnani S. Regulation and deregulation of human IgE synthesis. *Immunol Today* 1990; 11:316–21.
- Schultz CL, Coffman RL. Control of isotype switching by T cells and cytokines. *Curr Opin Immunol* 1991; 3:350–4.
- De Vries JE, Gauchat J-F, Aversa GG et al. Regulation of IgE synthesis by cytokines. *Curr Opin Immunol* 1991; 3:851–8.
- Romagnani S. Human TH1 and TH2 subsets: doubt no more. *Immunology* 1991; 12:256–7.
- El Rafei A, Peters SM, Harris N, Bellanti JA. Diagnostic value of IgG4 measurements in patients with food allergy. *Ann Allergy* 1989; 62:94–9.
- Morgan JE, Daul CB, Lehrer SB. The relationship among shrimp-specific subclass antibodies and immediate adverse reactions to shrimp challenge. *Allergy Clin Immunol* 1990; 86:387–92.
- Sloper K, Brostoff J. Milk and ovalbumin-specific IgG4 in childhood eczema: serum levels in relation to dietary changes. *Pediatr Allergy Immunol* 1991; 2:20–4.
- Lessof MH, Kemeny DM, Price JF. IgG antibodies to food in health and disease. *Allergy Proc* 1991; 12:305–7.
- Barnes RMR, Johnson PM, Harvey MM, Blears J, Finn R. Human serum antibodies reactive with dietary proteins: IgG subclass distribution. *Int Archs Allergy Appl Immunol* 1988; 87:184–8.
- Unsworth DJ, Walker-Smith JA, Holborow EJ. Gliadin and reticulon antibodies in childhood coeliac disease. *Lancet* 1983; 1:874–6.
- O'Farrelly CO, Kelly J, Hekkens W, Bradley B, Thompson A, Feigher DG. α -Gliadin antibody levels: a serological test for coeliac disease. *Br Med J* 1983; 286:2007–10.
- O'Mahony S, Ferguson A. Gluten-sensitive enteropathy (coeliac disease). In: *Food Allergy: Adverse Reactions to Food and Food Additives*. Metcalfe DD, Sampson HA, Simon RA, eds. Boston: Blackwell Scientific Publications, 1991: 186–98.
- Savilahti E, Perkkio M, Kalimo K et al. IgA anti gliadin

- antibodies: a marker of mucosal damage in childhood coeliac disease. *Lancet* 1983; i:320-2.
- 28 Labrooy JT, Hohmann AW, Davidson GP et al. Intestinal and serum antibody in coeliac disease: a comparison using ELISA. *Clin Exp Immunol* 1986; 66:661-8.
- 29 O'Mahony S, Barton JR, Crichton S, Ferguson A. Appraisal of gut lavage in the study of intestinal humoral immunity. *Gut* 1990; 31:1341-4.
- 30 O'Mahony S, Vestey JP, Ferguson A. Similarities in intestinal humoral immunity in dermatitis herpetiformis without enteropathy and in coeliac disease. *Lancet* 1990; i:1487-90.
- 31 Scott H, Ek J, Havnen J et al. Serum antibodies to dietary antigens: a prospective study of the usefulness in coeliac disease of children. *J Pediatr Gastroenterol* 1990; 11:215-20.
- 32 Main J, McKenzie H, Yeaman GR et al. Antibody to *Saccharomyces cerevisiae* (baker's yeast) in Crohn's disease. *Br Med* 1988; 297:1104-5.
- 33 Barnes RMR, Allan S, Taylor-Robinson CH, Finn R, Johnson PM. Serum antibodies reactive with *Saccharomyces cerevisiae* in inflammatory disease: is IgA antibody a marker for Crohn's disease? *Int Archs Allergy Appl Immunol* 1990; 92:9-15.
- 34 MacDonald TT. The role of activated T lymphocytes in gastrointestinal disease. *Clin Exp Allergy* 1990; 20:247-52.
- 35 Shakib F, Brown HM, Phelps A, Redhead R. Study of IgG sub-class antibodies in patients with milk intolerance. *Clin Allergy* 1986; 16:451-8.
- 36 Taylor CJ, Hendrickse RG, McGaw J, MacFarlane SBJ. Detection of protein cow's milk intolerance by an enzyme-linked immunosorbent assay. *Acta Paediatr Scand* 1988; 77:49-54.
- 37 Firer MA, Hoskings CS, Hill DJ. Humoral immune response to cow's milk in children with cow's milk allergy. *Int Archs Allergy Appl Immunol* 1987; 84:173-7.
- 38 Tainio V-M, Savilahti E. Value of immunologic tests in cow's milk allergy. *Allergy* 1990; 45:189-96.
- 39 Burks AW, Williams LW, Casteel HB, Fiedorek SC, Connaughton CA. Antibody response to milk proteins in patients with milk-protein intolerance documented by challenge. *J Allergy Clin Immunol* 1990; 85:921-7.

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