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Clinical significance of IgG subclass deficiency

IgG is quantitively and functionally the major class of immunoglobulin found in serum and all extravascular fluids except mucosal secretions. Four structurally and functionally distinct subclasses (IgG 1 to 4) have been described in man.[1] Deficiencies of individual subclasses of IgG were first described almost 20 years ago,[2] but their exact prevalence and significance is not accurately known.[3] They do appear, however, to be relatively common—possibly more common than IgA deficiency which occurs in 1:500 of the healthy population.[4] As with IgA deficiency, asymptomatic individuals are found both in blood donors[5] and among the relatives of patients with a variety of immunodeficiencies, including family members of patients with IgG subclass deficiencies.[6]

The different functions of individual IgG subclasses are partly related to their structure; only IgG 1 and IgG 3 effectively fix complement and similarly there is variability of crystallisable fragment (Fc) receptor binding to different leucocyte populations. Although antigenic stimulation may potentially give rise to antibody of any IgG subclass, usually it is restricted to one or two subclasses depending on the type of antigen.[7] IgG 1 and IgG 3 generally provide the response to protein antigens of bacteria, viruses, vaccines, and foods. IgG 2 antibodies are predominantly to carbohydrate antigens and are important in protection against polysaccharide encapsulated organisms such as *Streptococcus pneumoniae, Haemophilus influenzae,* and *Neisseria meningitidis*.[7] In infants and children of less than two years of age, however, the anticarbohydrate response is predominantly in the IgG 1 subclass which is possibly less protective, accounting for the increased susceptibility to invasive disease by encapsulated organisms. The *H influenzae* polysaccharide vaccine produces little or no protection in these children,[8] but by conjugating the polysaccharide to a protein carrier a protective immune response may be obtained.[9] It is not known whether this is due to a change in the IgG subclass of the antibody response to the vaccine. The role of IgG 4 is controversial. It is produced in response to repeated antigenic stimulation and it has been suggested that it may act as a blocking antibody in parasitic[10] and allergic[7] diseases or paradoxically be responsible for mediation of allergic responses.[11 12]

The mechanisms underlying IgG subclass deficiency are not clear. Deletions of sections of the immunoglobulin gene are extremely rare but have been found in a few healthy individuals with deficiencies of more than one IgG subclass in combination with IgA 1 deficiency.[13] Such deletions, however, have not been shown in symptomatic individuals with IgG subclass deficiency, nor have isolated deletions of single IgG subclass heavy chain regions been found.[14] The defect therefore probably resides at the level of regulation of immunoglobulin gene expression in B-lymphocytes. In some cases this may be due to abnormal T-lymphocyte control of B-lymphocyte function—IgG subclass deficiencies are often found in patients with T-lymphocyte deficiencies including AIDS[15] and after bone marrow transplantation.[16]

Among children with IgG subclass deficiencies there is 3:1 male:female predominance with IgG 2 deficiency being most common. This situation is reversed after puberty, women with IgG 3 deficiency becoming more common.[17] IgG subclass deficiencies may be transient in childhood, as seen with IgA deficiency. There appears to be more variation, however, in the levels of IgG subclass deficiency and more associations with other immunodeficiencies are found.[16] Low concentrations of IgG subclasses should be interpreted with caution before the age of 2 years as 'transient hypogammaglobulinaemia of infancy'[18] is relatively common and because of the late maturation of IgG 2 and IgG 4 immunoglobulin concentrations and antibody responses.[7]

IgG 1 to 4 respectively constitute 65%, 25%, 7%, and 3% of total serum IgG. In consequence deficiencies of IgG 2, 3, or 4 may occur in the presence of normal concentrations of total serum IgG. In fact high total concentrations of IgG may be found when as a result of one IgG subclass deficiency persistent stimulation of the other subclasses by repeated or chronic infection or inflammation occurs. In this situation even IgG 1 deficiency may occur in the presence of a normal total IgG.

Patients with IgG subclass deficiency are characterised by a vast array of symptoms and disease associations which are listed below.

(1) RESPIRATORY TRACT INFECTIONS

Recurrent or severe upper respiratory tract infections, otitis media, sinusitis, and bronchopulmonary infections are the most common manifestation of IgG subclass deficiency.[6 19] They occur particularly

in IgG 2 deficiency, but also in IgG 1 and IgG 3 deficiency. Organ damage resulting in deafness and bronchiectasis may occur, particularly when associated with IgA deficiency.[20] Occasionally organ damage may occur without symptoms of major infection being evident.

(2) GASTROINTESTINAL SYMPTOMS

We have observed a number of patients with diarrhoea, failure to thrive, and a variety of IgG subclass deficiencies, some of whom responded to intravenous immunoglobulin (IVIg) treatment. Similar symptoms were attributed to infection in another group of patients who also responded to IVIg.[21] Gastrointestinal symptoms may, however, be related to food intolerance in some cases.[17]

(3) OTHER INFECTIONS

Osteomyelitis, meningitis, urinary tract infection, and septicaemia are all described in patients with IgG subclass deficiencies. They may also have recurrent bacterial and viral (*Herpes simplex*) cutaneous infections.[6]

(4) ATOPY

A high incidence of significant allergic disease among people with IgG subclass deficiency has been noted,[17 22] particularly in IgG 3 deficiency[6 16]; IgG 4 concentrations may be reduced or raised, sometimes to very high levels.

(5) MULTISYSTEM DISEASE AND AUTOIMMUNITY

A number of groups have described associations of IgG subclass deficiencies with vasculitides including Henoch-Schönlein purpura, autoimmune cytopenias, and diabetes mellitus type I.[23 24] As with atopy it is unknown how and if IgG subclass deficiencies predispose to these disorders. The aetiology may be related to either a primary problem of dysregulation of immunity, or one which is secondary to frequent or abnormal handling of infections.

(6) NEUROLOGICAL DISORDERS

Three groups have described a remarkable response of severe anticonvulsant resistant epilepsy to intravenous immunoglobulin treatment.[25–27] About half of these patients had IgG subclass deficiency, and we have observed similar responses in two subclass deficient children with intractable fits.[16] Prospective studies in several centres are in progress to try and elucidate this phenomenon. IgG subclass deficiency is found in association with Freidreich's ataxia, and ataxia-telangiectasia.

(7) ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

Despite the hypergammaglobulinaemia characteristic of infection with human immunodeficiency virus 1, many patients have significant abnormalities of antibody production, and may be deficient in one or more IgG subclass.[15]

(8) OTHER IMMUNODEFICIENCIES

IgG subclass deficiency is often associated with IgA deficiency[4] and patients with this combination of immunodeficiencies usually have more symptoms and evidence of organ damage than those who have only one deficiency.[20] Patients with severe combined immunodeficiency, chronic granulomatous disease, and deficiency of major histocompatibility antigens (bare lymphocyte syndrome) may have low IgG subclass concentrations.[16 21]

(9) MISCELLANEOUS

Subclass deficiencies have been noted in both the early and late stages of recovery from bone marrow transplantation for immunodeficiency[28]—the immunoglobulin subclass concentrations of the donors are usually normal, giving further evidence for the role of dysregulation in the generation of IgG subclass deficiencies. Certain patients with pyrexia of unknown origin have been found to have IgG subclass deficiency, some of whom were characterised by marked lymphadenopathy and response to immunoglobulin infusions.[16]

The measurement of IgG subclasses and the interpretation of low concentrations may present considerable difficulty. There is a major variation of concentration with age, and establishing normal ranges presents major problems. There may also be inconsistency between and within different assays.[3] Faced with the problem that it may be difficult to interpret the finding of a low or even undetectable IgG subclass concentration in an individual, patients should be treated according to their symptoms and signs along the lines suggested for IgA deficiency.[4] The combination of judicious further investigation, observation, and escalation of preventative treatment (if required) should benefit most patients and allow identification of the minority who would benefit from intravenous immunoglobulin (IVIg) treatment. As IVIg can occasionally cause anaphylaxis[29] and transmit non-A non-B hepatitis,[30] the decision to prescribe it should only be taken after thorough evaluation of both the patient and other therapeutic options.

Finally, it is worth remembering that IgG subclass measurements are not the 'last word' in assessment of humoral immunity. Despite having normal concentrations of all immunoglobulin class and subclasses, patients have been reported who fail to

mount a protective antibody response to certain infections[31]—the quality of the immunoglobulin is probably as important as its quantity.

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