IgG Subclass Deficiency

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For the past two decades, IgG subclass deficiency has been popularized as a potential explanation for apparent infection-susceptibility in children and adults with normal total serum concentrations of IgG, IgA and IgM. This has led to the indiscriminate use of intravenous immunoglobulin (IVIG) replacement therapy in patients with low levels of one or more of the four IgG subclasses. This article will review the problems and pitfalls of basing IVIG therapy solely on such a finding, the potential implications of low levels of these proteins, and the optimal approach to diagnosis and management of patients with deficiencies of one or more IgG subclasses.

Functions of IgG

IgG is the immunoglobulin molecule normally present in highest concentration in both intra- and extravascular spaces, with a mean normal adult serum concentration of 1200 mg/dl. It is of particular importance in secondary antibody responses (immunologic memory), and it subserves a major role in host defense against infection. Molecules of the IgG isotype are involved in complement fixation, opsonization and fixation to macrophages. It is the only class of immunoglobulin transported across the placenta from the mother to the fetus.

IgG Subclasses

In the 1960’s, four subclasses of IgG were identified on the basis of unique heavy chain antigenic epitopes, and it was soon appreciated that there were differences among them in terms of concentration, structure and function (Table 1). The relative proportion of each of the IgG subclasses is generally constant within the total amount of IgG present in a given individual: IgG1 constitutes 60% to 65%, IgG2 20% to 25%, IgG3 3% to 10%, and IgG4 3% to 6% of total IgG. The mean normal adult serum concentration of IgG1 is 840 mg/dl, of IgG2 is 240 mg/dl, of IgG3 is 80 mg/dl, and of IgG4 is 40 mg/dl; however, there is a wide range of normal absolute values for each. Because of this variability and the much higher concentration of IgG1, it is possible to have deficiencies of all of the other subclasses and still have a normal total IgG level. Conversely, a low IgG2 concentration usually results in a low total IgG level. It is well to point out that low concentrations of IgG4 occur with high frequency among healthy individuals, and undetectable serum levels of IgG4 have been reported in

Table 1: Property of IgG Subclasses

<table>
<thead>
<tr>
<th>Property</th>
<th>IgG1</th>
<th>IgG2</th>
<th>IgG3</th>
<th>IgG4</th>
</tr>
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<tbody>
<tr>
<td>Percent of total IgG</td>
<td>60%</td>
<td>25%</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Serum half life (days)</td>
<td>23</td>
<td>23</td>
<td>9</td>
<td>23</td>
</tr>
<tr>
<td>Complement fixation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Binding to macrophage</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fc Receptors (opsonization)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Antibodies to protein antigens</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Antibodies to polysaccharide antigens</td>
<td>+</td>
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up to 15% of healthy children and 10% of healthy adults. Because of differences in their structure, particularly in the hinge regions, there are differences in the biologic properties of molecules in the four different subclasses. With regard to their abilities to fix complement by the classical pathway, there is a rank order of affinity of the different subclass molecules for Clq: IgG2 > IgG1 > IgG4 does not bind Clq and, therefore, does not fix complement. Similarly, IgG2 and IgG3 bind with higher affinity to Fc receptors on phagocytic cells than do IgG1 and IgG4. There are further differences with respect to their susceptibility to proteolytic digestion: IgG2 > IgG3 and IgG1 > IgG4. The latter contributes to differences in their half-lives: IgG1, IgG2 and IgG4 have a T 1/2 of 23 days, whereas IgG3 has a T 1/2 of only 9 days. Molecules of the four subclasses all cross the placenta, but IgG3 does so most efficiently and IgG2 least well. There are also differences in the acquisition of adult concentrations of the four subclasses: IgG1 reaches adult levels by 1 to 4 years of age, whereas concentrations of the other three subclasses are usually less than half those in adults until 4 to 5 years of age and do not reach adult levels until adolescence.

One of the earliest observations made about the different subclasses had to do with their content of antibodies of certain specificities. Thus, anti-protein antibodies (such as those to tetanus toxoid) were found in high concentration in the IgG2 and IgG3 subclasses, while conversely anti-polysaccharide (PS) antibodies were found in highest concentration in the IgG2 subclass. This predominance of particular antibody types within certain subclasses has particular relevance for the neonate, who does not receive as much IgG2 as IgG1, and for the normal human infant who does not readily make anti-polysaccharide antibodies until after the age of 2 years. However, soon after that young children begin to compensate for their lower IgG2 levels by making anti-polysaccharide antibodies of the IgG2 subclass to a much greater extent than do adults.

IgG Subclass Measurement

Because all but 5% to 10% of the amino acid sequences of the constant regions of the four IgG subclasses are identical, it was difficult to develop truly specific antisera for IgG subclass immunosassays. This impeded the development of sensitive, specific and reproducible assays and accounted for large discrepancies in results of IgG subclass determinations among different laboratories. The development of monoclonal antibodies allowed the development of much more specific and reliable assays, but there are still quality control problems when different methods are used (Table 2). Thus, these measurement problems (that continue to exist) result in numerous errors in diagnosis and are but one of several reasons that a decision to treat a patient with an ‘IgG subclass deficiency’ with IVIG is ill-founded.

Table 2: Problems Associated with the Measurement of IgG Subclasses

- Discrepancies in results obtained in different laboratories on aliquots of the same serum sample.
- Measurement of an IgG subclass concentration provides no information about antibody function.
- In young children, there is marked variability in normal concentrations of IgG subclasses.
- Most commercial laboratories do not have age-appropriate normal ranges for the specific method being used.

Table 3: IgG2 Subclass Deficiency Does Not Always Correlate with Antibody Deficiency

- Patients with the Wiskott-Aldrich syndrome, who have a profound anti-polysaccharide antibody deficiency, have normal levels of IgG2. (Nahm MH et al. J Immunol 1986; 137:3484.)
- Marked deficiencies in anti-polysaccharide antibodies have been noted in some children and adults (non-Wiskott-Aldrich) with recurrent infections despite the presence of normal levels of IgG2 and all other immunoglobulin isotypes. (Ambrosino DM et al. J Allerg Clin Immunol 1988; 81: 1175.)
- Asymptomatic individuals have been reported who totally lacked IgG1, IgG2, IgG4, and/or IgA1 owing to immunoglobulin heavy chain deletions. (LeFranc MP Immunol Rev 1991; 2:265.)
- Healthy children have been described with low levels of IgG2 but normal antibody responses to polysaccharide antigens after immunization. (Shackelford PG et al. Pediatr Res 1990; 27:16.)

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IgG2 subclass deficiency does not always correlate with antibody deficiency. The development of monoclonal antibodies allowed the development of much more specific and reliable assays, but there are still quality control problems when different methods are used (Table 2). Thus, these measurement problems (that continue to exist) result in numerous errors in diagnosis and are but one of several reasons that a decision to treat a patient with an ‘IgG subclass deficiency’ with IVIG is ill-founded.

IgG2 subclass deficiency may occur as an isolat-
ed finding in asymptomatic persons who are homozygous for the G3m(g) or G3m(b) allotypes. In symptomatic individuals, IgG3 deficiency has usually been noted primarily in association with deficiencies of other IgG subclasses. One exception was in a group of 30 patients with CT proven chronic sinusitis. However, IgG3 levels normalized with time in most of those patients after intensive antibiotic (not IVIG) therapy of their sinusitis, suggesting that the IgG3 deficiency was a secondary phenomenon due to consumption of antibodies in this subclass, which has the shortest half-life and the greatest susceptibility to degradation (Table 4).

The role of selective IgG4 deficiency in infection-susceptibility is unknown, since it occurs in many apparently normal individuals. Undetectable serum levels of IgG4 have been reported in up to 15% of healthy children and up to 10% of healthy adults.

Other causes of IgG subclass deficiency include 1) use of systemic corticosteroids and 2) gastrointestinal and renal protein-losing states. However, in both the steroid-induced and protein-loss types of IgG subclass deficiency, production of antibodies to protein and polysaccharide antigens is normal.

Approaches to Evaluation
Once an ‘IgG subclass deficiency’ has been identified in a patient, it becomes exceedingly important to ascertain the biologic significance of the finding. Assessing the patient’s capacities to respond to both protein and polysaccharide antigens is of crucial importance. In the case of responsiveness to protein antigens, obtaining serum before and two weeks after a DPT or a DT immunization will permit determination not only of the titers of tetanus and diphtheria antibodies but also of the magnitude of the response after the booster. Unfortunately it is often difficult to interpret the results reported from commercial laboratories, which usually report a level as ‘protective’ but often do not give any information as to what would be expected two weeks after a booster immunization. (Table 5)

Evaluating the patient’s capacity to respond to polysaccharide antigens is somewhat more problematic. Polyvalent pneumococcal vaccines are the most useful in this regard; however, they would not be expected to induce an antibody response even in normal infants in the first two years of life. IgG subclass measurement is also fraught with other problems in that age-group, where marked variability in the normal concentrations for these proteins is seen, and most commercial laboratories do not have their own age-appropriate normal ranges. Thus, obtaining IgG subclass determinations in the first two years of life is not a very cost-effective means of assessing immune function.

After the age of 2-3 years, pneumococcal vaccine immunization can provide reliable information about the patient’s immunocompetence. Certain of the serotypes are more immunogenic than others, particularly Type 3 polysaccharide, which appears to be immunogenic even in young children who are unable to respond to the other serotypes. Nevertheless, even if the patient responds to only that one serotype with more than a 2-fold rise in titer or quantity that is indicative of the capacity to produce anti-polysaccharide antibodies. Previous to the development of the conjugated Hemophilus influenzae type b (HIB) vaccine the HIB polysaccharide vaccine was also useful in the assessment of anti-polysaccharide antibody responses. However, response to the conjugated HIB vaccine is still useful in assessing overall immunocompetence, because a failure to respond to it signifies an inability to respond to the protein carrier and indicates a potentially serious abnormality of B cell function.

Management of IgG Subclass Deficiency
Patients with IgG deficiency who have been clearly demonstrated to have impaired abilities to produce anti-polysaccharide antibodies (but normal responses to protein antigens) should be immunized with polysaccharide-protein conjugate vaccines. In addition to the ones available for Hib, pneumococcal and meningococcal conjugate vaccines will soon be available. Titers should be monitored post-immunization, and patients should be maintained on antibiotic prophylaxis until they are protective.

* IVIG should be reserved for those with broad deficiencies of antibodies to both protein and polysaccharide antigens.

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<td>* In symptomatic individuals, IgG3 subclass deficiency usually occurs in association with deficiencies of other IgG subclasses.</td>
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<th>Table 5: Evaluation of Patients with IgG Subclass Deficiency</th>
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<td>* Assess abilities to produce antibodies to both protein and polysaccharide antigens.</td>
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<tr>
<td>* Protein antigens: tetanus and diphtheria most useful. Obtain serum before and two weeks after booster.</td>
</tr>
<tr>
<td>* Polysaccharide antigens: pneumococcal antibody titers before and three weeks after polyvalent vaccine. (Not generally useful in children during the first two years of life.)</td>
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<tr>
<td>* Care should be taken not to conclude that commercial laboratories’ reporting of ‘protective’ levels equates with a significant rise after immunization. It is most helpful to have paired pre- and post-immunization samples sent to same laboratory for quantitative measurement of antibody.</td>
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<td>* Based on results of antibody studies.</td>
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<tr>
<td>* IgG deficient patients unable to make anti-polysaccharide antibodies, but capable of producing anti-protein antibodies, should be immunized with all available polysaccharide-conjugate vaccines.</td>
</tr>
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Conclusions
From these observations, it can be concluded that IgG subclass measurement is not very helpful in the general assessment of immune function. Such assays provide no information about the patient’s capacity to produce specific antibodies to protein,
polysaccharide, or viral antigens. Moreover, there is considerable variability in values reported for the different subclasses when aliquots of the same serum sample are tested in different commercial laboratories. Thus, when ‘abnormalities’ are detected, one is still left with the more relevant question, i.e. “what is the capacity of the patient to make specific antibodies to protein and polysaccharide antigens?” Care should be taken not to overinterpret ‘low’ levels of antibodies to pneumococcal polysaccharide serotypes 6A, 9N, 14 and 23F, which have very low immunogenicity even in healthy children. Finally, IVIG should not be given to ‘IgG subclass deficient’ patients unless they are known to have a deficiency of antibodies to a broad array of protein and polysaccharide antigens.

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