IgG Subclass Deficiencies:

To Treat or Not to Treat?

It is unknown what causes IgG subclass deficiencies, but their symptoms can be managed, and many children outgrow them.

By E. Richard Stiehm, MD

IGG SUBCLASS DEFICIENCIES are common (usually mild) primary antibody immunodeficiencies that too often are treated with immune globulin (IG) therapy. This article discusses the discovery and function of the subclasses, their role in host defense, their deficiencies and a brief mention of IgG4-related disease.

An IgG subclass deficiency is present if one or more of the four IgG subclasses are low, but the total IgG level is normal. Since up to 20 percent of normal subjects have one or more low levels of an IgG subclass, most often IgG4, a clinically significant IgG subclass deficiency requires the presence of recurrent infections and a significant defect in functional antibody responses.

Indications in patients who should be tested for an IgG subclass deficiency are shown in Table 1.

Discovery of the IgG Subclasses

Patients with the malignant lymphoma termed “multiple myeloma” have large amounts of a single malignant B-cell clone that make an enormous amount of a single subclass of IgG globulin. These myeloma IgGs can be readily purified and used to make rabbit antibodies to that myeloma IgG, to other myeloma IgGs of the same subclass and to normal IgG containing all subclasses.

Using these antibodies, four distinct subclasses of IgG were identified in the serum of most normal adults. These subclasses were named IgG1, IgG2, IgG3 and IgG4 in order of their decreasing amounts in normal IgG. All subclass immune globulins react to a polyclonal anti-IgG antibody, but only to one of the specific subclass antibodies used to measure the levels of each subclass.
IgG subclass deficiencies were first reported by Yount et al. in 1971 working in the same Rockefeller Institute Laboratory where the subclasses were first identified. Their cause is unknown, but gene deletions in some families result in hereditary subclass deficiency.

The relative frequency of symptomatic subclass deficiencies can be estimated by combining four immunodeficiency registries that included 2,082 antibody-deficient patients. Subclass deficiencies make up 5 percent of the patients compared to 29 percent for transient hypogammaglobulinemia of infancy, 29 percent for selective IgA deficiency and 15 percent for common variable immunodeficiency.

Properties of the IgG Subclasses (Table 2)

IgG1 subclass is the most abundant subclass (70 percent) with a mean adult level of 900 mg/dl. IgG1 and to a lesser extent IgG3 contain most of the antibodies acquired from past infection or vaccination. These antibodies kill viruses, neutralize bacterial toxins and coat bacteria for engulfment and death by white blood cells, a process called opsonophagocytosis. The latter is promoted by a series of nonspecific serum proteins collectively called complement.

The abundance of IgG1 and its long half-life make it the most important subclass for host defense, and it is the usual antibody component of therapeutic monoclonal antibodies. IgG1 and IgG3 readily cross the placenta in the second half of pregnancy to provide protective antibodies to the newborn infant. The gradual decline of these immunoglobulins after birth results in physiologic hypogammaglobulinemia of infancy from 3 months to 6 months of life. When there is a delay of the infant making its own immune globulin, the result is transient hypogammaglobulinemia of infancy starting after 6 months. Both of these conditions are predominantly IgG1 deficiencies and rarely require treatment since most infants will outgrow them.

IgG2 subclass makes up 20 percent of the serum IgG with a mean level of 240 mg/dl. IgG2 contains most of the antibodies to polysaccharide antigens present on the capsule of common pathogens, including Streptococcus pneumoniae, Haemophilus influenzae type b, Streptococcus...

Table 1. Indications for Subclass Analysis

- Recurrent respiratory infections despite normal total Ig levels
- Selective IgA deficiency
- Poor response to a polysaccharide vaccine
- Common variable immunodeficiency
- Hypogammaglobulinemia, primary or secondary
- Prolonged hypogammaglobulinemia of infancy
- Symptoms and/or signs suggestive of IgG4-related disease (autoimmune pancreatitis, sclerosing cholangitis, salivary gland enlargement, orbital proptosis, retroperitoneal fibrosis)

Table 2. Properties of the IgG Subclasses

<table>
<thead>
<tr>
<th>General Properties</th>
<th>IgG1</th>
<th>IgG2</th>
<th>IgG3</th>
<th>IgG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight (daltons)</td>
<td>150,000</td>
<td>150,000</td>
<td>170,000</td>
<td>150,000</td>
</tr>
<tr>
<td>Relative frequency (% of IgG)</td>
<td>70</td>
<td>20</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Mean adult serum level (mg/dl)</td>
<td>800</td>
<td>240</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>Half-life (days)</td>
<td>25</td>
<td>25</td>
<td>9</td>
<td>25</td>
</tr>
<tr>
<td>Placental transfer</td>
<td>++++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Complement activation</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>–</td>
</tr>
<tr>
<td>Antibody Responses to</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteins</td>
<td>+++</td>
<td>+/-</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Polysaccharides</td>
<td>+</td>
<td>+++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Allergens</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>++</td>
</tr>
</tbody>
</table>
pyogenes and Neisseria meningitidis. IgG2 antibodies do not cross the placenta well, contributing to the enhanced susceptibility of young infants to these infections.

IgG3 subclass makes up 7 percent of the serum IgG with an adult mean level of 80 mg/dl. IgG3 subclass deficiency is often associated with other subclass deficiencies. Although it is transferred well through the placenta, its low level and short half-life mean it has a minimal role in newborn immunity.

IgG4 subclass makes up only 3 percent of the serum IgG with a mean level of 40 mg/dl. It is the subclass most often associated with other subclass deficiencies. Antibodies to allergens are mostly in this subclass and often increase following allergy immunotherapy. IgG4 antibodies may have a protective effect on allergic reactions by blocking IgE reactions and inhibiting mast cell degranulation.7 A marked elevation of IgG4 (greater than 100 mg/dl) is associated with an illness called IgG-4-related disease,8 an immune-mediated fibroinflammatory disorder, including autoimmune pancreatitis, sclerosing cholangitis, enlarged inflamed salivary glands, orbital proptosis and retroperitoneal fibrosis. When this occurs, the IgG4 levels average 234 mg/dl! Diagnosis is confirmed by finding IgG4-staining plasma cells and fibrosis of the affected tissue or organ.

IgG Subclass Deficiencies (Table 3)

IgG1 subclass deficiency makes up 10 percent of symptomatic subclass deficiencies (Table 3). Only rarely is there an associated subclass deficiency. Complete absence of IgG1 is unusual, but Smith et al. reported familial absence of IgG1.9 IgG1 deficiencies are usually identified when hypogammaglobulinemic patients have subclass levels measured. Most of these patients have recurrent sinopulmonary infections, pharyngitis and ear infections similar to infants with transient hypogammaglobulinemia. Children with IgG1 subclass deficiency often outgrow the condition, especially if they make antibodies to vaccine antigens.

IgG2 subclass deficiency makes up 25 percent of the subclass deficiencies with a mean adult level of 240 mg/dl. It is the most common symptomatic subclass deficiency in children and is often accompanied by other subclass deficiencies and/or selective IgA deficiency. Manifestations include sinopulmonary infections, recurrent otitis and asthmatic bronchitis. Patients may have poor responses to polysaccharide vaccines, often aggravated by weak activation of the complement system. IgG2 deficiency is also present in some endocrinopathies (e.g., diabetes, growth hormone deficiencies) and other primary immunodeficiencies (e.g., mucocutaneous candidiasis, ataxia-telangiectasia).

### Table 3. Clinical Features of IgG Subclass Deficiencies

<table>
<thead>
<tr>
<th>General Properties</th>
<th>IgG1</th>
<th>IgG2</th>
<th>IgG3</th>
<th>IgG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative frequency (clinical)</td>
<td>10%</td>
<td>25%</td>
<td>15%</td>
<td>50%</td>
</tr>
<tr>
<td>Relative frequency (laboratory)</td>
<td>10%</td>
<td>20%</td>
<td>20%</td>
<td>50%</td>
</tr>
<tr>
<td>Relative frequency (&gt;1 subclass)</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Clinical severity</td>
<td>++++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Low levels: Age under 10 years</td>
<td>&lt;250 mg/dl</td>
<td>&lt;40 mg/dl</td>
<td>&lt;10 mg/dl</td>
<td>&lt;1 mg/dl</td>
</tr>
<tr>
<td>Low levels: Age over 10 years</td>
<td>&lt;350 mg/dl</td>
<td>&lt;50 mg/dl</td>
<td>&lt;15 mg/dl</td>
<td>&lt;1 mg/dl</td>
</tr>
</tbody>
</table>
IgG3 subclass deficiency makes up about 15 percent of the subclass deficiencies with a mean adult level of 80 mg/dl, and it is more common in adults. When symptomatic, it is usually associated with other subclass deficiencies. Findings then include viral respiratory infections, refractory sinusitis and asthma. Levels of IgG3 may decrease during an antibiotic-treated infection, suggesting its consumption during recovery. IgG3-deficient patients with an IgG4 deficiency and/or selective IgA deficiency often have atopic diseases with elevated IgE levels. And, familial cases have been reported.

IgG4 subclass deficiency, with a mean level of 40 mg/dl, is the most common but most benign subclass deficiency. An isolated deficiency occurs in 15 percent of children and 10 percent of adults, most of whom are asymptomatic. When associated with other subclass deficiencies and/or a selective IgA deficiency, sinopulmonary infections are common, including pneumonia and bronchiectasis. Heiner described a familial syndrome of IgG4 deficiency with bronchiectasis. Hill et al. found an IgG4 deficiency was present in 5 percent of their bronchiectasis patients compared to 2 percent for other subclass deficiencies. Additionally, an IgG4 deficiency may be a marker for susceptibility to respiratory infections.

Managing IgG Subclass Deficiencies
A subclass deficiency should be confirmed by a repeat test, preferably from a different laboratory.

Asymptomatic patients with a subclass deficiency but normal antibody responses require no treatment. Follow-up studies are recommended since some subclass deficiencies may evolve into common variable immunodeficiency. Mildly symptomatic subclass-deficient patients should first be tried on antibiotics, inhaled steroids or bronchodilators. Prophylactic antibiotics during the winter are sometimes valuable. Surgical treatment for chronic sinusitis should be considered.

Failure of these measures with persistent infections may be an indication for IG therapy either intravenously or subcutaneously at the same dosage for proven antibody-deficient patients. After several months of successful IG therapy, a trial off of IG therapy should be considered, followed by immunologic reassessment. This trial should be started in late spring or summer months when there is a reduced chance of contracting a respiratory infection. Parents or patients should be told that stopping IG therapy is often followed by more minor respiratory infections for several months, but it is worth the low risk and expense of lifelong IG therapy. Further, many patients, especially children, may outgrow their subclass deficiency.

References

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