

# Immediate hypersensitivity in adults with IgG deficiency and recurrent respiratory infections

Valentin Popa, MD and Stephen M Nagy, Jr, MD

**Background:** Little is known about the prevalence of atopy in adults with recurrent respiratory infections and IgG deficiency.

**Objective and methods:** To elucidate this aspect, we skin-tested 95 consecutive adults with respiratory infections, subnormal levels of IgG subclasses or common variable immunodeficiency and usually poor response to vaccination. In 50 subjects we also measured total IgE.

**Results:** We found 67 subjects with IgG subclass deficiency, 21 subjects with mild (partial) and 5 with usual common variable immunodeficiency, and 2 subjects with functional IgG deficiency. Atopy was encountered in 42/95 subjects, 33/44 (75%) with asthma, 7/19 (38%) with isolated rhinosinusitis, 1/27 (4%) with chronic obstructive lung disease, and 1/5 (20%) with both the latter disease and asthma, respectively. Atopy was preferentially clustered in subjects with asthma ( $P < .05$ ) who were less than 40 years of age ( $P < .05$ ) and nonsmoking. Atopy was not affected by the type of IgG deficiency, unless it was usual common variable immunodeficiency, in which case the skin tests tended to be negative (4/5). Total IgE was within normal range but less elevated than usually seen in asthma or chronic obstructive lung disease. Total IgE was independent of the type of IgG deficiency, except for usual common variable immunodeficiency in which it remained  $<10$  IU/mL.

**Conclusions:** In adults with symptomatic IgG deficiency, the prevalence of immediate hypersensitivity and its modulation by age and smoking are similar to the referred, non-IgG deficient population; however, total IgE may be lower in the former than in the latter. In common variable immunodeficiency, consistent with the literature data, both the prevalence of atopy and serum total IgE are decreased.

Ann Allergy Asthma Immunol 1999;82:567-573.

## INTRODUCTION

Immunoglobulin G deficiency is emerging as a relatively frequent abnormality in adults with recurrent respiratory infections. Many of these patients seem to suffer from rhinitis and asthma but the participation of atopy in this immunodeficiency is not clear.

Limiting our considerations to adults, several lines of evidence suggest that the subnormal levels of IgG subclasses associated with recurrent respiratory infections,<sup>1-4</sup> including IgG3 and IgG4,<sup>5-10</sup> are clinically relevant: IgG response to vaccination is

impaired,<sup>5</sup> intravenous IgG may have a beneficial effect<sup>6,11-14</sup>; the serum levels of other immunoglobulins, IgD,<sup>15</sup> IgA,<sup>16</sup> or IgM<sup>5,6,7</sup> may be subnormal; the relatives of patients may also be deficient in IgG subclasses<sup>14,15</sup>; and lymphocytic interstitial pneumonitis or bronchiolitis obliterans obstructive pneumonia, occasionally associated with common variable immunodeficiency, may also be encountered.<sup>17</sup>

In IgG subclass deficiency, asthma and chronic rhinosinusitis seem to be relatively frequent.<sup>5,6,8,10-12</sup> Unlike IgA<sup>18-21</sup> or IgM<sup>22,23</sup> deficiency, atopy was found to be less common in IgG subclass deficiency of both children<sup>10,14</sup> and adults<sup>8</sup> than in the general asthmatic population. The level of IgE in this immunodeficiency has not been reported. The opposite is true for se-

vere IgG deficiency in which the IgE values but not the prevalence of atopy are known. Indeed, in common variable immunodeficiency (mostly adult subjects), X-linked hypogammaglobulinemia (children) and hyper-IgM syndrome (children), all characterized by low IgG, total IgE is markedly reduced.<sup>24,25</sup> Would a low IgE and its expected corollary, a reduced prevalence of atopy, also be present in IgG subclass deficiency?

The prevalence of atopy in IgG subclass deficiency cannot be surmised from the prevalence of atopy in other bronchial diseases associated with repeated respiratory infections. In bronchiectasis or cystic fibrosis, serum IgG or IgG subclasses may be elevated rather than reduced.<sup>26-30</sup> Similar to chronic bronchitis<sup>31</sup> in these diseases, serum concentration of antibodies against the pathogenic flora of the bronchi and the response to bacterial antigens is not low but generally high.<sup>29,30</sup>

The aim of this report was to evaluate the prevalence of atopy in adults with recurrent respiratory infections and common variable immunodeficiency or IgG subclass deficiency. For the practicing allergist, pulmonologist, or primary care physician, this study could indicate whether the work up for IgG deficiency in atopy or for atopy in IgG deficiency is likely to be productive. For immunologists, this report may show whether there is a link between IgG and IgE in IgG subclass deficiency. In the 2-signal concept of IgE regulation, either signal modulates not only the switch to IgE but also to IgG isotypes.<sup>32</sup> For example, in X-linked hyper-IgM, the defective expression in CD40 ligand leads to an impairment in the switch to IgG, IgE, and IgA.

Department of Medicine, University of California at Davis, Sacramento, California.

Study supported in part by a grant from Physicians Clinical Laboratory and Schering, Inc.

Received for publication October 23, 1997.

Accepted for publication March 1, 1999.

## MATERIAL

Ninety-five consecutive adults with recurrent respiratory infections and IgG deficiency, were skin tested with a standard battery of allergens. The skin testing was part of the routine allergy evaluation of patients with chronic respiratory diseases who have acute exacerbations that may recognize an atopic determinism. Ninety-five out of 320 subjects with recurrent respiratory infections had immunoglobulin deficiency (30%). Seventy-five subjects were seen in our separate practices and 20 in the Sacramento Allergy Clinic of Martinez Veterans Administration Medical Center (1983–1987). As mentioned before, recurrent respiratory infections were defined as at least 5 “chest colds,” lasting each time 2 weeks or more in the past 2 years and/or two episodes of pneumonia encountered in healthy blood donors.<sup>37</sup> We applied current, usual criteria for the diagnosis of pneumonia, bronchial asthma, acute bronchitis, chronic obstructive pulmonary disease (COPD), or chronic sinusitis.<sup>38,39</sup> To avoid fragmentation of a relatively small sample, only the subjects smoking at least 20 cigarettes per day for 20 or more years were considered smokers.

## METHODS

All subjects were skin tested with Hollister-Stier/Miles allergens. The allergens used were those prepared from regional trees, grasses and weeds pollen, animal hair, house dust mite, and MMP molds (after Morrow, Meyer and Prince who devised the method). According to the history, additional allergens were applied in some subjects. The prick puncture method was used in all subjects. If the history was suggestive of sensitization to an allergen to which the prick test was negative, intradermal testing was also performed.

Immunoglobulin G subclass determinations were carried out on a commercial basis. For veterans, we used the Peter Brent Brigham Immunology laboratory (1983 to 1987; method: radial immunodiffusion). For non-veterans, between 1987 to 1994, we used

two laboratories: Associated Regional University Laboratory (Salt Lake City, UT), the method being radial immunodiffusion as performed with the “Binding Site” kit; and, Specialty Laboratories (Santa Monica, CA), where an immunoradiometric method was applied. For comparison purposes, in 15 non-veterans, duplicate measurements were carried out in the same serum sample at the two laboratories mentioned above. Total IgG, IgM, and IgA were measured with a nephelometric method and total IgE with a non-competitive radioimmunoassay (Pharmacia). The immunoglobulin classes were measured either at Martinez VA Medical Center, if the subjects were veterans, or Physicians Clinical Laboratory in Sacramento if they were non-veterans.

Values less than 76 mg% for IgA, 40 mg% for IgM, 650 mg% for total IgG, 422 mg% for IgG1, 117 mg% for IgG2, 41 mg% for IgG3, and 11 mg% for IgG4 were considered subnormal. These levels are below the 95% confidence limits reported by Silverman et al.<sup>38</sup> for total IgG, IgA and IgM, Schur<sup>39</sup> for IgG4, and Oxelius<sup>40</sup> for the remaining IgG subclasses. Similar to IgA and IgM deficiency, in which a cut-off value of the corresponding immunoglobulin discriminates between a partial and complete form of deficiency<sup>7,19</sup> we used an IgG level of 450 mg% to separate a partial or mild form and a complete or severe form of common variable immunodeficiency.<sup>5,6</sup> For IgE levels, we chose the geometric mean of normal values (32 IU/mL)  $\pm 1$  SD or 80 IU as the value offering the best combination of sensitivity and specificity for separating asthmatic from normal subjects of all adult age groups.<sup>41</sup> For IgE levels in smokers, we selected the study principles of Gerrard et al.<sup>42</sup> in which the geometric mean of IgE in age-matched smokers and non-smokers was 40 and 70 IU/mL, respectively. The latter value is very close to the value mentioned above for the separation of asthmatics from normals.<sup>41</sup>

The veterans were vaccinated with tetanus toxoid and *H. influenzae* (both from Lederle, Wayne, NY). The specific IgG antibodies were measured

by enzyme-linked immunoassay in Dr D Heiner's research laboratory at Harbor-UCLA Medical Center.<sup>5,6</sup> One group of non-veterans was immunized with tetanus toxoid (Lederle) and multivalent pneumococcal vaccine (Merck). Another group received conjugated tetanus and diphtheria toxoid (Pasteur Merieux Connaught), Prohibit, an *H. influenzae* b conjugate with diphtheria toxoid (Pasteur Merieux Connaught) and multivalent pneumococcus vaccine (Merck). For the latter vaccine, we measured the IgG antibody response against antigens 3, 7F, 9N, and 14. In all nonveterans, the specific IgG antibodies were measured by an enzyme-linked immunoassay at Specialty Laboratories (Santa Monica, CA). Failure to increase the specific antibody level by more than twice the basal level was considered insufficient, signalling functional IgG deficiency (6; review in 43). A basal preimmunization level of pneumococcal antibody against type 3, 7F, 9N, or 14 less than 200 ng N/mL<sup>44</sup> or less than 150 ng N/mL for anti-*H. influenzae* b antibody was felt to be unprotective.<sup>44</sup> In the absence of vaccination records, it was impossible to determine the significance of non-protective anti-tetanus and anti-diphtheria antibodies measured before vaccination.

No test was performed in our patients without a direct clinical need, no research on atopy was intended at the time of clinical evaluation and the data on consecutive patients was analyzed retrospectively. Thus, no consent form was used or could have been used.

### Statistical Analysis

The results obtained in different groups of subjects were compared by Student's *t* test for paired or unpaired observations and chi square test with Yates correction. The results of IgG subclass determinations performed in the same serum sample with two methods were analyzed by calculating the corresponding regression equations ( $Y = a + bx$ ) and the statistical significance of the slope (*b*).

RESULTS

As shown in Table 1, 21 subjects had partial common variable immunodeficiency, 5 had usual (complete) common variable immunodeficiency, 67 had IgG subclass deficiency, and 2 had normal immunoglobulin levels but functional deficiency demonstrated with pneumococcal vaccine. The range of abnormal values was 110 to 400 mg%, 50 to 98 mg%, 3 to 40 mg%, and 0 to 10 mg% for IgG1, IgG2, IgG3, and IgG4, respectively.

The duplicate measurements of IgG subclasses performed with two different methods in 15 subjects at Speciality Laboratories and Associated Regional University Physicians (Salt Lake City, UT) were closely correlated. The P value of the slope for all subclasses was less than .0001. These measurements, part of a quality control program of Physicians Clinical Laboratory, were entirely supported by this laboratory.

Seventy-five out of 95 subjects completed the vaccination protocol. Fifty-nine subjects (78%) had functional IgG deficiency, that is a poor response to vaccination mediated through isotypes IgG1 (25 subjects), IgG2 (50 subjects), or both (19 of the above). A low, non-protective level of one out of the 4 anti-pneumococcal antibodies tested was found in 45 subjects before vaccination. Eight of these subjects had nonprotective levels against three pneumococcal antigens. With two exceptions, all 75 subjects who com-

pleted the vaccination protocol had either an impaired response to vaccination or a non-protective level against *S. pneumoniae*. No subject had non-protective antibody levels against *H. influenzae*. The response to vaccination bore no relationship to a quantitative deficiency in a particular IgG isotype (preliminary report in 45).

Figures 1 and 2 indicate that out of 95 subjects, 44 had asthma (46%); 19 subjects had rhinosinusitis without asthma (20%); and 32 subjects had chronic obstructive lung disease, 5 with (6%) and 27 without asthma (28%). The subjects with chronic obstructive lung disease, with or without asthma had also rhinosinusitis but it was primarily acute. Except for usual common variable immunodeficiency, which was not associated with isolated rhinosinusitis, all forms of IgG subclass deficiency and the two types of functional IgG deficiency were represented in the clinical entities mentioned above.

In 35 subjects with asthma, 12 subjects with isolated rhinosinusitis and all 32 subjects with chronic obstructive lung disease, it was possible to relate the onset of recurrent respiratory infections to the onset of the corresponding chronic respiratory disease. In most cases, 31/35 subjects with asthma ( $P < .05$ ), 10/12 subjects with rhinosinusitis ( $P < .05$ ) and all subjects with chronic obstructive lung disease, the recurrent

respiratory infections developed after the onset of these chronic diseases. In the remaining subjects, the beginning of these diseases coincided with (5 subjects) or followed (1 subject) the onset of recurrent respiratory infections.

In 42 of 95 subjects (44%), henceforth called atopic, skin tests were positive to at least one allergen.

Table 1 indicates that atopy was not specifically restricted to a certain IgG deficiency. The deficient IgG1-mediated and IgG2-mediated responses were similar in atopic (11/25 and 24/50, respectively) and nonatopic subjects (14/25 and 26/50, respectively). In the usual form of common variable immunodeficiency, atopy seemed to be rare (1/5), but the small number of subjects precluded statistical analysis.

As shown in Figure 1 for nonsmokers and Figure 2 for smokers, the prevalence of atopy (hatched blocks) varied with the clinical entity: 33/44 subjects (75%) with asthma (27 nonsmokers and 6 smokers), 7/19 (38%) with rhinosinusitis (6 nonsmokers and 1 smokers), 1/27 (4%) with chronic obstructive lung disease (all smokers), and 1/5 (20%) with chronic obstructive lung disease + asthma (all smokers) were atopic. As a group, the subjects with asthma were more often atopic than nonatopic ( $P < .05$ ), the subjects with chronic obstructive lung disease were generally ( $P < .05$ ) nonatopic, while

Table 1. IgG Deficiency

| IgG                   | Subjects  |           |
|-----------------------|-----------|-----------|
|                       | Atopic    | Nonatopic |
| Subnormal             |           |           |
| IgG1                  | 2         | 6         |
| IgG2                  | 1         | 4         |
| IgG3                  | 19        | 16        |
| IgG4                  | 6         | 7         |
| IgG2 + IgG4           | 1         | 2         |
| IgG2 + IgA            | 1         | 2         |
| CVID                  | 10        | 16        |
| Normal                |           |           |
| Functional deficiency | 2         | 0         |
| <b>Total</b>          | <b>44</b> | <b>51</b> |

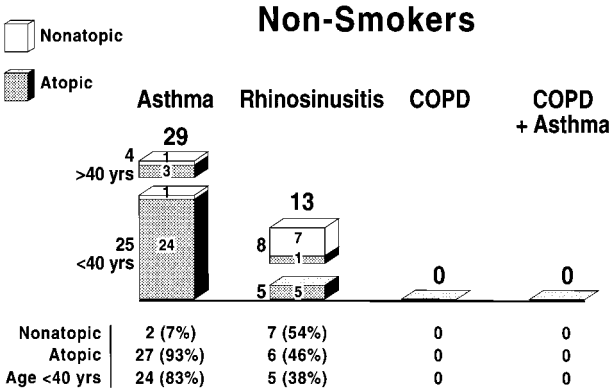


Figure 1. The figure shows the prevalence of atopy and its modulation by disease and age in 42 nonsmoking subjects with IgG deficiency. The clinical entities are displayed vertically. Within each entity, the subjects above or below age 40 are separated in two different blocks. In each block, hatched and clear zones represent the atopic or non-atopic subjects, respectively.

the small rhinosinusitis group showed a borderline difference, statistically not significant, between atopic and nonatopic subjects ( $P < .1$ ). All asthmatic subjects wheezed and felt short of breath during respiratory infections and also, intermittently, outside these episodes.

The subjects were divided into two groups according to the age at the time of diagnosis, above and below 40 years (Figures 1 and 2, upper and lower blocks, respectively). The majority of subjects with asthma (33/44) were less than 40 years of age ( $P < .05$ ) and atopic (28/33) rather than nonatopic ( $P < .05$ ). The rhinosinusitis group had 6/19 subjects less than 40 years ( $P < .1$ ) who were all atopic. With few exceptions, the smokers were above age 40 and most non-smokers were below this age, probably because the definition of smoking required a habit of at least 20 years. This habit lasted from 40–30 years (12 subjects), 29–25 years (33 subjects), and 20–24 years (8 subjects) in smokers and 1 to 5 years (3 subjects), 6 to 10 years (3 subjects) in nonsmokers. The individuals with chronic obstructive lung disease and asthma (28/32) were generally over age 40 ( $P < .05$ ) and nonatopic (30/32) ( $P < .05$ ). We also determined the prevalence of atopy in subjects with onset of asthma before and after age 30. This reduces the influence of smoking while sharpening the effect of age on the onset of the disease and atopy. In the general population, asthma beginning before age 30 is predominantly atopic, while asthma appearing after this age is nonatopic.<sup>46</sup> In 30 subjects, asthma began before age 30, 28 being atopic and 2 non-atopic ( $P < .05$ ). After age 30, 9 were non-atopic and 5 atopic ( $P > .05$ ).

In chronic obstructive lung disease, age (above or below 40 years), and smoking (more or less than 20 years), were interrelated; their separate effect on atopy could not be assessed.

Total IgE was measured in 50/95 subjects: all 32 subjects with chronic obstructive lung disease + asthma, 18 asthmatic subjects, 6 non-atopic and 12 atopic subjects. The four types of

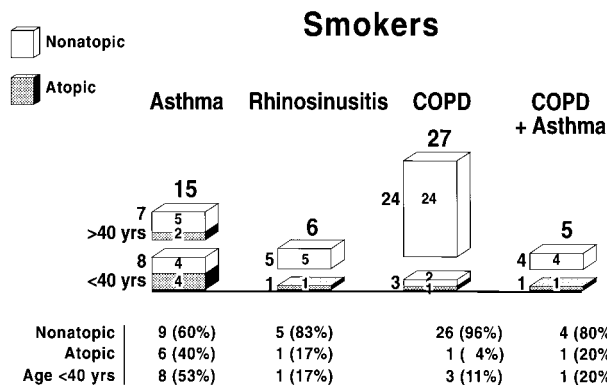


Figure 2. This figure presents the prevalence of atopy and its modulation by disease, age and smoking in 53 smokers with IgG deficiency. For legend, see figure 1.

quantitative IgG deficiency and the two types of their associated functional IgG deficiency were represented in these asthmatic or subjects with chronic bronchitis. In asthmatic subjects, the geometric mean  $\pm 1$  SD of IgE was  $22 \pm 7$ , within normal range but below asthmatic range; only one subject had a value above 80 IU/mL. In chronic bronchitis, IgE was  $17 \pm 6$ , again within normal range but substantially below the values reported in smokers. All 4 subjects with usual common variable immunodeficiency had IgE less than 10 IU/mL.

## DISCUSSION

Seventy percent (67/95) of the subjects included in this study had subnormal values of IgG subclasses with normal total IgG. The remaining subjects presented with partial or complete common variable immunodeficiency (26/95 or 27%), or functional IgG deficiency (2/95 or 3%). This series of adults with IgG subclass deficiency is the largest reported in this country. If one considers only the series with a vaccination protocol this series of adults with IgG subclass deficiency is the largest in the literature as well. It is also larger than any IgA<sup>18–21</sup> or IgM<sup>22,23</sup> deficiency series. Also, the IgA deficiency series did not provide data regarding the IgG-mediated and/or IgA-mediated responses to vaccination.

## Chronic Respiratory Diseases in IgG Deficiency

This and a previous study<sup>6</sup> indicate that in symptomatic IgG deficiency, nasal and bronchial symptoms persist at a variable degree between respiratory infections. These chronic, intercritical symptoms involve the same respiratory segments affected by the acute episodes<sup>6</sup> and may recognize an allergic component.

Neither the presence nor the pulmonary physiologic impact<sup>6</sup> of these chronic inflammatory diseases of the airways depend on a particular IgG isotype or IgG-mediated pattern of response to vaccination. Asthma seems more prevalent in symptomatic IgG subclass deficiency and partial common variable immunodeficiency than in complete (25–33%<sup>19,20</sup>) or partial (15%<sup>20</sup>) IgA deficiency. In IgG deficiency, unlike IgA deficiency, the more severe the deficiency, the less prevalent is asthma. In the three large series of common variable immunodeficiency of this country, asthma was not mentioned in one,<sup>47</sup> affected 10% of the subjects in the second,<sup>48</sup> while in the third,<sup>49</sup> it was probably amalgamated with other conditions in “chronic lung diseases” (32% of the subjects). In X-linked agammaglobulinemia, asthma is not listed as a manifestation.<sup>7,50</sup> In the present series, 3/5 subjects with the usual or complete form of common variable immunodeficiency had asthma.

Usually but not invariably, asthma, rhinosinusitis, and chronic bronchitis precede the onset of recurrent respiratory infections regardless of IgG subclass deficiency. This extends a previous report on 4 subjects with IgG2 deficiency.<sup>51</sup> The simple presence of repeated respiratory infections may increase the propensity to develop these chronic diseases in the general population. For instance, in bronchiectasis and cystic fibrosis<sup>26,27,52,53</sup>; asthma is more prevalent than in the general population but less frequent than in IgG subclass deficiency. It seems that with occasional exceptions, in IgG subclass deficiency associated with repeated infections, the development of these chronic respiratory diseases is independent of the immunologic mechanisms defining this immune deficiency (quantitative and functional IgG deficiency) and, to some extent, their clinical effect, repeated respiratory infections.

#### Atopy

This report indicates that in symptomatic IgG deficiency, acute exacerbations of asthma, rhinosinusitis and asthma + chronic obstructive lung disease may also be triggered by an environmental allergen. It is not known whether allergy to bacteria<sup>46,54-57</sup> or viruses<sup>58,59</sup> plays a role in the acute, infection-related manifestations of IgG deficiency.

The prevalence of atopy depends on the underlying respiratory disease, asthma > rhinosinusitis > chronic obstructive lung disease, and young age (<40 and even <30 years) but not on a particular IgG subclass deficiency or presence of recurrent infections. It seems that in IgG subclass deficiency or partial common variable immunodeficiency, atopy does not reflect an abnormality in isotype switching. Indeed, the prevalence of atopy is comparable across deficient IgG subclasses, regardless of the distance separating their exon from that of IgE.

In both general or referred populations, atopy is disease-dependent and age-dependent. The high prevalence of immediate hypersensitivity in asthma

(75%) and chronic rhinosinusitis (38%) observed in this series is comparable to that encountered in (presumably) non-immunocompromised<sup>46,54,55,60,61</sup> or IgA-deficient<sup>18,20</sup> and IgM-deficient<sup>23</sup> subjects referred to allergists. The prevalence of atopy in chronic obstructive lung disease associated with shortness of breath and wheezing (20%)<sup>62</sup> is identical to that observed in our subjects who have similar complaints during chest colds.<sup>6</sup> The findings regarding the prevalence of atopy in IgG deficiency may be explained by the fact that in most subjects asthma, rhinosinusitis, or chronic obstructive lung disease precede recurrent respiratory infections. When the latter appear, the factors responsible for atopy might have already made their mark. The recurrent respiratory infections may exert a minor if any influence on atopy, since its prevalence in diseases with repeated infections is inconsistent: normal,<sup>27</sup> increased,<sup>62</sup> or decreased.<sup>28</sup>

#### Total IgE

The average level of IgE in chronic obstructive lung disease or asthma associated with IgG deficiency, 17.0 IU and 22.0, respectively is lower than in subjects with the same respiratory diseases but without immune deficiency, 40 IU and 80.0 IU, respectively.<sup>41,42</sup> This suggests that atopy and total IgE are differently modulated in IgG deficiency. The simple presence of recurrent respiratory infections does not appear to modulate serum IgE in this immune deficiency. Indeed, total IgE is normal in bronchiectasis<sup>27</sup> or cystic fibrosis<sup>63</sup> and increased in chronic bronchitis.<sup>42,64</sup> The differences in IgE responses, along with the differences in IgG levels and, as mentioned before, specific antibacterial antibodies<sup>26-31,63</sup> suggest that the population with recurrent respiratory infections and subnormal values of IgG or IgG isotypes is immunologically different from the populations with chronic respiratory infections or chronic bronchitis but without such an immune abnormality.

The regulation of total IgE may be different in different immunoglobulin deficiencies. This immunoglobulin is

usually low in IgM deficiency. In IgA deficiency, IgE is reported as normal,<sup>21</sup> decreased,<sup>18,19</sup> increased<sup>20</sup> or variable, depending on the presence of atopy.<sup>65</sup> In IgG deficiency, total IgE seems to be lower in common variable immunodeficiency<sup>24,25</sup> (below 10 IU/mL in this study) than in isotype deficiency. This is reminiscent of severe combined immunodeficiency where IgE is increased in the partial form and decreased in the complete form.

In conclusion, allergy work-up can be performed in IgG subclass deficiency associated with repeated infections since the defining immunologic features and the presence of repeated respiratory infections do not diminish the prevalence of atopy. Total IgE is lower in IgG deficiency than in patients with similar chronic respiratory disease.

#### REFERENCES

- Schur PH, Borel H, Gelfand EW, et al. Selective gamma-G globulin deficiencies in patients with recurrent pyogenic infections. *N Engl J Med* 1970; 283:631-634.
- Oxelius V-A. Chronic infections in a family with hereditary deficiency of IgG2 and IgG4. *Clin Exp Immunol* 1974;17:19-27.
- Umetsu D, Ambrosino DM, Quinti I, et al. Recurrent sinopulmonary infection and impaired response to bacterial capsular polysaccharide antigen in children with selective IgG-subclass deficiency. *N Engl J Med* 1985;313: 124-125.
- Shackelford PG, Polmar SH, Mayus JL, et al. Spectrum of IgG2 subclass deficiency in children with recurrent infections. *J Pediatr* 1986;108: 647-653.
- Popa V. IgG deficiency in adults with recurrent respiratory infections. *Ann Allergy* 1993;70:418-423.
- Popa V. Airway obstruction in adults with recurrent respiratory infections and IgG deficiency. *Chest* 1994;105: 1006-1012.
- Ochs H, Winkelstein J. Disorders of the B-cell system. In: Stiehm ER, ed. *Immunologic disorders in infants and children*. Philadelphia: Saunders, 1996:296-338.
- Bjorkander J, Oxelius V-A, Hanson LA. IgG subclasses and asthma.

- Agents and Actions 1989;Suppl.28: 239–244.
9. Hanson LA, Soderstrom R, Avanzini A, et al. Immunoglobulin subclass deficiency. *Pediatr Infect Dis J* 1988;8: S17–S21.
10. Shapiro GG, Virant FS, Furukawa CT, et al. Immunologic defects in patients with refractory sinusitis. *Pediatrics* 1991;87:311–316.
11. Bjorkander J, Bengtsson U, Oxelius V-A, Hanson LA. Symptoms in patients with lowered levels of IgG subclasses, with or without IgA deficiency, and effect of immunoglobulin prophylaxis. In: Hanson LA, Soderstrom T, Oxelius V-A., eds. Immunoglobulin subclass deficiencies. Monographs in Allergy. Basel: Karger, 1986;20:157–163.
12. Hanson LA, Bjorkander J, Robbins JB, et al. IgG subclass deficiencies. *Vox Sang* 1986;51(suppl. 2):50–56.
13. Bernatowska-Matuszkiewicz E, Pac M, Skopcynska H, et al. Clinical efficacy of intravenous immunoglobulin in patients with severe inflammatory chest disease and IgG3 subclass deficiency. *Clin Exp Immunol* 1991;85: 193–197.
14. Heiner DC, Myers AS, Beck CS. Deficiency of IgG4: disorder associated with frequent infections and bronchiectasis that may be familial. *Clin Rev Allergy* 1983;1:259–266.
15. Van der Giessen M, Reerink-Brongers EE, Algra-van Veen A. Quantitation of Ig classes and IgG subclasses in sera of patients with a variety of immunoglobulin deficiencies and their relatives. *Clin Immunol Immunopathol* 1976;5: 388–398.
16. Oxelius V-A, Laurell AB, Lindquist B, et al. IgG subclasses in selective IgA deficiency. Importance of IgG2-IgA deficiency. *New Engl J Med* 1981;304: 1476–1477.
17. Popa V, Colby TV, Reich S. Interstitial lung diseases in immunoglobulin G deficiency. *Am J Respir Crit Care Med* 1994;149:A1046.
18. Buckley RH, Dees SC. Correlation of milk precipitins with IgA deficiency. *N Engl J Med* 1969;281:465–469.
19. Buckley RH. Clinical and immunologic features of selective IgA deficiency. In: Bergsma D, ed. Immunodeficiency in man and animals. Birth defects; original articles series, vol. 11, no. 1. Sunderland: Sinauer Ass., 1975: 134–142.
20. Burgio GR, Duse M, Monafó V, et al. Selective IgA deficiency: clinical and immunologic evaluation of 50 pediatric patients. *Eur J Pediatr* 1980;133: 101–106.
21. Plebani A, Monafó V, Ugazio AG, et al. Comparison of the frequency of atopic diseases in children with severe and partial IgA deficiency. *Int Archs Allergy Appl Immunol* 1987;82: 485–486.
22. Hobbs JR. IgM deficiency. In: Bergsma D, ed. Immunodeficiency in man and animals. Birth defects; original articles series, vol. 11, no. 1. Sunderland: Sinauer Ass., 1975: 112–116.
23. Guill MF, Brown DA, Ochs HD, et al. IgM deficiency: clinical spectrum and immunologic assessment. *Ann Allergy* 1989;62:547–552.
24. Stites DP, Ishizaka K, Fudenberg HH. Serum IgE concentrations in hypogammaglobulinemia and selective IgA deficiency; studies on patients and family members. *Clin Exp Immunol* 1972;10:391–399.
25. Buckley RH, Fiscus SA. Serum IgD and IgE concentrations in immunodeficiency diseases. *J Clin Invest* 1975; 55:157–165.
26. Hilton AM, Doyle L. Immunological abnormalities in bronchiectasis with chronic bronchial suppuration. *Br J Dis Chest* 1978;72:207–216.
27. Murphy MB, Reen DJ, Fitzgerald MX. Atopy, immunologic changes, and respiratory function in bronchiectasis. *Thorax* 1984;39:179–184.
28. Horan MA, Leahy BC, Fox RA, et al. Immunological abnormalities in patients with chronic bronchial suppuration: a possible relationship with endotoxaemia. *Br J Dis Chest* 1984;78:66–74.
29. Moss RB, Lewiston NJ. Immune complexes and humoral response to *Pseudomonas aeruginosa* in cystic fibrosis. *Am Rev Respir Dis* 1980;121: 23–29.
30. Fick RB, Olchowski J, Squier SU, et al. Immunoglobulin-G subclasses in cystic fibrosis. IgG2 response to *Pseudomonas aeruginosa* lipopolysaccharide. *Am Rev Respir Dis* 1986;133: 418–422.
31. Reichel N, Lewin EB, Rhoden DL, Weaver RR. Antibody responses to bacterial antigens during exacerbations of chronic bronchitis. *Am Rev Respir Dis* 1970;101:238–244.
32. Vercelli D, Geha RS. Regulation of IgE synthesis in humans; a tale of two signals. *J Allergy Clin Immunol* 1991; 88:285–295.
33. Soderstrom T, Soderstrom R, Enskog A. Immunoglobulin subclasses and prophylactic use of immunoglobulin in immunoglobulin G subclass deficiency. *Cancer* 1991;68:1426–1429.
34. Weinstein L. Diseases of the upper respiratory tract. In: Braunwald E, Isselbacher KJ, Petersdorf RG, et al, eds. Harrison's principles of internal medicine. 11th eds. New York: McGraw Hill 1987:1111–1115.
35. Ingram RH Jr. Chronic bronchitis, emphysema and airway obstruction. In: Braunwald E, Isselbacher KJ, Petersdorf RG, et al, eds. Harrison's principles of internal medicine. 11th eds. New York: McGraw Hill, 1987: 1087–1095.
36. Murray JF. Bronchiectasis and broncholithiasis. In: Braunwald E, Isselbacher KJ, Petersdorf RG, et al, eds. Harrison's principles of internal medicine. 11th edition eds. New York: McGraw Hill, 1987:1082–1085.
37. Burrows B, Lebowitz M, Barbee R. Respiratory disorders and allergy skin test reactions. *Ann Intern Med* 1976; 84:134–139.
38. Silverman LM, Christensen RH, Grant GH. Aminoacids and proteins. In: Tietz NW, ed. Textbook of clinical chemistry. Philadelphia: Saunders, 1986:573–579.
39. Schur P. IgG subclasses. A review. *Ann Allergy* 1987;58:89–96.
40. Oxelius V-A. IgG subclass levels in infancy and childhood. *Act Paediatr Scand* 1979;68:23–27.
41. Wittig HJ, Belloit J, De Fillipi I, Royal G. Age-related serum immunoglobulin E levels in health subjects and in patients with allergic diseases. *J Allergy Clin Immunol* 1980;66:305–313.
42. Gerrard JW, Heiner DC, Ko CG, et al. Immunoglobulin levels in smokers and non-smokers. *Ann Allergy* 1980;44: 261–262.
43. Hilleman MR, Carlson AJ, McLean AA, et al. Streptococcus pneumoniae polysaccharide vaccine: age and dose responses, safety, persistence of antibody, revaccination and simultaneous administration of pneumococcal and influenza vaccines. *Rev Infect Dis* 1981;3:S31–S42.
44. Granoff DM, Munson RS Jr. Prospects for prevention of *Haemophilus influ-*

- enzae type b disease by immunization. *J Infect Dis* 1986;153:448–458.
45. Popa V, Naghy S. The response to vaccination in adults with IgG deficiency. *Am J Respir & Crit Care Med* 1997;155(2):A10.
46. Rackemann FM. Studies in asthma. I. A clinical survey of 1074 patients with asthma followed for two years. *J Lab Clin Med* 1928;1185–1197.
47. Hermans PE, Diaz-Buxco J, Stobo J. Idiopathic late-onset immunoglobulin deficiency; clinical observations in 50 patients. *Am J Med* 1976;61:221–237.
48. Watts WJ, Watts MB, Dai W, et al. Respiratory dysfunction in patients with common variable hypogammaglobulinemia. *Am Rev Respir Dis* 1986;134:699–703.
49. Cunningham-Rundles C. Clinical and immunologic analyses of 103 patients with common variable immunodeficiency. *J Clin Immunol* 1989;9:22–33.
50. Lederman HM, Winkelstein JA. X-linked agammaglobulinemia: an analysis of 96 patients. *Medicine* 1985;64:145–156.
51. Barth J, Winkler I, Moelmann HW, et al. IgG2 deficiency in asthmatic patients; course of disease in four adults. *Agents and Actions (Suppl)* 1989;28:245–248.
52. Warner JO, Taylor BW, Norman AP, Soothill JF. Association of cystic fibrosis with allergy. *Arch Dis Child* 1976;51:507–511.
53. Wilmot RW. The relationship between atopy and cystic fibrosis. In: Moss RB, ed. *Clinical reviews in allergy*, vol. 9. Cystic fibrosis. Clifton: Humana Press, 1991:29–46.
54. Popa V, Teculescu D, Stanescu D, Gavrilescu N. The value of inhalation tests in perennial bronchial asthma. *J Allergy* 1968;42:130–137.
55. Popa V, Al-George S. Nasal provocation tests in allergic perennial rhinitis. A preliminary study. *Ann Allergy* 1969;27:45–54.
56. Bloom JW, Halonen M, Dunn AM, et al. Pneumococcus-specific immunoglobulin E in cigarette smokers. *Clin Allergy* 1986;16:225–230.
57. Pauwels R, Verschraegen G, Van der Straeten M. IgE antibodies to bacteria in patients with bronchial asthma. *Allergy* 1980;157:665–671.
58. Perlmutter I, Potvin L, Phipps P. Immunoglobulin E response during viral infections. *J Allergy Clin Immunol* 1979;64:127–133.
59. Welliver RC, Sun M, Rinaldo D, Ogra PL. Respiratory syncytial virus-specific IgE responses following infections: evidence for a predominantly mucosal response. *Pediatr Res* 1985;19:420–426.
60. Smith JM. Epidemiology and natural history of asthma, allergic rhinitis, and atopic dermatitis (eczema). In: Middleton E Jr, Reed CE, Ellis EF, et al, eds. *Allergy principles and practice*, St Louis: Mosby, 1988:891–929.
61. Lin FJ, Wong D, Chan-Yeung M. Immediate skin reactivity in adult asthmatic patients. *Ann Allergy Asthma Immunol* 1995;74:398–404.
62. Burrows B. Allergy and its relation to asthma, airway responsiveness, and chronic airways obstruction; an epidemiological perspective. In: Weiss ST and Sparrow D, eds. *Airway responsiveness and atopy in the development of chronic lung disease*. New York: Raven Press, 1989:241–270.
63. Tobin MJ, Maguire O, Reen D, et al. Atopy and bronchial reactivity in older patients with cystic fibrosis. *Thorax* 1980;36:807–813.
64. Merrill WW, Naegel GP, Olchowsky JJ, Reynolds HY. Immunoglobulin G subclass proteins in serum and lavage fluid of normal subjects. *Am Rev Respir Dis* 1985;131:584–587.
65. Kanok JM, Steinberg P, Cassidy JT, et al. Serum IgE levels in patients with selective IgA deficiency. *Ann Allergy* 1978;41:220–223.

*Request for reprints should be addressed to:*  
Valentine Popa, MD  
8100 Timberlake Way  
Sacramento, CA 95823