Antibody deficiency in chronic rhinosinusitis: Epidemiology and burden of illness

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ABSTRACT

Background: A subset of patients with chronic rhinosinusitis (CRS) has refractory disease. The risk factors for refractory CRS include atopy, a disrupted mucociliary transport system, medical conditions affecting the sinonasal tract mucosa, and immunodeficiency.

Methods: We review four primary immunodeficiencies reported in individuals with CRS: common variable immune deficiency (CVID), selective IgA deficiency, IgG subclass deficiency, and specific antibody deficiency. We also review treatment options for individuals with both CRS and a concomitant immune defect.

Results: There is a high prevalence of CRS in individuals with CVID and selective IgA deficiency. While many reports describe IgG subclass deficiency in individuals with CRS, the clinical relevance of this is unclear. Specific antibody deficiency may play a more significant role in the pathogenesis of refractory CRS.

Conclusion: Screening for a primary immunodeficiency should be part of the diagnostic workup of refractory CRS, as its identification may allow for more effective long-term therapeutic options.

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Chronic rhinosinusitis (CRS) is defined as inflammation of the paranasal sinuses lasting at least 12 weeks in duration.¹ CRS causes a great deal of disease burden in the United States, where up to 31 million people (12.5% of the population) are affected.¹ This, in turn, leads to a significant economic burden because of time lost from work and imposes a strain on the health care system. It is estimated that CRS annually results in 73 million restricted activity days and \$2.4 billion in direct medical costs.² In addition, CRS, as a disease, does not sit in isolation. The unified airway hypothesis illustrates how disease of the upper airways can negatively impact the lower airways. This is clearly evident in asthma because there is a high prevalence of sinus disease in asthmatic patients.^{3,4} Therefore, the burden of disease in CRS can greatly impact the asthmatic patient by contributing to asthma exacerbations.^{3,4}

CRS can be divided into two main subtypes: CRS without nasal polyposis, which accounts for ~60–65% of cases, and CRS with nasal polyposis, which accounts for up to 33% of cases. In general, CRS without nasal polyposis is characterized by more of a T-helper type 1 response, with less eosinophilic infiltrate in nasal tissue, and symptoms of facial pain and purulent drainage. On the other hand, CRS with nasal polyposis is characterized by a prominent T-helper type 2 immune response, nasal tissue eosinophilia, and symptoms of nasal obstruction and anosmia.⁵

REFRACTORY CRS

Treatment options for CRS include nasal and systemic corticosteroids, antibiotics, and surgery. A subset of individuals with CRS fails to adequately respond to therapy and develops refractory disease. They may have required multiple courses of antibiotics and sometimes multiple surgeries without long-term benefit.^{2,6} Risk factors for refractory CRS are many and include atopy, a disrupted mucociliary transport, multiple medical conditions that affect the sinonasal tract mucosa (such as Wegner's granulomatosis), and defects in the im-

mune system.^{2,6} An individual can have refractory CRS due to any one or combinations of these conditions. The challenging task confronting clinicians is that the severity or intervals of disease do not point to an underlying cause.⁷ In the case of immunodeficiency, the severity of CRS symptoms may not directly relate to an underlying immune dysfunction; however, an immunodeficiency may make disease more refractory to standard therapies.⁸ This points to the importance of identifying the etiology of disease in a patient with refractory CRS, because treatment decisions can be significantly influenced.

PRIMARY IMMUNODEFICIENCIES

A large number of primary immunodeficiencies have been characterized, ranging from relatively common conditions to extremely rare phenomena, with only a handful of cases identified.⁹ Diseases resulting from immunodeficiency vary greatly, ranging from fatal conditions if left untreated to asymptomatic phenotypes. Primary immunodeficiencies are classified according to the component of the immune system that is affected. Categories include (i) combined T- and B-cell immunodeficiencies; (ii) predominantly antibody deficiencies; (iii) well-defined immunodeficiency syndromes; (iv) diseases of immune dysregulation; (v) congenital defects of phagocyte number, function, or both; (vi) defects in innate immunity; (vii) autoinflammatory disorders; and (viii) complement deficiencies.⁹ Evidence pointing to primary immunodeficiency as an etiology of CRS is prevalent in the literature. This review will focus on common variable immunodeficiency (CVID), IgA deficiency, IgG subclass deficiency, and specific antibody deficiency (SAD), all of which fall under the category of antibody deficiencies.

CVID AND CRS

CVID is the most common symptomatic primary immunodeficiency in adults, estimated to affect ~1 in 25,000 individuals, and has a higher prevalence in people of northern European descent (Table 1).^{10,11} CVID constitutes a complex syndrome with various clinical phenotypes, making it difficult to define pathogenesis and find precise genetic defects.^{9,11} Age of onset is typically after puberty and before the age of 30 years. However, there is a significant gap between age of onset and diagnosis of CVID.^{11,12} Quinti examined 224 patients with CVID and found that the median age of onset of symptoms was 16.9 years and the mean age of diagnosis was 26.6 years. This translated into a diagnostic delay of 8.9 years.¹² Similarly, Oksenhendler characterized 252 patients with CVID and described the median age of diagnosis at 33.9 years. Interestingly, they found differences in the median delay

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Table 1 Summary of proposed diagnostic criteria and management/treatment options for selective IgA deficiency, specific antibody deficiency, and CVID

	IgA Deficiency	Specific Antibody Deficiency	CVID
Diagnostic criteria	<p>>4 yr of age</p> <p>Normal serum (IgG) and (IgM)</p> <p>Other causes of hypogammaglobulinemia have been excluded</p> <p>Partial deficiency/probable diagnosis: serum (IgA), >7 mg/dL, but below the lower limit of normal (2 SD below the age-adjusted mean)</p> <p>Severe deficiency/definitive diagnosis: serum (IgA) <7mg/dL</p>	<p>>2 yr of age</p> <p>Normal serum immunoglobulin concentrations</p> <p>Deficient specific antibody response to polysaccharide antigens: <7 of 14 pneumococcal serotypes $\geq 1.3 \mu\text{g/mL}$ after Pneumovax vaccination</p>	<p>>2 yr of age</p> <p>Significantly reduced total serum (IgG)</p> <p>2 SD below the mean for age</p> <p>Low serum (IgA) and/or (IgM)</p> <p>Poor or absent response to immunization</p> <p>Absence of any other defined immunodeficiency state (diagnosis of exclusion)</p>
Management and treatment	<p>Vaccination</p> <p>Symptomatic patients</p> <p>Treat concomitant disorders (CRS and asthma)</p> <p>Prophylactic antibiotics</p> <p>IVIG</p> <p>Asymptomatic patients</p> <p>No specific treatments</p>	<p>Aggressive management of other conditions predisposing to recurrent sinopulmonary infections (allergic rhinitis and asthma)</p> <p>Evaluation for coexistent pulmonary disease</p> <p>High-resolution chest CT</p> <p>Prophylactic antibiotics</p> <p>IVIG</p>	<p>IVIG</p> <p>Treatment of specific infections</p> <p>Evaluation for coexistent pulmonary disease</p> <p>High-resolution chest CT</p> <p>Evaluation for coexistent gastrointestinal and/or autoimmune disease</p> <p>Age-appropriate cancer screening</p> <p>Monitor for lymphoma</p>

CVID = common variable immunodeficiency; IVIG = intravenous immunoglobulin.

of diagnosis (2.9 years versus 15.6 years), depending on the year symptoms started—15.6 years if symptomatic before 1990 and 2.9 years if symptomatic after 1990.¹¹ This likely reflects the increased recognition of CVID as a clinical entity by physicians.

CVID is a primary humoral immunodeficiency that presents with recurrent respiratory tract infections as the major clinical feature of the disease. In addition to infection, CVID also has a wide range of clinical manifestations including autoimmunity, gastrointestinal disorders, and increased risk of malignancy. Chronic sinusitis is a common feature of CVID. Oksenhendler's study found that sinonasal symptoms were one of the most frequent initial symptoms in 36% (91 of 252) of the CVID patients he characterized.¹¹ The frequencies of the other initial comorbidities in CVID patients include bronchitis (38%), pneumonia (31%), and bronchiectasis (14%).¹¹ Treatment of CVID consists of either i.v. or subcutaneous immunoglobulin replacement. As will be discussed later, although antibody replacement has proven to be effective in reducing the frequency of respiratory infections, it is less effective in reducing sinusitis.¹²

IgA DEFICIENCY AND CRS

Selective IgA deficiency is defined as an isolated deficiency in serum IgA, in an individual with normal IgG and IgM levels, and in which other identifiable disorders associated with low IgA have been excluded. This is the most common immunodeficiency with a prev-

alence of ~1 in 600 individuals, with marked variability among different ethnic groups.¹⁰ The majority of IgA-deficient individuals are asymptomatic, making it difficult to accurately determine the prevalence in the general population. As such, the classification of selective IgA deficiency as a true immunodeficiency remains a subject of debate.^{13,14}

Although there is a high frequency of IgA deficiency in the general population, the prevalence of this condition is significantly higher in individuals with CRS. A retrospective study by Chee examined the contribution of primary immunodeficiency states in individuals with refractory CRS⁶; 16.7% (13 of 78) of individuals with CRS had low IgA levels (mean of 191; range, 6–605 mg/dL) and 6.2% had selective IgA deficiency.⁶ The relevance of selective IgA deficiency in contributing to the pathogenesis of CRS is unclear and may be insignificant in the absence of other immune deficiencies to be discussed.

IgG SUBCLASS DEFICIENCY AND CRS

IgG is the most predominant antibody isotype in humans and is composed of four subclasses that are numbered according to their concentration (IgG1 > IgG2 > IgG3 > IgG4). In terms of functional responses, IgG1 and IgG3 are induced in response to protein antigens, and IgG2 and IgG4 respond to polysaccharide antigens.¹⁵ IgG subclass deficiency is established when one or more IgG subclasses are 2 SDs below the age-adjusted reference range, along with normal total

serum IgG levels.¹⁶ Individual IgG subclass deficiencies and the corresponding phenotypes have been described.¹⁷ IgG1 deficiency has been associated with a predisposition to pyogenic airway infections. IgG2 deficiency is the most common subclass deficiency in children and results in recurrent upper respiratory tract infections (URIs) and lower respiratory tract infections, similar to what is observed in CVID. IgG2 deficiency is often isolated or seen in combination with IgG4 deficiency. Deficiency of the IgG3 subclass is the most common subclass deficiency in adults with individuals typically presenting with recurrent URIs and lower respiratory tract infections.

There are several published articles describing IgG subclass deficiency in individuals with CRS. A case report from Snowden describes a 35-year-old woman with IgG3 deficiency and a history of recurrent URIs and sinusitis who benefited from treatment with IVIG.¹⁸ A retrospective study by Vanlerberghe examined 307 patients with refractory CRS and found 21.8% with humoral defects: 2.2%, IgA deficiency; 2.0%, IgG2 deficiency; 17.9%, IgG3 deficiency; and 2.9%, combined deficits, and none had CVID.¹⁹ Neither of these studies measured specific antibody titers to common protein or polysaccharide antigens, nor did they examine specific antibody production in response to vaccination, which are addressed in other studies. Van Kessel examined 24 adults with selective IgG1 deficiency and a history of recurrent respiratory infections with encapsulated bacteria and found that 9 patients failed to produce adequate pneumococcal antibody titers after vaccination with Pneumovax (23-valent pneumococcal vaccine) (Merck & Co., Inc., Whitestone Station, NJ).²⁰ May examined 245 patients with refractory CRS and found that 5 individuals had CVID and 17 had IgG subclass deficiency: 10, IgG2; 5, IgG1; and 1 each, IgG3 and IgG4 deficiencies. One-half of the IgG subclass-deficient patients had abnormally low baseline pneumococcal titers and after Pneumovax vaccination, 3 of 17 had an inadequate response, and none of the CVID patients responded.⁷ A retrospective analysis by Abrahamian looked at individuals with IgG3 deficiency and recurrent infections that were not limited to CRS and included pneumonia, fungal skin infections, recurrent herpes infections, and cystitis.²¹ Six of 11 patients had low baseline pneumococcal titers, with 2 of the 6 failing to respond adequately to Pneumovax.²¹ A retrospective study by Alqudah looked at patients with refractory CRS and found 1 case of IgG2 deficiency, 3 cases of IgG3 deficiency, and 3 with IgG4 deficiency.² Sixty-seven percent of patients who subsequently received Pneumovax had a poor response. The authors concluded that an isolated subclass deficiency is not significant unless functional antibody responses are also inadequate.²

RELEVANCE OF IgG SUBCLASS DEFICIENCY

Although the aforementioned studies describe IgG subclass deficiency in patients with CRS, a causal relationship is far from established. Multiple peer-reviewed articles have questioned the relevance of IgG subclass deficiency.^{17,22–25} A study by Hoover examined 80 adults with extensive sinusitis. Three individuals had IgG3 deficiency that did not correlate with the extent of disease. The authors did report that total IgE and IgG4 levels positively correlated with extent of disease, but the significance of the relationship was lost under multiple stepwise regression analysis.²⁶

Buckley describes IgG3 deficiency, observed in some cases of refractory CRS, as a secondary phenomenon rather than a cause of disease.²² IgG3 has a half-life of only 9 days in serum and is the most susceptible to degradation. Therefore, IgG3 deficiency may be secondary to the disease process itself.²² Olinier-Nielsen questioned the usefulness of measuring IgG subclasses as they note that the combination of chronic lung disease and IgG subclass deficiency is common. Despite this relationship causality is not implied.¹⁷ Low levels of one or more of the IgG subclasses are observed in 2–20% of healthy individuals.¹⁶ IgG4 is undetectable in 15% of normal individuals, calling into question the relevance of its absence.^{22,23} Buckley's review and others also highlight the problem of accurate laboratory quantification of IgG subclass levels.^{22,27}

SAD AND CRS

More relevant than absolute antibody levels is the need to assess functional responses to protein antigens (with tetanus or diphtheria vaccination) and polysaccharide antigens (with pneumococcal vaccination).^{22,23} SAD is defined as dysfunctional IgG responses to immunization with polysaccharide antigens in the presence of normal serum concentrations of IgG, IgM, and IgA (Table 1).^{16,28} The definition of what constitutes a dysfunctional antibody response after pneumococcal immunization is unclear. The 2005 practice parameters defines an adequate antipneumococcal antibody response as a postimmunization antibody concentration of $\geq 1.3 \mu\text{g/mL}$ or at least fourfold over baseline.^{29,30} However, the exact number of antibodies of the 14 measured serotypes that must meet either of these criteria is not clearly defined. Our practice routinely uses a cutoff of 7 of 14 serotypes $\geq 1.3 \mu\text{g/mL}$ as an adequate response. We do not use the increase of fourfold over baseline criterion because patients with high baseline titers may not develop a fourfold increase after vaccination.³¹ This lack of consensus in the guidelines makes accuracy of diagnoses more challenging. The prevalence of SAD in the general population is not known. It is difficult to make this diagnosis in children <2 years of age, because they have inconsistent responses to polysaccharide vaccines.¹⁶ A retrospective study by Javier sought to determine the types of immunodeficiencies in a pediatric population with an 8-year history of recurrent infections.³² The majority of patients (67%) had predominantly antibody deficiencies, with the most common phenotype (23.1% of patients) being SAD (defined as postimmunization pneumococcal titers $< 1.3 \mu\text{g/mL}$ or $<$ fourfold over baseline titers in at least 5 of 9 serotypes).³²

The clinical significance of SAD has been addressed in a few studies.^{25,33–36} A retrospective study by Hidalgo characterized preimmunization and postimmunization pneumococcal antibody titers in a pediatric population with a history of recurrent respiratory infections, but no known immunodeficiency syndrome.³⁴ Before immunization, 50% of the patients did not have protective antibody levels against any of the serotypes tested. After immunization 6.4% of the patients failed to produce protective pneumococcal antibody, and the patients presented various infections including recurrent sinusitis, otitis, and pneumonia.³⁴ A prospective study by Misbah examined antibody levels against pneumococcus and *Haemophilus* in children with a history of recurrent otitis media requiring tympanostomy tube placement.²⁵ Although the majority of patients actually had significantly higher pneumococcal antibody titers compared with controls, 19.6% of the patients had pneumococcal titers below the 25th percentile, with 26% failing to adequately mount a response to Pneumovax. Interestingly, 25% of the children in the control group also had low pneumococcal antibody levels.²⁵ Boyle examined children with recurrent infections and found that 14.9% had SAD.³³ SAD was associated with otitis media and atopy, in particular allergic rhinitis.³³ A cohort study by Van Kessel examined the prevalence of SAD in patients with idiopathic bronchiectasis and found that ~50% of the patients failed to respond to Pneumovax.³⁵ Interestingly, the authors based this on an inadequate pneumococcal antibody response in IgA and the IgG2 subclass, referred to as isotype nonresponders.³⁵ A recent retrospective cohort study by Lim examined the prevalence of SAD in a pediatric population with a history of a wet cough lasting > 8 weeks, a diagnosis that is not further clarified in the article.³⁶ After vaccination with either Pneumovax or Prevnar (conjugated vaccine against seven pneumococcal serotypes) (Wyeth Pharmaceuticals, Philadelphia, PA), 58% of the patients failed to mount an adequate response. The population with SAD was more likely to require admission for i.v. antibiotics and had significantly more abnormal chest radiographs.³⁶

There is increasing evidence pointing to the contribution of SAD to the pathogenesis of CRS. Several of the studies detailed in this article focused on IgG subclass deficiency, but also provided data on SAD in CRS. A large proportion of CRS patients with IgG subclass deficiency

cies also had abnormally low baseline pneumococcal titers, with several individuals failing to adequately respond to Pneumovax.^{2,7,20,21} Although the aforementioned studies focused on IgG subclass deficiency and also described SAD in that context, there are very few studies that focus solely on the role of SAD in CRS. A recent retrospective study by Carr examined 129 patients with medically refractory CRS, requiring multiple surgeries.²⁸ Of the patient population, 72% had low baseline pneumococcal antibody titers (fewer than 7 of 14 measured pneumococcal serotypes were $\geq 1.3 \mu\text{g/mL}$ postimmunization). Out of 69 individuals who received Pneumovax, 15 patients (11.6% of original total) failed to respond and were diagnosed with SAD.²⁸ This was one of the largest studies of its kind to characterize SAD in refractory CRS.

TREATMENT OPTIONS AND RECOMMENDATIONS

The importance of identifying the etiology of CRS for a given patient becomes apparent when it comes to treatment options. Identifying a primary immunodeficiency such as SAD changes management options, because these individuals may have refractory disease because of their underlying immune dysfunction.⁸ As previously discussed current guidelines do not adequately define what is an inappropriate response to vaccination. We routinely classify an inadequate response to Pneumovax as <7 of 14 measured pneumococcal antibodies appropriately responding ($\geq 1.3 \mu\text{g/mL}$ postimmunization). In addition, when vaccination is warranted the proper vaccine should be used depending on the patient's age. The conjugated vaccine Prevnar should be reserved for patients <2 years of age, because unconjugated polyvalent pneumococcal vaccines, such as Pneumovax, do not typically induce an adequate antibody response in this age group.^{22,23} However, we do routinely challenge adult patients with Prevnar when they fail to produce an appropriate response to Pneumovax, with the hope that they will generate protective antibodies.

Recognizing humoral immune defects in CRS prompt the clinician to treat more aggressively with the use of prophylactic antibiotics, early culture-directed antibiotics for exacerbations, and IVIG if indicated.⁸ In addition, early implementation of surgery may be indicated as a study by Khalid showed that CRS patients with immune dysfunction had similar outcomes with endoscopic sinus surgery compared with CRS patients with normal immune function.³⁷ Prophylactic antibiotics may be considered in patients with primary immunodeficiency and refractory CRS or recurrent acute rhinosinusitis. Our practice routinely uses β -lactams, trimethoprim sulfamethoxazole, and azithromycin for prophylaxis. It is important to note that there are no consensus guidelines on the use of prophylactic antibiotics in refractory CRS. We consider prophylactic antibiotics a failure if an individual continues to get recurrent sinus infections over a 6-month period. Other options such as immunoglobulin replacement should be considered when antibiotic prophylaxis fails. However, IVIG therapy is not benign because it can have significant side effects and can be quite expensive. Therefore, we recommend that treatment with IVIG be reserved for patients with documented CRS and primary immunodeficiency who have coexistent pulmonary disease or have failed medical and surgical therapy.^{22,23} It should not be used in isolated IgG subclass deficiency, but instead in patients with documented lack of functional antibody response. In the study by Hidalgo, discussed previously, children with a history of recurrent infections (otitis, sinusitis, and pneumonia) were treated with IVIG, resulting in clinical improvement.³⁴ In the study by Abrahamian patients with recurrent infections, SAD, and concurrent IgG3 deficiency received IVIG therapy, with dosing adjusted to achieve normal IgG3 levels. Eleven of 13 patients responded to IVIG treatment with decreased frequency and severity of infections.²¹ Although IVIG has been shown to benefit individuals with CVID by reducing the number of serious infections, such as pneumonia, the long-term benefits of

antibody replacement treatment in controlling sinusitis is less encouraging. A multicenter prospective study by Quinti followed 224 patients with CVID on IVIG for a mean of 11.5 years.¹² They found that treatment with IVIG significantly reduced the incidence of acute pneumonia and otitis. Forty-nine percent of the patients had pneumonia at least once before being diagnosed with CVID. At follow-up 35.7% never experienced an episode of acute pneumonia after starting IVIG replacement, and 13.3% continued to have recurrent pneumonia.¹² As far as otitis, 29% of patients had acute otitis before their CVID diagnosis. At follow-up 25.5% never had an episode of acute otitis, and 13.3% had recurrent otitis.¹² In sharp contrast to acute pneumonia and otitis, IVIG therapy did not show benefit in sinusitis. Thirty-six percent of the patients had CRS at the time they were diagnosed with CVID. Although 8.6% of individuals did improve on follow-up, overall, the percentage of patients with CRS increased to 54% despite IVIG treatment.¹² A more concerning finding of this study was that the prevalence of bronchiectasis increased from 56 patients, at the time of CVID diagnosis, to 65 patients at follow-up.¹² The administration of IVIG carries risks such as hypersensitivity reactions and aseptic meningitis, along with high financial costs. Whether it is indicated in patients with refractory CRS who have failed prophylactic antibiotics, but have no signs of chronic lung disease, is unknown. Because the natural history of SAD is not known, more studies need to be undertaken to answer these questions and provide guidelines for clinicians.

The burden of CRS on the health care system warrants the medical and scientific communities to seek improvements in prevention and treatment. By its very nature, a chronic illness poses unique challenges. This review has discussed multiple studies that have attempted to elucidate the underlying immune defect in CRS. Several immunodeficiencies have been associated with CRS, from CVID, to IgA deficiency, to IgG subclass deficiency, and, finally, SAD. Although the absolute quantity of any particular antibody may be decreased in an individual with refractory CRS, the most important contributor to disease appears to be the quality of the antibody in the circulation. Therefore, evaluation for SAD should be performed in an individual with refractory CRS. A great deal of work from the research community is required to further characterize SAD as a clinical entity. This will hopefully lead to improved guidelines to aid clinicians in the treatment of this chronic illness.

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