

Humoral Primary Immunodeficiencies in Chronic Rhinosinusitis

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Abstract Chronic rhinosinusitis (CRS) may be the primary presenting symptom for primary immunodeficiencies (PID). PID can affect the humoral or the cellular immune system. This paper provides an overview of PID which affect the humoral immune system, with details around the diagnostic criteria, the epidemiology, the subtypes, the clinical manifestations, underlying molecular mechanisms, methods to screen for PID and the management of CRS in the context of PID. A high clinical suspicion of PID is required when assessing patients with CRS who are refractory to maximal medical therapy.

Keywords Primary immunodeficiencies · Humoral · Antibody · Chronic rhinosinusitis

Abbreviations

CRS	Chronic rhinosinusitis
CVID	Common variable immunodeficiency
Ig	Immunoglobulin
SAD	Specific antibody deficiency

Introduction

Chronic rhinosinusitis (CRS) is an inflammatory disorder of the paranasal sinuses characterized by persistent inflammation and bacterial colonization [1, 2]. CRS may be the initial presentation of an immunocompromised state in adults [1] and should especially be considered in cases of patients with refractory CRS who fail appropriate medical therapy [3, 4]. The primary presentation of immunodeficiency is increased susceptibility to infection, which may include several manifestations [3].

Primary immunodeficiencies (PID) are divided according to the part of the immune system that they affect [4]. There are many different phenotypes from relatively common conditions to extremely rare [4]. Certain phenotypes are completely asymptomatic and others fatal [4]. The main categories of PID 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) other defects in innate immunity; (vii) auto-inflammatory disorders; and (viii) complement deficiencies [4]. More than 50 % of PID are due to humoral immunity abnormalities [5]. In this review, we focus on defects in humoral immunodeficiencies.

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The Humoral Immune System

The adaptive immune system contains both humoral and cellular components. The humoral system is characterized by the production of specific antibodies or immunoglobulins (Ig) by certain B lymphocytes.

Deficiency in antibody production results in a defect in one of the most efficient host-defense mechanisms of fighting infections, which may cause more significant mucosal damage to the paranasal sinuses [3]. It has long been recognized that CRS is strongly associated with humoral deficiencies such as common variable immunodeficiency (CVID), IgA deficiency, specific antibody deficiencies (polysaccharide antibody deficiency), hyper IgE syndrome (HIES), and Bruton's agammaglobulinemia [6]. The underlying mechanism of humoral deficiencies may be due to abnormal T and B cell communication, resulting in a dysfunction in T helper cells, B cell heavy chain switching, or antigen presentation [6]. As an example of this, more than 200 different molecular defects have been recently identified [5•, 7•].

Primary Humoral Immunodeficiencies

Definition and Epidemiology

Humoral immunodeficiencies can be described as either primary or acquired. Patients with a primary immunodeficiency (PID) may present with recurrent acute rhinosinusitis or chronic rhinosinusitis. According to the Modell Foundation

and the American Red Cross, two or more serious sinus infections within 1 year are one of ten warning signs of PID [3]. More recently, the overall incidence of PID ranges between 30 and 50 per 100,000 [8, 9]. A large cohort study examining temporal trends in PID noted a nearly five-time increase in PID in the last decade compared to the late 1970s [8], which may in fact be due to increased awareness and better methods to screen for PID.

Subtypes

Several subtypes of PID may develop CRS (Table 1) including B cell defects such as Bruton's agammaglobulinemia, a complete lack of immunoglobulins, and dysgammaglobulinemia, deficiency in one or two main classes of immunoglobulins. Patients with primary antibody deficiencies have the highest incidence of CRS. The most common B cell defect is IgA deficiency in the general population and reported in approximately 30 % of cases [1, 8]. The second most common deficiency is IgG subclass (IgG2, IgG3, IgG4 deficiency) at 26 % and hypogammaglobulinemia (including IgG1 subclass deficiency) at 23 % [1, 8]. Combined B and T cell defects are less common (11 %), phagocytic defects (8 %) and complement defects (3 %) [1].

CVID is the most common symptomatic PID in North America and Europe and is present in 15 % of patients [1, 10•]. The incidence of CVID varies in the literature and ranges between 1:25,000 and 1:200,000 [1, 11, 12]. CVID is diagnosed with the presence of hypogammaglobulinemia of two or more immunoglobulin isotypes (IgG, IgA, and/or IgM),

Table 1 Summary of the main types of primary immunodeficiencies affecting the humoral immune system

Name	Description
Bruton's agammaglobulinemia	• Complete lack of immunoglobulins
Dysgammaglobulinemia	• Deficiency in one or two main classes of immunoglobulins
Common variable immunodeficiency (CVID) [6, 11]	• Most common symptomatic PID • Hypogammaglobulinemia of two or more immunoglobulin isotypes (IgG, IgA, and/or IgM) • Recurrent sinopulmonary infections • Impaired functional antibody responses to vaccine antigens
IgA deficiency	• Most common B cell defect
Specific antibody deficiencies (SAD) [10•, 13]	• Primarily due to the inability to make antibodies against the polysaccharide capsule around bacteria • Normal Ig levels • Older than >2 years of age • Recurrent respiratory tract infections (upper/lower)
Hyper IgE syndrome [13–15]	• Abnormal cell-cell signaling, potentially affecting Th17 cell, B cell, and neutrophil responses • Elevated serum IgE level greater than 2000 IU/ml • Eosinophilia • Eczema • Recurrent staphylococcal abscesses particularly in the oto-sino-pulmonary region.
Good's syndrome	• Rare • Hypogammaglobulinemia • B cell depletion • Variable defects in cellular immunity • Thymoma

recurrent sinopulmonary infections, and impaired functional antibody responses to vaccine antigens [6, 11]. Autoimmunity, lymphoproliferation, granulomatous disease, and neoplasia may also be present in patients with CVID [11]. Approximately 10 % of patients with CRS are diagnosed with CVID as well [1] and approximately 40 % of patients with CVID present with CRS as the primary presenting symptom. CVID is associated with autoimmune cytopenias, granulomatous disease, and splenomegaly [10•]. Genetic studies have shown that CVID tends to be heterogeneous as there are multiple loci, which are susceptible and variable, thus resulting in the multiple clinical phenotypes of the disease [1, 4•, 10•].

Selective antibody deficiency (SAD) is a PID of unknown origin and rarely, may be an early presentation of CVID [10•]. Antibody responses may be variable in SAD and is primarily due to the inability to make antibodies against the polysaccharide capsule around bacteria [13]. SAD can be considered as a diagnosis in patients with normal Ig levels who are older than 2 years of age and present with recurrent respiratory tract infections (upper/lower) [10•]. Although this deficiency may occasionally explain a patient's problems with infections, IgG subclass deficiency is a controversial diagnosis and experts are increasingly disagreeing about the importance of this finding as a cause of repeated infections. The misdiagnosis of IgG subclass deficiency as a cause of presumed immunodeficiency is common, often leading to an unnecessary long-term treatment.

HIES or Job syndrome is a rare form of a PID characterized by abnormal cell-cell signaling, potentially affecting Th17 cell, B cell, and neutrophil responses [14]. Patients with HIES have an elevated serum IgE level greater than 2000 IU/ml with eosinophilia and develop eczema, recurrent staphylococcal abscesses particularly in the oto-sinopulmonary region and cyst-forming pneumonia (pneumatoceles) [13, 15]. Most cases of HIES are sporadic, although it has been described as having an autosomal dominant and an autosomal recessive type as well [13].

Good's syndrome is a rare adult-onset form of immunodeficiency and has four main characteristics: hypogammaglobulinemia, B cell depletion, variable defects in cellular immunity, and thymoma. The underlying pathogenesis of Good's syndrome may involve cytokine abnormality in the bone marrow and genetic defects [10•]. Immunological abnormalities specific to Good's syndrome include hypogammaglobulinemia, few or absent B cells, abnormal CD4⁺/CD8⁺ T cell ratio, CD4 T cell lymphopenia and impaired T cell functional mitogenic responses [10•].

Mechanisms

Several immunological hypotheses have been developed to explain the underlying mechanism in CRS and PID (Fig. 1).

Furthermore, those patients with refractory CRS may in fact have low immunoglobulin titers of IgG, IgA, and IgM (18, 17, and 5 %, respectively) [1, 16].

Studies have found that patients with CRS undergoing an immunological workup may have T lymphocyte dysfunction [1, 16]. Deficiencies in lymphocytes including memory cells, natural killer (NK)-T cells and Th17 T cells may also be found. These patients may be more susceptible to severe viral and fungal infection. Certain T helper cell defects such as Th17 are associated with concomitant epithelial cell anomalies [17].

An abnormal complement system and an aberrant Th17 cell response result in a reduced immune response to pathogens. Particular mechanisms include inadequate coating of bacteria with antibody, reduced or absent phagocytosis, or abnormal lysis of microorganisms in the case of complement defects [10•, 18]. An abnormal Th17 defect could render the host susceptible to bacterial and fungal infections through several mechanisms which could include a defect in neutrophil recruitment and activation.

In CVID, there have been several polymorphisms, which have been linked to the abnormality of immunodeficiency. Co-stimulatory molecules CD18, CD19, CD20, CD21, inducible co-stimulator, transmembrane activator and calcium-modulating and cyclophilin ligand interactor (TACI), and B cell activator factor (BAF) of the TNF family have been linked to CVID [10•, 19, 20].

Furthermore, the research group of the senior author has been able to demonstrate that polymorphisms within the CD8A and TAPBP genes implicated in MHC-1 immunodeficiency syndromes are associated with a more severe phenotype of CRS [2]. This association is strongest for single nucleotide polymorphisms in CD8A gene and the TAPBP gene has less of an effect. Homozygotes of the CD8A gene polymorphism present with a more severe form of CRS as described by an earlier development of the disease, earlier need for surgical intervention and an increased tendency for disease recurrence, requiring multiple revision surgeries [2]. Patients with such genetic abnormalities may have a reduced ability to clear diseased epithelial and inflammatory cells infected with bacteria or viruses [2].

In patients with antibody immunodeficiency, the major microbial pathogens that play a role in CRS in patients with PID are *Streptococcus pneumoniae* and *Haemophilus influenzae type B* [3]. Both of these microorganisms are pyogenic and have capsular polysaccharide exteriors. IgG1 and IgG3 are important for response to protein antigens and IgG2 and IgG4 respond to polysaccharide antigens. IgG1 antibodies are important in host defenses to encapsulated bacteria as they allow for the neutralization of protein antigens such as tetanus toxoid and for biological reactions to polysaccharide encapsulated antigens [21]. More specifically, IgG2 class antibodies are important for protection against such microbes [21]. IgG3 antibodies are important for viral defense, and it is well known

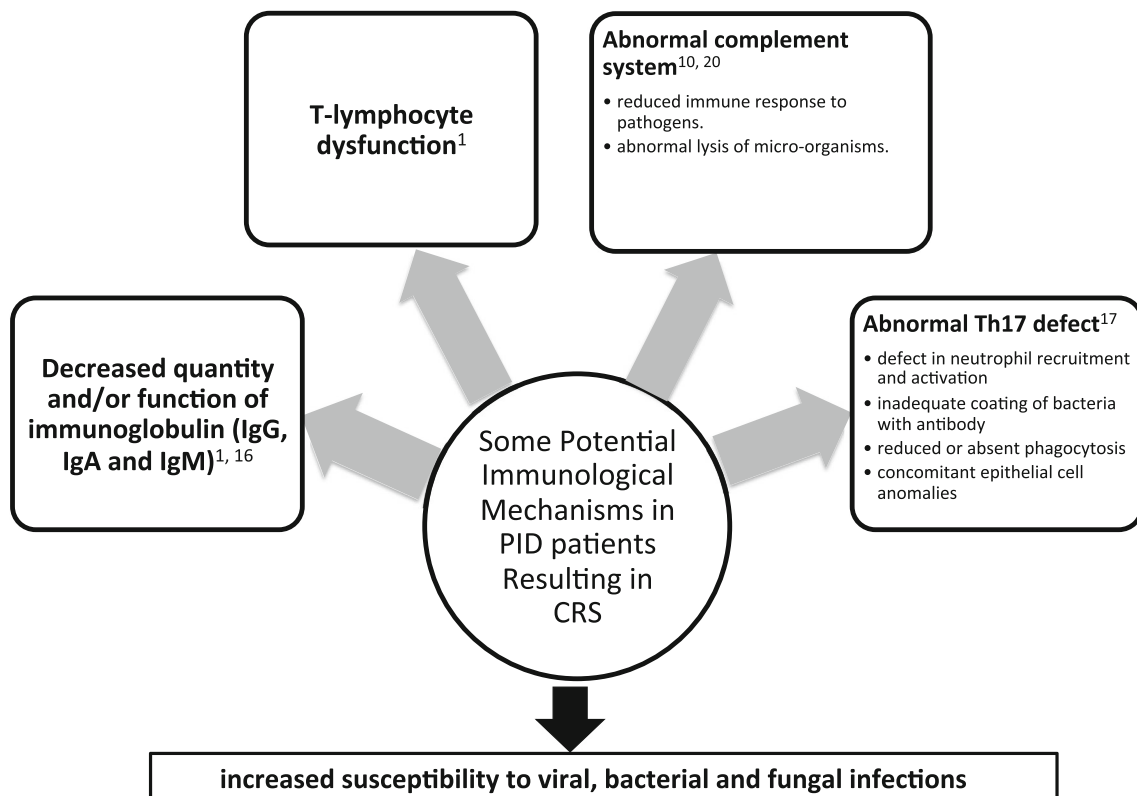


Fig. 1 Primary immunological mechanisms contributing to chronic rhinosinusitis in primary immunodeficiency

that rhinovirus initiates an inflammatory reaction in the mucosa, which can be followed by a bacterial infection [1, 21]. However, patients may have low subclass levels of these Ig and be healthy. In addition, some patients with recurrent oto-sino-pulmonary infections and functional antibody deficiencies can have normal IgG subclasses. For this reason, the diagnosis of IgG subclass deficiencies are now less in vogue and IgG sub-types are rarely measured by clinical immunologists who prefer a functional humoral assessment in such patients using protein and polysaccharide antigen immunization and measurement of the humoral response pre- and post-exposure. Patients with medically refractory CRS tend to have a high prevalence of low pre-immunization anti-pneumococcal titers and specific antibody deficiency [10•].

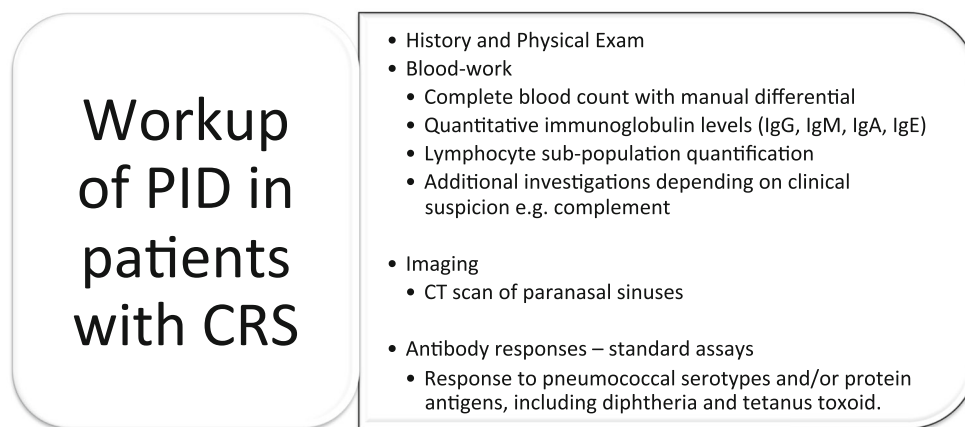
Diagnosis and Clinical Presentation

Given the increased awareness of PID, the delay in diagnosis has significantly been reduced compared to 30 years ago where the median delay in diagnosis was 17.5 years [8]. However, the diagnosis of PID continues to be difficult and the majority of patients are still not diagnosed and/or investigated despite being symptomatic for many years. A high clinical suspicion is required to ensure the diagnosis of PID [1]. Up to 20 % of patients with IgG subclass deficiency and 90 % of IgA deficient patients are asymptomatic.

The combination of recurrent infections and a defect in antibody responsiveness is clinically significant. Patients with PID may present with the following manifestations: increased frequency or severity of infections, prolonged duration of infection, recurrent infections without symptom-free interval, increased dependency on antibiotics and an absence of response to oral antibiotics or the need for admission for intravenous antibiotics, unexpected or severe complications of infection, or infection caused by an unusual organism which is often an opportunistic organism [3]. While adult patients are most likely to present with CRS that is difficult to manage, pediatric patients may also present with failure to thrive or recurrent oto-sino-pulmonary infections. Approximately 25 % of patients presenting to a tertiary immunology clinic with IgG immunodeficiency presented with CRS as the primary finding [5•, 22].

Patients with agammaglobulinemia or a deficiency of main classes of Ig tend to present with a more severe clinical course of bacterial infections in comparison to other patients with PID [3]. Patients with CVID and CRS most commonly have computed tomography (CT) findings of mucosal thickening consistent with CRS [1] and rarely, osteitis, or nasal polypsis [1]. A retrospective study by Hagan et al. showed patients primarily developed osteitis on CT when the serum IgM level was less than 25 mg/dl ($p=0.0074$) [11]. In the context of recurrent skin abscesses with the absence of an inflammatory response, HIES should be considered [14].

Fig. 2 Workup of primary immunodeficiency and chronic rhinosinusitis



Earlier diagnosis and identification of patients with PID would allow for appropriate management therapies to be initiated. Most PID patients with CRS who are recognized early and are effectively treated do not necessarily evolve more poorly than standard CRS patients.

Screening CRS Patients for ID

Recent advances in understanding the underlying molecular mechanisms of immunodeficiencies and the associated genetic influences have led to a better understanding of the different clinical phenotypes [23].

Refractory CRS may be due to several reasons including atopy, a disrupted mucociliary transport, underlying medical conditions such as granulomatous with polyangitis and immunodeficiencies [4•]. The difficulty in diagnosis lies in the fact that the severity of intervals of disease may not directly point to the underlying cause [4•]. Evaluating patients for immunodeficiencies is important in pediatric patients with recurrent respiratory tract infections as to rule out PID [1]. Similarly, adults with recurrent infections involving multiple systems such as the lungs and middle ears resulting in pneumonia, bronchitis, otitis media, or patients who fail maximal medical therapy and surgery for the treatment of CRS would benefit from a thorough immunological evaluation to rule out PID [1]. A detailed evaluation would provide a dramatic improvement in morbidity and quality of life in these patients.

A detailed immunologic workup would include immunization with protein and polysaccharide-based vaccines to exclude a functional humoral defect [21]. Standard immunoassays allow for thorough investigation of immunodeficiency in the different isotypes of Ig and specific antibodies [21]. In our experience, we obtain serum immunological levels as part of the workup on all patients who present to our tertiary rhinology clinic. This allows us to detect particular abnormalities within the workup and establish a personalized clinical phenotype of each patient.

In addition to the history, physical examination, and microbiological investigation, a positive family history is more common in patients with complement defects (25 %) or those with combined B and T cell defects (20 %) [8].

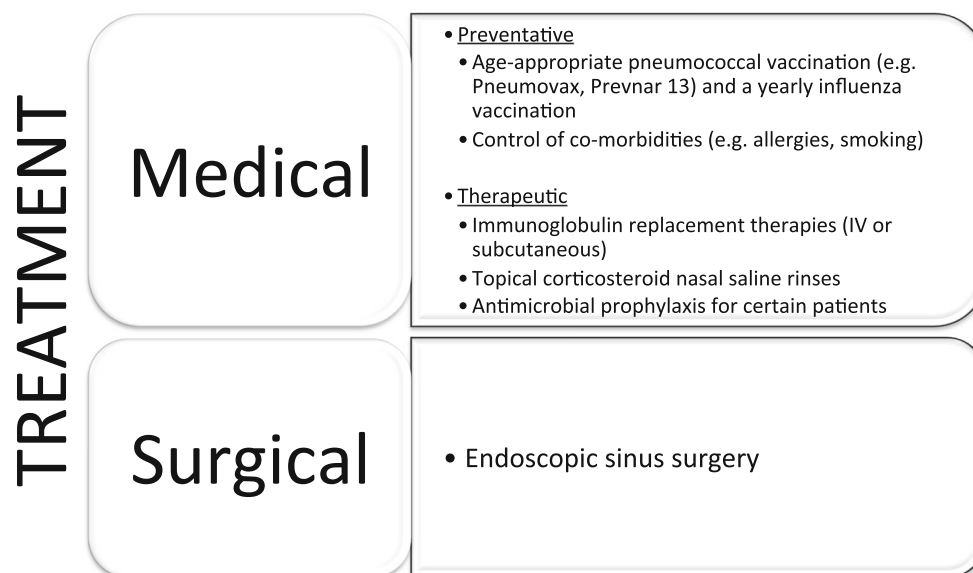
Management

Patients with recurrent CRS and an inadequate response to antibiotics should be thoroughly assessed (Fig. 2) through a complete blood count, quantitative immunoglobulin levels including IgG, IgM, IgA, and IgE, lymphocyte sub-population quantification, and a CT scan to detect anatomic abnormalities as well as have an evaluation of antibodies to pneumococcal serotypes and/or protein antigens, including diphtheria and tetanus toxoid. Patients with low antibody titers should be vaccinated. Follow-up antibody titers should be done within 4 to 6 weeks post-immunization to confirm a relevant disorder or an adequate response of the humoral immune system [10•]. The evaluation of the other arms of the immune system would depend on the global evaluation and the clinical suspicion of the treating physician. Should an abnormality persist or in the case of high clinical suspicion, consulting an immunologist is important. An immunodeficiency may make CRS more refractory to standard therapies [4•].

Preventive strategies such as age-appropriate pneumococcal vaccination and a yearly influenza vaccination are important for a subset of patients with PID who can mount an adequate immune response [8]. A polyvalent pneumococcal vaccine, such as Pneumovax, is important as the polysaccharide-encapsulated antigens induce specific antibody production belonging predominantly to subclass IgG2 and less to IgG1. Thus, immunodeficient patients can be safely vaccinated with Pneumovax without increasing the risk of an infection.

Prophylactic antibiotics have also been considered for patients with CVID, IgA deficiency, and SAD [4•]. At present however, there are no high-quality studies or consensus guidelines. The issue remains widely debated in the literature as

Fig. 3 Treatment options for primary immunodeficiency and chronic rhinosinusitis



these antibiotics may have little clinical benefit in preventing recurrent infections.

Immunoglobulin replacement therapies (IV or subcutaneous) can be considered in patients with a documented humoral defect where CRS and coexistent pulmonary disease who have failed medical or surgical therapy. Ig replacement can significantly reduce the number of acute and recurrent respiratory tract infections in patients with a documented humoral defect [3, 10•, 24]. The risk:benefit ratio must be evaluated with prudence as Ig replacement therapy can result in significant side effects and is expensive [4•]. Ig replacement may improve overall survival and decrease the rate of serious life-threatening infections in this patient group [1]. However, significant proven clinical benefit appears to be lacking in the case of CRS [1, 4•].

Ig replacement has been shown to be beneficial in the treatment of patients with agammaglobulinemia [3]. CVID patients respond to Ig replacement although 54–63 % of patients with CVID will still develop CRS despite treatment with IVIG [1, 10•]. Ig replacement thus is unlikely to reduce the frequency of CRS in the same fashion as it is able to reduce the frequency of lower respiratory tract infections in CVID patients [4•]. In patients with Good's syndrome, Ig replacement is the most effective way of improving clinical symptoms [10•]. Patient morbidity and mortality is reduced as defective signaling is restored, reestablishing immune homeostasis [10•]. Other candidates for Ig replacement include patients with normal Ig levels who have varying degrees of responsiveness to the polysaccharide vaccine and fail additional immunization with the conjugate vaccine as well as patients with HIES [10•, 13].

Surgical management through an endoscopic sinus surgery would also be important to open the paranasal sinuses and

reduce mucosal thickening or nasal polyposis. Postoperatively, PID patients would be able to use the same therapies as standard CRS patients, namely, topical corticosteroid nasal saline sprays, which may be beneficial. A large prospective study comparing immunocompetent and immunocompromised patients with CRS found that surgical outcomes of both groups were similar [25•] and that early surgical intervention may be warranted [4•].

A summary of the management options for patients with CRS and a diagnosis of PID is summarized in Fig. 3. Interestingly, there are certain patients who present with a clinical phenotype of immunodeficiency and yet standard laboratory evaluations are normal. These patients may have a yet-to-be described immunodeficiency or other known conditions such as primary ciliary dyskinesia or an atypical form of cystic fibrosis among other things and may benefit from being managed as patients who are immunodeficient.

Conclusion

PID patients are challenging to detect and manage. High clinical suspicion of PID must be maintained in the setting of refractory CRS not responding to standard therapy as the early diagnosis and management of PID has a significant impact on their overall morbidity and quality of life. Strong collaboration between immunology and otorhinolaryngology is important to ensure that the treatment of CRS is optimized.

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Compliance with Ethics Guidelines

Conflict of Interest This material has never been published and is not currently under evaluation in any other peer-reviewed publication. The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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