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Specific Antibody Deficiency

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Abstract: Patients with recurrent infections generate a large number of outpatient infectious disease referrals. While the differential diagnosis is vast, primary immunodeficiency is a consideration, but frequently overlooked. A subset of these maladies is Specific Antibody Deficiency. By definition, this diagnosis requires levels of both quantitative immunoglobulins and IgG subsets to be normal. Therapy is available, making identification of this immunodeficiency critical.

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Introduction

Patients with recurrent infections are commonly referred for an outpatient infectious disease (ID) evaluation. Frequently, the patient may hope to receive more definitive or prolonged antibiotic therapy. While this is occasionally the most prudent approach, the differential diagnosis of this problem is vast. Primary immunodeficiency (PID) is a definitive consideration. A subset of these maladies, specific antibody deficiency (SAD), is easy to overlook, difficult to diagnose, and is estimated to be the eighth most common PID [1]. This article will review the clinical presentations, evaluations, and therapeutic options of SAD.

Definitions

Specific antibody deficiency was previously known as selective antibody deficiency with normal immunoglobulins (SADNI). The diagnosis of SAD depends on normal immunoglobulin and IgG subclass levels, as well as a normal reaction to protein-based and conjugate vaccinations. The only immunologic deficiency in patients with SAD is an abnormal response to polysaccharide antigens, as found in the PPV23, known as the twenty-three valent pneumococcal vaccine.

Clinical Presentations

Recurrent infection of the upper respiratory tract (URI) and/or lower respiratory tract (LRI), and, more specifically, chronic sinusitis, are the most common clinical presentations [2]. A more severe and potentially life-threatening presentation is an invasive infection with an encapsulated organism, such as Streptococcus pneumoniae, Hemophilus influenzae, or Neisseria species. Bronchitis, otitis media, and pneumonia may also be presenting manifestations [3].

Bronchiectasis is an overlooked presenting manifestation of PID, with an incidence as high as 30% [4,5].

Incidence

The incidence of SAD in adults has been widely debated in the literature, ranging from 8 to 40% [2,6]. Recently, Stabler et al. studied 118 patients between the ages of 18 and 65 with one of three presentations: two benign URI or LRI for at least two years, one severe URI or LRI requiring intravenous antibiotics or hospital admission, or at least one invasive infection (such as meningitis, bacteremia, or arthritis) due to an encapsulated organism [7]. Patients were excluded from analysis if they had an underlying disease that could potentially preclude them from responding appropriately to polysaccharide antigens. Patients with HIV, diabetes, neutropenia, sickle cell disease, intravenous drug usage, and splenectomy, as well as those deemed immunocompromised, comprised the excluded group. By utilizing the standard process of evaluation delineated below, 47 patients (39.8%) were diagnosed with an immunodeficiency, and 37 (78.7%) of these were diagnosed with SAD. Other diagnoses included common variable immune deficiency (CVID) and IgG subset deficiency.

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The differential diagnosis of polysaccharide nonresponse includes a number of disease states as well as medications. More information on these diagnoses is listed below.

a. IgG subclass deficiency—most of the antibodies directed against bacterial polysaccharides are of the IgG2 subset.
b. CVID—URI, LRI, and gastrointestinal infections are most common; hypogammaglobulinemia may be present at an initial diagnosis.
c. Ataxia telangiectasia—usually a pediatric disease with neurologic abnormalities, URI, and skin rash.
d. Hyper IgE syndrome—characteristic facial anatomic anomalies and eczema.
e. HIV infection—decreased response to polysaccharide antigens may be experienced with increasing CD4 suppression.
f. Asplenia—invasive infections with encapsulated organisms are common.
g. Lymphocytic malignancies—chronic lymphocytic leukemia patients have varying degrees of hypogammaglobulinemia; patients with lymphoma are frequently treated with immunoglobulin-depleting therapy (such as rituximab).
h. Medications—glucocorticoids and any other immunosuppressive medication that could decrease the ability to produce immunoglobulins.

Clinical Evaluation

Clinical evaluation requires a four-step process. Initially, an extensive history and physical exam must be performed to identify the symptoms of any of the above diseases. In patients with recurrent sinusitis, sinus imaging may be used to eliminate anatomic obstructions. If identified, referral to an ear,

nose, and throat surgeon may be appropriate. Laboratory evaluation should include CBC, chemistry profile, HIV, quantitative immunoglobulins, IgE, and IgG subsets. The only abnormality in patients with SAD is the inability to respond to polysaccharide antigens. Accordingly, it would be expected that these labs in patients with SAD would be normal.

The next step involves measuring the baseline 23 pneumococcal serology antibody titers. Protective levels from invasive disease equate to 1.3 mcg/mL. Low baseline titers have been found to be predictive of SAD [8]. The third step involves administering the 23 valent polysaccharide pneumococcal vaccine (PPV23). Finally, one month after the administration of the PPV23, the pneumococcal antibody titers should be re-measured. Normally, at least 70% of the titers should be 1.3 mcg/mL or greater. Some authors have stratified the severity of deficiency by the percent of titers below the normal level [9], but the clinical utility of this is unclear.

If the baseline levels are greater than 1.3 mcg/mL, a two-fold increase in the titers is considered a normal response.

Therapeutic Options

Optimally, an intervention to decrease the incidence or severity of the recurrent infections should be considered. Therapeutic antibiotics should be used to aggressively treat acute infections. Once the patient has responded, a trial of prophylactic antibiotics may be indicated and has been shown to be effective at decreasing the number of clinical infections [10]. Unfortunately, prophylactic antibiotics may induce a multidrug-resistant organism, making future therapeutic interventions more difficult. An alternative approach is the usage of intravenous immunoglobulin (IVIG) at a monthly dose of 400 mg/kg. Setting patient expectations at the onset of therapy is very important since occasional infections may still be experienced despite IVIG therapy. A more realistic outcome is a decrease in the number of infections and courses of antibiotics over a period of time. The duration of therapy is poorly defined but should proceed for at least 6–12 months [6]. At that time, the intervention should be re-evaluated. This should include the efficacy of the therapy, patient adverse reactions and compliance, as well as financial considerations.

To optimize protection, vaccination with conjugate or protein-based vaccines, directed against encapsulated pathogens, should be administered.

Summary

ID clinicians are frequently consulted to evaluate patients with recurrent infections. SAD, a disease state that may present with recurrent or potentially life-threatening infections, should be considered. Aggressive management, including IVIG, has been shown to be beneficial in decreasing the frequency and intensity of these infections.

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