GUIDELINES

Diagnosis and Management of Immunodeficiencies in Adults by Allergologists

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Abstract

Primary immunodeficiencies (PIDs) are genetic diseases that cause alterations in the immune response and occur with an increased rate of infection, allergy, autoimmune disorders, and cancer. They affect adults and children, and the diagnostic delay, morbidity, effect on quality of life, and socioeconomic impact are important. Therapy (γ-globulin substitution in most cases) is highly effective. We examine adult PIDs and their clinical presentation and provide a sequential and directed framework for their diagnosis. Finally, we present a brief review of the most important adult PIDs, common variable immunodeficiency, including diagnosis, pathogenesis, clinical signs, and disease management.

Key words: Immunologic deficiency syndromes. Common variable immunodeficiency. Adult. Allergologist.

Resumen

Las inmunodeficiencias primarias (IDP) son enfermedades genéticas que ocasionan alteraciones en la respuesta inmunológica y que cursan con aumento de infecciones, alergia, autoinmunidad y cáncer. Afectan tanto a adultos como a niños, y el retraso diagnóstico, la morbilidad, la afectación de calidad de vida de los pacientes y el impacto socioeconómico que implican son considerables. El tratamiento (sustitutivo con gammaglobulina en la mayoría de los casos) es altamente eficaz en todos estos aspectos. Se enumeran las IDP que se pueden manifestar en adultos, los patrones de presentación clínica, y una pauta secuencial y dirigida de diagnóstico de las mismas. Finalmente se revisa brevemente (diagnóstico, patogenia, clínica y manejo) la IDP relevante más frecuente en adultos, que es la inmunodeficiencia variable común.

Palabras clave: Inmunodeficiencias. Inmunodeficiencia variable común. Adultos. Alergólogos.

Primary immunodeficiencies (PIDs) are genetic diseases in which the effector mechanisms of the immune system are weakened, the capacity to eliminate microorganisms is reduced, and susceptibility to infection is increased. Therefore, patients are more susceptible to allergic, autoimmune, and oncologic disorders. More than 150 PIDs are known, and the genetic basis of many of them has been identified [1].

Primary Immunodeficiencies in Adults

The perception of PIDs as a pediatric condition is changing, due to increased life expectancy of those affected and the late diagnosis of milder variants than previously known [2,3], and because some of the most common PIDs, such as antibody production deficiency (common variable immunodeficiency [CVID] [4], immunoglobulin [Ig] A deficiency, and IgG subclass deficiency), frequently appear during adolescence or adulthood. Between 25% and 40% [5,6] of all PIDs are diagnosed in adulthood, and in several national PID registries, there are as many cases in adults as in children.

Epidemiology studies on PIDs are scarce, especially those involving adults. National registries provide a reasonable impression of global prevalence [5,7,8]; prevalence in the European Union is estimated to be 1 case/10 000 people [9]. PIDs are considered rare diseases, and each of the different forms can be considered as such individually.

Experts suspect that the prevalence of these diseases is higher than previously reported, and a recent North American population study [10] revealed an estimated prevalence for PIDs of 1 case/1200 people, suggesting that it affects more people than, for example, cystic fibrosis. This could mean that there are around 38 000 cases of PID in Spain (albeit taking into account the necessary caveats for such an extrapolation); however, there is no reason to believe that the prevalence of PIDs in countries in our region would be very different from that of North America.

Infectious diseases are the result of the germ–host interaction, and there is growing interest in the understanding of individual immunological phenotypes (genetic polymorphisms providing different degrees of defense against infection and neoplasm, as well as tolerance mechanisms, gene regulation, and environmental and epigenetic factors). It is therefore foreseeable that the field of PIDs will be expanded and redefined with respect to these factors. In this context, immunodeficiencies will no longer be considered rare diseases. Much research is being performed on innate immunity, particularly polymorphisms in toll-like receptors (TLR), nod-like receptors (NLR), and mannose-binding lectin (MBL), and their role in immunopathologic processes such as infectious, allergic, and autoimmune diseases. Some studies have already analyzed the role of MBL polymorphisms in the phenotypic expression of CVID [11] and in the autoinflammatory diseases caused by alteration of signaling in TLRs or NLRs—and which present periodic fever and inflammation—that will probably become more numerous in allergology clinics in the near future.

Diagnostic Delay

The perception of PIDs as rare congenital diseases that are difficult to manage contributes to the lack of interest in their diagnosis [13]. Several registries have shown that it can take many years for PIDs to be diagnosed [5-7], and this delay may even be increasing, from an average of 4.7 years for patients diagnosed before 1970 to 9.9 years for those diagnosed after 2000 [6]. Although this increase is due in part to late diagnosis of milder forms that went unnoticed some decades ago, these data give cause for concern. A better understanding of the condition by physicians can shorten this period [12]. Diagnosis is often delayed, as clinicians consider signs and symptoms (eg, bronchitis, pneumonia, sinusitis, diarrhea) to be infection-related without taking the underlying immunological process into account, even in specialized centers [12,13]. A common risk is progress towards chronicity and permanent damage [6], with associated morbidity—many patients require several hospital admissions before diagnosis [13]—and repercussions on quality of life and life expectancy [14,15].

Economic Impact

The morbidity associated with diagnostic delay—cancer, hepatitis, neurological complications, diabetes, other autoimmune processes, chronic lung disease—represents an important economic burden, for both patients and their families, health systems, and society at large [6,16].

Treatment Options

Despite the negative impact of PIDs, the range of therapeutic options is wide. In particular, replacement therapy with γ-globulins (intravenous and subcutaneous), which is required in around 70% of adult patients with PID, leads to a significant decrease in airway infections (pneumonia, bronchitis, sinusitis, and otitis) and diarrhea (albeit to a lesser extent), and up to a 50% reduction in admission rates after treatment has started. Furthermore, two-thirds of patients with PID who are being treated describe their current state of health as good and with little or no restriction of daily activity [6].

Other effective measures include judicious use of antibiotics as treatment or prophylaxis, the use of certain cytokines (eg, interferon [IFN] γ in chronic granulomatous disease [CGD], hematopoietic stem cell transplantation [HSCT] in cellular and macrophage immunodeficiencies, and monoclonal antibodies such as rituximab [anti-CD20] in autoimmune complications) [17], and adjuvant treatments with possible utility in the management of acquired and primary immunodeficiencies, such as the use of vitamin D supplements, which could boost the immune response, particularly the innate response.

To summarize, the implementation of initiatives to improve understanding and diagnosis of PID in adults will depend on the increasing prevalence of this condition, the significant diagnostic delay due to lack of awareness, the development of treatment options that can improve prognosis and quality of life, and economic impact [18]. Progress in this area will require a multidisciplinary effort (internal medicine, immunology, pneumology, otorhinolaryngology, and allergology) directed toward an etiological, functional, and inclusive approach that considers PID as a systemic disease.

The present work describes the clinical manifestations of PIDs in adults, establishes the corresponding differential diagnoses and indications, and presents options for management. Finally, we present up-to-date information on CVID, the most common PID in adults after IgA deficiency (which is usually asymptomatic or causes little morbidity).

Traditional Classification of PIDs

PIDs are traditionally classified according to defects in the immune response. Such a classification usually leads to clinical descriptions based on infections caused by specific groups of pathogens [19], as follows:

1. *Defects in humoral immunity (antibody deficiencies):* These are a consequence of the effect on B lymphocytes and the production of immunoglobulins and antibodies. They lead to recurrent respiratory infections by encapsulated microorganisms.
2. *Defects in cellular immunity:* These are a consequence of the effect on T lymphocytes, with a predisposition to severe infections by viruses, fungi, and other opportunistic pathogens (*Pneumocystis jiroveci*, mycobacteria).
3. *Defects in phagocytosis:* These defects predispose patients to recurrent cutaneous and deep-seated abscesses due to *Staphylococcus aureus*, gramnegative bacteria (*Escherichia coli, Serratia marcescens, Burkholderia* species, *Pseudomonas* species), fungi (*Aspergillus* species), *Nocardia* species, and mycobacteria.
4. *Defects in the complement system:* recurrent infections by *Streptococcus pneumoniae* and *Neisseria* species, or recurrent angioedema.

This classification has undergone several revisions for different reasons: the existence of complex mechanisms affecting more than one branch of the immune system, immunodeficiencies associated with major phenotype defects, reports of defects in innate immunity, clinical descriptions in which the main manifestations are not infectious (anti-inflammatory syndromes), and variants susceptible to specific germs in which traditional immunological evaluation does not yield abnormal findings. In particular, the International Union of Immunological Societies [1] has established the following groups of PIDs:

1. Combined T-cell and B-cell immunodeficiencies
2. Predominantly antibody deficiencies
3. Other well-defined immunodeficiency syndromes (associated with larger defects)
4. Diseases of immune dysregulation
5. Congenital defects of phagocyte number, function, or both
6. Defects of innate immunity
7. Autoinflammatory disorders
8. Complement deficiencies

More detailed information is available in the classification of the International Union of Immunological Societies [1].

Which PIDs Can Present in Adults?

Almost all PIDs can present in adults, although the frequency varies somewhat in comparison with children. The classification for adults by Riminton et al [20] is useful, and divides PIDs into 5 types:

1. *Defects of B-lymphocyte differentiation and antibody production* [21]: IgA deficiency, CVID, IgG subclass deficiencies, and deficiencies in the production of specific antibodies. There is some relation between these deficiencies and they may be part of a continuum. Of note, thymoma-associated immunodeficiency is not common, but is typically found in adults.
2. *Complement deficiencies:* These deficiencies affect a mechanism of innate immunity and so tend to improve with age due to maturation of the adaptive response, although they can present at any time in life. They include defects of the classic and alternative activation pathways (C1 to C4, factors D, I, H, and P) and defects in the lectin pathway (MBL, mannose-binding protein-associated serine protease 2 [MASP2]), which may operate as "low-efficiency" polymorphisms. Other diseases can act as cofactors in phenotypic expression.

Hereditary angioedema caused by C1 inhibitor deficiency is characterized by recurrent episodes of angioedema [22] and no recurrent infections. This condition is clinically very different from other PIDs.

3. *Adult presentation of PIDs that typically present in childhood* [23-40].
4. *Mendelian susceptibility to infection:* This type of susceptibility involves monogenic defects in certain pathways of the immune response that mediate infections by specific germs, such as mycobacteria and other intracellular pathogens in defects of the interleukin (IL) 12/23–IFN-γ pathway [41], or *Neisseria* species in defects of the terminal complement pathway (membrane attack complex). To date, there have been no reports of alteration in the defense against *Herpes simplex* virus and *S pneumoniae* or other encapsulated germs in adults due to defects in the 2 activation pathways of the TLRs.
5. *Emerging genetic polymorphisms in innate immunity:* As mentioned above, deficits in MBL and MASP2 and polymorphisms in TLRs generate susceptibility or resistance to various types of germs and to other diseases (eg, autoimmune disorders, some types of cancer, coronary disease) [42].

Patterns of Clinical Presentation of PIDs in Adults

Traditionally, the clinical manifestations of PIDs have been described according to defects in the immunological mechanism that causes them. However, the reverse path is more practical for the clinician, that is, to know the common clinical presentations, suspect different PIDs, and perform the corresponding differential diagnosis. Some recently published guidelines follow this path [43]. We shall attempt to adopt this approach in the present work.

A) Infections with special characteristics: recurrent, caused by rare or opportunistic germs, very severe (poor response to treatment, uncommon complications), or found in uncommon locations.

1. Recurrent or persistent upper and lower respiratory infections, unexplained bronchiectasis. The recurrence

and/or severity of such a condition (need for admission to hospital/intravenous antibiotic therapy) make it possible to rule out an underlying pathology, such as PID. Systemic diseases must also be taken in account in the case of persistent infiltrates. The PIDs that predispose to recurrent respiratory infections are as follows:

Antibody deficiencies: These deficiencies typically involve respiratory infections (rhinosinusitis, otitis, bronchitis, pneumonia) caused by encapsulated germs (*S pneumoniae, Haemophilus influenza*), and include IgA deficiency (the most common PID, asymptomatic in 70% of patients), CVID (the most important clinically, with 2 peaks of age at onset [during adolescence or young adulthood and in the fourth or fifth decade of life]), IgG subclass deficiency, and specific antibody production deficiency. They can affect the digestive tract (diarrhea and malabsorption, inflammatory bowel disease) and produce inflammatory symptoms (granuloma) in the lungs and intestine, and may have a higher incidence of lymphoproliferative disorders, solid tumors (gastric carcinoma), and autoimmune diseases (cytopenia in CVID, celiac disease in IgA deficiency). The genetic defect is not known in most cases and in many respects CVID is an undefined group of diseases. Thymoma with immunodeficiency is characterized by hypogammaglobulinemia, recurrent infections, and broadening of the mediastinum (on x-ray), and may be associated with myasthenia gravis. It typically appears in adulthood. Finally, when there are clinical signs and analytical findings compatible with antibody deficiency in adults, the possibility of late presentation of X-linked agammaglobulinemia (Bruton disease) should also be considered, as should HIV infection.

Complement deficiencies: Deficiencies in classic and alternative pathways (defect in C1 to C4, factors I, D, and H, and P) occur with infections by encapsulated germs and by *Neisseria* species and with lupus-like syndromes. C2 deficiency is the most common (incidence of 1 case in 10 000 people).

Phagocytic defects (CGD, neutropenia, hyper-IgE syndrome)

2. *Other infections:* recurrent abscesses—both superficial (cutaneous, mucosal) and deep-seated (lung, bone, liver, lymph nodes)—occur when there are phagocytosis defects (CGD, neutropenia, hyper-IgE syndrome, defects in leukocyte adhesion).
3. *Diarrhea and malabsorption:* These can be the main symptoms in CVID and IgA deficit. They may also occur secondary to infection by Giardia species, enterovirus, and cytomegalovirus (CMV), or associated with celiac disease and inflammatory bowel disease. The differential diagnosis has to be made with a large number of digestive, endocrine, and metabolic processes.
4. *Especially severe or opportunistic infections* (*P jiroveci*, *Aspergillus* species, *Cryptococcus* species, *Cryptosporidium* species, *Nocardia* species, severe infections by viruses such as CMV, Epstein-Barr virus [EBV], varicella-zoster virus [VZV], human herpes virus [HHV]) with or without malabsorption, diarrhea, and weight loss; less severe forms of cellular or combined immunodeficiencies—possibly associated with respiratory infections by encapsulated pathogens—that can start and persist into adulthood; other isolated poorly defined deficiencies in cellular immunity; and Wiskott-Aldrich syndrome. The differential diagnosis should be made with HIV infection and other cases of secondary immunosuppression (chemotherapy, corticosteroid therapy, malnutrition, and other metabolic processes such as diabetes, renal failure, hepatic disease).
5. *Infections by certain pathogens suggest specific defects.* We have already mentioned mendelian susceptibility to infection by mycobacteria and *Neisseria* infections secondary to deficiencies in the terminal complement pathway (membrane attack complex C5-C9), with recurrent meningococcal meningitis, or by rare serogroups (not B or C), or presence of susceptibility in several members of the family. Also noteworthy are infections by *Pneumococcus* and other encapsulated species in the signaling deficiencies of TLR (IRAK4/NEMO/MyD88), invasive pneumococcal infections in asplenia (acquired and congenital), verrucae (epidermodysplasia verruciformis), and EBV in X-linked lymphoproliferative syndrome. Chronic mucocutaneous candidiasis (CMC) is also recognized, and some forms—autoimmune polyendocrinopathy [APECED] caused by a mutation in the *AIRE* gene—occur with autoimmune multiple endocrinopathy.

B) Immunopathologic manifestations

6. *Allergy:* Asthma and food allergy are principally associated with IgA deficiency and other PIDs that rarely have their onset in adulthood (Wiskott-Aldrich and hyper-IgE syndromes).
   Despite not being an allergic process, hereditary angioedema is generally managed by the allergologist. It occurs as a consequence of a functional deficiency in the C1 inhibitor, which is transmitted as an autosomal dominant trait. Characterized by recurrent nonpruritic episodes at several sites (eg, pharynx, larynx, face and mouth, skin, and abdomen), it is not usually associated with urticaria. While 50% of patients show clinical onset before 10 years of age, other cases appear later [22].
7. *Autoimmunity and inflammation:* These manifestations include cytopenia (in CVID, which can also occur with inflammatory granuloma, and in IgA deficiency), and, more rarely, systemic diseases such as systemic lupus erythematosus, rheumatoid arthritis (which can occur in IgA and complement deficiencies, and probably in the long term in DiGeorge syndrome), and endocrinopathies (eg, chronic mucocutaneous candidiasis-APECED). Autoinflammatory syndromes caused by defects of apoptosis pathways (autoimmune lymphoproliferative syndrome) are characterized by autoimmune features (cytopenia) and polyclonal and monoclonal lymphoproliferation. Periodic fever syndromes are recurrent familial inflammatory diseases (eg, familial Mediterranean fever, hyper-IgD syndrome).
8. *Cancer:* PIDs rarely present as cancer in adults

(X-linked lymphoproliferative syndrome). Noticeable increases have been reported in the prevalence of cancer in patients with CVID (lymphoma, gastric cancer), advanced Wiskott-Aldrich syndrome, ataxia telangiectasia, and autoimmune lymphoproliferative syndrome.

C) Other conditions

9. *Typical associations with rare phenotypic characteristics:* DiGeorge syndrome (cardiopathy, hypoparathyroidism with hypocalcemia that can be partial and become more evident in situations of stress [eg, after surgery], dysmorphic features, severe cellular immunodeficiency, or more frequently a mild form associated with allergy and/or autoimmunity), Wiskott-Aldrich syndrome (eczema, thrombocytopenia, immunodeficiency, risk of lymphoproliferative disease), and ataxia telangiectasia (with variable immunodeficiency there is also an increase in the incidence of lymphoma). Many other signs and symptoms appear in certain immunodeficiencies, for example, light sensitivity, partial albinism, poor wound healing, microcephaly, dysmorphia, alterations in teething, and bone alterations. There may also be a certain level of immunodeficiency in several congenital syndromes affecting patients into adulthood [44].
10. *Abnormal laboratory findings:* Neutropenia (congenital, associated with antibody defects such as X-linked agammaglobulinemia and some forms of hyper-IgM syndrome or autoimmune syndrome), neutrophilia (as in leukocyte adhesion deficiency), lymphopenia (cellular or combined immunodeficiency, especially adenosine deaminase deficiency), lymphocytosis, eosinophilia (some cases of severe combined immunodeficiency [SCID], hyper-IgE syndrome, and Wiskott-Aldrich syndrome), hypocalcemia (DiGeorge syndrome), hypouricemia (purine nucleoside phosphorylase deficiency), and hypergammaglobulinemia (defects in phagocytosis or the complement system, any situation of recurrent or persistent infection with intact antibody production, HIV). We must rule out the possibility that hypogammaglobulinemia is secondary to loss (protein-losing enteropathy, nephrotic syndrome, burns), hypercatabolism (myotonic dystrophy [Steinert disease]), HIV infection, or medication (carbamazepine, hydantoins, rituximab and other immunomodulators, and—rarely and only in the long term—corticosteroid therapy).

PIDs: An Aid for Diagnosis

Below, we present the steps to be followed when making a diagnosis. More detailed information is available in the literature [45].

1. Medical history and physical examination. The differential diagnosis is made against secondary immunodeficiencies and other localized and generalized processes.

History: Infections with the characteristics mentioned above are the hallmark of PIDs.

Autoimmune diseases, allergy, or cancer could also be present.

The causal microorganisms provide important diagnostic information.

Family history: Recurrent infections, autoimmune processes, cancer, or higher infant mortality. A family history of immunodeficiency is very suggestive, although it is found in only 18% of cases [46] and its absence does not rule it out. Most cases are autosomal recessive diseases; therefore, there may be no family history. Twenty-five percent of cases linked to the X chromosome are caused by de novo mutations, autosomal dominant diseases may have incomplete penetration, and in all cases there may be associated factors that result in major variability in clinical expression within the same family, including lack of manifestation in some members.

Physical examination: The physical examination can provide data on chronic diseases (pallor, thinness, acropachy, lung sounds indicative of disease) and on other nonspecific but suggestive conditions such as hepatosplenomegaly and lymphadenopathy (although the absence of lymphoid tissue and tonsil hypoplasia are typical in agammaglobulinemia and in many forms of SCID). The phenotypic traits of the immunodeficiency associated with the major defects mentioned above are very suggestive.

Differential diagnosis: As well as suspecting PIDs and—sometimes earlier—secondary immunodeficiencies, (aging, malnutrition, and metabolic diseases [eg, diabetes mellitus, uremia, liver disease]), clinicians should also take into account the following: surgery, trauma, environmental conditions, radiation, chemotherapy, corticosteroids, other immunosuppressors, altitude, chronic hypoxia, infection, AIDS, hypogammaglobulinemia secondary to protein-losing syndromes, hypercatabolism, or drugs as should other disorders (localized and generalized) and hereditary diseases other than PIDs.

Below, we present a series of clinical settings in which specific conditions should be suspected.

Recurrent Respiratory Infections

Asthma/allergic rhinitis: In young adults and children, these factors are more commonly associated with pneumonia and recurrent sinusitis and, occasionally, with atypical or unknown manifestations.

α1-antitrypsin deficiency and cystic fibrosis are more often diagnosed in adults.

Localized alterations including obstructive bronchial disorders (tumors, foreign bodies, aspiration associated with gastroesophageal reflux, congenital malformations), bronchiectasis, allergic bronchopulmonary aspergillosis, and pulmonary vasculitis. In general, persistent atelectasis and infiltrates at the same sites point to localized disorders, whereas a variable location is indicative of systemic disorders, although this is not always the case.

Rhinosinusitis: localized processes in the ear, nose, and throat must be ruled out (eg, nasal septum deviation, foreign bodies).

Recurrent Abscesses

If abscesses occur at the same site, they may be due to anatomical factors such as bronchopulmonary malformations, bronchial cysts, and foreign bodies.

Recurrent Cellulitis

In adults, this condition can be caused by several processes, such as multiple myeloma, chronic lymphocytic leukemia, hemoglobinopathy, HIV infection, secondary neutropenia (cancer, toxins), skin barrier disruption (burns, severe eczema, catheters, dermatophytosis with bacterial superinfection), and lymphedema.

Recurrent Meningitis

In cases of recurrent meningitis, the clinician should suspect the following: post-traumatic CSF fistula or asplenia (*S pneumoniae*), extension of ENT infections (*S pneumoniae, H influenzae, Branhamella catarrhalis*), epidermoid cysts (gram-negative bacilli), infected ventricle peritoneal shunts (*Staphylococcus epidermidis*), and Mollaret meningitis (benign recurrent aseptic meningitis related to herpes simplex virus).

Finally, the list of warning signs for PIDs in adults recently produced by the European Society of Immunodeficiencies is relevant (Table) [47].

Table. The 6 ESID Warning Signs for Adult Primary Immunodeficiency Diseases [47]

1. Four or more infections requiring antibiotics within 1 year (otitis, bronchitis, sinusitis, pneumonia).
2. Recurring infections or infection requiring prolonged antibiotic therapy.
3. Two or more severe bacterial infections (osteomyelitis, meningitis, septicemia, cellulitis).
4. Two or more radiologically proven pneumonia within 3 years.
5. Infection with unusual localization or unusual pathogen.
6. PID in the family.

Abbreviation: ESID, European Society of Immunodeficiencies.

2. **General investigations** (screening and exclusion of other disorders)

Complete blood count and quantification of IgG, IgA, IgM, and IgE, as well as serum chemistry (eg, calcium, uric acid, liver enzymes).

Imaging (directed). The absence of adenoid tissue in the nasopharynx or absence of the thymus (difficult to visualize on plain chest x-ray) suggests a primary immunodeficiency (antibody or cellular/combined), mainly in children.

There must be an attempt to identify the microorganisms directly (eg, cultures, PCR for virus), as serological tests in infectious diseases could give false-negative results if there is an antibody defect. Secondary immunodeficiencies such as HIV and CMV must be ruled out.

Tests must also be directed towards differential diagnosis (eg, asthma, allergy, cystic fibrosis, malabsorption, gastroesophageal reflux, bronchial foreign body, local problems).

3. **Immunodeficiency investigations**

Progressive levels should be established, as follows:

Level 1

Complete blood count, with a manual count of leukocytes and careful verification of absolute values (eg, neutropenia or neutrophilia, lymphopenia, eosinophilia).

Quantification of serum IgG, IgA, IgM, and IgE and comparison with the reference values for age (and individual laboratory values where possible).

Level 2

1. Antibody response investigations, with repeated quantification of IgG, IgA, IgM, and IgE, and IgG subclasses
   - Antitetanus and/or antidiphtheria (protein antigens). Levels are related to vaccine status; if they are low, a booster dose of the vaccine and further tests to determine the presence of these antibodies are necessary. To consider a response normal, the baseline titer must increase at least 4-fold.

     IgG antibodies for rubella: immune status must also be taken into account, but vaccination is contraindicated until an antibody defect is clearly ruled out, as the vaccine is prepared with a live—albeit highly attenuated—virus.
   - Natural antibodies (isohemagglutinin, anti-ABO, antistreptolysin O titer).
   - Antipneumococcal antibody and monitoring after polysaccharide vaccine (Pneumo 23): normal response is a 2-fold increase in the baseline titer. Note that baseline levels could be influenced by the conjugate vaccine (heptavalent); therefore, ideally, the response of serotypes not included in the vaccine should be determined.
   - IgG subclasses
2. Investigation of lymphocyte subpopulations (basic protocol): $CD3^+$ (total T lymphocytes), $CD3^+CD4^+$ (helper T lymphocytes), $CD3^+CD8^+$ (cytotoxic T lymphocytes), $CD19^+$ or $CD20^+$ (B lymphocytes), $CD3^-/CD16^+$ or $CD3^-/CD56^+$ (NK cells). Compare with normal values for age and evaluate absolute and relative values.
3. Study of complement: C3, C4, CH50 (integrity of the classic and terminal complement pathway).

Level 3

1. Oxidative capacity of neutrophils (burst test).
2. Quantification of other complement factors and of the activity of the alternative and lectin pathways. In the case of angioedema, normal C4 titers rule out 95% of cases of hereditary angioedema. If values are low, or in suspicious cases despite normal C4 levels, C1 inhibitor antigen and functional values must be investigated to rule out hereditary angioedema.
3. Lymphocyte subpopulations (extended protocol). The selection of markers at this level will be directed according to clinical suspicion:

Common γ chain (CD132), CD40 ligand (CD154) in T lymphocytes/CD40 in B lymphocytes, HLA II (DR), CD45RA/45RO, CD18/11, CD15s, HLA I ($ß_2$-microglobulin), TCR α-ß.

4. Lymphocyte cultures (stimulation and measurement of response), as follows:
   - Mitogen stimulation assays (PHA, ConA)
   - Tritiated thymidine incorporation assay.
5. Special studies:
   Standard karyotype, karyotype with methotrexate, FISH (study of deletion of 22q11.2 to investigate DiGeorge syndrome), alpha fetoprotein/carcinoembryonic antigen.
   Parathormone.
   Biopsy (intestinal, lymph nodes), bone marrow examination.

Level 4

Lymphocyte cultures (stimulation and response measurement), with several variables:

• Stimulation with mitogens (PWM, PMA/ionoCa), monoclonal antibodies (anti-CD3 or anti-$CD2^+$ anti-CD28), and antigens (tetanus toxoid, Candida).

• Addition of IL-2 or other cytokines.

• Measurement of activation markers, cytokines, and/or immunoglobulins in supernatant fluids.

• Intracellular cytokines (eg, IL-2, IFN-γ, IL-4)

• IL-12/IL-12Rß/IFN-γR

• Proteins (flow cytometry, Western blot [eg, ZAP 70, Jak3, TAP1/2])

• Genetic studies (eg, BTK, RAG1/2, CD40L/CD40, IFNγR, ATM, WASP)

The study is sequential, becoming more specific with each new level. Assignment of the different determinations at the levels referred to should not be too rigid. In practice, a high level of suspicion, subsequent execution of simple complementary tests (blood cell count, IgG, IgA, IgM, IgE), and checking the results carefully make it relatively easy to detect half of all immunodeficiencies. However, if the suspicion of immunodeficiency remains due to the clinical symptoms observed, it is necessary to monitor the patient and to repeat certain investigations (immunoglobulins), or to progress with the study despite the normality of the previous basic results. Collaboration between levels of care through consultation with experts in the field and performance of advanced studies in different reference laboratories [48] is frequently necessary.

Common Variable Immunodeficiency

Common variable immunodeficiency is a heterogeneous syndrome of primary antibody production failure. It affects 1 in 10 000 to 50 000 individuals, and is the most frequent primary immunodeficiency producing relevant clinical symptoms in adults and children. The hallmark of this disease is recurrent bacterial infections, usually of the respiratory and gastrointestinal tract. Onset is mainly in children aged 1-5 years, adolescents aged 16-20 years, and adults (fifth decade).

Diagnosis

The diagnostic criteria are as follows [49]:

Recurrent bacterial infections.

Serum IgG and IgA with a marked decrease (at least 2 SD below the mean for age) in serum and fulfillment of all of the following criteria:

Onset of immunodeficiency at more than 2 years of age.

Absence of isohemagglutinins and/or poor response to vaccines.

Exclusion of defined causes of hypogammaglobulinemia.

Clinical Picture

To date, only 2 studies have analyzed high numbers of patients with CVID [4,49]. In the study by Chapel et al [49], the patients were classified into 5 different groups or phenotypes according their clinical signs and symptoms:

1. Immunodeficiency: Patients with recurrent infections as the only manifestation.
   These infections are usually produced by encapsulated microorganisms such as *H influenzae, Moraxella catarrhalis* and *S pneumoniae*, which are the 3 most frequent agents in the respiratory tract, and *Campylobacter jejuni* and *Giardia lamblia* in the gastrointestinal tract. This group represents 48% of patients.
2. Lymphocytic infiltration (22% of patients). This group includes patients with any of the following symptoms: lymphoid interstitial pneumonitis, hepatomegaly, splenomegaly, extensive and persistent lymphadenopathy or granulomas.
3. Autoimmunity (11% of patients). The most common autoimmune disorders are idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, pernicious anemia, or atrophic gastritis, which can cause megaloblastic anemia.
4. Enteropathy (2% of patients). Diarrhea and/or malabsorption with intestinal lymphocytic infiltration that is not sensitive to gluten withdrawal.
5. Malignancy. Fifty percent of cases involve cancer (eg, lymphoma, gastric cancer). In association with other subgroups of symptoms, cancer affects 3% of patients.

Different combinations of groups 2-4 (above) affect 17% of patients.

Survival of these patients is lower than that of the general population, mainly due to cancer (lymphoma or gastric cancer) and infections [4].

Pathogenesis

Molecular defects are observed in less than 10% of CVID cases. Nevertheless, at least 5 genetic defects associated with CVID have been described: *ICOS* defects in T cells, *TACI* (7-10% of cases of CVID), *BAFF-R* needed for B cell maturation and survival, *MSH5* that regulates Ig class switch recombination, and absence of CD19. Some of these mutations (*ICOS, MSH5*) can present in healthy controls, suggesting incomplete penetrance for the CVID phenotype. No mutations are found in 90% of patients.

A European multicenter study of 303 patients with CVID revealed different subgroups according to the phenotype of the B-cell population [50]. In most patients, the number of B cells was within the lower normal range. In more than 80% of patients there was a reduction in switched memory B cells ($IgM^- IgD^- CD27^+$). This reduction correlates with the decrease in serum IgG and IgA levels; however, more importantly, the decrease in memory B cells rather than the decrease in serum Ig levels is associated with infectious diseases in these patients.

Management

The elective form of treatment in CVID patients is intravenous immunoglobulin replacement. The usual dose is 400-800 mg/kg every 3-4 weeks, and the main objective is to maintain serum IgG levels above 500 mg/dL, with a clinical course that is free (or almost free) of infections. The overall goals of treatment are to decrease the incidence of infection and to prevent bronchiectasis and decreased pulmonary function [51,52]

Subcutaneous infusion of IgG, which was introduced more than 20 years ago, has gained ground in recent years. Smaller doses of IgG are infused weekly, and less variable levels are obtained. Systemic adverse effects are less frequent, patient autonomy and quality of life improve, and vascular access is not required. On the other hand, a limited volume of the product can be administered at any one time, so more frequent doses are needed, and the patient or his/her family must be reliable [53].

Other standard procedures are rational use of broad-spectrum antibiotics in therapy and prophylaxis when needed, respiratory physical therapy, nutritional support, and supplements (eg, iron, vitamin B12, other vitamins).

Long-term follow-up is necessary, mainly to monitor health status and Ig levels and to avoid bronchiectasis (biannual thoracic computed axial tomography is recommended, as are lung function tests, in particular spirometry and carbon monoxide transfer factor).

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