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REVIEW

Educational paper

Primary antibody deficiencies

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Abstract Primary antibody deficiencies (PADs) are the most common primary immunodeficiencies and are characterized by a defect in the production of normal amounts of antigen-specific antibodies. PADs represent a heterogeneous spectrum of conditions, ranging from often asymptomatic selective IgA and IgG subclass deficiencies to the severe congenital agammaglobulinemias, in which the antibody production of all immunoglobulin isotypes is severely decreased. Apart from recurrent respiratory tract infections, PADs are associated with a wide range of other clinical complications. This review will describe the pathophysiology, diagnosis, and treatment of the different PADs.

Keywords Primary antibody deficiency · Child · Agammaglobulinemia · Common variable · Immunodeficiency · IgA deficiency · IgG2 deficiency · Specific anti-polysaccharide antibody deficiency

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Introduction

Primary antibody deficiencies (PADs) are the most common primary immunodeficiencies [24]. The hallmark of PADs is a defect in the production of normal amounts of antigen-specific antibodies. These antibodies or immunoglobulins are indispensible for the adaptive immune response against a wide variety of pathogens. A defect in antibody production results in recurrent and/or severe infections. PADs represent a heterogeneous spectrum of conditions, ranging from often asymptomatic selective IgA and IgG subclass deficiencies to the severe congenital agammaglobulinemias, in which antibody production of all immunoglobulin isotypes is severely decreased. The majority of patients with symptomatic PADs present with recurrent ENT and airway infections and are difficult to discover among the many children presenting to pediatric practice. Therefore, a diagnostic strategy for immunodeficiency in children has been recently presented in this journal [16]. Apart from recurrent infections, there is a wide range of other clinical complications associated with primary antibody deficiency [13, 15, 43], affecting the child's quality of life and life expectancy. After an introduction on normal B cell development, this review will describe the pathophysiology, diagnosis, and treatment of the different PADs.

Normal B cell differentiation and maturation

Plasma cells and memory B cells represent the end stages of B cell differentiation and maturation (Fig. 1). They are responsible for the continuous production of specific antibodies and long-lasting immunological memory, respectively [59]. Memory B cells are able to rapidly differentiate in new plasma cells in case of reinfections. B cells originate from

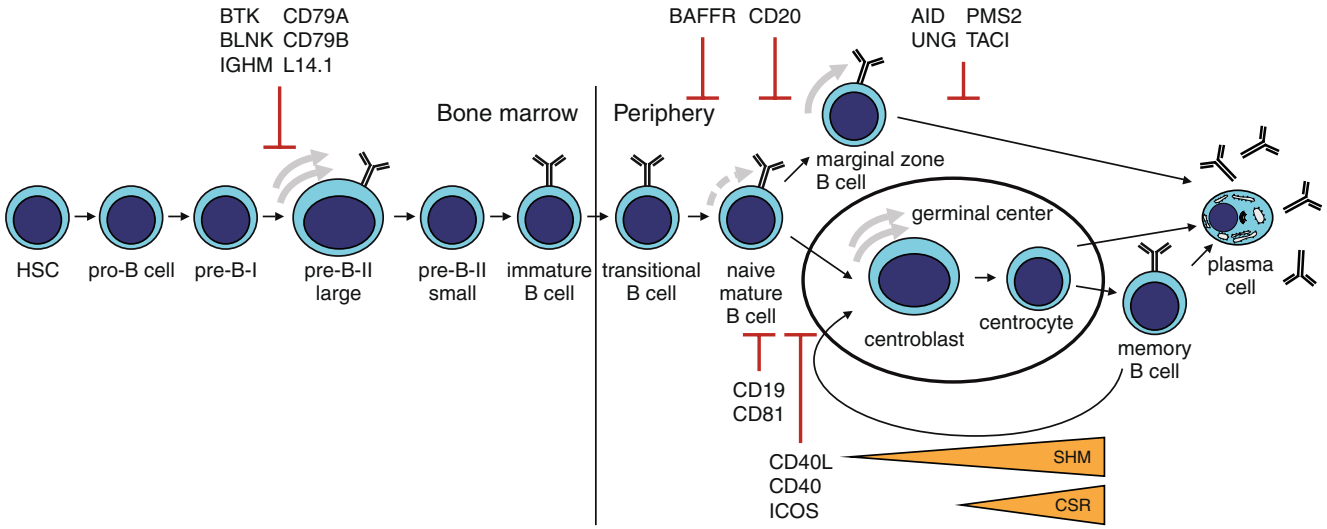

Fig. 1 Antigen(Ag)-independent B cell differentiation occurs in the bone marrow, whereas Ag-dependent B cell differentiation occurs in the periphery. After activation by Ag, B cells develop in a T cell-dependent way in the germinal center and in a T cell-independent way in the marginal zone of the spleen. Defects of survival, Ag stimulation, B–T interaction, TI response, CSR/SHM can result in PAD. Identified PAD genes affecting these processes are indicated

lymphoid precursors in the bone marrow, where a large repertoire of B cells with different B cell receptors (BCRs) is formed, consisting of a signaling complex and a membrane bound IgM molecule. These BCRs are able to recognize a wide variety of antigens. After leaving the bone marrow, IgM positive B cells can be activated by antigen and enter a germinal center in lymphoid tissue. Here, the interaction of B and T cells, characteristic for the T cell-dependent antibody response, is contributing to the generation IgG, IgA, and IgE positive plasmacells and memory B cells by initiation of class switch recombination (CSR). Somatic hypermutation (SHM) of the variable region of Ig heavy and Ig light chains increases the affinity of the BCR for antigen (affinity maturation). The production of antibodies to polysaccharide antigens, present in the cell wall of encapsulated bacteria like pneumococci and meningococci, is supported by a second T cell-independent B cell response, which localizes in the marginal zone of the spleen. The T cell-independent B cell response is still immature in healthy children below the age of 2 years, hence their susceptibility to severe complications of pneumococcal and meningococcal infections.

The spectrum of primary antibody deficiencies

Defects in all critical stages of B cell development have the potential to cause PAD (Fig. 1); however, the immunological and genetic defects of most patients with PAD are still unknown. Evaluating a child with a suspected PAD, the secondary causes for the antibody deficiency, such as nephrotic syndrome, protein-loosing enteropathy, use of certain drugs, and hematological malignancies have to be excluded. Depending on the nature of the B cell defect, PADs can be separated in different categories (Table 1), with their own clinical, immunological, and genetic characteristics. In this section, we will discuss the different PADs in more detail including specific diagnostic features and most important clinical complications (Table 2).

Congenital agammaglobulinemias

The first report of a congenital agammaglobulinemia dates from 1952 [6], when Bruton described a boy with recurrent infections and a deficiency of gammaglobulins. Many years later, it appeared that boys with X-linked agammaglobulinemia (XLA) suffer from a defect in the gene for Bruton's tyrosine kinase or *BTK* [62], which is crucial for (pre)B cell receptor signalling. *BTK* deficiency causes an early block in B cell development in the bone marrow, resulting in the (near) absence of B lymphocytes in peripheral blood and peripheral lymphoid tissues. As a result, antibody production of all immunoglobulin isotypes, including the response to vaccinations is severely impaired. XLA accounts for 85% of all cases of congenital agammaglobulinemia. Patients with autosomal recessive forms also have B cell defects affecting the pre-BCR or the downstream signalling cascade (Fig. 1, Table 1). The clinical problems of these patients are comparable to XLA, but the clinical phenotype tends to be more severe because of a more absolute block in early B cell development [23].

Over half the XLA patients present before 1 year of age and more than 90% are diagnosed at the age of

Table 1 The heterogeneous spectrum of primary antibody deficiencies

Disease	Circulating B cells	Serum Ig decrease
Congenitial agammaglobulinemias		
X-linked		
BTK deficiency	Severe decrease	All isotypes
Autosomal recessive		
μ Heavy chain deficiency	Severe decrease	All isotypes
λ 5 deficiency	Severe decrease	All isotypes
Ig (or CD79) α deficiency	Severe decrease	All isotypes
Ig (or CD79) β deficiency	Severe decrease	All isotypes
BLNK	Severe decrease	All isotypes
Class switch recombination deficiency		
X-linked		
CD40 ligand deficiency	Normal	IgG, IgA
Autosomal recessive		
CD40 deficiency	Normal	IgG, IgA
AID deficiency	Normal	IgG, IgA
UNG deficiency	Normal	IgG, IgA
Anhydrotic ectodermal dysplasia with	Normal	IgG and/or IgA and/or
Immunodeficiency (NEMO deficiency, syndromic)		Specific anti-polysaccharide
PMS2 deficiency	Normal/decrease	IgG variable, IgA
Other PADs with known genetic defect		
CD19 deficiency	Normal	IgG, IgA, and/or IgM
CD81 deficiency	Normal	IgG, IgA, and/or IgM
ICOS deficiency	Normal	IgG, IgA, and/or IgM
BAFF receptor deficiency	Decrease	Variable
TACI deficiency (increased disease susceptibility)	Normal	Variable
Idiopathic primary antibody deficiencies		
Common variable immunodeficiency disorders[b]	Normal/decrease	IgG, IgA, and/or IgM[c]
Possible CVID/CVID-like disorders	Normal/decrease	IgG
Transient hypogammaglobulinemia of infancy	Normal	IgG, IgA, and/or IgM
Selective IgM deficiency	Normal	IgM
Selective IgA deficiency[a]	Normal	IgA
IgG_2 deficiency[a]	Normal	IgG_2
Specific anti-polysaccaride antibody deficiency[a]	Normal	Specific anti-polysaccharide
Other PIDs associated with antibody deficiency		
Severe combined immunodeficiency	Normal/decrease[d]	All isotypes
DNA repair disorders	Normal/decrease	Variable
AD Hyper-IgE syndrome	Normal	Specific antibodies
Wiscott–Aldrich syndrome	Normal	IgM, specific anti-polysaccharide

BTK Bruton's tyrosine kinase, *CVID* common variable immunodeficiency, *TACI* transmembrane activator and CAML interactor, *AID* activation-induced cytidine deaminase, *UNG* uracil-n glycosylase, *PMST2* postmeiotic segregation increased 2, *ICOS* inducible costimulator, *BAFF* B cell-activating factor, *PID* pelvic inflammatory disease

[a] Often combined in one patient

[b] Can be preceded by conditions marked with [a]

[c] Age >2–4 years and decreased response to vaccination

[d] T-cells show a severe decrease in most patients

5 years [66]. Fewer than 10% of the patients have symptoms in the first 3 months because of protection by placentally transferred maternal antibodies. Recurrent ENT and airway infections are the most frequent presenting symptoms, but children may also present with severe bacterial infections in other organ systems [66]. Apart

Table 2 Clinical complications of primary antibody deficiency

Clinical complications	Predominantly associated with	Occurrence[a]
Recurrent URTI	All PAD	Very common
Recurrent ENT infections	All PAD	Very common
Recurrent severe pneumonia	Cong. agamma., CSR def., CVID	Very common
Bronchiectasis	Cong. agamma., CSR def., CVID	Common
Interstitial pulmonary abnormalities	CVID	Rare
Sepsis	Cong. agamma., CSR def., CVID	Rare
Bacterial osteomyelitis/arthritis	Cong. agamma., CSR def., CVID	Rare
Bacterial meningitis	Cong. agamma., CSR def., CVID	Rare
Chronic enteroviral meningoencephalitis	Cong.agamma., CD40L def	Rare
Recurrent giardiasis	All PAD	Common
Campylobacter gastroenteritis	All PAD	Rare
Nodular lymphoid hyperplasia	CVID	Rare
Inflammatory bowel disease	AID, CVID	Rare
Enteropathy (chronic diarrhoea of origin)	CVID, cong. agamma, sIgAD, AID	Common unknown
Autoimmune disease	CVID, sIgAD, AID	Common
Allergic disorders	CVID, sIgAD	Common
Granulomas (lung, bowel, other)	CVID	Rare
(Hepato)splenomegaly	CVID	Common
Lymphoid hyperplasia	CVID, AID	Common
Malignancies, Mainly lymphoma	CVID	Rare
Neutropenia	XLA, CD40L	Common

URTI upper respiratory tract infection, *BTK* Bruton's tyrosine kinase, *AID* activation-induced cytidine deaminase, *PAD* primary antibody deficiencies, *ENT* cong. agamma congenital agammaglobulinemias ears, nose, throat, *XLA* X-linked agammaglobulinemia, *CVID* common variable immunodeficiency, *sIgAD* selective IgA deficiency

[a] Estimated occurrency rate; rare (<10%), common (10–50%), very common (>50%)

from a severe antibody deficiency, 11% of children with XLA suffer from concomitant neutropenia, which can be misdiagnosed as congenital neutropenia. Following the diagnostic strategy for children with recurrent ENT and airway infections, congenital agammaglobulinemias can be easily suspected by low immunoglobulin levels of IgG, IgA, and IgM [16]. Subsequent lymphocyte subset analysis will reveal that B cells in the peripheral blood are severely decreased. In case B cells are present, other PADs have to be considered, especially transient hypogammaglobulinemia of infancy and class switch recombination deficiencies (discussed below). When B cells are absent, a definite diagnosis can be made by genetic analysis of the candidate genes.

Treatment consists of immunoglobulin replacement therapy and antibiotic treatment of suspected bacterial infections. If neutropenia is present, it disappears on immunoglobulin replacement. Chronic lung disease is the most frequent long-term complication. XLA patients are susceptible to chronic enteroviral meningoencephalitis, which is an important cause of death [66].

Class switch recombination deficiencies

Class switch recombination deficiencies, formerly known as hyper IgM syndromes, are rare conditions characterized by decreased serum IgG and IgA levels, but normal or increased levels of IgM [28]. The disease-causing mechanism is either a disturbed co-stimulation of B cells and T cells in the germinal centre, affecting the initiation of CSR, or a deregulation of the class switch process itself (Fig. 1).

The prototype of a co-stimulation defect is X-linked CD40-ligand deficiency [1, 2, 18, 67]. CD40L deficiency not only causes a PAD, but also results in a profound T cell deficiency because the antibody deficiency is secondary to decreased CD40L expression on T cells. Therefore, CD40L deficiency is nowadays primarily classified as a T cell disorder [28]. Because of the T cell deficiency, an important difference with other PADs is the occurrence of opportunistic infections. Apart from a bacterial pneumonia, which occurs in 80% of the children, 41% suffer from *Pneumocystis jiroveci* pneumonia [67]. Severe combined immunodeficiency (SCID) is part of the differential diagnosis of CD40L deficiency (van der Burg M, Gennery A, the expanding spectrum of severe combined immunodeficiency, EJP in press), but in contrast to most cases of SCID, analysis of lymphocyte subpopulation in PAD patients will show normal T cell counts. Similar to XLA patients, neutropenia can be present and CD40L patients also share the increased susceptibility chronic enteroviral meningoencephalitis. Furthermore, CD40L patients are prone to a fatal sclerosing cholangitis secondary to a *Cryptosporidium parvum* infection. Initial treatment consists of immunoglobulin replacement and Pneumocystis

jiroveci prophylaxis, but because of the high frequency of life-threatening complications before the age of 25 years [36], hematopoietic stem cell transplantation is now the treatment of choice [19].

A deregulation of the CSR process itself is caused by AID [45], UNG [27], NEMO [30], and PMS2 [40] deficiency. X-linked anhidrotic ectodermal dysplasia with immunodeficiency secondary to mutations in NEMO gives a much broader immunodeficiency in addition to the CSR defect and has been described in the EJP review on syndromic primary immunodeficiencies of Kersseboom et al. [34] in this journal. The immune defect in AID and UNG deficiency is limited to the B cell lineage. These patients usually present at an older age than patients with CD40L deficiency. Apart from recurrent infections, they often suffer from lymphoid hyperplasia, inflammatory bowel disease, and autoimmunity [27, 42].

Common variable immunodeficiency

Common variable immunodeficiency (CVID) is an idiopathic antibody deficiency with an estimated prevalence of 1:25,000. It is defined by serum IgG levels below 2 SD of normal controls in the presence of decreased IgA and/or IgM levels, recurrent infections, impaired response to immunization, exclusion of defined causes of hypogammaglobulinemia, and an age above 2 years (ESID-PAGID-criteria "probable CVID", www.esid.org). A considerable group of patients suffer from a similar idiopathic hypogammaglobulinemia, but do not fulfil all the diagnostic criteria. These patients are usually diagnosed as "possible" CVID or as having a "CVID-like" disorder. The clinical characteristics are indistinguishable from CVID. Less than 10% of the CVID patients have a positive family history [13] and a genetic defect has only been identified in less than 10% of the patients who have been reported to the ESID primary immunodeficiency database with the clinical phenotype of CVID [24]. Reported defects involve B cell activation (CD19 [60] and CD81 deficiency [61]), co-stimulation (ICOS deficiency [25]) and B cell survival (BAFF-R deficiency [64]). Moreover, genetic defects have been identified that do not cause hypogammaglobulinemia per se, but increase disease susceptibility (TACI deficiency [8, 41, 44, 47, 48]). The heterogeneity of the immunological and clinical features of CVID hampers the discovery of underlying disease-causing mechanisms, clinically relevant prognostic factors, and genetic defects.

Most of the CVID patients present in young adulthood, but symptoms start in childhood in more than half of the cases [43]. Consequently, a diagnostic delay of more than 5 years is the rule [13, 54]. Sometimes CVID is preceded by IgA deficiency, IgG subclass deficiency, or a specific anti-polysaccharide antibody deficiency.

The presenting symptoms in CVID are diverse, but recurrent ENT and airway infections are present in more than 90% of the patients. Some patients present with autoimmune disease, most often autoimmune cytopenias (Table 2). Other clinical features are granulomatous inflammation of the lungs and gastrointestinal tract, chronic diarrhoea secondary to unexplained enteropathy, and haematological malignancies, which are important causes of death. CVID patients who suffer from at least one non-infectious complication have higher mortality than patients who only suffer from infectious complications [9].

Treatment consists of immunoglobulin replacement and antibiotic treatment of infections. Immunosuppressants are indicated in some cases with autoimmunity, but therapeutic guidelines on how to use these agents in CVID patients are lacking. A low number of switched memory B cells in the peripheral blood is associated with autoimmunity, granulomas, and respiratory infections [7, 57, 63, 65]. Also, children who are non-responders to pneumococcal polysaccharide vaccination more often suffer from respiratory infections and bronchiectasis [46]. Growth monitoring is important because one third of the patients develops a growth retardation [54], which is associated with recurrent infectious episodes, but can also develop irrespective of infectious complications secondary to disturbances of the growth hormone axis [17, 55]. A combination of short stature and antibody deficiency may also have its origin in a syndromic form of primary immunodeficieny [34].

Transient hypogammaglobulinemia of infancy

Transient hypogammaglobulinemia of infancy (THI) has to be considered in the differential diagnosis of every young child with hypogammaglobulinemia. It is best defined by low levels of IgG (<2 SD below the mean for age), with or without a decrease of IgA or IgM while other causes of the hypogammaglobulinemia have been excluded [52]. The pathophysiology is unknown. In some patients, THI might be a variation of the physiological hypogammaglobulinemia secondary to the disappearance of maternal IgG from the circulations that normally occurs between 3 and 6 month of age. Many cases probably go unnoticed because they are asymptomatic. Of the symptomatic cases, most children present with recurrent ENT and airway infections before the age of 1 year. Much rarer presenting symptoms are sepsis [51] or meningitis [26, 50]. Other symptoms include recurrent diarrhoea, severe varicella infection, or prolonged oral candidiasis [52]. In more than two thirds of the children, immunoglobulin levels normalize before the age of 2 years, but in some children, the condition can persist up to the age of 5 years [14]. A minority of children will appear to suffer from a long-lasting PAD. Children who do not recover from a suspected THI have more infectious

complications, lower switched memory B cells, and lower levels of IgM compared to children with a self-limiting course [38]. Treatment consists of prophylactic antibiotics; immunoglobulin replacement is usually only given to patients with severe or frequent infections despite antibiotic prophylaxis.

Selective IgA, IgG_2 subclass, and specific anti-polysaccharide antibody deficiency

These three PADs are the most prevalent in children and tend to appear in combination. As single conditions they are often asymptomatic, but a combination more often leads to a clinically significant immunodeficiency. This implies that if one of these conditions is diagnosed, it is useful to search for the others.

Selective IgA deficiency (sIgAD) is defined as a decrease of serum IgA <2 SD of age-matched controls. The prevalence of sIgAD in Europe varies between 1:163 and 1:875 [11, 33]. The incidence is much lower in Asian populations [32]. Although the cause of sIgAD is unknown, mutations in TACI increase disease susceptibility, similar to CVID [44].

Secretory IgA, secreted in the dimeric form, is the prominent immunoglobulin in luminal secretions of the respiratory and gastrointestinal tract and as such an important component of mucosal immunity. Secretory IgA cannot be measured in the serum; the serum level of monomeric IgA is rather an indirect reflection of the level of secretory IgA in the body. The diagnosis of sIgAD is usually made by analysis of immunoglobulin levels during the evaluation of recurrent respiratory infections. However, sIgAD is also often diagnosed "by accident" as part of a laboratory evaluation for celiac disease, allergy, or autoimmune disease. The clinical course is asymptomatic in many patients. If children have complaints, they usually suffer recurrent ENT and airway infections. A minority of patients develop recurrent lower respiratory tract infections and/or bronchiectasis. Patients with sIgAD are especially at risk of chronic diarrhoea and giardiasis because of their defect in mucosal immunity. Furthermore, sIgAD is associated with a higher prevalence of allergy/atopy and a range of autoimmune diseases, including autoimmune cytopenias [12, 20, 29].

The four IgG subclasses are defined by the structure of their constant regions. Of the IgG subclass deficiencies, at least IgG_2 deficiency is clinically relevant. A decrease in IgG_1 cannot be considered as an IgG subclass deficiency a decrease of IgG_1 in it results in hypogammaglobulinemia. Most patients with IgG_3 deficiency also suffer from a deficiency in another subclass, whereas IgG_4 subclass deficiency is very common, but asymptomatic as a rule. In healthy children, IgG_2 antibodies are low in the first years of life, after which they gradually increases with age. Antibodies against encapsulated bacteria are mainly of the IgG_2 subclass, and IgG_2 deficiency increased the susceptibility to these bacteria. Children often present with recurrent respiratory tract and ENT infections. Symptomatic children with IgG_2 subclass deficiency should be tested for a concomitant specific anti-polysaccharide antibody deficiency (SPAD) if they are older than 2 years [20]. Children under the age of 10 years may recover spontaneously [52].

If patients continue to experience recurrent respiratory tract or ENT infections despite normal levels of IgG, IgA, and IgM, a SPAD has to be excluded. Although the pathophysiology is unknown, a deficiency of CD20 has recently been linked to SPAD in one patient [35]. The antibody response to polysaccharide antigens is impaired in healthy children under the age of 2 to 3 years, which contributes to their susceptibility to infections with encapsulated bacteria. However, some infants are able to produce normal responses to certain pneumococcal serotypes [3, 5]. After the age of 2 to 3 years, children should be able to mount a sufficient response to pneumococcal polysaccharides. An insufficient response after this age defines the presence of a SPAD. However, the interpretation of the pneumococcal serology for the diagnosis of SPAD is problematic. Jeurissen et al. [31] and Borgers et al. [4] published the best available serotype-specific cut off values for anti-pneumococcal antibodies in children and adults so far. Their fifth percentiles of normal controls of an ELISA for six different serotypes [31] and a commercially available bead assay for 14 serotypes [4] can be used for the diagnosis of SPAD. Pneumococcal antibodies are measured before and 2 to 4 weeks after pneumococcal vaccination. Healthy children should be able to respond to at least seven of the 14 serotypes, above a level of 0.23 to 1.66 mg l, depending on age and serotype (Table 3). Furthermore, an increase of two to fourfold of the pre-vaccination anti-pneumococcal antibody level is often used as additional criteria. If children received previous vaccinations with pneumococcal conjugate vaccines, the serotypes present these vaccines cannot be used for the interpretation of the anti-pneumococcal polysaccharide response (Table 3), so the introduction of pneumococcal conjugate vaccines in national vaccination programs limits the usage of these assays for the diagnosis of SPAD. The assays measuring the anti-pneumococcal IgA or IgM response might be able to overcome these limitations.

Treatment for IgAD, IgG_2 deficiency, or SPAD consists of antibiotic prophylaxis in symptomatic cases, especially during autumn and winter. If children present with bronchiectasis or severe recurrent lower respiratory tract infections, immunoglobulin replacement therapy has to be considered, especially in case of a combination of sIgAD

Table 3 Cut off values of antipneumococcal antibodies for the diagnosis of SPAD as defined by Jeurissen et al. [31] and Borgers et al. [4] in relation to serotypes in pneumococcal conjugate vaccines

Pneumococcal serotype	Serotypes of pneumococcal conjugate vaccine			Anti-pneumococcal antibodies by ELISA (mg/L)[a]			Anti-pneumococcal antibodies by multiplex bead assay (mg/L)[a]
	PCV-7	PCV-10	PCV-13	Age 3–15 years	Age 19–30 years	Age 3–30 years	Age 3–30 years
1		x	x				0.53
3			x	0.99	0.58	0.67	0.64
4	x	x	x	0.73	0.37	0.45	0.49
6B	x	x	x				0.80
7F		x	x				1.45
8							1.02
9N				0.78	0.23	0.46	0.63
9V	x	x	x				0.69
12F							0.46
14	x	x	x				0.57
18C	x	x	x	0.55	0.31	0.31	0.34
19A			x				0.96
19F	x	x	x	1.66	0.91	1.04	0.74
23F	x	x	x				0.24

Serotypes present in 23-valent pneumococcal polysaccharide (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F)

[a] Fifth percentile of normal controls

x serotypes cannot be used for the interpretation of the pneumococcal polysaccharide response, if the child received one of the PCV, *PCV* pneumococcal conjugate vaccines, *ELISA* enzyme-linked immunosorbent assay

and/or IgG_2 deficiency with a SPAD. Data for the efficacy of immunoglobulin replacement for this indication is lacking, but clinical studies are ongoing. If diagnosed at young age, children tend to recover from IgG_2, sIgAD, and SPAD. For individuals diagnosed at an older age, these conditions are usually permanent. Follow-up with large intervals is necessary to check for the development of CVID [21].

Treatment and follow-up of PAD

Immunoglobulin replacement therapy

Before the introduction of immunoglobulin replacement therapy, the life expectancy of patients with a- or hypogammaglobulinemia was severely reduced due to chronic lung disease secondary to recurrent pneumonia and bronchiectasis. Immunoglobulin replacement prevents many, but not all, pulmonary complications. Over the past years, it has become obvious that individual dosing, rather than supplementation above a certain "through level" of IgG is necessary to prevent infections complications in PAD patients [37]. There is no difference in efficacy between subcutaneous substitution or IV treatment [10]. Home therapy is very well possible and increases the quality of life [22].

Antibiotic prophylaxis

The use of prophylactic antibiotics to prevent infections in PAD is widely practiced, but is not evidence based. There is an urgent need for controlled trials to address this issue because besides immunoglobulin replacement, it is one of the few therapeutic options in patients with PAD.

Follow-up and prognosis

The long-term follow-up of PAD patients on immunoglobulin replacement should focus on the early detection of chronic lung disease. Apart from regularly pulmonary function tests, it is advisable to perform at least one high resolution CT thorax in these patients to exclude bronchiectasis or other pulmonary abnormalities [53]. Follow-up with high resolution low-dose CT thorax is promising, but needs further evaluation [58]. An increased incidence of respiratory complications and early onset of disease have been associated with polymorphisms in mannose-binding lectin in CVID patients [39], so once a PAD has been

diagnosed, it is useful to check MBL levels. Furthermore, attention should be paid to symptoms suggesting non-infectious complications such as autoimmunity, granulomas, splenomegaly, and enteropathy. A decrease of memory B cells in CVID patients is associated with a higher incidence of clinical complications [49, 56, 65, 68]. The use of age-related normal values is important for the interpretation of the results.

Conclusions, learning points

1. PADs represent a heterogeneous spectrum of conditions, ranging from often asymptomatic selective IgA and IgG subclass deficiencies to severe congenital agammaglobulinemias.
2. Patients with PAD most often present with recurrent or severe respiratory tract and ENT infections.
3. PADs have a range of non-infectious complications, such as autoimmunity and enteropathy, which might be the only presenting symptom.
4. Severe PADs can be easily detected by the determination of total IgG, IgA, and IgM levels.
5. Previous pneumococcal conjugate vaccinations limit the use of pneumococcal serology for the diagnosis of specific anti-polysaccharide antibody deficiency.
6. Intravenous or subcutaneous immunoglobulin replacement is the treatment of choice for PAD patients with reduced IgG levels.

Conflicts of interest None to declare for all authors

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