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Evaluation of B Lymphocyte Deficiencies

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Abstract: The most common of the primary immunodeficiency diseases are those that involve inadequate antibody production. The characteristic presentation of these disorders is recurrent sinopulmonary infections. An arrest in B cell development at the pre-B cell stage leads to agammaglobulinemia and an insignificant number of B cells. X-linked agammaglobulinemia is the most common of these developmental arrests while the autosomal recessive agammaglobulinemias comprise a small minority of the total cases. Likewise, the most common form of the hyper-IgM syndromes (CD40 ligand deficiency) is X-linked. Of the autosomal recessive forms, CD40 deficiency is basically identical to the X-linked form in its clinical phenotype where, in addition to inadequate antibody production, there is defective T cell signaling through the CD40-CD40L interaction. Aside from CD40 deficiency, the other recessive forms of hyper-IgM syndrome have adequate T cell function. IgA deficiency is the most common and the most benign of the B cell disorders. Common variable immunodeficiency is diverse in its presentation and clinical course. The pathophysiology of this disease is multifactorial and frequently ill defined, often making it a diagnosis of exclusion. A working knowledge of identifiable PIDDs is essential in both recognizing when to suspect immunodeficiency and making a diagnosis.

Keywords: B Lymphocyte, Antibody, Deficiencies, Clinical Evaluation.

INTRODUCTION

The incidence of primary immunodeficiency diseases (PIDDs) as a whole is 1 in 2000 live births [1]. A little more than half of these are antibody deficiencies [2, 3]. Less than 1% of the PIDDs are complement deficiencies, and the remaining are roughly equally divided among cellular, combined, and phagocyte deficiencies [1]. As research progresses in the field of innate immunity, these numbers will likely change to include a significant amount of innate immunity defects. Nevertheless, most cases of PIDDs relate to an inability to adequately produce antibodies to protect the host against pathogens.

The characteristic presentation of humoral defects is recurrent sinopulmonary infections [1]. This pattern alone is not pathognomonic, and patients with the prototypical antibody defect, X-linked agammaglobulinemia, have been hospitalized for a variety of other infections including viruses, bacterial skin infections, and even vaccine associated polio [4]. They are also susceptible to protozoa infections like *Giardia lamblia* [5]. However, these non-sinopulmonary infections may not ever manifest or do so at a later age with otherwise preventable sequelae. An appropriately vaccinated patient who seems to have a susceptibility to respiratory infections with encapsulated bacteria should arouse the suspicion of humoral PIDDs.

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INITIAL APPROACH TO SUSPECTED B CELL DEFECTS

For a patient who has had recurrent sinopulmonary infections, immunodeficiency should be on the list of differential diagnoses. However, there are several other conditions that can predispose one to repeated infections. A partial list [1] includes allergic inflammation, adenoidal hypertrophy, cystic fibrosis, ciliary dyskinesia, abnormal lung anatomy, immunosuppressive therapy, malignancies, and AIDS. In the author's experience, the most common etiology found in recurrent sinopulmonary infection evaluations is allergic disease. Based on history, physical exam, and index of suspicion, some of the more common conditions should generally be considered or evaluated before an extensive PIDD evaluation is begun as the prognosis and management are vastly different. Recognizing genetic inheritance patterns, along with patient gender is helpful in considering which diagnosis to pursue.

Allergic rhinitis is characterized by nasal congestion, rhinorrhea, sneezing, and/or nasal itching triggered by an allergen [6]. Rhinosinusitis and recurrent otitis media have been associated with adenoid hypertrophy and are potentially caused by mechanical obstruction from enlarged adenoids [7]. Cystic fibrosis is suspected by an abnormal sweat chloride test in the vast majority of patients [8]. Genetic studies confirm this diagnosis. Nasal exhaled nitric oxide can be used to screen for ciliary dyskinesia, but the diagnosis must be confirmed by ciliary biopsy and electron microscopy [9]. Lung anatomy can most easily be assessed by radiographic studies. A review of the medication history will reveal iatrogenic susceptibilities to infection. Screening for

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cancer is done on an age appropriate basis. A positive ELISA for HIV must be confirmed by a Western blot or indirect immunofluorescent assay. Because seroconversion can occur 2-12 weeks after exposure, a repeat ELISA may need to be performed [10]. Malnutrition has various aspects to its evaluation. The World Health Organization has published a guide on the evaluation and management of malnutrition [11]. The role of exposure to day care in increasing the frequency of upper respiratory infections cannot be underestimated, but these children should manifest fewer infections as they progress through early school age.

Once it has been determined that a separate cause does not sufficiently explain the patient's symptoms and that the case is clinically consistent with a PIDD, then a work-up can be initiated. A logical starting point when considering antibody deficiencies is determining quantitative serum immunoglobulin levels for the isotypes IgG, IgA, and IgM. These values must be compared to age matched controls as they vary based on age, and reference lab values may differ if age is not taken into account. Reference IgG levels in very young infants (from birth until 3-4 months of life) reflect the mothers' rather than the patients' ability to produce antibodies. If the patient loses antibodies, due to a protein losing enteropathy or nephrotic syndrome, low levels of immunoglobulins may predispose to infection but not because of a lack of production by B cells. Profound hyopgammaglobulinemia refers to a serum IgG level less than < 100 mg/dL in an infant or less than 2-3 g/L in adults [1]. Not only should the total levels of circulating immunoglobulins be determined, but the patient's ability to produce specific antibody responses should be assessed. Vaccine response titers and isohemagglutinins demonstrate how well the adaptive immune system can induce and sustain humoral immunity. A review of vaccination records is required for accurate interpretation. If vaccine tiers are lower than expected, a booster dose is given and titers are repeated. For adults, a significant rise in antibody titers to 8 of 12 serotypes of pneumococcus 3-4 weeks after Pneumovax 23 vaccination is considered a good response, but children under 2 years of age have a less robust antibody increase to unconjugated vaccines [12]. The current recommendation [13] for pneumococcal vaccination is to use the 13-valent conjugated vaccine in all children under the age of 5 years to be given in a series of 4 rounds with the initial immunization at 2 months of age and then boosters at 4 months, 6 months, and 12-15 months.

If profound hypogammaglobulinemia is present, then the proportion and absolute numbers of different types of circulating lymphocytes should be determined. Since absent B cells and/or a lack of antibody production can be present in severe combined immunodeficiency (SCID), T cell function may also need to be assessed. If T cells are normal in number and function with the B cell population being exceedingly low, one of the agammaglobulinemias is likely present. Two exceptions to this are 1.) Omenn syndrome where a combined T and B cell deficiency exists, but the T cell count is normal or elevated due to a defective oligoclonal expansion of T cells and 2.) maternal engraftment and expansion of oligoclonal T cells [14].

B CELL DEVELOPMENTAL DEFECTS LEADING TO AGAMMAGLOBULINEMIAS

The journey from a hematopoietic stem cell to an antibody producing B cell or plasma cell has multiple stages with various checkpoints. One critical checkpoint occurs in the progression from pre-B cells to immature B cells. Here, several genetic mutations have been identified that lead to an arrest in further development. In Fig. (**1**), B cell

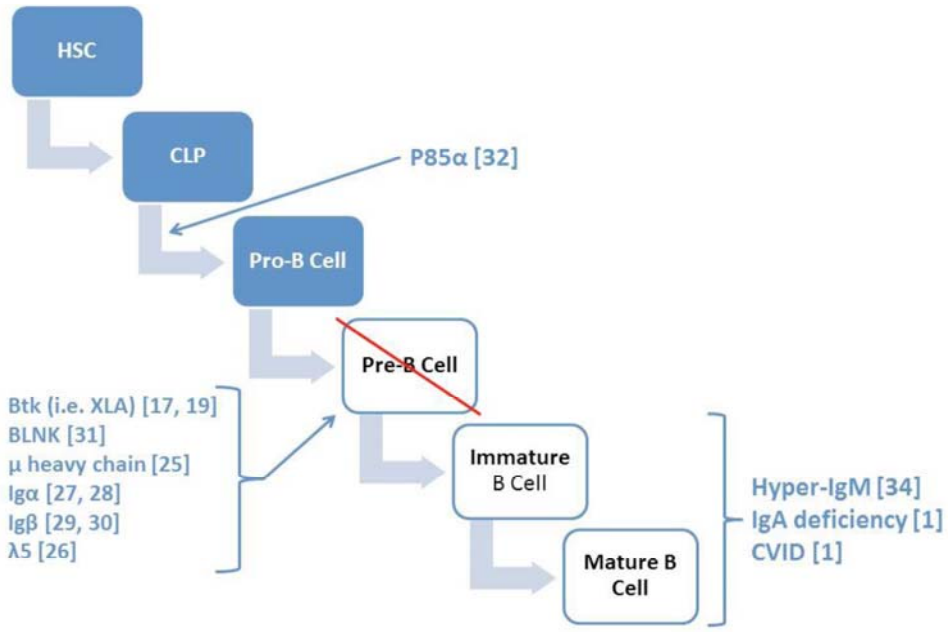

Fig. (1). B cell development with PIDDs occurring at different stages. HSC = hematopoietic stem cell, CLP = common lymphoid progenitor.

developmental stages are listed in sequential order. As noted in the diagram, there are several primary B cell immunodeficiencies where development fails to progress through the pre-B cell stage. Other B cell immunodeficiencies, such as hyper-IgM syndromes and selective IgA deficiency, allow for the development of mature B cells, but they do not function adequately.

In order to progress through the pre-B cell stage, a competent pre-B cell receptor (pre-BCR) must be assembled and activated. V-D-J rearrangement occurs in one of the two alleles for the immunoglobulin heavy chain, producing the μ heavy chain (μHC). This combines with the surrogate light chain (SLC), which acts as a placeholder for the immunoglobulin light chain. The SLC is composed of 2 components, VpreB and λ5. The membrane bound μHCs and coupled SLCs associate with two other surface molecules, immunoglobulins α (Igα (CD79a)) and β (Igβ (CD79b)), which initiate intracellular signaling. This entire complex comprises the pre-BCR [15, 16]. Once a viable pre-BCR is produced and activated, light chain rearrangement begins. Defects in any of these components of the pre-BCR or its signaling pathway result in an inability to make a significant amount of antibody producing cells. The basic pre-BCR structure and proteins where immunodeficiencies are involved are seen in Fig. (**2**).

X-LINKED AGAMMAGLOBULINEMIA (XLA, BRUTON'S AGAMMAGLOBULINEMIA)

One of the initial components of the pre-BCR's intracellular signaling is Bruton's tyrosine kinase (Btk) which is encoded on the X-chromosome at Xq21.33-q22 [17]. It was named after Dr. Odgen Bruton who first published a description of the disease in 1952 [18]. Mutated Btk was found to be the cause in 1993 by Tsukada and colleagues [19] as well as Vetrie and colleagues [17]. XLA accounts for about 85% of disorders characterized by profound hypogammaglobulinemia, extremely low B cells, and a lack of other lymphocyte abnormalities [20]. Even though the structurally normal pre-BCR cannot properly initiate downstream signaling, its function is slightly "leaky," indicating that some meaningful gene transcription occurs despite a faulty signaling pathway. This leads to the production of a minuscule amount of circulating CD19 positive lymphocytes that may not be detectable by many laboratory assays. The most consistent finding in XLA is lymphocyte population of <1% B cells. These few B cells cause the IgG level to be profoundly low but not zero.

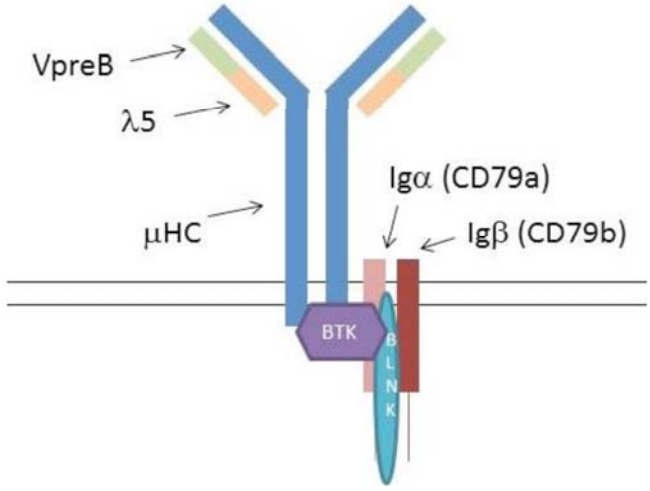

Fig. (2). Structure of the pre-BCR. The μHCs combine with surrogate light chains the pre-BCR. The SLCs are composed of VpreB and λ5. Except for VpreB, mutations in each of the diagramed components of the pre-BCR have been identified that in turn lead to a primary B cell immunodeficiency [15, 16]. VpreB = VpreB protein; λ5 = lambda 5; μHC = mu heavy chain; Igα (CD79a) = immunoglobulin alpha; Igβ (CD79b) = immunoglobulin beta; BTK = Bruton's agammaglobulinemia tyrosine kinase; BLNK = B cell linker protein.

Diagnostic criteria with differing degrees of certainty have been established for XLA [21]. All categories of diagnosis require that there be less than 2% $CD19^+$ cells on lymphocyte subset analysis. A *definitive diagnosis* means that there is a 98% chance that the diagnosis will remain the same over the next 20 years. In addition to the above $CD19^+$ cell percentage, to be considered *definitive*, one or more of the following need to be established: 1.) mutation in Btk, 2.) absent Btk mRNA on Northern blot analysis of neutrophils or monocytes, 3.) absent Btk protein in monocytes or platelets, or 4.) maternal cousins, uncles, or nephews with less than 2% $CD19^+$ B cells. A *probable diagnosis* carries an 85% probability of a consistent diagnosis over the next 20 years. For this category, all of the following must be present: 1.) onset of recurrent bacterial infections in the first 5 years of life, 2.) serum IgG, IgM, and IgA more than 2 SD below normal for age, 3.) absent isohemagglutinins and/or poor response to vaccines, and 4.) other causes of hypogammaglobulinemia have been excluded. The final category is a *possible diagnosis* where in addition to ruling out other causes of hypogammaglobulinemia, one or more of the following criteria are met: 1.) onset of recurrent bacterial infections in the first 5 years of life, 2.) serum IgG, IgM, and IgA more than 2 SD below normal for age, and 3.) absent isohemagglutinins.

A United States registry [22] of 201 XLA patients examined the clinical characteristics of this disease. In decreasing order of prevalence, reported infections were: upper respiratory, pneumonia, chronic/recurrent diarrhea, conjunctivitis, skin infections, meningitis/encephalitis, sepsis, septic arthritis, hepatitis, osteomyelitis, and vaccine related polio. Clearly, the most common infections preceding diagnosis were otitis media, pneumonia, and sinusitis. Half of the patients had symptom onset sometime between ages 6 and 12 months, and about 90% had developed symptoms by the age of 3 years. Encouragingly, the death rate of those receiving treatment was less than 1% per year. Additionally, the prevalence of chronic lung disease increases with age of diagnosis [23], making early diagnosis paramount.

Family history, when positive for known or suspected cases of XLA, is exceedingly helpful in diagnosis. In fact, it represents one of the definitive diagnostic criteria [21]. When a family has a known mutation in Btk, then pre- and post-natal diagnoses can be made fairly rapidly, allowing for early treatment before the onset of severe infections. Forty-one percent of patients had a positive family history at the time of diagnosis, and these patients were diagnosed at a younger age (mean 2.59 years) compared to those without a family history (mean 5.37 years) [22]. The physical exam finding that is consistent with XLA and other agammaglobulinemias is an absence of tonsilar tissue and no palpable lymph nodes. Otherwise, unless sequelae from infection have developed, the physical exam is unremarkable.

AUTOSOMAL RECESSIVE AGAMMAGLOBULINEMIAS

More rare, but clinically very similar to XLA, are the autosomal recessive agammaglobulinemias. Reports of females with an XLA phenotype began to surface in the 1970s, which, along with using the discovery of mutated Btk in 1993 to rule out XLA, ushered in research that lead to the discovery of distinct autosomal recessive forms [24]. As in XLA, there is defective signaling from the pre-BCR which results in a block in development at the pre-B cell stage. Defects in the μHC were first described in 1996 [25] and comprise 5% of agammaglobulinemias [5]. A handful of patients have been reported with identified defects in λ5 [26], Igα [27, 28], Igβ [29, 30], and a signal scaffolding protein called BLNK [31]. (See Fig. **2**) Like μH chain defects, problems with λ5, Igα, and Igβ result in malfunctioning pre-BCRs. Similar to mutations in Btk, BLNK abnormalities result in faulty downstream signaling from the pre-BCR. The autosomal recessive agammaglobulinemias are pheno-typically similar to XLA.

A report [32] of a single female patient with a premature stop codon mutation in the p85α gene (PIK3R1) was recently published. The patient had agammaglobulinemia and less than 1% CD19 cells. Phosphoinositide 3-kinase (PI3K) is regulated by p85α, but the exact role p85α plays in B cell development is not yet defined. It is clear that p85α operates in very early B cell lineage commitment, and the reported patient's B cell development was arrested before the pro-B cell stage. Simultaneous CD34 and CD19 surface expression indicate pro B-cells, and less than 0.1% of the patient's bone marrow cells expressed both of these markers. This is in contrast to the other defects causing agammaglobulinemias, which all inhibit progression through the pre-B cell stage but do produce pro-B cells. Additionally, the numbers of NK cells in this patient were below normal.

HYPER-IGM SYNDROMES

After B cells reach the mature stage, they circulate through secondary lymphoid tissue. Here, a B cell may encounter a pathogen and CD4 positive T cells that trigger it to play an active role in host defense *via* pathogen specific antibody production. Helper T cells express CD40 ligand (CD40L) that binds to its receptor (CD40) which is constitutively expressed on B cells. This interaction induces immunoglobulin isotype class switching (termed class switch recombination), a process that is dependent on B cell expression of activation-induced cytidine deaminase (AID) and uracil DNA glycosylase (UNG). This results in a change in expression of the heavy chains from IgM to the isotypes IgG, IgE, or IgA [33]. When the class switch recombination process is faulty, IgM can be expressed while there is a lack of adequate production of the other isotypes, resulting in a hyper-IgM syndrome (HIgMS).

X-LINKED HYPER-IGM SYNDROME (CD40 LIGAND DEFICIENCY)

Discovered in 1993 [34], the most common HIgMS is CD40L deficiency, accounting for 70% of the cases [35]. CD40L is encoded on Xq26.3 [36, 37]. Therefore, this is an X-linked disease, but there have been reports of symptomatic females with skewed lyonization [38, 39], the process by which cells undergo random X chromosome inactivation. CD40L also binds to CD40 on monocytes and macrophages where they feedback on T cells to generate a T-helper cell type 1 (T_H1) response [40]. Consequently, CD40L deficiency is not just a problem of immunoglobulin production but also lacks the full functioning of cellular immune defense. In addition to susceptibility to sinopulmonary infections, patients also suffer from opportunistic intracellular pathogens like *Pneumocystis jiroveci* [41, 42], cryptosporidium species [43], *Toxoplasma gondii* [44] and Mycobacteria species [45]. Cryptosporidial infections may be subclinical and missed on stool microscopy. Thus, PCR analysis may be needed [46]. Additionally, 50% of cases have neutropenia [41], which can respond to G-CSF. The rate of autoimmunity is higher in these patients [41, 42, 47], and they are at increased risk for malignancy of the biliary tree [41, 43], intestinal cancer [48, 49], and neuroendocrine tumors [49].

Despite the term "hyper-IgM," the serum IgM level is elevated in only half of the patients when the diagnosis of immunodeficiency is first considered and normal in the remaining [41]. This likely represents a normal baseline production of IgM in the absence of infection, whereas once signaling for isotype switching is put in place due to an infection, the result is instead a rise in IgM due to failed class switch recombination. Although detecting CD40L expression on stimulated T cells will, in most all cases, show an absence of the protein, mutations in the cytoplasmic tail [50] and at some splice sites [51] will result in surface expression of a faulty CD40L. The CD40L gene is 12kb long encoding only 5 exons [52], and it may be more practical to perform mutation analysis in lieu of examining CD40L surface expression.

As with XLA, there are similar diagnostic criteria providing a *definitive*, *probable*, and *possible diagnosis* [21]. For all categories, the age adjusted serum IgG level must be two or more standard deviations below normal. For a *definitive diagnosis*, there must be either 1.) a mutation in the CD40L gene or 2.) maternal cousins, uncles, or nephews with confirmed diagnosis of CD40L deficiency. A *probable diagnosis* includes all of the following: 1.) normal number of

T cells and normal T cell proliferation to mitogens, 2.) normal or elevated numbers of B cells but no antigen-specific IgG antibody, 3.) one or more of the following infections or complications: a.) recurrent bacterial infections in the first 5 years of life, b.) *Pneumocystis jiroveci* infection in the first year of life, c.) neutropenia, d.) Cryptosporidium-related diarrhea, e.) sclerosing cholangitis, or f.) Parvovirus-induced aplastic anemia, and 4.) absent CD40 ligand cell surface staining on activated $CD4^+$ T cells as assessed by binding to soluble CD40 or by binding of monoclonal antibody to CD40 ligand. For a *possible diagnosis*, the T and B cell numbers are normal, and one or more of the following is present: 1.) Serum IgM concentration at least 2 SD above normal for age, 2.) *P. jiroveci* infection in the first year of life, 3.) Parvovirus-induced aplastic anemia, 4.) Cryptosporidium-related diarrhea, or 5.) severe liver disease (sclerosing cholangitis).

There are also exclusion criteria [21] that, if present, make the diagnosis of CD40L deficiency unlikely. These include defects in T cell activation, HIV Infection, congenital rubella, MHC Class II deficiency, CD4 T cell deficiency, and exposure to drugs or infections known to influence the immune system.

AUTOSOMALLY INHERITED HYPER IGM SYNDROMES

Deficiency of AID [53-55] is the second most common type [35]. It is inherited in both a recessive [54] and dominant [56] manner. These patients have recurrent bacterial infections, mostly pneumonia, and the onset of infections develops before the age of 2 years. Twenty percent develop some form of autoimmunity, and 1/2 to 2/3 develop lymphoid hypertrophy without malignant transformation [57, 58]. In contrast to CD40L deficiency, the CD40-CD40L interaction is intact, leaving only antibody production insufficient.

Deficiency of UNG is much rarer and therefore more difficult to definitively characterize the phenotype. UNG follows step with AID in the class switch recombination process, and the clinical course is similar to AID deficiency [59].

Likewise, CD40 deficiency is rare with autosomal recessive inheritance, but the clinical phenotype is similar to CD40L deficiency [60, 61].

SELECTIVE IgA DEFICIENCY

These patients have an undetectable amount of serum IgA by most routine clinical studies in the presence of adequate numbers of other antibody classes. Even if it is below the age adjusted lower limit of normal, the patient is not considered to have selective IgA deficiency (SIgAD) unless IgA is below a certain threshold that has been reported to be in the range of 7 mg/dL to 15 mg/ dL [1, 62]. The clinical significance of "slightly low" IgA is not clear. The incidence of SIgAD ranges from 1 in 400 to 3000 [63, 64] people, making it a fairly common condition. One third of these individuals have recurrent viral, sinopulmonary, and GI infections [65, 66], while the majority of those with selective IgA deficiency do not suffer from a noticeable susceptibility to infections. For the third that are vulnerable, invasive infections are not typical [67]. The etiology of SIgAD is not understood, but these individuals are at risk for autoimmune disease [68], malignancies [69], asthma [66], and allergic diseases [66]. Some cases may evolve into common variable immunodeficiency [70].

COMMON VARIABLE IMMUNODEFICIENCY

As its name suggests, common variable immuno-deficiency (CVID) is relatively common with a prevalence of 1 in 30,000 to 1 in 75,000 people [1, 3]. Likewise, there are multiple clinical phenotypes [71], making CVID a varied disorder. In contrast to most other PIDDs, CVID is predominantly an adult disease with an average age of symptom onset being in the third decade of life, but the diagnosis can also be made in children [71, 72]. It affects both sexes, and these patients can have recurrent upper and lower respiratory tract infections [72, 73]; lung disease including granulomas, bronchiectasis, and lymphocytic interstitial pneumonitis [72, 74-76]; gastrointestinal com-plications such as lymphonodular hyperplasia, inflammatory bowel disease, malabsorption, Giardiasis, *Campylobacter jejuni* enteritis, Salmonellosis, viral hepatitis, and severe CMV enteritis [72, 77]; chronic cystitis from *Ureaplasma uraelyticum* [78]; autoimmunity with a prevalence of 20% [72]; various lymphoproliferative disorders [72, 77, 79] and malignancies [72, 74, 77, 80, 81]; and impaired antibody production [5, 63] with high, normal, or reduced numbers of circulating B cells [71].

As with XLA and CD40L deficiency, there are also diagnostic criteria for CVID, but only for a *probable* or *possible diagnosis* and not a *definitive* one [21]. For a *probable diagnosis*, both serum IgA and IgG must be at least 2 SD below the mean for age along with all of the following: 1.) onset of immunodeficiency at greater than 2 years of age, 2.) absent isohemagglutinins and/or poor response to vaccines, and 3.) defined causes of hypogammaglobulinemia have been excluded. A *possible diagnosis* entails having one of the major isotypes (IgM, IgG, or IgA) less than 2 SD below the mean for age and all of the following: 1.) onset of immunodeficiency at greater than 2 years of age, 2.) absent isohemagglutinins and/or poor response to vaccines, and 3.) defined causes of hypogammaglobulinemia have been excluded.

In only a minority of cases, has a genetic defect been identified, which has led to CVID being mainly a diagnosis of exclusion. One could argue that for this handful of patients, they have a distinct disease defined by the mutated gene and should therefore not be labeled with CVID. Nonetheless, these defects generally fall under the heading of CVID, and more are likely to be added to their number as research progresses. Mutations in inducible T cell costimulator (ICOS) [82] and CD19 [83, 84] have been identified that cause a CVID phenotype. Polymorphisms in tumor necrosis factor receptor superfamily member 13B (TNFRSF13B or TACI) [85], TNFRSF13C (BAFFR) [86],

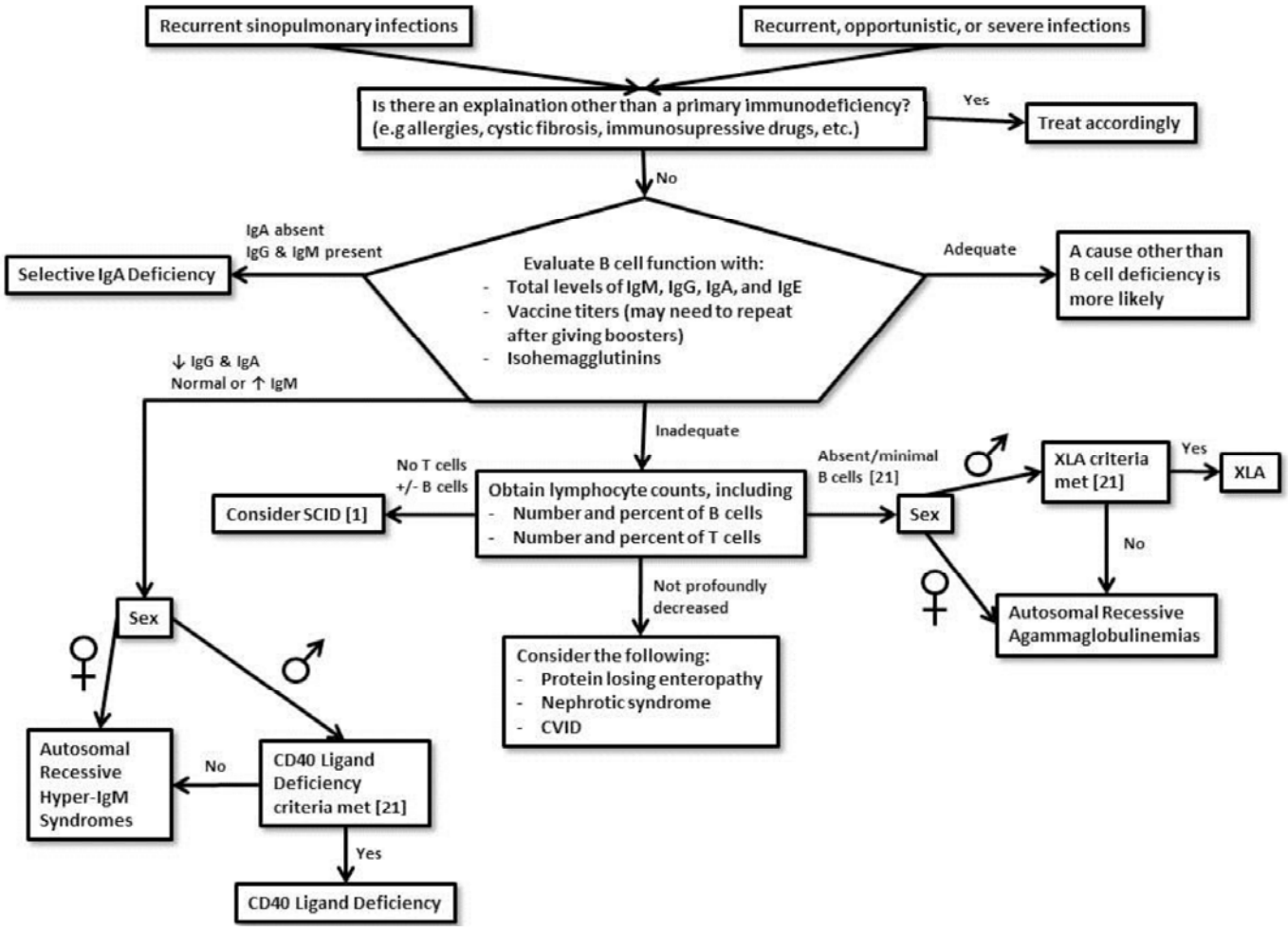

Fig. (3). Diagnostic algorithm for B cell deficiencies. SCID = Severe combined immunodeficiency, XLA = X-linked agammaglobulinemia, CVID = Common variable immunodeficiency.

and Msh5 [87] have been identified that predispose individuals to CVID. Various other genes have been identified that may have a disease modifying effect on CVID and include TNF [88], IL10 [88, 89], NOD2 [90], SERPINA1 [91, 92], MBL2 [93-95], IL12 & INFγ [96], and vitamin D receptor [89].

RECENT DISCOVERIES

The PIDDs discussed above represent the more well established B cell defects. Others are continuing to be elucidated. In addition to the p85α mutation, some more recent discoveries are as follows: CD81 is a transmembrane protein that amplifies signal through BCR [97], and CD19 expression is dependent on expression of CD81 [98]. A case report of CD81 defect showed severe nephropathy in conjunction with profound hypogammaglobulinemia [98]. CD20 (or MS4A1) was found to be mutated in a Turkish girl of consanguineous parents after she was previously diagnosed with CVID [99]. A mutation in CD21 (complement receptor 2) was discovered in a young adult male who had recurrent infections, reduced class-switched memory B cells, and hypogammaglobulinemia [100]. Two different groups found autosomal recessive mutations in LPS-responsive beige-like anchor (LRBA) among 10 patients in 5 unrelated families [101, 102]. In addition to hypogammaglobulinemia, autoimmunity, particularly colitis, seems to be part of the disease, possibly due to decreased apoptosis.

CONCLUSIONS

Humoral immunodeficiencies are the most common class of PIDDs with inadequate antibody production by B cells. The hallmark finding in these patients is recurrent sinopulmonary infections, but by no means is that the only malady. Poor growth or weight gain and those with a family history concerning for immunodeficiency may also need to be considered for evaluation. Although the most frequently encountered of the PIDDs, humoral immunodeficiencies are less common causes of sinopulmonary infection symptoms than other conditions such as asthma and daycare attendance. Obtaining circulating absolute lymphocyte counts, serum levels of immunoglobulin classes, vaccine titers, and isohemagglutinins are generally the first laboratory investigations obtained once a PIDD is suspected. Fig. (**3**) shows an algorithm to assist in the diagnostic process.

Normal B cell development is critical for antibody production. Arrest at the pre-B cell stage represents a flawed pre-BCR or its downstream signaling, resulting in agammaglobulinemia. The most common of these defects is XLA with a near absent amount of B cells, and diagnostic criteria for XLA have been established to categorize the certainty of the diagnosis. The more rare autosomal recessive agammaglobulinemias have a very similar clinical phenotype. Of the hyper-IgM syndromes, the X-linked form, CD40L deficiency, is also the most common and has defined diagnostic criteria. Of the autosomal recessive forms, CD40 deficiency has a near, if not completely, identical clinical phenotype which includes inadequate cellular immune function which depends on the CD40-CD40L interaction. The remaining recessive forms are less severe as only antibody production is malfunctioning.

Selective IgA deficiency is by far the most common PIDD, and the pathogenesis is not well understood. It is the least severe of the antibody deficiencies with two thirds of these patients being asymptomatic. Thus, the clinical significance is not entirely clear. However, there is an increased risk of allergy, autoimmune disease, and malignancy.

Also not entirely understood is CVID, which is characterized by recurrent infections, decreased serum immunoglobulin levels, deficient specific antibody production, and a wide range of clinical manifestations. The presenting symptoms can be attributed to autoimmune phenomenon in the absence of susceptibility to infections. Diagnostic criteria for CVID exist but do not include a *definitive diagnosis* class. It most often becomes a diagnosis of exclusion. A few genetic defects and polymorphisms have been linked to CVID, but the majority of cases have unknown etiologies.

Despite tremendous advancement in the field of therapeutics, there are few published data pertaining to the comparative outcome of different treatment regimen to minimize infectious complication in children and adolescent with PIDDs. For the most part, averting complications from B cell defects focuses on preventing infections through replacement immunoglobulin and prophylactic antibiotics [5]. Both subcutaneous (SCIg at 100 mg/kg/wk) and intravenous (IVIg at 400 mg/kg per 21 days) are effective. SCIg has more stable IgG trough levels and fewer adverse reactions, whereas IVIg can be given in higher doses for enteroviral meningoencephalitis, bronchiectasis, or autoimmune complications. One center [103] with expertise in B cell defects has found that XLA patients placed on early immuno-globulin replacement therapy had very few problems. This same group recommends the following strategy for XLA monitoring: yearly complete blood count with differential, a chemistry panel that includes liver and renal function tests as well as total protein, serum immunoglobulins and chest and sinus radiographs; follow-up clinic visits every 6 months or more frequently if needed. Use of continuous prophylactic antibiotics may be beneficial in patients with bronchiectasis and recurrent sinusitis [5].

A working knowledge of identifiable PIDDs is essential in both recognizing when to suspect an immunodeficiency and in making a diagnosis. While not wanting to miss or underestimate the seriousness of PIDDs, more common causes and mimickers of recurrent sinopulmonary infections, such as allergic rhinitis, right middle lobe atelectasis secondary to asthma, and adenoidal hypertrophy should be addressed first. As advancements in the field of genetics and therapeutics are made, an understanding of B cell development is as important as ever in making a timely and accurate diagnosis of known and yet to be discovered antibody deficiencies.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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Declared none.

ABBREVIATIONS

AID	=	activation-induced cytidine deaminase
AIDS	=	acquired immune deficiency syndrome
BAFFR	=	B cell-activating factor receptor
Btk	=	Bruton's tyrosine kinase
CD40L	=	CD40 ligand
CVID	=	common variable immunodeficiency
HIgMS	=	hyper-IgM syndrome
HIV	=	human immunodeficiency virus
ICOS	=	inducible T cell costimulator
Igα (CD79a)	=	immunoglobulin α
Igβ (CD79b)	=	immunoglobulin β
IL10	=	interleukin 10
IL12	=	interleukin 12
INFγ	=	interferon gamma
IVIg	=	intravenous immunoglobulin
LRBA	=	LPS-responsive beige-like anchor
μHC	=	μ heavy chain
MBL2	=	mannose-binding lectin 2
Msh5	=	MutS, E. coli, homolog of, 5
NK cell	=	Natural Killer cell
NOD2	=	nucleotide-binding oligomerization domain-containing protein 2
PI3K	=	Phosphoinositide 3-kinase
PIDD	=	primary immunodeficiency disease

pre-BCR	=	pre-B cell receptor
SCID	=	severe combined immunodeficiency
SCIg	=	subcutaneous immunoglobulin
SD	=	standard deviation
SERPINA1	=	serpin peptidase inhibitor, clade A, member 1
SIgAD	=	selective IgA deficiency
SLC	=	surrogate light chain
TACI	=	transmembrane activator and calcium-modulator and cyclophilin ligand interactor
T_H1	=	T-helper cell type 1
TNF	=	tumor necrosis factor
TNFRSF13B	=	tumor necrosis factor receptor super-family member 13B
TNFRSF13C	=	tumor necrosis factor receptor super-family member 13C
UNG	=	uracil DNA glycosylase
XLA	=	X-linked agammaglobulinemia

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