

Hypogammaglobulinaemia

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KEYWORDS

- Hypogammaglobulinaemia • Primary immunodeficiency
- Primary antibody deficiency • Agammaglobulinaemia
- Common variable immunodeficiency
- Class switch recombination defects

Hypogammaglobulinemia generally can be divided into primary/genetic causes or secondary causes due to other factors, such as sequelae of certain infectious diseases, malignancy, various medications, including immunosuppressants and anticonvulsants and systemic diseases that result in hypercatabolism or excessive loss of immunoglobulin (Ig).¹ Depending on the symptoms and severity of the hypogammaglobulinemia, various treatment options are available including replacement Ig therapy, antibiotic treatment or just careful follow-up observation.

The International Union of Immunological Societies (IUIS) has produced regular reports on the classification of primary immunodeficiency diseases (PIDs), with the most recent update in 2007.^{2–5} PIDs that resulted in hypogammaglobulinemia were categorized within several groups, which included those that caused a combined T and B cell defect, those that resulted in predominantly antibody deficiency, and those that incorporated other well-defined immunodeficiency syndromes. Other groups of PIDs did not have significant hypogammaglobulinemia, including diseases of immune dysregulation, congenital disorders of phagocyte numbers or function or both, defects in innate immunity, autoinflammatory disorders, and complement deficiencies.

This article discusses primarily PIDs that result in hypogammaglobulinemia generally following the order in the most recent IUIS classification (**Table 1**),⁵ with particular focus on the more common ones that typically require Ig replacement therapy. Several of the PIDs classified in this section (ie, X-linked lymphoproliferative syndrome, CD40 ligand deficiency, and CD40 deficiency) are also classified elsewhere in the IUIS scheme and are discussed in greater depth elsewhere in this issue because they result from T-cell dysfunction or immune dysregulation.

Predominantly antibody deficiency syndromes as a whole make up the greatest proportion of PID diagnoses—up 67% to 77% of all PIDs, as recently published by the European and Australian registries.^{6,7} Of the individual antibody deficiency

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Table 1 The International Union of Immunological Societies classification of predominantly antibody deficiencies	
Disease	Genetic Defects
Severe reduction in all serum Ig isotypes with profoundly decreased or absent B cells	
<i>BTK</i> deficiency	<i>BTK/BTK</i>
μ Heavy chain deficiency	<i>IGHM</i> / μ heavy chain
$\lambda 5$ Deficiency	<i>CD179B</i> / $\lambda 5$
Ig α deficiency	<i>CD79A</i> /Ig α
Ig β deficiency	<i>CD79B</i> /Ig β
BLNK deficiency	<i>BLNK/BLNK</i>
Thymoma with immunodeficiency	Unknown
Myelodysplasia	Monosomy 7, trisomy 8, and dyskeratosis congenita have been reported
Severe reduction in serum IgG and IgA with normal, low, or very low numbers of B cells	
Common variable immunodeficiency disorders	<i>TNFRSF13B/TACI</i> <i>TNFRSF13C/BAFFR</i> <i>MSH5/Msh5</i>
ICOS deficiency	<i>ICOS/ICOS</i>
CD19 deficiency	<i>CD19/CD19</i>
X-linked lymphoproliferative syndrome	<i>SH2D1A/SAP</i> <i>XIAP/XIAP</i>
Severe reduction in serum IgG and IgA with normal/elevated IgM and normal numbers of B cells	
CD40L deficiency	<i>TNFSF5/CD154</i>
CD40 deficiency	<i>TNFRSF5/CD40</i>
Activation-induced cytidine deaminase deficiency	<i>AICDA/AID</i>
Uracil-DNA glycosylase deficiency	<i>UNG/UNG</i>
Isotype or light chain deficiencies with normal numbers of B cells	
Ig heavy chain deletions	Deletion at chromosome 14q32
κ Chain deficiency	Mutation in κ constant gene
Isolated IgG subclass deficiency	Unknown
IgA deficiency associated with IgG subclass deficiency	Unknown
Selective IgA deficiency	Unknown
Specific antibody deficiency with normal Ig concentrations and normal numbers of B cells	Unknown
Transient hypogammaglobulinemia of infancy with normal numbers of B cells	Unknown

disorders, common variable immunodeficiency (CVID) made up the largest proportion of entries at 31.6% and 38.4% of all PIDs, respectively.

DISEASES RESULTING IN SEVERE REDUCTION IN ALL SERUM IMMUNOGLOBULIN ISOTYPES WITH PROFOUNDLY DECREASED OR ABSENT B CELLS

***BTK* Deficiency/X-linked Agammaglobulinemia**

X-linked agammaglobulinemia (XLA), or Bruton's agammaglobulinemia, first described in 1952,⁸ is the prototypic B-cell immunodeficiency resulting in agammaglobulinemia

because of a block in B-cell maturation. Almost 40 years later, in 1993, two groups identified *BTK*, the gene responsible for XLA, which encodes a protein tyrosine kinase—Bruton tyrosine kinase (Btk).^{9,10} The disease is typically characterized by marked reduction in serum Ig levels (IgG < 2 g/L, IgA and IgM < 0.2 g/L) and circulating B cells of less than 2%.¹ A recent US registry estimated the birth rate for XLA at 1 in 379,000 live births, although this number was thought to be an underestimate.¹¹ Other registry data have estimated a live birth rate as high as 1 in 100,000 in Norway and as low as 1 in 20 million in Spain, however.^{12,13}

Btk is encoded over 19 exons spanning 37 kb at Xq22¹⁴ and belongs to the Tec family of cytoplasmic tyrosine kinases.¹⁵ It is present in all stages of B-cell differentiation except plasma cells and myeloid cells and platelets but not T cells.^{16,17} Cross-linking of the B-cell receptor results in phosphorylation and activation of Btk.¹⁸ Initially Btk is phosphorylated by src family members and then undergoes autophosphorylation.¹⁹ Receptor-associated src family members also phosphorylate the immunoreceptor tyrosine activation motifs on the cytoplasmic tails of Ig α and Ig β , which escort the μ -heavy chain to the cell surface. Full phosphorylation of the immunoreceptor tyrosine activation motifs allows Syk, another cytoplasmic tyrosine kinase to dock and be activated via transphosphorylation.²⁰ Syk then phosphorylates downstream targets, including B-cell linker protein (BLNK).²¹ This process allows Btk and PLC γ 2 to bind to BLNK, resulting in phosphorylation of PLC γ 2 by Btk.²² PLC γ 2 then generates inositol triphosphate (IP3), a second messenger that binds to receptors on the endoplasmic reticulum leading to calcium release.

Btk mutations

There is significant variability in Btk mutations, with more than 170 different mutations identified and no single mutation accounting for more than 3% of patients in one series.²³ The issue as to whether specific mutations are associated with more significant disease has been difficult to clarify, because in addition to the nature of the mutation and compensating genetic factors, the age of first diagnosis is influenced by environmental exposure to infectious organisms, the level of suspicion of the physician, and the amount of antibiotic use. One study does raise the suggestion that patients with less “severe” mutations (ie, persons with amino acid substitutions or base pair substitutions at sites within the splice consensus site that are conserved, but not invariant) are more likely to have a later diagnosis, higher B-cell percentage, and plasma IgM.²⁴ It should be noted, however, that patients with “severe” mutations (eg, premature stop codons or mutations in the start codon) can have mild disease^{25–27} and that patients with the same mutation in the same family can have varying degrees of severity,^{25,27,28} which implies that other factors play a role in determining outcomes in XLA.

Clinical features

XLA is an X-linked recessive disorder that is fully penetrant and manifests in affected men. In general, female carriers are asymptomatic, although there are rare exceptions to the rule, with a recent case report of a daughter of a man with XLA who had all the features of XLA caused by extremely skewed X-inactivation.²⁹

There is marked variability in the clinical course of patients with XLA. In general, most patients become clinically symptomatic by the age of 1 year with nearly all patients manifesting by the age of 5.^{11,30} It should be noted that 10% to 25% of patients develop symptoms before 3 to 4 months of age, when some degree of maternal antibody would still be expected to be present.^{11,30} Most patients had reduced levels of all Ig isotypes and markedly reduced circulating B cells, although in most of the series of

patients, a handful developed symptoms only after the age of 5 and some had Ig levels within the normal range, despite confirmed Btk mutations.^{11,31,32}

The mean age at diagnosis was 3.5 years in the Italian series³¹ and 4 years in the Iranian series.³⁰ The most recent American series showed that patients with a family history were diagnosed at a mean of 2.59 years but patients without a family history were diagnosed significantly later at a mean age of 5.37 years.¹¹ In general, there was an inverse correlation between the age at diagnosis and the year of birth, hopefully indicating greater awareness of the disease.^{11,30,31} Approximately 25% to 40% of patients had a positive family history at the time of birth;^{11,31,32} however, even in the most recently published series, only approximately a third of patients with a positive family history were diagnosed before the onset of clinical symptoms.¹¹ This finding indicates the need for improved genetic counseling in affected families.

Infection is the commonest feature in XLA before diagnosis and during follow-up. The commonest infections involve the respiratory tract (including pneumonia, sinusitis, and otitis media) and affect 60% to 80% of patients, most commonly with *Streptococcus pneumoniae* but also with *Haemophilus influenzae*, staphylococcus, and pseudomonas species.^{11,30–32} Diarrhea affects approximately 25% of patients (most commonly with *giardia lamblia* but also rotavirus, campylobacter, enterovirus, salmonella, and shigella species).^{11,30–32} A few cases of vaccine-associated paralytic polio and wild polio have been reported in the various case series.^{11,31,32} A handful of cases of *Pneumocystis jirovecii* infection was reported despite the fact that Btk mutations are not known to affect T-cell function.^{11,33,34} This was attributed to poor nutrition in the children affected.

One case series described a constellation of symptoms in patients who presented in infancy, including pyoderma gangrenosa, perirectal abscess, cellulitis, or impetigo associated with pseudomonas or staphylococcal sepsis and neutropenia.³² In addition to recurrent infections, patients with XLA also have poorly developed lymphoid tissue, which can be noted clinically in the absence of tonsils and lymph nodes and should alert the clinician to consider the diagnosis.

Patients are prone to long-term complications of chronic lung damage and chronic sinusitis from infection; data have shown that the factors that significantly influenced the likelihood of chronic lung damage were “higher mean age at diagnosis” and “duration of follow-up”.³¹

In addition to conventional pathogens, patients with XLA have been noted to be susceptible to certain more unusual infections. Enteroviral infection (eg, coxsackie and echoviruses) can cause meningitis/encephalitis and, more rarely, hepatitis, pneumonia, and dermatomyositis, resulting in significant morbidity and mortality.^{35–38} Mycoplasma arthritis and urethritis were reported in 7 of 52 patients with XLA in one study,³⁹ although the more recent case series did not note this as a frequent complication.^{11,30,31}

The incidence of malignancy in XLA is unclear. Gastric adenocarcinoma, lung cancer, lymphoproliferative disease, dermatofibrosarcoma protuberans, and colorectal cancer have been reported to occur in patients who have XLA.^{11,40–44} There was an increase in colorectal cancer in 3 of 52 patients in one report⁴³ but no other cases in two series of 44⁴⁵ and 73 patients,³¹ respectively, and only one case in the largest series of 201 patients.¹¹ Without formal epidemiologic studies, it is not possible to state definitively if patients with XLA are more prone to malignancy and if any tumors occur more frequently.

Autosomal Recessive Agammaglobulinemia

Approximately 15% of patients with congenital agammaglobulinemia and absent circulating B cells do not have a mutation in Btk.²³ Mutations in the μ heavy chain

(IGHM) are thought to account for approximately 20% to 30% of patients without Btk mutations.^{46,47} Defects in $\lambda 5$ (CD179B), Ig α (CD79A), Ig β (CD79B), and BLNK (BLNK) have been identified in a small number of patients with autosomal recessive agammaglobulinemia.^{48–53} In approximately 5% to 10% of all patients with defects in early B-cell development, no clear molecular defect has been identified.

Clinically, patients with the autosomal recessive forms of agammaglobulinemia are not easily distinguishable from patients with XLA, although there is heterogeneity in the clinical presentation. Patients with μ heavy chain deficiency, for example, were noted to generally present at an earlier age with a higher incidence of complications, although two patients in one series had a relatively mild course and were still alive at age 53 and 49 years despite receiving what would currently be considered suboptimal doses of Ig.⁴⁶

Thymoma with Immunodeficiency

The association of thymoma with immunodeficiency or Good's syndrome was originally described in 1955,⁵⁴ and although there is no formal diagnostic criteria, it is recognized as a separate entity in the IUIS classification.⁵ Patients generally present in their 50s,⁵⁵ but Good's syndrome can occur in children.⁵⁶ It occurs with a similar frequency in men and women. Immunodeficiency can either precede or follow the diagnosis of the thymoma and does not resolve with thymectomy.⁵⁵

The etiology of Good's syndrome is not clear, although three possible hypotheses have been suggested: (1) the possibility that cytokines (eg, limitin in a murine model) can cause B-cell arrest or impair maturation, (2) the loss of the naive or memory T-cell population (and thereby the T-cell help for B cells) in view of the opportunistic infections, and (3) autoimmune destruction of the B cells in view of the studies in thymoma patients showing that T cells or autoantibodies can inhibit erythropoiesis.⁵⁷

Clinically, these patients are susceptible to recurrent infection with encapsulated bacteria and diarrhea,⁵⁵ similar to other patients with agammaglobulinemia. Susceptibility to opportunistic infections also suggests a cell-mediated defect. Cytomegalovirus colitis and retinitis and chronic mucocutaneous candidiasis occur relatively frequently,⁵⁵ infections with *P jirovecii* pneumonia, human herpesvirus 8, herpes simplex, varicella zoster, and babesiosis have been reported.^{56–59} Autoimmune phenomena, including myasthenia gravis, pure red cell aplasia, pernicious anemia, diabetes mellitus, polymyositis, and idiopathic thrombocytopenia, also can occur.^{2,58} Prognosis is generally thought to be worse compared to other antibody deficiency syndromes. In one series, 10 years after diagnosis only 33% of patients who had Good's syndrome were alive compared to 95% of patients with XLA or CVID.⁴⁵ The increased mortality was thought to be caused by disease complications (eg, infection, autoimmune disease, and hematologic complications) rather than the underlying thymoma, although patient numbers in the largest series were small (7 patients who had Good's syndrome vs 240 patients who had CVID).

Apart from the reduced/absent B cells and hypogammaglobulinemia, various other immunologic abnormalities have been described, including abnormal CD4+/CD8+ T-cell ratios, CD4+ lymphopenia, and reduced T-cell proliferation to mitogens.⁶⁰

Myelodysplasia

Myelodysplastic syndromes can mimic XLA, and this diagnosis has been included in the most recent IUIS classification.^{5,61} A small number of pediatric patients have been reported in the literature. They can have monosomy 7, trisomy 8, or dyskeratosis congenita and recurrent infection and low B cells at the onset of disease and the pancytopenia associated with myelodysplasia.^{61–63} These patients can have normal specific

antibody titers and isohemagglutinins titers and low numbers of pro- and pre-B cells in the bone marrow (unlike patients with XLA who have normal numbers of pro-B cells).^{62,63}

SEVERE REDUCTION IN SERUM IgG AND IgA WITH NORMAL, LOW, OR VERY LOW NUMBERS OF B CELLS

Common Variable Immunodeficiency

The first description of CVID in 1953 has been credited to Janeway.⁶⁴ It is currently understood to be a heterogeneous group of predominantly antibody deficiency disorders that make up the greatest proportion of patients with symptomatic primary hypogammaglobulinemia, with an estimated population prevalence of between 1 in 10,000 and 1 in 50,000.² Clinically, it is defined by the presence of recurrent infection, a reduction in IgG (of at least two standard deviations below the mean), and at least one other Ig isotype and a failure to generate a significant specific antibody response after vaccination or natural infection after other known genetic or acquired causes of hypogammaglobulinemia have been excluded.^{1,2}

Clinical features

CVID affects both genders equally, and symptoms can begin at any age, although there are peaks in the first and third decades.⁶⁵ A significant diagnostic delay of between 4 and 9 years exists in the published case series.^{6,65,66} In approximately 10% of patients, familial clustering of CVID has been documented, although typically the illness is sporadic.⁶⁷ IgA deficiency (discussed later) can occur in family members of patients with CVID,⁶⁸ which is consistent with the observation that some patients with IgA deficiency progress to CVID.⁶⁹

Recurrent infections (with a similar spectrum to patients with agammaglobulinemia, possibly reflecting antibody deficiency rather than the intrinsic genetic defect) are the most frequent complications in CVID. Recurrent respiratory tract infections occur in up to 98% of patients who have CVID.⁶⁵ Recurrent sinopulmonary infection can result in chronic sinusitis, hearing loss, and bronchiectasis, which are the principal sources of morbidity and (along with lymphoma) mortality in CVID.⁶⁵ In one cohort, bronchiectasis was present in a third of patients at baseline, with a further 12.2% developing it during follow-up despite appropriate treatment.⁶⁶ In general, most patients are not more susceptible to most viral infections and opportunistic infections are rare. Similar to patients with agammaglobulinemia, however, there is also infrequently a predisposition to mycoplasma infection of the joints (11 of 306 patients in one series,³⁹ although these numbers were not replicated in another series of similar size)⁶⁵ and enteroviral meningoencephalitis (with no more than 30 patients identified in the literature, most of whom were on inadequate doses of replacement Ig).^{37,70}

Gastrointestinal disease also occurs frequently in patients who have CVID, affecting up to 20% to 25% of patients.⁶⁵ The most common infections are with *Giardia lamblia*, *Campylobacter jejuni*, and *Salmonella* species; other prominent findings include nodular lymphoid hyperplasia, inflammatory bowel disease, and nonspecific malabsorption.⁶⁵ Severe cytomegalovirus enteritis also has been reported.⁷¹

Autoimmune disease complicates CVID in up to 20% to 25% of patients. Autoimmune cytopenias (particularly autoimmune thrombocytopenia and autoimmune hemolytic anemia) are the most commonly reported conditions, but various other conditions, including rheumatoid arthritis, sicca syndrome, pernicious anemia, and systemic lupus erythematosus, have been described.^{65,66} One series reported that the autoimmune thrombocytopenia preceded the hypogammaglobulinemia in 62% of cases.⁷²

Nonmalignant lymphoproliferation and granulomatous disease have been described in patients who have CVID. Up to a third of patients with CVID can develop lymphoproliferation, which is reflected as splenomegaly, intestinal lymphoid hyperplasia, or lymphadenopathy.⁶⁵ Lymphoid interstitial pneumonitis also has been reported.⁷³ Granulomatous inflammation most commonly affects the lung and has been reported in 8% to 22% of patients with CVID.^{65,74,75} Multisystemic involvement is not infrequent; granulomatous disease has been described in lymph nodes, spleen, liver, parotid glands, meninges, and bone marrow⁷⁶ and is often associated with a poor prognosis.⁷⁴

Patients with CVID are also at greater risk of malignancy, particularly non-Hodgkin's lymphoma and gastric carcinoma, with rates between 18 and 10 to 16 times greater than that of healthy individuals, respectively.^{65,66,77} Other malignancies, such as colorectal cancer, prostate cancer, breast cancer, ovarian cancer, melanoma, and Waldenström's macroglobulinemia, also have been described, but numbers in the various series have been too small to determine if there was a significant increased risk.^{65,66}

Immunopathology and classification schemes

A host of immunologic abnormalities have been described in the innate and adaptive immune systems in patients who have CVID.^{78–91} It is unclear if these changes are pathogenic or merely represent epiphenomena. In the innate immune system, abnormalities have been described in monocytes,⁷⁸ monocyte-derived dendritic cells,^{79–81} and blood myeloid and plasmacytoid dendritic cells.⁸² Signaling defects in the TLR9 pathway in plasmacytoid dendritic cells and B cells have been reported.⁸³

There has been a greater focus on the adaptive immune system, and multiple T-cell abnormalities in antigen and mitogen-induced proliferation,⁶⁵ cytokine production,⁸⁴ generation of antigen-specific T cells after vaccination,⁸⁵ cell surface molecule expression (CD40L, attractin),^{86,88} and T-cell apoptosis⁸⁷ have been described.

More recent work has shown elevation in serum IL-7 (which plays a role in homeostatic proliferation of lymphocytes) in a subset of patients who have CVID who had increased numbers of CD8+ T cells with decreased apoptosis and a greater incidence of splenomegaly and autoimmunity.⁸⁹ Abnormalities in T-cell receptor signaling affecting the cytoplasmic guanine nucleotide exchange factor Vav⁹¹ and ZAP-70⁹⁰ have been demonstrated.

Based on the immunologic abnormalities seen in patients who have CVID, various classification schemes, mostly based on B-cell phenotype, have been developed to help stratify patients for research and prognostic reasons. Bryant and colleagues⁹² originally divided patients who have CVID based on the ability of lymphocytes to produce Ig on stimulation *in vitro*. This method was labor intensive and not widely adopted; subsequently, two flow cytometric classification systems based on memory B-cell phenotype were published.^{93,94} These systems had some differences, and to further refine these schemes, the EUROClass scheme was developed after a large trial involving 303 patients.⁹⁵ EUROClass separated patients who had nearly absent B cells (< 1% of lymphocytes), severely reduced switched memory B cells (< 2% of total B cells), and expansion of transitional (> 9% of total B cells) or increased CD21^{low} B cells (> 10% of total B cells). There was a degree of clinical correlation, albeit relatively imprecise, with splenomegaly and granulomas more frequently seen in patients with reduced switched memory B cells and elevated CD21^{low} B cells and lymphadenopathy more frequently seen in patients with elevated transitional B cells. In addition to the B-cell classification schemes, investigators also classified patients who have CVID using T cells⁹⁶ and dendritic cells,⁹⁷ with a degree of clinical correlation.

Genetics

The past few years have seen the discovery of mutations/polymorphisms in five genes that result/contribute to a CVID phenotype, representing a significant advance in the understanding of what was previously poorly understood at a molecular level. The genes identified so far affect inducible costimulator ([ICOS] gene: *ICOS*) on T cells,⁹⁸ transmembrane activator and calcium-modulator and cyclophilin ligand interactor ([TACI] gene: *TNFRSF13B*),^{99,100} B-cell activating factor receptor ([BAFF-R] gene: *TNFRSF13C*),¹⁰¹ CD19^{102,103} (gene: *CD19*) on B cells, and *MSH5*, which is involved in regulating meiotic homologous recombination and contributes to class switch recombination (CSR).¹⁰⁴

Inducible Costimulator Deficiency

ICOS is expressed on activated T cells and belongs to the CD28 family of costimulatory surface molecules. It plays a significant role in activating T helper cells and providing B-cell help by superinduction of IL-10 necessary for terminal B-cell differentiation into memory and plasma cells and by binding to ICOS-ligand, which is present on antigen-presenting cells, including naive B cells.^{105,106}

So far, a total of nine individuals from four families have been identified with the same homozygous mutation (resulting in a truncated protein) in ICOS since it was first described in 2003.^{98,107} All affected patients have the same homozygous haplotype at the D2S2289 locus near the ICOS gene; all four families are believed to originate from a common founder and are either linked by the House of Habsburg or the River Danube.¹⁰⁷

Phenotypically, ICOS deficiency results in hypogammaglobulinemia and reduced B-cell numbers, particularly in the IgM memory and switched memory B-cell subsets. This further strengthens the evidence that ICOS plays an important role in late B-cell differentiation, class switching, and memory B-cell development.⁹⁸ Patients who have ICOS deficiency were able to generate IgM responses during infection, however.

TACI Deficiency

TACI is a member of the tumor necrosis factor receptor superfamily (TNFRSF) and belongs to a group of TNFRSF receptors that also includes B-cell maturation antigen and BAFF-R, which play important roles in B-cell survival, development, and antibody production.¹⁰⁸ The ligands for TACI and B-cell maturation antigen are BAFF and a proliferation-inducing ligand.

Mutations in TACI that result in CVID were first described in 2005^{99,100} and are thought to be present in 8% to 10% of patients with CVID.¹⁰⁹ A complicated pattern of inheritance with homozygous, heterozygous, and compound heterozygous mutations were identified, suggesting that there were autosomal dominant and autosomal recessive patterns of inheritance. Extracellular (C104R, S144X), transmembrane (A181E), and intracellular (S194X, R202H, Ins204) portions of the molecule were all found to possess mutations.^{99,100}

The role of heterozygous mutations in CVID is not completely clear because it was subsequently shown that patients with CVID had unaffected family members with the same TACI mutation.¹¹⁰ In a large study, the C104R and A181E (but not the R202H) mutations were present in greater frequency in patients who had CVID compared to the general population.^{111,112} This finding suggested that TACI mutations (at least in the heterozygous state) might result in increased disease susceptibility rather than being solely responsible. No clear genotype-phenotype correlation has been shown in patients with TACI mutations, although there is a suggestion that these patients are at increased risk of autoimmunity and lymphoid hyperplasia.⁹⁹

B-cell Activating Factor Receptor Deficiency

BAFF-R deficiency has so far been identified in only one patient—a 60-year-old man who had a 24 base pair homozygous deletion in exon 2, which codes for the trans-membrane portion of the receptor.¹⁰¹ This deficiency resulted in a block at the transitional B-cell stage, leading to low total peripheral B-cell numbers and a percentage increase in transitional B cells, indicative of the BAFF–BAFF-R role in peripheral B-cell survival. These findings have only been published in abstract form so far; the full publication is awaited.

CD19 Deficiency

CD19 is a B-cell surface molecule that forms a co-receptor complex with CD21, CD81, and CD225. The co-receptor complex reduces the signaling threshold after antigen binding to the B-cell receptor,¹⁰⁶ and the CD21 component can bind antigen-bound C3d, thus linking recognition of complement to CD19 signaling.¹¹³

Five patients with a CVID phenotype from three families have been found to have a total of four different mutations in CD19.^{102,103} Three patients (born to unrelated Colombian parents) had a homozygous two base pair deletion that resulted in a frameshift and premature stop codon leading to deletion of a large portion of the intracellular domain. One patient (born to consanguineous Turkish parents) had a single base pair insertion that resulted in a frameshift and premature stop codon in the proximal region of the intracellular domain.¹⁰² The final patient (born to unrelated Japanese parents) was a compound heterozygote with a splice acceptor site mutation of intron 5 on the maternal allele, which resulted in skipping of exon 6 and a truncated protein, and a gross deletion on the paternal allele that encompassed the *CD19* and at least the neighboring *ATP2A1* and *NFATC2IP* genes.¹⁰³ All patients presented in childhood with recurrent infections and hypogammaglobulinemia. One patient was found to have mild thrombocytopenia, which raised the possibility of autoimmunity.¹⁰³ Peripheral B-cell numbers were normal, but CD5+ and memory B cells were reduced. Patients had normal germinal center formation but poor antibody responses to vaccination. Other publications on patients with CD19 deficiency are underway, which suggests that the defect may not be that rare.

MSH5 Mutations

MSH5 is a gene encoded in the major histocompatibility class III region that plays role in homologous recombination in meiosis but was found to be involved in CSR in mice.¹⁰⁴ Subsequently, several nonsynonymous single nucleotide polymorphisms (SNPs) in *MSH5* were found in greater frequency in patients who have IgA deficiency (C580G, L85F/P786S, rs3131378) and CVID (Q292H, rs3131378).¹⁰⁴ *MSH5* was found to have reduced binding affinity to its heterodimerization partner *MSH4* in patients who had the L85F/P786S allele. Patients who have CVID with heterozygous nonsynonymous *MSH5* polymorphisms were found to have abnormalities in the S_{μ} - $S_{\alpha 1}$ joints; although controls with heterozygous *MSH5* polymorphisms did not have hypogammaglobulinemia, there were some subtle differences in the S joint phenotype. Consequently, it is more likely that *MSH5* is a disease susceptibility gene rather than pathogenic.¹⁰⁴

X-linked Lymphoproliferative Syndrome

X-linked lymphoproliferative syndrome was originally described in 1974¹¹⁴ as a rapidly fatal illness after Epstein Barr virus infection in men with a strong genetic linkage. The illness can result in fulminant infectious mononucleosis (60% of patients), lymphoma

(30%), or dysgammaglobulinemia (30%), and patients can present with any or all of these features.¹¹⁵ It also has been recognized that Epstein Barr virus infection is not necessary to trigger the onset of the disease. The mutation responsible for X-linked lymphoproliferative syndrome was identified in the signaling lymphocyte activation molecule-associated protein ([SAP] gene: *SH2D1A*) in 1998.^{116,117} SAP mutations only accounted for approximately 60% of familial X-linked lymphoproliferative syndrome, however, and defects in the gene encoding the X-linked inhibitor of apoptosis (XIAP) were identified in 2006 in a cohort of some of these patients with no molecular diagnosis.¹¹⁸ X-linked lymphoproliferative syndrome can mimic CVID, although in one series only 1 of 60 patients with CVID had an *SH2D1A* mutation.¹¹⁹

CLASS SWITCH RECOMBINATION DEFECTS: SEVERE REDUCTION IN SERUM IgG AND IgA WITH NORMAL/ELEVATED IgM AND NORMAL NUMBERS OF B CELLS

Reductions in serum IgG and IgA with a normal or elevated IgM are suggestive of a defect in the machinery required for CSR and result in the so-called “hyper-IgM syndrome” (HIGM), which is somewhat of a misnomer because the IgM can sometimes be in the normal range. These syndromes can be inherited in an X-linked, autosomal recessive or autosomal dominant manner.¹²⁰ Limited epidemiologic data are available, but X-linked HIGM is thought to have an estimated frequency of approximately 1 in 500,000 live male births in the United States.¹²¹

The first mutation that accounted for these syndromes to be discovered was in CD40 ligand ([CD40L] gene: *TNFSF5*), which results in the X-linked HIGM syndrome that makes up approximately 30% of patients with CSR defects.^{122,123} CD40L is present on the surface of T cells and interacts with CD40 on the surface of B cells (required for Ig class switching) and dendritic cells/monocytes (required for T cell responses). Patients are susceptible to recurrent bacterial infections similar to other patients with hypogammaglobulinemia but are also prone to infections with opportunistic organisms, such as *P. jirovecii*, cryptosporidium, toxoplasma, and cytomegalovirus, and neutropenia and autoimmune disease.^{120,121} A mutation in CD40 (gene: *TNFRSF5*) resulting in a similar clinical phenotype but inherited in an autosomal recessive manner also was described in a small number of patients.¹²⁴ Another form of an X-linked HIGM syndrome in association with anhidrotic ectodermal dysplasia was described with mutations in NF- κ B essential modulator (NEMO or IKK γ), which is required for CD40 induced signaling of the transcription factor NF- κ B.^{125,126}

CD40L, CD40, and NEMO deficiency all result in a combined antibody and cellular immune deficit and are discussed elsewhere in this issue. The remaining 70% of patients with class switch defects possess some form of intrinsic B-cell defect that is usually inherited in an autosomal recessive (sometimes autosomal dominant) manner. Mutations in activation-induced cytidine deaminase ([AID] gene: *AICDA*) and uracil-DNA glycosylase ([UNG] gene: *UNG*) have been described to account for approximately 40% of these patients, although there remains a substantial group with an as-yet uncharacterized molecular defect.

Activation-Induced Cytidine Deaminase Deficiency

AID deficiency is typically inherited in an autosomal recessive fashion and is characterized by defects in CSR and somatic hypermutation (SHM).¹²⁷ Clinically, these patients are prone to recurrent bacterial infections and diarrhea, similar to other patients with hypogammaglobulinemia, but they also frequently possess marked enlargement of lymphoid organs, in contrast to patients with XLA who have sparse lymphoid tissue. Giant germinal centers (five to ten times the normal size) filled with

intensely proliferating B cells have been found in lymphoid tissue biopsies. This finding is thought to be caused by continuous antigen stimulation due to lack of SHM secondary to defective AID.¹²⁸ Lymphoid hyperplasia has been noted to decrease with Ig replacement.¹²⁹ IgM-mediated autoimmunity (mostly cytopenias) is seen in approximately one fourth of these patients.^{127,129} In a case series of 29 patients, the median age of onset of clinical symptoms was 2 years (range 0.3–12.9) with recognition of immunodeficiency at 3.8 years and diagnosis of a HIGM syndrome at 4.9 years.¹²⁹ IgM levels ranged from 1 to 37 g/L, whereas IgG levels ranged from undetectable to 1.5 g/L and IgA ranged from undetectable to 0.2 g/L.¹²⁹

AID possesses a cytidine deaminase activity domain, an apolipoprotein-B mRNA-editing cytidine deaminase 1 (APOBEC-1)-like domain, and a nuclear localization signal and nuclear export signal in the N and C terminal portions of the protein, respectively. It is thought to be essential for initiation of the DNA cleavage required for CSR and SHM; 35 different recessive mutations have been identified in 73 patients.^{128–131} The mechanism by which AID exerts its function is not completely clear, although studies in patients with AID deficiency have helped to shed some light on this. It is thought to act as a DNA-editing enzyme and a docking protein by forming multimeric complexes.¹³²

Mutations in AID generally result in defective CSR and SHM in keeping with its role as the inducer of DNA breaks required for these processes, although mutations in the C-terminal portion in a small number of patients have been shown to result only in defective CSR but not SHM.¹³³ This information and additional data showing that AID truncated for the last ten amino acids was unable to generate CSR but was able to generate mutations in the S μ region¹³⁴ was taken to indicate that the C-terminal portion of AID played a role in binding a CSR-specific cofactor that helped target AID to S μ regions. A particular heterozygous mutation (R109X) in the C-terminal portion has been shown to result in an autosomal dominant form of a HIGM defect.^{128,135} This is thought to arise because of a dominant negative effect of the mutated allele, which implies that a multimeric AID complex is necessary for optimal CSR and SHM.

Uracil-DNA Glycosylase Deficiency

A similar clinical picture to AID deficiency with recurrent infections and lymphadenopathy was described in three patients with a homozygous defect in UNG, which is a member of a family of glycosylases able to deglycosylate uracil residues on DNA.¹³⁶ UNG deficiency results in defective CSR but with SHM in normal frequency, albeit with a biased pattern, with almost all mutations at G/C residues being transitions as opposed to an equal frequency of transitions and transversions at A/T residues.^{136,137} This finding has been cited as a strong argument for the DNA-editing activity of AID. AID is thought to deaminate cytosine into uracil. Subsequently, UNG deglycosylates and removes the uracil residues, which creates an abasic site and allows creation of single-stranded DNA breaks. UNG deficiency interferes with this pathway and results in defective CSR and skewed SHM.^{136,137}

Uncharacterized Molecular Defects that Result in Deficiencies in Isotype Class Switching

There are still many cases of CSR defects caused by an intrinsic B-cell abnormality that are not caused by AID or UNG deficiency.

A CSR defect titled HIGM4 has been described in a group of 15 patients with clinical features similar to AID deficiency, although slightly milder with some residual IgG production.¹³⁸ The specific defect has yet to be identified, although it is thought to be

downstream to AID and probably due to a selective defect in either a CSR-specific factor of the DNA machinery or survival signals delivered to B cells.

Another defect thought to be upstream of S region DNA cleavage was described in a group of 16 patients with HIGM and a generally good prognosis, with no autoimmunity or lymphoma.¹²⁸ It was speculated that this condition could be caused by problems with AID targeting (which is poorly understood) to switch regions.

ISOTYPE OR LIGHT CHAIN DEFICIENCIES WITH NORMAL NUMBERS OF B CELLS

Most of the deficiencies in Ig isotypes or light chains occur in otherwise healthy individuals, and the question of Ig replacement is controversial in persons who are symptomatic. They are covered here briefly for completeness.

Immunoglobulin Heavy Chain Deletions

Deletions and duplications that affect the heavy chain constant regions in chromosome 14q32 have been described in 5% to 10% of the healthy white population who have no history of recurrent infection.^{2,139} One or more IgG and IgA subclasses and IgE have been shown to be affected.¹³⁹ Homozygous individuals lack the relevant subclasses, and heterozygotes may show diminished levels. Most patients are well, although a few individuals have presented with recurrent infections, which casts doubt on the relevance of the immunologic abnormalities.

κ Chain Deficiency

κ chain deficiency has been reported in two families.^{2,140} B cells seemed to be normal, although all of them possessed the λ light chain. Point mutations in the κ chain gene were reported in one family.¹⁴¹

Isolated IgG Subclass Deficiency

Isolated deficiencies in one or more IgG subclasses were first described in 1970 in patients with recurrent sinopulmonary infections¹⁴² and are defined as a reduction in one or more IgG subclasses more than two standard deviations from the mean. By definition, however, approximately 2.3% of the healthy population will have an IgG subclass deficiency and up to 10% to 15% actually do have an IgG4 level below the limit of detection.¹⁴³ Many healthy individuals have been identified with significantly decreased IgG subclass levels. Consequently, controversy exists as to whether isolated IgG subclass deficiency does represent a true PID. Some authors have argued that there is no clinical value in IgG subclass measurement.^{144–146}

Selective IgA Deficiency

Selective IgA deficiency is defined as complete absence of IgA (usually less than the detection limit of 0.07 g/L in most laboratories) with a normal IgG and IgM in patients older than age of 4 and in whom other causes of hypogammaglobulinemia have been excluded. It is the commonest Ig deficiency and has a prevalence of 1 in 300 to 1 in 700 in whites.^{2,147–149} Most patients with IgA deficiency are asymptomatic, although there is an increased prevalence of infections, autoimmune disease, atopy, and celiac disease.^{150–152} There was a suggestion of increased rates of gastrointestinal malignancy and lymphoma in patients who have IgA deficiency,¹⁵³ but this was not replicated in a later study.¹⁵⁴ The molecular mechanisms underlying IgA deficiency are unclear, although as noted in some patients, there is a family history of IgA deficiency and CVID, and some patients can progress to CVID.^{67–69}

IgA Deficiency Associated with IgG Subclass Deficiency

IgG subclass deficiency has been noted to occur in association with IgA deficiency, and both can present with specific antibody deficiency. The molecular, clinical characteristics and frequency of these combined deficiencies in the healthy and patient populations remain poorly understood and characterized, although small studies suggest that a combination of these defects is more likely to result in clinical disease.¹⁵⁵

SPECIFIC ANTIBODY DEFICIENCY WITH NORMAL IMMUNOGLOBULIN CONCENTRATIONS AND NORMAL NUMBERS OF B CELLS

Specific antibody deficiency with normal Ig was first described in 1980¹⁵⁶ and is characterized by normal levels of IgG, IgA, and IgM but a failure to make antibody responses to vaccination, typically with polysaccharide antigens. Clinically, these patients are prone to recurrent sinopulmonary infections; bronchiectasis, diarrhea, and autoimmune disease also have been reported.¹⁵⁷ There is no universal definition as to what constitutes a failure to respond, however. Normal responses are age dependent and not well characterized. Pure polysaccharide antibody responses are unreliable in children younger than age 2 years.¹⁵⁸

The components necessary to define what constitutes an adequate response include (1) the increase in antibody titers above baseline, (2) the final antibody concentration, and (3) the percentage of serotypes in the vaccine to which the patient has responded.

The American practice parameter defines an adequate response to individual serotypes as a postimmunization antibody titer of 1.3 mcg/mL or more or at least fourfold over baseline.^{145,158} Patients between 2 and 5 years of age are expected to respond to at least half the vaccinated serotypes; for patients 5 years or older, the consensus recommendation was that there should be a response to 70% of the serotypes, although it was acknowledged that there was a degree of controversy regarding this. The IUIS classification is a lot less specific than this.² The increasing use of conjugated pneumococcal vaccines in routine immunization is likely to influence how a diagnosis of specific antibody deficiency is made in the future.

A further point about the diagnosis of specific antibody deficiency is whether patients who fail to make responses to polysaccharide antigens but not to protein antigens should be considered a separate group than patients who cannot make responses to polysaccharide and protein antigens.¹⁵⁹

Much work still needs to be done with regard to diagnosing and working out the molecular mechanisms underlying specific antibody deficiency. The entity does serve to make the point that in patients with normal Ig levels who have recurrent infections, further detailed evaluation is necessary.

TRANSIENT HYPOGAMMAGLOBULINEMIA OF INFANCY WITH NORMAL NUMBERS OF B CELLS

In 1956, Gitlin and Janeway¹⁶⁰ described two infants with temporary hypogammaglobulinemia and coined the description "transient hypogammaglobulinemia of infancy" (THI). This was thought to be caused by prolongation of the nadir in gammaglobulins normally seen in infants in the first few months of life after the decline in maternally transferred Ig. Despite this, until now this group of patients remains poorly characterized with little understanding of the molecular mechanisms underlying the condition.

The IUIS classification had noted that THI can take up to 36 months to resolve,² although it has been noted that the period of hypogammaglobulinemia can extend significantly beyond infancy. Only approximately half the infants had resolution of

hypogammaglobulinemia by 24 months in one case series, with resolution seen at up to 14 years of age,¹⁶¹ and a definitive diagnosis of THI can be made only retrospectively. Patients with THI were more likely to be male (60%–80%) and generally presented with mild infections, including ear/nose/throat infections, respiratory infections, and diarrhea,^{161–165} although isolated case reports have documented more severe infection.¹⁶⁶ An increased risk of atopic disease has been noted in patients with THI.^{164,165}

Generally, patients with THI have reductions in IgG and IgA below the lower limit of normal and less frequently in IgM; specific antibody production and cell-mediated immunity is usually intact.^{161,165} A few individuals have reduced vaccine responses that recover by 3 to 4 years.¹⁶² Some recent data indicated that in vitro Ig secretory responses were poorer in patients who had THI and that in vitro IgG and IgA (but not IgM) responses did not normalize at the same time as serum Ig.¹⁶⁴ This was interpreted as possibly caused by some deficiency in class switch mechanisms.

SUMMARY

The predominantly antibody deficiency PIDs that result in hypogammaglobulinemia represent an important group of diseases, both clinically and for furthering understanding of the immune system. Combined, they represent the largest group of PID diagnoses that possess a relatively good outcome with Ig replacement therapy. A significant delay in diagnosis still remains, which can result in significant morbidity and long-term complications and emphasizes that the need for greater awareness of these conditions still remains. This heterogeneous group of disorders has provided many useful insights into our understanding of the immune system, particularly with regard to B-cell development and antibody responses and is likely to continue doing so.

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