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# Neutropenia Associated With Primary Immunodeficiency Syndromes

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**The primary immunodeficiency diseases are a heterogeneous group of more than 75 disorders characterized by intrinsic defects in the functions of the immune system. Many are associated with abnormalities of hematopoiesis as well. This article will review those primary immunodeficiency syndromes in which neutropenia is a prominent finding, including X-linked agammaglobulinemia (XLA), hyper IgM syndrome, common variable immunodeficiency (CVID), IgA deficiency, cartilage-hair hypoplasia (CHH), and reticular dysgenesis, with regards to pathophysiologic findings and treatment. *Semin Hematol* 39:107-112. Copyright 2002, Elsevier Science (USA). All rights reserved.**

PRIMARY IMMUNODEFICIENCY diseases involve virtually every component of the immune system. There are disorders of B-cell function (such as X-linked agammaglobulinemia [XLA]) or T-cell function (purine nucleoside phosphorylase deficiency), and some that affect both B- and T-cell function (severe combined immunodeficiency disease [SCID] and Wiskott–Aldrich syndrome); others complement (C2 deficiency), and still others, phagocytic cells (chronic granulomatous disease).

## General Manifestations of the Primary Immunodeficiency Diseases

Most of the primary immunodeficiency diseases are genetically determined and inherited as single-gene defects.<sup>2,12,26</sup> However, the etiologies of the two most common disorders, selective IgA deficiency and common variable immunodeficiency disease (CVID), remain unknown.

Accurate information on the prevalence of the different primary immunodeficiency diseases has been difficult to obtain and is available for only a few of the disorders. For example, population surveys of serum immunoglobulin levels have established a prevalence of selective IgA deficiency of between 1/1,000 and 1/333 in the general population of adults.<sup>8,18,19</sup> Molecular genetic analysis for C2 deficiency among normal populations has estimated its prevalence at 1/10,000.<sup>58</sup> Finally, a national registry of US residents with chronic granulomatous disease provided a minimal estimate of 1/200,000 live births.<sup>67</sup> Thus, although some of the disorders are relatively rare, others, such as selective IgA deficiency, are relatively common.

Because many of the primary immunodeficiency diseases were first described in infants and children, they were initially viewed as diseases that were characteristic of, if not largely confined to, infancy and early childhood. It has become apparent, however, that these disorders occur just as frequently in older children and adults as they do in infants.<sup>54</sup> Some of

the primary immunodeficiency diseases (for example, CVID and selective IgA deficiency) usually present in adults.<sup>21</sup> Many of the disorders that typically appear in infancy (XLA and adenosine deaminase deficiency) include patients who have a mild enough clinical phenotype to allow initial clinical presentation in later childhood and adult life.<sup>32,47</sup> Improvements in supportive care and specific therapy have allowed many infants and children with primary immunodeficiency diseases to survive into adulthood.

The most common clinical presentation of patients with a primary immunodeficiency disease is an increased susceptibility to infection, involving pathogens that usually affect normal hosts or opportunistic organisms that more commonly infect immunodeficient hosts. Most patients present with recurrent or chronic respiratory infections, although infectious diarrhea and blood-borne infections are also seen.

Patients can have a variety of other clinical manifestations as well. Autoimmune and inflammatory disorders are relatively common in some of the primary immunodeficiency diseases. A single organ or tissue may be involved, as in idiopathic thrombocytopenic purpura (ITP) or autoimmune hemolytic anemia, or there may be a more global syndrome, such as occurs in systemic lupus erythematosus (SLE), rheumatoid arthritis, and sarcoidosis. Finally, the clinical presentation may occur in the context of a recognized syndrome, such as the Wiskott–Aldrich

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syndrome, rather than with symptoms related to the immunodeficiency itself. For example, the typical infant with Wiskott-Aldrich syndrome may initially manifest thrombocytopenia rather than infection.<sup>57</sup>

### Specific Immunodeficiency Diseases Associated With Neutropenia

Although neutropenia may occur in any of the primary immunodeficiency diseases as a consequence of either an intercurrent infection or an autoimmune disease, the following disorders have been selected for discussion because neutropenia is a frequent occurrence and may be a prominent part of the patient's clinical picture. Additional syndromes in which neutropenia is prominent are listed in Table 1.<sup>1,3</sup>

#### X-Linked Agammaglobulinemia

**Pathophysiology.** XLA was the first recognized primary immunodeficiency disease.<sup>9</sup> Inherited in an X-linked recessive fashion, XLA is caused by mutations in the gene encoding a tyrosine kinase named Bruton's (or B-lymphocyte) tyrosine kinase (BTK).<sup>61,62</sup> More than 250 different mutations in the human *Btk* gene have been recognized to date.<sup>63</sup> Most parts of the coding portions of the gene have been involved, and there has not been any clear correlation between the location of the mutation and the clinical phenotype. Apparently, BTK is necessary for the maturation of B

lymphocytes, as patients with this disorder have very few mature B cells.<sup>48</sup> Laboratory testing reveals markedly decreased levels of all three major immunoglobulin classes. In addition, patients with XLA fail to make specific antibodies following antigenic stimulus. Lymph node biopsies indicate a depletion of follicles and germinal centers. In contrast, T-cell number and function are normal.

**Clinical manifestations.** Patients are generally asymptomatic for the first few months of life. As maternally acquired IgG levels decline, recurrent infections develop.<sup>36</sup> Respiratory tract infections such as otitis, sinusitis, and pneumonia are most common, but other infections may also occur.<sup>36</sup> Infections are usually caused by pyogenic bacteria such as pneumococcus, streptococcus, and *Haemophilus influenzae*, but these patients are also prone to enteroviruses, hepatitis viruses, and mycoplasma organisms.<sup>36,66</sup>

The mainstay of treatment is prophylactic immunoglobulin replacement aiming to maintain trough levels of IgG greater than 400 mg/dL, usually achieved by monthly injections of intravenous gammaglobulin (IVIG).<sup>40</sup> Although infections are significantly reduced with this therapy, not all can be prevented and antibiotics are often necessary. Early diagnosis and prompt treatment of infections have improved prognosis significantly.

**Neutropenia.** Neutropenia has been reported in a significant proportion of patients with XLA. XLA

**Table 1.** Immunodeficiency Disorders Associated With Neutropenia

MIM	Syndrome	Inheritance (gene map locus)	Associated Features	Immune Abnormality
300300	X-linked agammaglobulinemia	XL (Xq22)	Recurrent bacterial infections; rare incidence of neutropenia; defect in Bruton tyrosine kinase (BTK)	↓ B cells, ↓ IgG, ↓ IgM, ↓ IgA, normal T-cell function
250250	Cartilage-hair hypoplasia	AR (9p13)	Neutropenia and lymphopenia, short-limbed dwarfism, metaphyseal chondrodysplasia, fine sparse hair	↓ CD4 ↓, CD8, ↓ PHA, cytotoxic activity
240500	Common variable immunodeficiency	Unknown	Heterogenous group, characterized by hypogammaglobulinemia, sinopulmonary infections, autoimmune disorders	Variable T- & B-cell numbers, ↓ IgG, ↓ IgM, ↓ IgA
223370	Dubowitz syndrome	AR	Recurrent neutropenia, growth deficiency, mental retardation, microcephaly, eczema, dysmorphic facies	↓ IgA, ↓ IgG ↑ IgM
214450	Griscelli syndrome	AR (15q21)	Episodic neutropenia, thrombocytopenia, partial albinism, lymphohistiocytosis	↓ IgA, ↓ IgG, ↓ IgM, defect NK
308230	Hyper IgM syndrome	XL, AR (Xq26) (Xq28) (12p13)	Recurrent bacterial infections, frequent autoimmune hematologic disorders (neutropenia, hemolytic anemia, thrombocytopenia)	↓ IgA, ↓ IgG, ↑ IgM
137100	Selective IgA deficiency	Unknown	Autoimmune disorders, autoimmune neutropenia	Anti-IgA, selective ↓ IgA
267500	Reticular dysgenesis	AR	Neutropenia, thrombocytopenia	↓ T- and B-cell numbers
193670	WHIM	XL	Warts, hypogammaglobulinemia, infection, myelokathexis	↓ IgG/IgA, ↓ T & B cells

Abbreviations: MIM, Mendelian inheritance in man; AR, autosomal recessive; AD, autosomal dominant; XL, X-linked; NK, natural killer; PHA, phytohemagglutinin; WHIM, warts, hypogammaglobulinemia, infections, and myelopathies.

patients who manifest neutropenia may be more prone to develop fungal infections or infections with *Pneumocystis carinii*.<sup>34</sup>

That the XLA gene is expressed in cells of myeloid lineage may explain the associated neutropenia. Intermittent neutropenia, which is often manifest at the beginning of an infection,<sup>34</sup> may be reflective of BTK being only one of several signaling molecules participating in myeloid maturation; neutropenia would be observed in XLA only when rapid production of such cells is needed.<sup>11</sup>

There are no specific reports regarding granulocyte colony-stimulating factor (G-CSF) treatment of the associated neutropenia, which tends to be intermittent. Nevertheless, in the face of significant infection with concomitant neutropenia, a short-course of G-CSF in conjunction with antibiotics might be warranted.

### Immunodeficiency With Elevated IgM (Hyper IgM Syndrome)

**Pathophysiology.** Immunodeficiency with elevated IgM may be caused by one of at least three different molecular genetic defects. The most common form is inherited as an X-linked recessive trait and is caused by mutations in the gene for CD40 ligand<sup>4,6,23,33</sup> This T-lymphocyte surface molecule interacts with CD40 on the surface of B lymphocytes to induce class switching from production of IgM to IgG and IgA; absence of this interaction results in the defective production of IgG and IgA as well as elevated levels of IgM. Thus, these patients have markedly reduced levels of IgG, IgA, and IgE with normal to elevated levels of IgM.<sup>39</sup> Normal or increased levels of isohemagglutinins are usually detected, indicating that the functional activity of IgM molecules is retained.<sup>45</sup> Immunization may result in normal primary (IgM-restricted) antibody responses but repeated immunization rarely leads to IgG production. The interaction of CD40 ligand on T lymphocytes with B lymphocytes, and other antigen-presenting cells such as macrophages, also plays an important role in antigen processing by T lymphocytes. As a result, patients with CD40 ligand-deficiency have defective in vitro T-lymphocyte proliferation on antigen exposure, although their responses to mitogens are normal.<sup>5,39</sup> Numbers of circulating B cells are normal or increased and T cell numbers are normal.

Recently, patients with another X-linked form of the hyper IgM syndrome associated with anhidrotic ectodermal dysplasia have been shown to have a defect in the gene encoding NF- $\kappa$ B essential modulator (NEMO).<sup>24,29</sup> Finally, an autosomal recessive form of the hyper IgM syndrome has been found to be caused by defects in the gene for activation-induced cytidine deaminase (AID).<sup>50</sup>

**Clinical manifestations.** Symptoms develop during the first or second year of life. The most common problems are recurrent pyogenic bacterial infections.<sup>35,39,45</sup> In addition, patients have difficulty with opportunistic organisms for which T lymphocytes play an important defensive role including *P carinii*, histoplasmosis, cryptosporidium, and toxoplasma.<sup>35,37,39,45</sup> Patients with X-linked hyper IgM syndrome due to CD40 ligand deficiency are also prone to develop autoimmune diseases and malignancies, especially of the liver.<sup>39,45</sup>

The mainstay of treatment is regular, prophylactic IVIG. However, in view of their T-cell defect and propensity to develop opportunistic infections, including sclerosing cholangitis due to cryptosporidial infections, some patients have been treated with bone marrow transplantation in order to correct the underlying T-cell defect.<sup>59</sup>

**Neutropenia.** In addition to the increased susceptibility to infection, many patients have chronic neutropenia. In a report from the Registry of Primary Immunodeficiencies of the European Society for Immune Deficiency, 56 patients with X-linked hyper IgM were described.<sup>39</sup> Thirty-eight of the patients (68%) were reported as having neutropenia, which was chronic in 25 (45%). The pattern was cyclic in seven of the patients and episodic in six. The etiology of the neutropenia is not known. Some investigators have hypothesized an autoimmune basis, as there are other manifestations of autoimmunity in these patients. In the European experience, four patients had autoantibodies against parietal cells and thyroid microsomes but were asymptomatic; one was found to have a Coomb's positive hemolytic anemia. However, the patients with neutropenia have not had antineutrophil antibodies.<sup>35,39</sup> This negative finding may reflect the difficulty of detecting these antibodies but may also indicate another etiology. Interaction between CD40 on stromal cells and CD40 ligand on T cells may stimulate synthesis of G-CSF, and the abnormality of CD40 ligand might thus contribute to the neutropenia.<sup>44</sup>

In the European Registry, 11 patients received G-CSF for severe symptomatic neutropenia, and eight responded.<sup>39</sup> Other reports have likewise demonstrated a clinical response to this therapy.<sup>65</sup> Patients who have a cyclical pattern to their neutropenia may continue to be cyclical following treatment with G-CSF although the nadir of the absolute neutrophil count is neither as low nor as prolonged as prior to therapy (unpublished data from the Severe Chronic Neutropenia International Registry).

### Common Variable Immunodeficiency

**Pathophysiology.** CVID is used to describe a group of patients in whom the hypogammaglobuline-

mia is of unknown etiology. CVID is the most common of the primary immunodeficiency diseases in which there are significant symptoms,<sup>20,21,52,55</sup> and both the laboratory and clinical findings vary from patient to patient.<sup>20,21</sup> It is likely that this disorder represents more than one disease.

There is some evidence that CVID is genetically influenced, at least in some cases. In a small subset of patients, a number of first-degree relatives have either CVID or a related disorder, IgA deficiency,<sup>7,53,68</sup> although several patterns of inheritance have been described. Families whose members include some persons with CVID and others with IgA deficiency often have a characteristic major histocompatibility complex (MHC) haplotype.<sup>53,64</sup> A susceptibility gene, or genes, for both CVID and selective IgA deficiency likely is located within the class III region of the MHC on chromosome 6, possibly between the *C4B* and *C2* genes.<sup>53,64</sup>

Laboratory findings demonstrate depressed levels of IgG and variable levels of IgM and IgA.<sup>20,21</sup> In some patients, there appears to be an inability of terminal differentiation of the B cell: although there are normal circulating immunoglobulin-bearing B lymphocytes and the presence of lymphoid follicles, they do not differentiate normally into immunoglobulin-producing cells when stimulated with pokeweed mitogen (PWM) in vitro.<sup>20,56</sup> Total lymphocyte counts, T-cell numbers, and T-cell subset numbers may be normal or depressed.

**Clinical presentation.** Although CVID usually becomes clinically apparent in the second or third decade of life, some patients present in early childhood. The most common clinical manifestation is recurrent bacterial infections of the sinopulmonary tract.<sup>20,21</sup> A few patients may initially show infections involving opportunistic organisms such as *P. carinii*, mycobacteria, or various fungi.<sup>20,21,55</sup>

In addition to an increased susceptibility to infection, patients also have an unusually high incidence of malignancies of the lymphoreticular and gastrointestinal systems.<sup>20,21,30</sup> Additionally, they are prone to develop autoimmune disorders, such as ITP, SLE, and thyroiditis,<sup>20,21,55</sup> as well as noncaseating granulomas of the skin, gut, and other viscera, which resemble sarcoidosis.<sup>21,25</sup> First-degree relatives of patients with CVID have an increased rate of autoimmune phenomena.<sup>28</sup>

As with other primary immunodeficiency diseases characterized by hypogammaglobulinemia, IVIG is the main therapy.

**Neutropenia.** Neutropenia may occur in CVID, probably on an autoimmune basis. The neutropenia has been reported to be responsive to G-CSF,<sup>60</sup> and this therapy may be helpful if the patient is symptomatic despite IVIG and appropriate antibiotics.

## IgA Deficiency

**Pathophysiology.** Selective IgA deficiency is the most common primary immunodeficiency, with a frequency as high as 1/333 reported among some blood donors,<sup>8,18,19</sup> although it is often asymptomatic. The basic defect(s) responsible for this disorder is unknown, but there is evidence that genes located in the MHC class III region of chromosome 6 influence the expression of both CVID and IgA deficiency.<sup>53,64</sup> By definition, patients with selective IgA deficiency have normal IgG and IgM levels and mount normal primary and secondary responses to vaccination. Their cell-mediated immunity also is unaffected. Some patients with this disorder have concurrent IgG2 and IgG4 deficiency.<sup>46</sup>

**Clinical presentation.** Infections in IgA deficiency tend to affect the respiratory and gastrointestinal tracts.<sup>10</sup> There is an increased incidence of autoimmune disorders and occurrence of malignancy, similar to patients with CVID.<sup>27,49</sup> Affected individuals may develop anti-IgA antibodies and they can experience severe or fatal anaphylactic reactions after receiving blood products that contain IgA.<sup>17</sup> Patients with IgA deficiency should only receive washed erythrocytes or other blood products from donors deficient in IgA.

**Neutropenia.** Neutropenia may occur in this disorder, on an autoimmune basis. There are no published cases of IgA-deficient patients with neutropenia who have received G-CSF.

## Cartilage-Hair Hypoplasia

**Pathophysiology.** Cartilage-hair hypoplasia (CHH) is a specific form of short-limbed dwarfism characterized by metaphyseal dysplasia, fine hair, and immunodeficiency.<sup>41</sup> The disease is inherited in an autosomal-recessive fashion and is particularly common among the Finnish and Amish. CHH is due to mutations in the *RMRP* gene, which encodes the RNA component of a ribonuclear protein ribonuclease.<sup>51</sup>

Laboratory investigations confirm the disorder as primarily one of T-cell function deficiency, but abnormalities of the humoral immune system have been demonstrated as well. The T lymphocytes of the majority of patients demonstrate diminished proliferative responses in vitro to concavalin A and phytohemagglutinin.<sup>31</sup> Up to 35% have humoral immune deficiencies, including IgA deficiency and IgG subclass deficiencies.<sup>42</sup>

**Clinical presentation.** Patients with CHH suffer from recurrent severe infections, particularly varicella zoster.<sup>41,43</sup> A cohort of 120 patients followed in Finland demonstrated increased mortality, primarily in the younger patients and attributable to infection.<sup>43</sup>

**Neutropenia.** CHH is associated with moderate to severe neutropenia with absolute neutrophil counts in the range of 100 to 2,000/ $\mu\text{L}$ .<sup>41</sup> There are no reports of the use of G-CSF in this disorder.

## Reticular Dysgenesis

**Pathophysiology.** Severe combined immunodeficiency disease (SCID) includes a group of diseases characterized by defective T-lymphocyte and B-lymphocyte function. There are at least nine different molecular genetic causes of SCID, each of which may produce a characteristic phenotype.<sup>2,12,13,26</sup> Some forms of SCID are associated with neutropenia, in particular, reticular dysgenesis,<sup>22</sup> which is characterized by complete failure of development of both myeloid and lymphoid cells. Hypogammaglobulinemia, lymphopenia, absent cell-mediated immunity, and neutropenia lead to severe and often fatal infections in the first year of life. The genetic defect predisposing to this disorder has not been determined.

**Clinical presentation.** SCID is among the most severe of the primary immunodeficiency diseases.<sup>2,12,13,26</sup> Patients present early with failure to thrive, persistent oral candidiasis, chronic diarrhea, and pneumonia (often interstitial). If SCID is unrecognized and untreated in the first year of life, the mortality rate is high.<sup>13</sup>

**Neutropenia.** Bone marrow transplantation has been reported to be curative in patients with reticular dysgenesis, reconstituting lymphocyte function and resolving the neutropenia.<sup>14,38</sup> G-CSF has been ineffective,<sup>15,16</sup> at least at conventional doses (4 to 5  $\mu\text{g}/\text{kg}/\text{d}$ ).<sup>15</sup>

## Summary

A number of the primary immunodeficiency diseases have associated neutropenia. Children or adults presenting with repeated infection and neutropenia should be evaluated for immunodeficiency, with laboratory investigations tailored to the type of infections experienced. Additional research into the genetic causes of these disorders is likely to shed further light on myelopoiesis and the mechanisms of neutropenia.

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