

Pulmonary complications of primary immunodeficiencies

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Summary In the fifty years since Ogden Bruton discovered agammaglobulinemia, more than 100 additional immunodeficiency syndromes have been described. These disorders may involve one or more components of the immune system, including T, B, and NK lymphocytes; phagocytic cells; and complement proteins. Most are recessive traits, some of which are caused by mutations in genes on the X chromosome, others in genes on autosomal chromosomes. Until the past decade, there was little insight into the fundamental problems underlying a majority of these conditions. Many of the primary immunodeficiency diseases have now been mapped to specific chromosomal locations, and the fundamental biologic errors have been identified in more than 3 dozen.

Within the past decade the molecular bases of 7 X-linked immunodeficiency disorders have been reported: X-linked immunodeficiency with Hyper IgM, X-linked lymphoproliferative disease, X-linked agammaglobulinemia, X-linked severe combined immunodeficiency, the Wiskott–Aldrich syndrome, nuclear factor κ B essential modulator (NEMO or IKK γ), and the immune dysregulation polyendocrinopathy (IPEX) syndrome. The abnormal genes in X-linked chronic granulomatous disease (CGD) and properdin deficiency had been identified several years earlier. In addition, there are now many autosomal recessive immunodeficiencies for which the molecular bases have been discovered. These new advances will be reviewed, with particular emphasis on the pulmonary complications of some of these diseases. In some cases there are unique features of lung abnormalities in specific defects. Infections obviously account for most of these complications, but the host reaction to infection often leads to characteristic findings that can be helpful diagnostically. Finally, advances in treatment of the underlying diseases as well as their infectious complications will be covered.

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HUMORAL IMMUNODEFICIENCY DISORDERS

Humoral immunodeficiencies, i.e. those characterized by defective antibody production, are the most common, accounting for about 70% of all primary immunodeficiencies.^{1,2} Clinically, affected individuals are susceptible to infections with pyogenic agents, particularly the encapsulated bacteria,

such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Staphylococci*. Recurrent pneumonia, otitis media, sinusitis, and septicemia are the most common clinical manifestations. Most patients with defects involving predominantly humoral immunity have the ability to recover from viral infections because of their normal T-cell responses.

X-linked agammaglobulinemia

X-linked agammaglobulinemia (XLA) was the first primary immunodeficiency disorder to be recognized and was reported by Ogden Bruton in 1952.³ The

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Table 1
Locations of faulty genes in primary immunodeficiency diseases

Chromosome	Disease
1q21	MCH class II antigen deficiency caused by RFX5 mutation*
1q25	Chronic granulomatous disease (CGD) caused by gp67 ^{phox} deficiency*
1q42–43	Chediak–Higashi syndrome*
2p11	Kappa-chain deficiency*
2q12	CD8 lymphocytopenia caused by ZAP70 deficiency*
5p13	SCID due to IL-7 receptor alpha chain deficiency*
6p21.3	MHC class I antigen defect caused by mutations in <i>TAP1</i> or <i>TAP2</i> *
6p21.3	(?) Common variable immunodeficiency and selective IgA deficiency
6q22–23	Interferon- γ R1 mutations*
7q11.23	CGD caused by p47 ^{phox} deficiency*
8q21	Nijmegen breakage syndrome due to mutations in <i>Nibrin</i> *
9p13	Cartilage hair hypoplasia due to mutations in endoribonuclease <i>RMRP</i> *
10p13	SCID (Athabascan, radiation sensitive) due to mutations in the <i>Artemis</i> gene*
10p13	DiGeorge's syndrome/velocardiofacial syndrome
11p13	IL-7 receptor alpha chain deficiency*
11p13	SCID caused by RAG-1 or RAG-2 deficiencies*
11q22.3	Ataxia telangiectasia (AT), attributable to AT mutation, causing deficiency of DNA-dependent kinase*
11q23	CD3 gamma- or epsilon-chain deficiency*
12p13	Autosomal recessive Hyper-IgM caused by mutations in the activation-induced cytidine deaminase (<i>AID</i>) gene*
13q	MHC class II antigen deficiency caused by RFXAP mutation*
14q13.1	Purine nucleoside phosphorylase (PNP) deficiency*
14q32.3	Immunoglobulin heavy-chain deletion*
16p13	MHC class II antigen deficiency caused by CIITA mutation*
16q24	CGD caused by gp22 ^{phox} deficiency*
17	Human nude defect*
19p13.1	SCID caused by Janus kinase 3 (Jak3) deficiency*
19p13.2	Agammaglobulinemia caused by mutations in <i>Igα</i> gene*
20q13.11	SCID caused by adenosine deaminase (ADA) deficiency*
21q22.3	Leukocyte adhesion deficiency, type 1 (LAD 1), caused by CD18 deficiency*
22q11.2	Agammaglobulinemia caused by mutations in λ 5 surrogate light chain gene*
22q11.2	DiGeorge syndrome
Xp21.1	CGD caused by gp91 ^{phox} deficiency*
Xp11.23	Wiskott–Aldrich syndrome (WAS) caused by WAS protein (WASP) deficiency*
Xp11.3–21.1	Properdin deficiency*
Xq13.1	X-linked SCID caused by common gamma-chain (γ_c) deficiency*
Xq22	X-linked agammaglobulinemia caused by Bruton tyrosine kinase (Btk) deficiency*
Xq24–26	X-linked lymphoproliferative syndrome caused by mutations in the <i>SH2D1A</i> gene*
Xq26	Immunodeficiency with hyper-IgM caused by CD154 (CD40 ligand) deficiency*
Xq28	Anhidrotic ectodermal dysplasia with immunodeficiency caused by mutations in the nuclear factor kappa B essential modulator (NEMO)*

* Gene cloned and sequenced; gene product known.

incidence is unknown, but XLA is thought to be less common than IgA deficiency or common variable immunodeficiency (CVID).⁴ Serum immunoglobulins and antibodies of all isotypes are almost completely lacking. Those affected have less than 1% circulating B cells. They also lack germinal centers in their lymphoid tissue, accounting for their small tonsils and lymph nodes. There is a block in differentiation at all stages of B-cell development. The responsible mutated gene has been identified on the X chromosome and it encodes Bruton's tyrosine kinase, a key regulator of B-cell maturation (Table 1).^{5,6} T-cell numbers and functions are normal, as is thymic size and architecture.

During the first 6–9 months of life, patients with XLA are protected from infections by maternally derived IgG antibodies. As this source of antibodies diminishes, patients begin to develop pyogenic bacterial infections, with recurrent sinopulmonary infections being most common. As a consequence bronchiectasis frequently develops before the underlying condition is diagnosed. While most children develop recurrent bacterial infections during infancy, 20% of presentations occur from about 3–5 years of age, probably due to the widespread use of antibiotics.¹ Unfortunately, this often masks the diagnosis until after structural damage to the lungs has already occurred. Less common complications include chronic conjunctivitis, giardiasis, malabsorption, and persistent CNS enteroviral infections with resultant chronic meningoencephalitis.⁷

The standard treatment for XLA is intravenous immunoglobulin (IVIG) replacement therapy. Despite apparently adequate treatment with IVIG, however, many patients still develop pansinusitis or post-infectious chronic lung diseases, most commonly bronchiectasis. Rotating antibiotics in treatment doses are then needed in addition to monthly IVIG infusions.

Chest radiographs may demonstrate findings of pulmonary infection, including atelectasis and bronchial wall thickening or bronchiectasis. Bronchiectasis is most commonly found in the middle or lower lobes; upper-lobe distribution is very uncommon.⁸ Splenomegaly is not seen and tonsils, adenoids and cervical lymph nodes are typically extremely small. Infectious involvement of the central nervous system may demonstrate diffuse leptomeningeal thickening and enhancement or encephalitis with MR imaging.

IgA deficiency

This is the most common primary immunodeficiency disorder, with an estimated incidence of from 1:333–1:700 in Caucasians, who are affected much more

frequently than Asians or African Americans.⁹ Both genetic and environmental factors contribute to the pathogenesis of this disorder. Some children with IgA deficiency may be clinically healthy,² while others are susceptible to respiratory and gastrointestinal infections, allergy, autoimmune diseases, and malignancy. Pulmonary complications are predominantly due to bacterial pneumonias. However, since most can make IgG antibodies, bronchiectasis is not as common as in XLA. Treatment of this disorder is usually with antibiotics for specific infections.

Common Variable Immunodeficiency

Common variable immunodeficiency (CVID) is a syndrome encompassing probably several different genetic disorders.¹⁰ It is characterized by impaired antibody production of all major classes. CVID has an estimated incidence of up to 1:10,000.^{1,13} The diagnosis is usually made by the finding of low to absent serum immunoglobulins but normal numbers of circulating B cells. Upon antigen stimulation, these B cells do respond and proliferate, but fail to differentiate into antibody-secreting plasma cells. T-cell-mediated immunity is often intact; however, T-cell abnormalities have also been noted in up to 60% of individuals.^{1,13} Both males and females are affected equally, and the pattern of inheritance in many cases appears to be autosomal dominant with incomplete penetrance. In contrast to XLA where onset is always in early childhood, onset of symptoms may occur in early or late childhood or adulthood.

Clinically, CVID and XLA share a number of common features such as increased susceptibilities to recurrent pyogenic sinopulmonary infection leading to frequent development of bronchiectasis, gastrointestinal involvement, and (less often than in XLA) fatal enteroviral meningoencephalitis.¹⁵ Unlike in XLA, tonsillar tissue is normal in amount in CVID, and 15–25% of individuals develop lymphadenopathy or splenomegaly. Lymphoid interstitial pneumonia and nodular follicular lymphoid hyperplasia of the gastrointestinal tract are frequently observed as a part of a generalized lymphoproliferative process.¹⁶ CVID is also associated with an increased cancer risk, predominantly with lymphoreticular tumors.¹⁷ Approximately 20% of individuals with CVID will develop autoimmune diseases.¹⁰ Treatment for patients with this group of disorders consists of IVIG replacement and rotating antibiotics if bronchiectasis or pansinusitis is present.

Other humoral deficiencies

Other defects characterized by antibody deficiency include both X-linked and non-X-linked

hyper-IgM (both characterized by recurrent bacterial infections).^{12,18} X-linked lymphoproliferative disease (an inadequate response to Epstein–Barr viral infection) results in either death from acute infectious mononucleosis, malignancy or severe antibody deficiency.¹¹ These conditions have the same pulmonary complications as seen in XLA and CVID.

CELLULAR AND COMBINED IMMUNODEFICIENCY DISORDERS

Patients with inadequate cellular immunity are highly susceptible to opportunistic infections with viruses, such as the herpes viruses (herpes simplex, varicella zoster, and cytomegalovirus). They often have progressive pneumonia caused by parainfluenza 3 virus, respiratory syncytial virus, cytomegalovirus, varicella, or *Pneumocystis carinii*. T-cell immunodeficiencies are also accompanied by abnormalities in antibody production, because B-cell function is T-cell dependent. Hence, patients with these defects may also have infections with high-grade pathogens, similar to those with primarily antibody deficiencies.

DiGeorge syndrome

DiGeorge syndrome (thymic hypoplasia) is a typical example of a primary T-cell deficiency.¹ DiGeorge syndrome is most often due to gene defects on chromosome 22, which lead to abnormal development of the third and fourth pharyngeal pouches during early embryogenesis.¹⁹ As a result, the organs that develop from these structures, most importantly the thymus, parathyroid glands, and the heart, can be affected. Impaired functions of these organs account for a unique constellation of clinical presentations including variably severe T-cell deficiencies secondary to hypoplasia (most common) or aplasia of the thymus, neonatal hypocalcemic tetany due to hypoparathyroidism, and congenital cardiovascular anomalies, especially of the great vessels and septa. Another distinctive abnormality associated with this syndrome is facial dysmorphism, which presents as micrognathia, low-set ears, shortened philtrum of the upper lip, and hypertelorism.¹⁹ B cells are present in normal numbers. Nevertheless, antibody responses may still be affected due to an inadequate number of T cells, which is highly variable depending on the degree of thymic hypoplasia. In up to 80% of patients, the immunodeficiency is mild (partial DiGeorge syndrome). However, those with more severe forms of this disease (complete DiGeorge syndrome) may resemble children with severe combined immunodeficiency. These children, as is the case for all children

with cellular immunodeficiencies, are susceptible to infections with opportunistic organisms (i.e., viruses and *Pneumocystis carinii*), and to graft-versus-host disease (GVHD) from non-irradiated blood or blood-product transfusions. Viral pneumonias or PCP pneumonia are the most common pulmonary complications. Chest radiographs may reveal narrow upper mediastinal contour and retrosternal lucency due to absence of the thymus. Cardiovascular anomalies such as right-side aortic arch, interrupted aortic arch, truncus arteriosus, tetralogy of Fallot, atrial or ventricular septal defects are frequently present.¹⁹

Immunologic treatment is usually unnecessary in the partial form. However, the cardiac defects may need early correction. Thymic epithelial transplants or unfractionated HLA-identical sibling bone-marrow transplantation are recommended only for those with the complete DiGeorge syndrome.²⁰

Severe combined immunodeficiency

Severe combined immunodeficiency (SCID) is a syndrome characterized by the absence of T- and B-cell (and sometimes natural killer cell) function.²¹ Recently, several molecular defects responsible for SCID have been identified. X-linked SCID accounts for 46% of all cases and is caused by defects in the chain (γ c) common to the IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 receptors.^{22–26} Mutations in the genes encoding adenosine deaminase,²⁷ Janus kinase 3 (Jak3),²⁸ the α chain of the IL-7 receptor,²⁹ recombinase activating genes 1 or 2,³⁰ CD45³¹ or the Artemis gene³² also result in SCID and are inherited in an autosomal recessive pattern (Table 1). Regardless of the molecular cause, SCID patients with this syndrome are similar in many of their clinical and histopathological features.

Affected children frequently start to develop severe infections with opportunistic organisms soon after the neonatal period. Typical presenting features include failure to thrive, chronic diarrhea, persistent oral thrush, severe diaper rash or other skin rashes, pneumonia, and sepsis. Due to lack of graft-rejection capability, these infants are also at risk for severe GVHD from transfusion of non-irradiated blood products. Immunization with live attenuated viruses, such as poliovirus, bacille Calmette–Guerin (BCG), measles or varicella vaccines must be avoided due to risk of severe or systemic infection which can be fatal. Pulmonary manifestations of SCID include recurrent severe pneumonias due to *Pneumocystis carinii*, Parainfluenza 3, respiratory syncytial virus, adenovirus, cytomegalovirus, or bacterial organisms. The pneumonias may be due to multiple organisms. *Pneumocystis* typically

produces interstitial infiltrates, which progress to alveolar infiltrates. However, viral pneumonitis can be indistinguishable from *Pneumocystis* pneumonia. An important feature to recognize in children with SCID, as opposed to immunocompetent children or children with other immunodeficiencies with an acute pulmonary infection, is that the thymic shadow is absent.

ADA-deficient SCID is noteworthy from a radiologic standpoint due to skeletal abnormalities and because infants and children with this disorder usually have more profound lymphopenia than other infants with SCIDs.²⁷ Skeletal abnormalities, while not present in all cases, are unique to this form of SCID and are usually limited to the axial skeleton. These abnormalities include cupping and flaring at the costochondral junctions anteriorly, metaphyseal cupping, and irregularity at the costovertebral junction with increased separation between the rib head and vertebral body. In addition, a "bone-in-bone" appearance of the vertebral bodies, and squaring of the scapula tip have also been reported.³³

SCID is fatal without immune reconstitution. Current therapy is most commonly bone-marrow transplantation, which has been highly successful.²⁵ The first successful gene therapy for X-linked SCID was reported from France and was successful in 9 such patients.³⁴ However, 2 of the 9 developed a leukemia-like complication and gene therapy trials are currently on hold.

Purine nucleoside phosphorylase deficiency

Purine nucleoside phosphorylase (PNP) is an enzyme deficiency affecting lymphocyte function somewhat similar to the mechanism in ADA deficiency.³⁵ Clinically, immunodeficiency associated with PNP deficiency varies in age of onset of symptoms. The infections are similar to those experienced by patients with SCID. Milder forms may present later with diverse neurologic findings such as developmental delay, hypotonia, and spasticity. However, PNP deficiency is uniformly fatal in childhood unless corrected by bone-marrow transplantation.³⁶ Unlike ADA deficiency, this disorder is not associated with skeletal anomalies.

Wiskott–Aldrich syndrome

Wiskott–Aldrich syndrome is an X-linked recessive immunodeficiency disorder characterized by a triad of eczema, thrombocytopenia with small defective platelets, and recurrent infections.^{1,2} The responsible gene on the X chromosome encodes a protein called the Wiskott–Aldrich syndrome protein (or WASP)

that is expressed in lymphocytes, megakaryocytes, spleen, and thymus.³⁷ The function of this protein, however, is still unclear, but it is thought to have a major role in actin polymerization.³⁸ Immunologically, serum IgA and IgE levels are elevated, the IgM level is decreased, and the IgG level remains normal or slightly decreased. However, despite the presence of normal or elevated levels of immunoglobulins, including IgG subclasses, there are consistently impaired antibody responses to polysaccharide antigens and a moderately impaired response to protein antigens. Therefore, such patients are particularly susceptible to infection with polysaccharide-encapsulated organisms (e.g., pneumococcus, *Haemophilus influenzae*, meningococcus). T-cell function is also impaired, resulting in a partial combined immunodeficiency.

Clinically, affected infants often first present with prolonged bleeding from the circumcision site, bruising, or bloody diarrhea during infancy. Pyogenic infections usually start before 1 year of age and may include meningitis, otitis media, pneumonia, and sepsis. Pulmonary infections with agents such as pneumococci, *Pneumocystis carinii* and herpes viruses are common. Imaging findings include recurrent pneumonia, sinusitis and mastoiditis. Patients rarely survive beyond teenage years without bone-marrow transplantation. Death usually results from massive bleeding, infection, vasculitis, autoimmune cytopenias or lymphoreticular malignancy.

Therapy includes monthly IVIG infusions to compensate for the antibody deficiency and transfusions of fresh irradiated platelets for acute bleeding episodes. Bone marrow transplantation has completely corrected both the hematological and immunologic abnormalities in many patients.³⁹ If no HLA-identical donor is available, splenectomy may improve platelet count and reduce bleeding complications.⁴⁰

Ataxia telangiectasia

Ataxia telangiectasia (AT) is an autosomal recessive disorder characterized by progressive cerebellar ataxia (evident as the child begins to walk), oculocutaneous telangiectasia (evident beginning at 3–6 years of age), recurrent bronchopulmonary infections (in approximately 80% of individuals), and a high incidence of malignancy. The mutated gene (ATM) responsible for this defect is on the long arm of chromosome 11 (11 q22–23) and was cloned.⁴¹ The gene product is a DNA-dependent protein kinase localized predominantly to the nucleus and believed to be involved in mitogenic signal transduction, meiotic recombination, and cell cycle control.^{42–44} Defects in the AT gene compromise DNA repair mechanisms thus rendering the affected

cells highly susceptible to radiation-induced chromosomal damage. Immunologic features include selective IgA deficiency, hypogammaglobulinemia and moderately severe T-cell dysfunction. The degree of immunodeficiency is highly variable. The thymus is markedly hypoplastic.

Pulmonary complications include recurrent sinopulmonary infections with bronchiectasis and fibrosis. Because of the increased risk of cancer from radiation exposure, imaging studies utilizing ionizing radiation should be performed sparingly. Children that survive the first decade are at high risk for both solid (i.e., adenocarcinoma) and lymphoproliferative malignancies. Patients usually die from chronic pulmonary disease, neurologic deterioration, or malignancy by early adulthood. Both AT and Wiskott–Aldrich syndrome have the highest malignancy rates of all of the primary immunodeficiencies. Treatment is limited to antibiotics, IVIG if hypogammaglobulinemic and other supportive care. No cure is available. Bone-marrow transplantation has not been successful and would likely not correct the neurologic defect.

The hyper-IgE syndrome

The hyperimmunoglobulinemia E (hyper-IgE) syndrome is a condition characterized by staphylococcal abscesses of the skin, lungs, viscera or other sites beginning in infancy in association with markedly elevated serum IgE concentrations.^{45,46} The mode of inheritance appears to be autosomal dominant with variable penetrance.^{46,47} No gender or racial discrepancy in incidence has been noted. The most common infectious agent is staphylococci. Eczema, mucocutaneous candidiasis, and coarse facial features are frequently associated with this syndrome.^{45,46} Delayed eruption of teeth, scoliosis and osteopenia leading to fractures are also unique features of this immune disorder.^{46,47}

Pulmonary complications include recurrent staphylococcal pneumonias with subsequent and usually persistent pneumatocele formation.^{45,46} The presence of persistent single or multiple pneumatoceles is the most striking radiographic feature of this syndrome. These lung cysts may persist, expand, and become superinfected with bacteria and fungi, and may require surgical excision. Osteoporosis involving predominantly the spine and, to a lesser degree, the limbs in the epiphyseal-metaphyseal regions may also occur with resultant recurrent fractures.⁴⁹

The mechanism of this osteoporosis is not known. The underlying molecular defect is unknown. Treatment is usually supportive, with an emphasis

on long-term anti-staphylococcal antibiotic prophylaxis.

DISORDERS OF PHAGOCYtic CELLS AND ADHESION MOLECULES

Phagocytic cells are of great importance in host defence against pyogenic bacteria and fungi as well as other intracellular microorganisms. Defects in phagocyte production and/or function predispose affected patients to recurrent pyogenic and fungal infections. Common organisms include bacteria such as *Pseudomonas*, *Serratia marcescens*, *Staphylococcus aureus*, and fungi such as *Aspergillus* and *Candida*. Phagocytic disorders are not associated with increased susceptibility to viral or protozoal infections, nor is there an increased risk of malignancy. Disorders include chronic granulomatous disease, leukocyte adhesion deficiency, and Chediak–Higashi syndrome.

Chronic granulomatous disease

Chronic granulomatous disease (CGD) is the most common phagocytic disorder, affecting roughly 1 in 125,000 live births.⁵⁰ This disorder is inherited in an X-linked fashion in two-thirds of cases, but three forms of autosomal recessive CGD exist as well.

Diagnosis of this disorder is established with a respiratory burst assay. CGD is actually a collection of four different molecular defects that result in defective NADPH oxidase activity in leukocytes.⁵¹ NADPH oxidase catalyses a reaction producing important bactericidal products following phagocytosis: superoxide radical, singlet oxygen and hydrogen peroxide. Catalase-negative organisms such as streptococci and pneumococci provide oxidative products and can be killed. However, catalase-positive bacteria such as *Staphylococcus aureus* and *Serratia marcescens*, and some fungi such as *Aspergillus* destroy the very oxygen radicals they produce. Prolonged intracellular existence of these catalase-positive microorganisms in CGD triggers a cell-mediated response, resulting in granuloma formation.

The onset of symptoms usually occurs before 1 year of age. In a recent review of the US CGD registry, pulmonary infection was the most frequent occurrence (79%), and fungal organisms accounted for the majority. Other features included suppurative adenitis (53%), subcutaneous abscess (42%), liver abscess (27%), osteomyelitis (25%), and sepsis (18%). Gastric outlet obstruction, urinary tract obstruction, and enteritis or colitis occur in

10–17% of individuals. Trimethoprim sulfamethoxazole prophylaxis and recombinant human interferon gamma, in addition to chronic antifungal therapy, are standards of care for this disorder.⁵¹

Chest radiographs or CT may demonstrate chronic or recurrent pneumonia, pleural reaction, osteomyelitis from chest wall invasion (e.g., aspergillus, candida), hilar or mediastinal adenopathy, and esophagitis or esophageal stricture. Radionuclide imaging is indicated when clinical signs of infection are present without a source. The sedimentation rate is a useful clinical barometer, since this is elevated with acute, occult or persistent infection.

Leukocyte adhesion deficiency

Leukocyte adhesion deficiency type 1 (LAD 1) is attributable to mutations in the gene on chromosome 21 at position q22.3 encoding CD 18, a 95-kD β subunit shared by three adhesive heterodimers: LFA-1 on B, T, and NK lymphocytes; complement receptor type 3 (CR3) on neutrophils, monocytes, macrophages, eosinophils, and NK cells; and p150,95 (another complement receptor).^{52–54} Neutrophils cannot migrate out of the blood vessels into areas of infection. Common clinical features in LAD include impaired wound healing, severe periodontal disease and recurrent widespread pyogenic infection (otitis media, pneumonia, peritonitis, and cellulitis) later in childhood. The severity of symptoms can be highly variable, depending on the nature of the gene defect. Treatment options for LAD include aggressive antibiotic therapy and bone-marrow transplantation.³⁹

Complement deficiencies

Complement disorders represent the rarest form of primary immunodeficiencies, accounting for only 1% to 3% of these diseases; such rarity attests to the importance of complement proteins in host defence.¹ Inherited deficiencies in almost all the complement proteins have been discovered, with C2 deficiency occurring most commonly.^{55,56} All but one of these proteins are encoded by genes on autosomal chromosomes; however, the gene encoding properdin is on the X chromosome.⁵⁷ There is an increased incidence of autoimmune disease and pyogenic infections with deficiencies of early components (C1 to C4) of the classical pathway. Deficiencies of the terminal complement components (C5 to C9) are associated with increased susceptibility to serious infections from *Neisseria* species. C3 deficiency usually results in serious complications such as recurrent pneumonia, meningitis, and peritonitis. Its clinical presentations

often mimic those of the antibody deficiency disorders. On the other hand, some patients with deficiencies in C2, C4, or C9, can remain completely asymptomatic. Treatment usually involves prophylactic antibiotics and specific vaccination against encapsulated organisms. Complement replacement therapy is not effective in treating these disorders.

CONCLUSIONS

Primary immunodeficiency diseases include a broad spectrum of disorders with enormously diverse intrinsic defects involving one or multiple components of the immune system. Immunodeficiency is characterized clinically by an increased susceptibility to infection, malignancy, and autoimmunity. The pulmonologist can play an important role in the child with a primary immunodeficiency. This role is facilitated with familiarity with the classification and mechanisms of these deficiencies, clinical manifestations, and pulmonary complications.

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