Oral manifestations of primary immune deficiencies in children

Aleksandra Szczawinska-Poplonyk, MD, PhD,[a] Karolina Gerreth, DDS,[b]
Anna Breborowicz, MD, PhD,[c] and Maria Borysewicz-Lewicka, DDS, PhD,[d] Poznan, Poland
KAROL MARCINKOWSKI UNIVERSITY OF MEDICAL SCIENCES

An important task for both dentists and pediatricians dealing with patients manifesting different oral lesions is to be able to differentiate changes signaling systemic disease from those appearing without any concomitant serious health problem. In this article, symptomatology of selected primary immune deficiency diseases are discussed with particular emphasis on oral manifestations reported in this group of disorders. Facial, dental, and oral findings compose a constellation of symptoms observed in immunodeficiency diseases. Predisposition to bacterial invasion, cytokine dysregulation, tissue inflammatory process, and necrosis lead to early-onset oral lesions and periodontitis. Developmental abnormalities, periodontal disease, and oral lesions may accompany immunodeficiency and require particular awareness directed toward diagnosis of an underlying disease of the immune system. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;108:e9-e20)**

Primary immune deficiencies are a group of genetically heterogeneous disorders affecting anatomical structure, maturation, differentiation, and function of organs and cells of the immune system. In this group of disorders, the World Health Organization recognizes more than 100 of distinct disease entities, and for more than 80% of these, the genetic background has been identified. The division of most important primary immunodeficiencies based on the predominating disorder of the immune response is displayed in Table I. Epidemiology of primary immune deficiency diseases varies depending on the geographic region, ethnic factors, race, and gender. The median prevalence of diagnosed immunodeficiencies in the United States is estimated at 1:2000 in children and 1:1200 in people of all ages. The most frequently recognized disorders are humoral immunodeficiencies, responsible for more than 50% of all cases; among them selective IgA deficiency is the most prevalent in the Caucasian race.

Facial, dental, and oral findings compose a heterogeneous group of manifestations occurring frequently in patients with primary immunodeficiency diseases. Developmental abnormalities, periodontal disease, and oral lesions can therefore be a manifestation of an underlying systemic defect of immunity. Physicians evaluating children with oral manifestations must be able to detect numerous possible immune disorders, perform the correct differential diagnosis, and establish an appropriate treatment plan. Considering the fact of a wide variability in the prevalence and in the character of oral findings assisting different immunodeficiency diseases, particular awareness of both dentists and pediatricians should be directed toward identifying patients manifesting abnormalities that signal underlying systemic disease (Table II).

The most frequently reported oral lesions in the pediatric population include recurrent aphthous stomatitis, recurrent herpes labialis, tongue diseases (coated tongue, geographic tongue, fissured tongue), traumatic lesions (bites, ulceration), and oropharyngeal candidiasis. Despite of the association among many of the previously mentioned lesions and host factors, such as patient's age, allergy, congenital extraoral anomalies, history of smoking, nourishment status, and presence of concomitant illnesses (metabolic disorders, primary and secondary immunodeficiencies), all of these oral lesions may occur also in high frequency in healthy individuals.[1] Primary immunodeficiency diseases are very often accompanied by processes of tissue necrosis with ulceration and bacterial invasion leading to early-onset, aggressive gingivitis and periodontitis.[2-4]

PRIMARY IMMUNE DEFICIENCIES ASSOCIATED WITH ORAL DISEASE

T-cell disorders and combined immunodeficiencies

In this group of heterogeneous immune disorders, clinical manifestations result from quantitative and/or functional defects of T lymph cells, variably associated

[a]III Chair of Pediatrics, Department of Pediatric Pneumonology, Allergology and Clinical Immunology, Karol Marcinkowski University of Medical Sciences, Poznan, Poland.
[b]Assistant, Department of Pediatric Dentistry, Karol Marcinkowski University of Medical Sciences, Poznan, Poland.
[c]Head, Department of Pediatric Pneumonology, Allergology and Clinical Immunology, Karol Marcinkowski University of Medical Sciences, Poznan, Poland.
[d]Head, Department of Pediatric Dentistry, Karol Marcinkowski University of Medical Sciences, Poznan, Poland.
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Table I. Categories of primary immune deficiencies

Combined immunodeficiencies

- Severe combined immunodeficiency (SCID)
  - T-B+SCID: XL - gamma chain of the interleukin 2,4,9,7,15 receptor deficiency
    AR – Jak3 kinase deficiency, Omenn syndrome, alpha chain of the interleukin 7 receptor deficiency
  - T-B-SCID: RAG1/RAG2 deficiency, Artemis gene deficiency, adenosine deaminase deficiency, reticular dysgenesis
- Hyper-Immunoglobulin (Ig)M syndrome X-linked
- Purine nucleoside phosphorylase deficiency
- Major histocompatibility complex (MHC) II antigens deficiency (transcription factors CIITA or RFX5 mutations)
- ZAP-70 kinase deficiency
- MHC I antigens deficiency (TAP2 transporter deficiency)
- CD3 gamma, CD3 epsilon deficiency

Other well-defined immunodeficiency syndromes

- DiGeorge syndrome
- Ataxia – telangiectasia
- Nijmegen breakage syndrome
- Wiskott – Aldrich syndrome

Immune deficiencies with predominantly antibody production defects

- Agammaglobulinemia X-linked (Bruton's disease)
- Hyper-IgM syndrome non X-linked
- Immunoglobulin heavy chain deficiency
- Immunoglobulin kappa light chain deficiency
- Selective IgG subclass deficiency with or without IgA deficiency
- Common variable immunodeficiency
- Selective IgA deficiency
- Transient hypogammaglobulinemia of infancy

Phagocytic disorders

- Neutropenias: severe congenital (Kostmann syndrome), cyclic
- Leukocyte adhesion defects (LAD I, LAD II)
- Chediak–Higashi syndrome
- Shwachman syndrome
- Chronic granulomatous disease X-linked and autosomal recessive
- Neutrophil glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Myeloperoxidase deficiency
- Hyperimmunoglobulin E syndrome

Complement deficiencies

- Classical pathway
  - C1q deficiency
  - C1r/s deficiency
  - C4 deficiency
  - C2 deficiency
- Alternative pathway
  - Factor D deficiency
- C3 and terminal components
  - C3 deficiency
  - C5 deficiency
  - C6 deficiency
  - C7 deficiency
  - C8 deficiency
  - C9 deficiency
- Control proteins
  - C1 inhibitor deficiency
  - C4 binding protein deficiency
  - Factor H deficiency
  - Factor I deficiency
  - Properdin deficiency

Table I. Continued

Immune deficiencies associated with other congenital/hereditary conditions

- Chromosomal defects
- Skeletal abnormalities
- Immunodeficiency with generalized growth retardation
- Dermatological defects
- Hereditary metabolic defects

with abnormal development of other lymphocyte lineages—B and NK cells. In the United States severe combined immunodeficiencies represent 5% of primary immune deficiencies; the overall frequency of these disorders is estimated to be 1 in 50,000 to 100,000 live births. Among combined immunodeficiencies the forms with most severe T-cell depletion are termed severe combined immunodeficiencies (SCID); the approximate division of the various types of SCID is shown in Table I.

Independently of the pathogenesis of particular disease entities, clinical presentation of combined immunodeficiencies is distinctive. An early onset of symptoms, such as neonatal sepsis, severe infections such as progressive interstitial pneumonia caused by opportunistic pathogens (*Pneumocystis (carinii) jiroveci*, Candida, cytomegalovirus, adenoviruses, RSV [respiratory syncytial virus]) and poor response to antibiotic therapy may point to this type of immunodeficiency. Among other manifestations, local and generalized complications can occur after administration of live bacterial (BCG [bacillus Calmette-Guerin]) and viral (polio) vaccines. Graft versus host disease resulting from transplacental passage of alloreactive maternal T lymphocytes may occur in SCID infants. Although usually asymptomatic, the maternal cells may cause skin rashes, increased liver enzymes, eosinophilia, and pancytopenia. Transfusions of unirradiated blood products invariably cause overwhelming proliferation of alloreactive T lymphocytes with rapidly fatal course. Other features in some patients include chronic hepatitis, sclerosing cholangitis, chronic encephalopathy, and cutaneous lesions such as severe eczema, alopecia, warts, and cellulitis.

A wide spectrum of oral manifestations may be present in children with combined immunodeficiencies; these disorders may exhibit an early onset, tendency to rapid rate of progression, and pertinacious, recurrent course. The most frequent findings involving oral mucosa are candidiasis and aphthous ulceration; predisposition to periodontal disease also may occur.[4] The mechanism underlying this association may be related to cytokine production dysregulation, and both tumor necrosis factor (TNF) and interleukin-1 (IL-1) have been impli-

Table II. Important oral and facial manifestations in primary immune deficiencies

Disease	*Oral and facial symptoms*
Ataxia-telangiectasia (AT)	Periodontal disease (4)
Chediak-Higashi syndrome (CHS)	Early-onset aggressive periodontitis, extensive loss of alveolar bone leading to tooth exfoliation (35) Increased tendency for postoperative bleeding (4) Severe gingivitis, ulcerations on the buccal mucosa, the tongue, and hard palate (3)
Chronic granulomatous disease (CGD)	Gingivitis, recurrent aphthous-like ulceration, prepubertal periodontitis (28,29,30)
Chronic mucocutaneous candidiasis (CMC)	Oral candidiasis
Common variable immunodeficiency (CVID)	Gingivitis and lichenoid lesions with Wickham striae, necrotizing ulcerative periodontitis (19)
Cyclic neutropenia	Mucosal ulcers, gingivitis, periodontal disease, aphthous lesions (38)
DiGeorge syndrome (DGS)	Dysmorphic face with hypertelorism, low and posteriorly settled auricles, short philtrum, thick and reflected lips, micrognathia (11) Cleft or arched palate (12) Delayed formation and eruption of permanent teeth, aberrant tooth shape, and enamel hypoplasia along with enamel hypocalcification (13) Dental caries with multiple active incipient caries lesions (14) Solitary median central incisors (15)
Griscelli syndrome type 2 (GS2)	Periodontal disease (29) Oral ulcers (40)
Hyper-Immunoglobulin (Ig)E syndrome (HIES)	"Double rows" of teeth due to primary teeth failure to exfoliate on the eruption of the permanent dentition (45) Chronic multifocal oral candidiasis (46,47) Angular cheilitis and recurrent aphthous ulceration (46) Mid-face anomalies and arched palate (44) Generalized aggressive periodontitis (48)
Hyper-IgM syndrome (HIGM)	Recurrent aphthous ulcers (4,5,6) Ulcers can begin to erode the gingiva and may mimic periodontal disease (4)
Leukocyte adhesion deficiency I (LAD I)	Severe progressive periodontitis with alveolar bone loss, periodontal pockets, and partial or total premature loss of the deciduous and permanent dentitions (34)
Selective IgA deficiency (sIGAD)	Periodontitis (16,17) Hyperplastic candidal infection (17)
Severe congenital agranulocytosis (Kostmann syndrome)	Severe gingival inflammation with apical abscesses and periodontitis with extensive bone loss (41,42,43)
Wiskott-Aldrich syndrome (WAS)	Gingivitis and periodontitis, petechiae in oral mucosa, and bleeding in the oral cavity (4)
X-linked agammaglobulinemia (XLA)	Necrotizing stomatitis (22)
X-linked anhydrotic ectodermal dysplasia with immunodeficiency (EDA-ID)	Adontia/hypodontia, delayed eruption of teeth and conical incisors (9)

Note. Numbers in parentheses are reference numbers.

cated; in addition, secondary humoral and neutrophil abnormalities in the setting of T-cell dysfunction may be involved. Therefore, the number of patients seen with advanced periodontal disease attributable to SCID is relatively small as they usually undergo curative treatment with hematopoietic stem cell transplantation at a young age before the development of advanced periodontal disease. The natural course of combined immunodeficiencies is severe with high mortality rates within the first years of life unless treated properly. Use of immune polyvalent gammaglobulins, *Pneumocystis (carinii) jiroveci* pneumonia prophylaxis, aggressive treatment of infectious episodes, and use of irradiated blood products are only a supportive therapy. Allogeneic hematopoietic stem cell transplantation may result in permanent cure with survival rate exceeding 90% if an HLA-identical family donor is available.

The immunodeficiencies with elevated immunoglobulin (Ig)M levels, hyper-IgM syndromes (HIGM), are characterized by profound hypoimmunoglobulinemia G, A, and E but normal or increased levels of IgM. The X-linked hyper-IgM syndrome type 1 is a result of a mutation of a T-cell ligand CD40L (CD154) that interacts with B-cell antigen CD40. This interaction induces the formation of memory B cells and facilitates isotype switching from IgM to IgG and IgA synthesis. Although the dominant feature in this syndrome is an antibody deficiency, this abnormality is secondary to an intrinsic T-lymphocyte defect resulting in lack of specific T-cell–mediated switch signal. CD40 molecule, in addition to its effect on B lymphocyte proliferation and differentiation, may play an important role in the functional responses of other cell types (including monocytes, thymic epithelial cells, and dendritic cells).

Hyper-IgM syndrome is associated with recurrent aphthous stomatitis; over time oral ulcers lead to erosion of the gingiva mimicking periodontal disease.[4] A predisposition to periodontal disease is in fact mild in this syndrome, and other features of the immunodefi-

ciency are dominant, such as recurrent purulent sinopulmonary infections, often caused by opportunistic pathogens, *Pneumocystis (carinii) jiroveci* and Cryptosporidium, as well as splenomegaly and lymphadenopathy. About two thirds of patients have neutropenia associated with oral and perirectal ulcers.[5,6] Neutropenia and trauma have been suggested to be responsible for recurrent oral ulceration; however, oral ulcers have also been found in relation to autoantibodies having cytopathic effect on mucosal antigens.[5]

An X-linked anhydrotic ectodermal dysplasia with immunodeficiency (EDA-ID) is a disorder with developmental and immunologic abnormalities caused by mutations in IKK gamma gene encoding nuclear factor kappaB essential modulator (NEMO/IKKgamma), a key regulatory subunit of IKB kinase that regulates activation of nuclear factor kappaB (NFkB), which plays an important role in T- and B-cell function.[7] Immunologic assessment shows hypogammaglobulinemia with low IgG concentration and variable IgA and IgM levels, normal lymphocyte subsets with impaired proliferative response, specific antibody production, and natural killer cell function.[8] Patients present with hypotrichosis, hypo- or anhydrosis, and dental abnormalities such as adontia/hypodontia, delayed eruption of teeth, and conical incisors.[9] They are also at increased risk of severe infections caused by pyogenic bacteria (such as sepsis, meningitis, pneumonia, infections of bones and soft tissues) and atypical mycobacteria.[10]

Other well-defined immunodeficiency syndromes

Significant T-cell disorders are also noted in other well-defined immunodeficiency syndromes. Wiskott-Aldrich syndrome (WAS), an X-linked disease, is characterized by a triad of symptoms: thrombocytopenia and abnormal small platelets, eczema, and recurrent infections. The product of the defective gene, WAS protein (WASP), contains well-defined domains with unique functions suggesting a critical role of this complex protein in signal transduction in hematopoietic cells and cytoskeletal reorganization by regulating actin polymerization. The WAS protein is expressed in all hematopoietic cells including CD34-positive stem cells, platelets, and lymphocytes including NK cells. In WASP-deficient peripheral blood macrophages, IgG-mediated phagocytosis is impaired. WASP also plays a role in apoptosis, which may be relevant to progressive immunodeficiency in WAS owing to T-cell depletion as a direct result of a defect in the cell death signaling pathway.

The prevalence of WAS in the United States is approximately 1 case per 250,000 births. Patients experience recurrent infections such as otitis media, pneumonias, urinary tract infections, and meningoencephalitis. Hemorrhagic diathesis occurs early in the infancy and is responsible for severe bleeding episodes; profound lymphopenia develops later in childhood. Wiskott-Aldrich syndrome is one of the disorders specifically associated with gingivitis and periodontitis; moreover, petechiae in oral mucosa and bleeding in the oral cavity may also be found.[4] In about 40% of WAS patients autoimmune diseases have been reported. The risk of malignant lymphoreticular neoplasia is also markedly increased; the most frequent malignancy is an Epstein Barr virus (EBV)-positive B-cell lymphoma, suggesting a direct relationship with the defective immune system.

In DiGeorge syndrome (DGS) (22q11 deletion syndrome), also described with an acronym CATCH22 (cardiac defect, abnormal facies, thymic hypoplasia, cleft palate, hypocalcemia), numerous abnormalities result from impaired embryogenesis of organs originating from the third and fourth branchial arches. This 22q deletion is one of the most common chromosomal abnormalities known with a frequency in the general population of approximately 1:4000 (in the United States the estimates range from 1:4000 to 1:6400). Clinical manifestations of the syndrome include hypoplasia of the thymus and parathyroid glands resulting in episodes of hypocalcemia, congenital cardiac malformation, particularly a conotruncal heart defect, and characteristic features such as dysmorphic face with hypertelorism, low and posteriorly settled auricles, short philtrum, and thick and reflected lips, as well as micrognathia.[11] Developmental abnormalities, including hypoplasia of the oropharynx or cleft or arched palate may also be observed.[12] Dental examination may reveal delayed formation and eruption of permanent teeth, aberrant tooth shape, and enamel hypoplasia, along with enamel hypocalcification.[13] A common oral health problem is dental caries with multiple active incipient caries lesions.[14] In patients with DiGeorge syndrome, such abnormality as solitary median central incisor may be seen.[15]

The immunodeficiency in DGS has been characterized as either partial (incomplete) form, occurring in 80% of patients, with a tendency for spontaneous immunocorrection within the first year of life, and complete form, observed in 20% of cases, with profound, progressive impairment of T-cell mediated immunity and impaired B-cell function. These severely affected subjects also have abnormalities in their T-cell repertoire, with T-cell receptor excision circles (TRECs), serving as a measure of newly emigrated thymic cells, significantly diminished. Functional antibody defects may also be noted, such as impaired antibody response to pneumococcal polysaccharide antigens, selective

IgA deficiency, and autoimmune antibodies. Patients suffer from pulmonary and gastrointestinal infections caused by viruses, invasive fungi, and *Pneumocystis (carinii) jiroveci*. Affected children presenting with both complete and incomplete forms of DiGeorge syndrome may experience the aforementioned orofacial and dental problems, with congenital heart malformation and immune deficiency significantly influencing their course.

Predominantly T-cell function impairment and assisting hypogammaglobulinemia is also noted in ataxia-telangiectasia (AT), a disease representative for the group of chromosomal breakage syndromes. The prevalence rate of AT is approximately 1 in 40,000 people in the United States. A mutation in the ataxia-telangiectasia gene (ATM), mapped to 11q chromosome, compromises DNA repair mechanisms and in this way renders the affected cells highly susceptible to radiation-induced chromosomal damage.[11] ATM is a sensor of double-strand breaks in DNA and transduces this information to enzymes involved in the repair of DNA damage and in cell cycle checkpoint control. In AT, defective mechanisms of DNA repair account for the unusual hypersensitivity to radiation resulting in reduced survival and increased levels of chromosomal aberrations. The chromosomal damage tends to occur in chromosomes 7 and 14 within immunoglobulin and T-cell receptor genes, pointing to a role of ATM protein in recognition and processing of DNA double-strand breaks during the ontogeny of T and B cells. A wide range of abnormalities involving both humoral and cellular immunity have been identified in AT patients. A marked decrease of IgA, IgG subclasses, and IgE along with impaired antibody response to protein and polysaccharide antigens are the most commonly reported humoral defects; T-cell function may be variably depressed. Clinical manifestations in AT include chronic sinopulmonary infections as a result of immunodeficiency as well as swallowing dysfunction and aspiration in advanced disease with cerebellar ataxia and neurodegeneration.

Profound dental caries and oropharyngeal candidiasis are frequent manifestations. Both DiGeorge syndrome and ataxia-telangiectasia may be associated with periodontal disease, although this predisposition is mild and it is infrequently a defining feature.[4]

An immunodeficiency disease, specifically associated with infection caused by Candida, is chronic mucocutaneous candidiasis (CMC). The impaired T-cell response to Candida is recognized as an underlying immune defect. Affected individuals suffer from infection localized to the oral cavity and other mucous membranes, skin and nail beds, and typically a coexisting endocrinopathy, particularly hypoparathyroidism. In one clinical variant of CMC, the autosomal recessive polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED), a mutation of AIRE (autoimmune regulator) gene has been identified. The proposed function of AIRE protein is to regulate expression of ectopic antigens (such as insulin, myelin basic protein) present on thymic medullary epithelial cells. In the absence of AIRE protein the potentially autoreactive thymocytes would not encounter the ectopic antigens and not be eliminated of the thymic population, predisposing to autoimmunity.

Predominantly antibody deficiencies

Antibody deficiencies are the most numerous of the primary immunodeficiencies. They can be divided into 3 categories:

1. Profound antibody deficiencies: X-linked agammaglobulinemia and related syndromes, common variable immunodeficiency, the hyper-IgM syndromes. These patients require immune globulin therapy.
2. Common but less severe antibody deficiencies: eg, transient hypogammaglobulinemia of infancy, IgG subclass deficiency. In these patients immune globulin therapy is rarely used.
3. Unusual and less severe antibody deficiencies: eg, Transcobalamin 2 deficiency, selective IgM deficiency.

The 2005 survey of primary immunodeficiencies conducted by the Jeffrey Modell Foundation in the United States reported selective IgA deficiency in 15.5%, IgG subclass deficiency in 8%, and transient hypogammaglobulinemia of infancy in 2% of patients. Antibody deficiencies are also present in the combined immunodeficiencies and in several specific immunodeficiency syndromes as well as in a number of genetic syndromes (termed syndromic immunodeficiencies) and in secondary immunodeficiencies (malignancy, malnutrition, protein loss, chemotherapy).

Selective IgA deficiency (sIGAD) is the most common primary immunodeficiency in the Caucasian race; it appears in Europe with a frequency of 1:500 to 1:700 live births, in the United States its prevalence ranges from 1 in 223 to 1000 persons. The serum IgA level used to establish the diagnosis of IgA deficiency is 5 mg/dL or lower.[7] The clinical course of this immune deficiency may be asymptomatic, particularly in partial IgA deficiency in which production of secretory IgA may be unimpaired. Complete IgA deficiency with a lack of IgA2 subclass enhances penetration of allergens and antigens in the respiratory and gastrointestinal tract. This form of the disease may be associated with recurrent bacterial and viral sinopulmonary, gastroin-

testinal, and cutaneous infections; the risk of allergies and development of autoimmunity (rheumatoid arthritis, endocrinopathies, myasthenia, diabetes mellitus, thrombocytopenia) is also increased. In about 20% to 30% of patients, IgG subclass deficiency may coexist. A fundamental defect in IgA deficiency is the failure of IgA-bearing lymphocyte to mature to IgA-secreting plasma cells. The circulating B cells have an immature phenotype with positive IgM and IgD. The failure of terminal B-cell differentiation has been attributed to both defective T-helper cells and IgA-specific T-cell suppressors, as well as to intrinsic B-cell defect or cytokine skewing and receptor abnormalities.

The role of salivary IgA in local immune response, and the question of whether IgA-deficient patients have an increased risk of aggressive periodontitis as a result of decreased oral secretory immunity has yet to be elucidated.[16,17] Clinical studies show contradictory results, indicating both a predisposition to oral diseases such as hyperplastic candidal infection,[17] and no increased susceptibility either to periodontitis or recurrent aphthous ulceration.[18]

Common variable immunodeficiency (CVID) is a clinically heterogeneous disorder characterized by hypogammaglobulinemia, impaired antibody response despite the presence of B cells, and normal (or near-normal) T-cell immunity. CVID is the most common form of severe antibody deficiency. In the United States its incidence lies between 1:25,000 and 1:50,000 and the international prevalence is similar to that in the United States. CVID does not show a predilection for any race and equally affects males and females. Either a single genetic or precise molecular defect resulting in the disease has not been identified. Pathogenesis of CVID is associated with wide variety of B- and T-cell abnormalities. Despite normal numbers of mature B lymphocytes in the peripheral blood and lymphoid tissue, they show various defects of differentiation into immunoglobulin-secreting plasma cells, including defects in expression of the B cell co-receptor CD27 and CD134 ligand, phenotypic characteristics of immature B lymphocytes with lack of somatic hypermutation, deficient numbers and activation of memory B cells, and a severe deficiency of switched memory B cells. Some CVID patients have associated T-cell defects (decreased numbers of CD4 lymphocytes and reduced CD4:CD8 ratio, lack of antigen-specific T cells and reduced T-cell receptor repertoire, accelerated T-cell death). Monocyte/macrophage defects have also been identified in CVID, and monocyte activation may be involved in the pathogenesis of chronic inflammatory and granulomatous complications.

Clinical manifestation of CVID includes recurrent bacterial respiratory infections, resulting in rapid development of bronchiectasis, gastrointestinal symptoms (malabsorption syndrome, recurrent giardiasis, splenomegaly), as well as lymphadenopathy. Affected individuals are at high risk of development of malignancies—particularly lymphomas and gastric adenocarcinomas, and of autoimmune diseases (cytopenias, Crohn-like enteritis, arthritis).

Oral manifestations may include gingivitis and lichenoid lesions with Wickham striae. Necrotizing ulcerative periodontitis has also been described in patients with CVID and its course correlated with a patient's systemic condition during immunoglobulin therapy.[19] Concomitant autoimmune processes may also manifest with oral lesions.[20,21]

X-linked agammaglobulinemia (XLA) is characterized by a profound deficiency of all isotypes of immunoglobulins, mature B cells, and plasma cells secondary to mutation in Btk (Bruton's tyrosine kinase) gene, which maps to the long arm of the X chromosome. Btk is representative of the Tec family of nonreceptor tyrosine kinases and plays an important role in pre-B- and B-cell receptor–dependent signaling. Its defect interferes progressively at several points of B lymphocyte development, with both pre-B-cell expansion and mature B-cell survival and activation. Btk-deficient cell populations fail to proliferate and undergo apoptosis.

Bacterial infections usually caused by pyogenic encapsulated bacteria are the most common clinical manifestation of XLA; these patients are also unusually susceptible to enteroviral infection of the gastrointestinal tract and secondary spread to central nervous system. Abnormalities in physical examination directly related to agammaglobulinemia include markedly hypoplastic lymphatic tissue normally rich in B lymphocytes (tonsils, adenoids, lymph nodes).

There are reports concerning patients with common variable immunodeficiency and X-linked agammaglobulinemia presenting with a type of necrotizing stomatitis in which clinical patterns appear distinct from the periodontal forms of the disease. These lesions yield bacterial cultures positive with *Pseudomonas aeruginosa*, so it may be assumed that this pathogen may be responsible for selected necrotizing lesions with a clinical presentation differing from that seen in typical necrotizing periodontal disease.[22] Moreover, this condition may represent the intraoral counterpart of ecthyma gangrenosum.[23-25]

Phagocytic disorders

Functional and quantitative disorders of phagocytic cells result in recurrent infections, most frequently caused by bacteria and fungi, localized in the respiratory tract, subcutaneous tissue, skin, mucous membranes, and lymph nodes. An extremely severe course

of infection, caused by common microorganisms, with predisposition to abscesses and granuloma formation, as well as poor wound healing is a hallmark of this group of immune deficiencies. A defect at any step of neutralization of pathogens by phagocytic cells due to altered cell function or quantitative defect also leads to high risk of periodontal disease.[26] On the other hand, in experimental studies the role of neutrophils in pathogenesis of periodontitis and expression of inflammatory molecules (IL-1beta, TNFalpha, IL-8) has been shown.[27]

Chronic granulomatous disease (CGD) is a genetically heterogeneous disorder with 4 closely related genetic defects and 2 different inheritance patterns, resulting in defects in the NADPH oxidase that are involved in the pathogenesis and determination of the phenotype. The most common genotype, an X-linked CGD, accounts for about 70% of cases, and involves mutations in gp91phox (CYBB gene), composing the chain of the cytochrome b558 in the phagocyte vacuole membrane, an enzymatic unit of NADPH oxidase. Autosomal recessive CGD caused by mutations of a smaller membrane cytochrome subunit, p22phox (CYBA gene on 16q chromosome), accounts for approximately 5% of cases. Other forms of autosomal recessive CGD comprise defects of cytosolic components of NADPH oxidase, including p47phox (NCF1 gene on 7q chromosome) responsible for 25% cases, and p67phox (NCF2 gene on 1q chromosome) accounting for less than 5% of cases. After cell activation, the cytosolic components translocate to the cytochrome resulting in an active NADPH oxidase complex. Impaired formation of an active NADPH oxidase complex leads to a defective production of reactive oxygen metabolites in phagocytic cells, particularly neutrophils, and are indispensable for extracellular killing of ingested microorganisms. Failure of production of superoxide anion, singlet oxygen, and hydrogen peroxide occurs as a result of impaired respiratory burst upon activation of the hexose monophosphate shunt pathway during phagocytosis. Recurrent infections involving skin; mucous membranes; lymph nodes; and deep abscesses localized in liver, brain, and lungs; as well as anorectal abscesses, tendency for granulomas formation in the gastrointestinal and genitourinary tracts are characteristic of this immunodeficiency. The infective microorganisms are usually catalase producing, such as *Staphylococcus aureus*; infections caused by *Escherichia coli*, *Serratia*, or *Pseudomonas aeruginosa*, as well as by invasive fungi, including *Candida* and *Aspergillus*, may also occur. Patients with chronic granulomatous disease present with significant gingivitis and may develop recurrent aphthous-like ulceration of the oral mucosal membranes. Prepubertal periodontitis has also been reported.[28-30]

Recurrent severe bacterial infections involving soft tissues are observed in patients with leukocyte adhesion deficiency (LAD). A hallmark of LAD I syndrome is omphalitis in the newborn period and delayed separation of the umbilical cord. Also, impaired wound healing, as well as recurrent widespread pyogenic infections, are seen in LAD.[11] In LAD I, pathogenesis is related to a defect in beta chain (CD18) common for all beta2-integrins (CD11/CD18 complex). Lack of integrin CD11/CD18 receptor complex on neutrophil surface results in impairment in their adhesion to the endothelium and migration from the vascular bed to the site of infection.[4] In patients with a milder form of LAD I, in which there is residual expression of CD18, clinical features include severe progressive periodontitis with alveolar bone loss, periodontal pockets, and partial or total premature loss of the deciduous and permanent dentitions.[31] LAD II syndrome is dependent on defective fucose metabolism leading to the lack of fucosylated sialyl-LewisX ligand for selectins, which play a role in neutrophil adhesion to the endothelium, particularly in the first phase of this process (leukocyte rolling).[32-34]

Neutropenia, impaired neutrophil chemotaxis, and NK cell activity, as well as defective intracellular killing are the most important immune abnormalities recognized in Chediak-Higashi syndrome (CHS). Patients experience recurrent severe bacterial infections, neurological involvement (epilepsia, psychomotor regression, peripheral neuropathy), hypopigmentation, and development of hematological accelerated phase of the disease, manifesting with fever, hepatosplenomegaly, lymphadenopathy, pancytopenia, and lymphohistiocytic infiltrations in different organs. In Chediak-Higashi syndrome, a mutation of the gene coding for LYST protein results in impaired membrane fusion and intracellular granule transporting. As a consequence, neutrophils, basophils, eosinophils, and other granule-containing cells, including lymphocytes, mast cells, thrombocytes, Schwann cells, and neutrocytes, are characterized by giant organelles built up from fused primary granules.

In Griscelli syndrome type 2 (GS2) a clinical appearance similar to that seen Chediak-Higashi syndrome occurs with recurrent infections, neuropathy, and hypopigmentation, as well as development of accelerated phase and hemophagocytic syndrome. A mutation of Rab27A gene, coding for GTPase playing a role in membrane transporting, its docking and fusion particularly in melanocytes and in lymphocytes leads to impaired activity of cytotoxic T lymphocytes and immunological disorders presenting as generalized lymphohistiocytosis.

These aforementioned intrinsic neutrophil defects (LAD I, LAD II, CHS, GS2) predispose patients to periodontal disease.[29] Reports of Chediak-Higashi patients indicate for early-onset aggressive periodontitis, accompanied by extensive loss of alveolar bone leading to tooth exfoliation.[35] In subgingival plaque samples, bacteria often associated with periodontitis may be detected, including *Fusobacterium, Campylobacter, Prevotella, Peptostreptococcus, and Clostridium*. Moreover, massive bacterial invasion of epithelium and connective tissue may be revealed in microscopic examination.[36,37] Severe gingivitis as well as ulcerations of the buccal mucosa, tongue, and hard palate are also common findings in the disorder.[3,38,39] In rare cases of patients with Griscelli syndrome type 2 and clinical manifestation of hematological accelerated phase of the disease with hemophagocytic syndrome, oral ulcers have been observed.[40]

Quantitative neutrophil defects include congenital neutropenias resulting from arrested maturation during myelopoiesis wherein myeloid stem cells are present in the bone marrow, but rarely differentiate beyond the promyelocyte stage. In severe congenital agranulocytosis (Kostmann syndrome) the course of the disease may be fulminant, with sepsis and endotoxic shock, or it may manifest as recurrent infections of the respiratory tract, as well as skin and mucous membranes. Cyclic neutropenia is characterized by regularly recurrent episodes of neutropenia at average intervals of 21 days owing to a defect in the pluripotent stem cell maturation process. In Shwachman syndrome, enzymatic insufficiency of the pancreas coexists with bone marrow insufficiency leading to neutropenia; moreover, neutrophils exhibit defective chemotaxis and intracellular killing. Congenital agranulocytosis is usually associated with complete absence of peripheral granulocytes, and in cyclic neutropenia, there are cyclical episodes where neutrophil counts are diminished. Decrease of the circulating neutrophil count has the potential of contributing to rapidly destructive periodontal disease; particularly, patients with Kostmann syndrome experience severe gingival inflammation with apical abscesses and periodontitis with extensive bone loss.[41-43] Moreover, in patients with cyclic neutropenia, oral findings include mucosal ulcers, gingivitis, and aphthous-like lesions.[38]

Hyper-immunoglobulin E syndrome (HIES) (Job's syndrome) is an immunodeficiency manifesting with a constellation of abnormalities in the immune, skeletal, and dental systems, as well as connective tissue. Neither the precise host genetic defect nor the fundamental pathogenesis of the disease has been found. The defect in some patients with an apparent autosomal dominant inheritance has been mapped to chromosome 4, but the candidate gene has not been identified precisely. In HIES, because of the apparent abnormal regulation of IgE synthesis, excessive production of IL-4 or failure to produce interferon (IFN) gamma and TNFalpha have been proposed. These abnormalities may be due to a T-cell defect with Th1/Th2 lymphocyte imbalance and cytokine dysregulation. Recently, in a group of patients with autosomal dominant HIES, a mutation in transcription factor STAT3 (signal transducer and activator of transcription) has been noted and a protein tyrosine kinase (TYK-2) mutation has been identified in few patients with the autosomal recessive form of the disease.

A clinical triad of symptoms found in about 75% of cases in autosomal dominant type hyper-IgE syndrome includes recurrent abscesses localized in skin, subcutaneous tissue, and deep organs such as lungs, bones, joints, and lymph nodes; recurrent airway infections; and increased concentration of total IgE in serum. This finding is a hallmark of the syndrome, yet the importance of increased value of IgE remains unexplained; moreover, in the course of the disease, fluctuations of IgE concentration may be observed and they do not correlate with clinical manifestations and severity of infection.[44] A specific immune defect invariably present in all patients with hyper-IgE syndrome has not been identified; hence, there is an absence of one characteristic diagnostic parameter. Heterogeneous disorders of the immune system may be revealed, including a decreased number of CD8 T-lymphocytes, an impaired response of lymph cells to antigenic and alloantigenic stimulation, with the most frequently recognized and the most characteristic abnormality being defective neutrophil chemotaxis. Dental abnormalities in patients with hyper-IgE syndrome often appear as "double rows" of teeth owing to the failure of primary teeth to exfoliate on the eruption of the permanent dentition.[45] Permanent teeth development and eruption usually occur on time[44]; however, in other cases, failure of primary dentition to exfoliate may result in delayed eruption of the permanent teeth.[45] The causes of primary teeth resorption failure or delay is still unknown; however, they may involve cytokine activation of osteoclasts, macrophages, or both.[39] Also, an abnormal persistence of Hertwig's epithelial root sheath on the roots of primary teeth as well as several Malassez epithelial rests located in the periodontal ligament were suggested to have some association with delayed resorption of primary teeth roots.[46] Timely intervention and elective extractions of primary teeth are frequently necessary to allow normal eruption of permanent teeth. A consistent feature of hyper-IgE syndrome is a chronic multifocal oral candidiasis.[46,47] Also, changes such as angular cheilitis and recurrent aphthous ulceration are seen in patients with hyper-IgE syndrome.[46] In a num-

ber of affected individuals, mid-face anomalies and arched palate are observed.[44] In the less frequently occurring autosomal recessive type of hyper-IgE syndrome, severe, pharmacotherapy-resistant viral and mycotic infections predominate in its clinical presentation, as well as characteristic neurological complications such as partial paresis of the facial nerve or hemiparesis. In the autosomal recessive form of the disease, skeletal abnormalities, pathological bone fractures, dental disorders, or characteristic facial features do not occur. Generalized aggressive periodontitis in a pediatric patient with this immune deficiency has been reported.[48]

Complement deficiencies

The clinical expressions of complement deficiencies include an increased susceptibility to infection, rheumatic disease, and angioedema. The kinds of microorganisms that most commonly cause infection in a specific complement deficiency, reflect the biologic function of the missing component. In C3 (an important opsonin) deficiency or in a deficiency of a component in the pathways necessary for the activation of C3, patients have an increased susceptibility to infections with encapsulated bacteria (eg, *Haemophilus influenzae*, *Streptococcus pneumoniae*) for which opsonization is the primary host defense. Patients with deficiencies of C1, C4, or C2 have a lower prevalence of infection than seen in patients with C3 deficiency, because their alternative pathway is intact and able to activate C3. The terminal components, C5 to C9, form the membrane attack complex and are therefore responsible for the bactericidal and bacteriolytic functions of complement. Patients with deficiencies of C5 to C9 can opsonize bacteria normally because they possess C3 and the components necessary for its activation. These patients are, however, markedly susceptible to *Neisseria* species, because serum bactericidal activity is an important host defense mechanism against these microorganisms.

The pathophysiologic basis for the development of rheumatic disorders in patients with complement deficiencies may be related to a number of different functions of the complement system: host defense against viral infections, generation and expression of an adequate antibody response, and the clearance of the apoptotic cells. The rheumatic diseases seen in complement-deficient patients include systemic lupus erythematosus (SLE), scleroderma, dermatomyositis, vasculitis, and membranoproliferative glomerulonephritis. The strongest known genetic risk factor for SLE is C1q deficiency.

An inhibitor of active C1 (C1 INH) is grossly lacking in hereditary angioedema and this can lead to recurrent episodes of circumscribed noninflammatory edema comprising lips, tongue, soft palate, and larynx, mediated by a vasoactive C2 fragment. In patients with type I C1 INH deficiency, the diagnosis can be established easily by demonstrating a decrease in serum C1 INH protein when assessed with immunohistochemical technique. In patients with type II C1 INH deficiency, the diagnosis rests on demonstrating a decrease in C1 INH functional activity.

Human autoinflammatory diseases

Human autoinflammatory diseases are a heterogeneous group of pathologies characterized by seemingly unprovoked inflammation in the absence of autoimmune or infective causes.[49,50] These processes may be classified into 2 categories:

1. Hereditary: autosomal dominant TNF superfamily 1A-associated periodic syndrome (TRAPS), autosomal recessive familial Mediterranean fever (FMF), hyper-IgD syndrome (HIDS), Muckle-Wells syndrome, and familial cold urticaria.
2. Non-hereditary: periodic fever, aphthous stomatitis, pharyngitis, adenopathy syndrome (PFAPA, Marshall's syndrome), chronic infantile neurological, cutaneous, and articular syndrome (CINCA).[51]

All of these syndromes share an intermittent expression in the form of acute attacks of fever associated with serosal, synovial, and cutaneous inflammation. The most severe complication related to TRAPS and FMF is amyloidosis. Among these autoinflammatory diseases, PFAPA invariably manifests with recurrent episodes of aphthous stomatitis[52-57]; nevertheless, symptoms suggestive of periodic fever, aphthous stomatitis, and adenopathy syndrome, with coexisting conjunctivitis have been noted in a patient diagnosed with TRAPS.[58] In contrast, oral lesions are not a part of clinical course of hyper-IgD syndrome owing to mevalonate kinase deficiency.[59]

DENTAL MANAGEMENT OF PATIENTS WITH SUSPECTED OR DIAGNOSED PRIMARY IMMUNE DEFICIENCIES

As described by Atkinson et al.,[39] a dentist should suspect a patient may have an undiagnosed primary immune deficiency disorder when:

- The child presents with a history of atypically severe, recurrent, or persistent infections, and/or failure to thrive. As a general basis for comparison, children with normal immune functions have an average of 6 to 8 respiratory infections per year for the first 10 years of life, and up to 6 cases of otitis and 2 cases of gastroenteritis per year for the first 2 to 3 years. They may have more if they stay in child care centers or have older siblings.

- The child presents with oral complications that might signal abnormal immune functions including prepubertal periodontitis, persistent candidiasis, and herpetic infections, as well as prolonged or unusual dental infections.

For patients diagnosed with a primary immune deficiency disorder, special precautions and considerations relating to their dental treatment, as described by Atkinson et al.,[39] are outlined as follows.

- Predental treatment evaluation of the patient with a primary immune deficiency disorder includes a comprehensive medical history that includes information regarding recent hospitalizations, infections, and medications. Also, the results of a current complete blood cell count with white cell differential and platelet count need to be evaluated before initiating most invasive dental procedures. Consultation by the dentist or hygienist with the physician(s) managing the immunodeficient patient regarding the patient's oral/dental diagnosis and procedures planned for the patient is also essential.
- Aggressive preventive dental care including oral hygiene instructions, nutritional counseling, and fluoride gel applications can maintain oral health and may help avoid the need for invasive dental procedures in the future.
- Pre- and postprocedural antibiotic prophylaxis often is indicated to prevent local (oral) and systemic infections that may arise secondary to invasive dental treatment. This is particularly important because bacteremias from dental procedures could be fatal to these patients. Because many patients with a primary immune deficiency disorder are maintained on continuous antibiotic therapy that permits the selection and growth of antibiotic-resistant oral organisms; prophylaxis with antibiotics from another pharmacologic class other than the one currently being used for the patient may be necessary. Consultation with infectious disease specialists can help dental clinicians select alternative antibiotics to use for perioperative prophylaxis for invasive dental procedures.
- Appropriate diagnosis and aggressive treatment of oral soft-tissue infections is essential in a patient with a primary immune deficiency disorder. Both the risk of infections in general, and the risk of infections caused by opportunistic organisms are increased in the immunodeficient patient. Therefore, viral, fungal, and bacterial cultures are often needed to establish the causative agent of oral infections, ulcerations, and lesions, and to help ascertain the appropriate treatment. For example, herpetic infections of oral soft tissues in an immunocompromised host can resemble major aphthous stomatitis, Also, higher concentrations of the antiviral agent acyclovir are usually needed to effectively treat herpes zoster as compared with herpes simplex. Antibiotic sensitivity/susceptibly testing is also recommended for patients with a primary immune deficiency disorder with an orodental bacterial infection because of the increased risk of infection by antibiotic-resistant organisms.

CONCLUSIONS

This article has outlined the most frequently occurring primary immune deficiency disorders in children along with their etiology and clinical presentation, as well as highlighted the associated orodental manifestations and complications of these disorders.

It is important that the dentist be able to identify and differentiate various oral lesions and abnormalities that may signal a previously undiagnosed primary immune deficiency disorders from those that are not associated with any concurrent, underlying systemic disease or associated health problem.

Equally important, the dentist must recognize, address, and implement the special management considerations and precautions needed to ensure the safe dental treatment of a patient with a primary immune deficiency disorder, as well as safeguard the health of the oral cavity in these patients.

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Reprint requests:

Aleksandra Szczawinska-Poplonyk, MD, PhD
Department of Pediatric Pneumonology, Allergology and Clinical Immunology
III Chair of Pediatrics
Karol Marcinkowski University of Medical Sciences
27/33 Szpitalna Street
60-572 Poznan, Poland
ola@malwa.com.pl