Oral manifestations of primary and acquired immunodeficiency diseases in children

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Abstract
Immunodeficiency diseases in children can have significant oral manifestations. Oral changes appear to depend on the nature of the host defect. Children with IgA deficiency and hypogammaglobulinemia do not demonstrate severe oral pathology or abnormalities in craniofacial development. Phagocytic cell defects are associated with mucosal lesions or rapidly progressive forms of periodontal disease. Candidiasis, recurrent aphthous ulceration, and herpes simplex infections are reported frequently in children with T-cell and combined immunodeficiency disorders. Oral changes in pediatric acquired immunodeficiency syndrome are similar to those seen in patients with primary phagocytic cell and T-cell defects, and can also include parotitis and severe gingivitis. In addition, human immunodeficiency virus infection in utero can produce an embryopathy with craniofacial abnormalities.

Immune defects in children, whether caused by primary immunodeficiency, by human immunodeficiency virus (HIV) infection, or by immunosuppressive therapy, have profound effects on the oral tissues. In general, infection is the major cause of morbidity and mortality in these patients. Oral infections are caused by organisms that normally are either nonpathogens or are a minor component of the oral microflora. Moreover, septicemia from an oral focus can cause a life-threatening infection in the immunocompromised host. This review will examine the oral features and dental management of children and young adults with primary and acquired immunodeficiency diseases.

Primary Immunodeficiencies
Primary immune disorders considered here include B-cell defects (selective IgA deficiency, hypogammaglobulinemia), T-cell defects (mucocutaneous candidiasis, DiGeorge's syndrome), combined immunodeficiency diseases (severe combined immunodeficiency, Nezelof's syndrome, ataxia-telangiectasia, Wiskott-Aldrich syndrome) and phagocytic cell defects. Immunological and clinical features of these diseases have been reviewed in detail by Ammann (1984), Ammann and Wara (1975), and Buckley (1986). Immune disorders are separated by system for purposes of discussion; however, defects in one immune system may have major consequences for other systems.

Selective IgA deficiency is the most common disorder of the immune system, and estimates of prevalence range from 1 in 200 to 1 in 800. IgA levels are less than 5 mg/dL, but other immunoglobulins are usually normal or may be increased, and cell-mediated immunity is normal. These patients show an increased incidence of sinopulmonary infection and may have an associated immunoglobulin subclass deficiency in IgG2 and/or IgG4. Treatment is primarily symptomatic, and gamma-globulin therapy generally is contraindicated. Patients with X-linked hypogammaglobulinemia show symptoms of recurrent infections at an early age, an absence of B cells in peripheral blood, IgG levels less than 200 mg/dL, and low to absent levels of IgM, IgA, IgD, and IgE. The clinical features of acquired hypogammaglobulinemia (common, variable immunodeficiency) are similar to those of X-linked hypogammaglobulinemia; however, B-cell numbers usually are normal. Total immunoglobulins are less than 250 mg/dL. Both X-linked and acquired hypogammaglobulinemia respond well to gamma-globulin treatment.

Chronic mucocutaneous candidiasis is a syndrome of skin and mucous membrane infection which may be associated with absent lymphocyte proliferation to Candida antigens, absent or delayed hypersensitivity skin test response to Candida antigens, impaired macrophage function and, in some studies, neutrophil chemotactic defects. Multiple endocrinopathies also...
may be present. The infecting agent is usually *Candida albicans*. B-cell function and antibody response to *C. albicans* typically are normal. Oral candidiasis and other oral mucosal lesions are a consistent feature of the disease. Candidiasis also can be a feature of DiGeorge’s syndrome (congenital thymic aplasia). This syndrome includes abnormal facies, hypoparathyroidism, congenital heart disease, aplasia or hypoplasia of the thymus, decreased numbers of T cells, and absent T-cell function in peripheral blood. Thymus transplantation and/or thymic factor therapy have been successful in prolonging survival.

**Severe combined immunodeficiency disease** is inherited in X-linked recessive or autosomal recessive forms and may be characterized by absence of both T-cell and B-cell function, resulting in susceptibility to infection by any opportunistic organisms. Combined immunodeficiency associated with the absence of the purine pathway enzymes adenosine deaminase and nucleoside phosphorylase is usually less severe, both clinically and immunologically. In the past, combined-immunodeficient patients rarely survived more than 1 year of age. Bone marrow transplantation has been successful in establishing some immunocompetence and offers promise for an improved prognosis. Nezelof’s syndrome includes a diverse group of immunodeficient patients who exhibit the sequelae of a variety of viral, bacterial, fungal, and protozoal infections but do not show the specific clinical symptoms or enzyme defects characteristic of other combined immunodeficiency diseases. These patients have depressed T-cell function, but serum levels and function of the immunoglobulin classes are highly variable. Many patients formerly classified in this category have adenosine deaminase or nucleoside phosphorylase deficiencies.

**Immunodeficiency with ataxia-telangiectasia** is an autosomal recessive disorder associated with progressive cerebellar dysfunction resulting in ataxia, slurred speech and nystagmus; telangiectasia involving the bulbar conjunctivae, nose, ears, perioral area, and other skin surfaces; recurrent sinopulmonary infections; and, in about 70% of cases, selective IgA deficiency, which may be associated with IgG deficiency. Increased chromosomal breakage as well as abnormal DNA repair following irradiation may be associated with the observed incidence of lymphoma in these patients. Although careful supportive treatment has prolonged survival, definitive therapy has not been established. **Wiskott-Aldrich syndrome** is an X-linked recessive immunodeficiency consisting of eczema, thrombocytopenia, and recurrent infections. Serum antibody patterns show low IgM levels and elevated levels of IgA and IgE. Bone marrow transplantation is under study in the management of these patients, but treatment approaches are not well defined.

A number of phagocytic dysfunction diseases have been described. Clinical effects of phagocytic cell defects range from mild skin infections to life-threatening systemic infections. **X-linked chronic granulomatous disease** is a severe form of phagocytic dysfunction. It usually is detected before 2 years of age, based on marked lymphadenopathy, hepatosplenomegaly, chronic draining lymph nodes, and susceptibility to infections caused particularly by organisms normally of low virulence which have in common catalase positivity. Nonspecific references to oral stomatitis is common to most case reports. Other symptoms include rhinitis, osteomyelitis, and chronic diarrhea. Mothers and sisters of affected boys may also show abnormal neutrophil metabolism. However, the neutrophil defect of female carriers is much less profound, in vitro, than that of boys with chronic granulomatous disease, and unusual susceptibility to infections is uncommon.

**Acquired Immunodeficiency Syndrome (AIDS) in Children**

Human immunodeficiency virus infection has been identified in increasing numbers of children with otherwise unexplained immune deficiency and opportunistic infections of the type found in adults with AIDS. For the limited purposes of epidemiologic surveillance, the Centers for Disease Control (CDC) characterize a case of pediatric HIV infection as a reliably diagnosed disease in children that is at least moderately indicative of underlying cellular immunodeficiency, and with which no known cause of underlying cellular immunodeficiency or any other reduced resistance is reported to be associated.

A recent CDC report (1986) described 231 AIDS patients under 13 years old, 59% of whom had died. Nineteen per cent were white, 60% black, and 20% Hispanic. Fifty-five per cent were male. Fifty-eight per cent were diagnosed with *Pneumocystis carinii* pneumonia; 19% with disseminated cytomegalovirus; 15% with candidal esophagitis; 6% with cryptosporidiosis; 4% with Kaposi’s sarcoma; and 22% with other opportunistic diseases. One hundred seventy-four (75%) pediatric patients came from families in which 1 or both parents had AIDS or were at increased risk for developing AIDS; 33 (14%) had received transfusions of blood or blood components before onset of illness, and 11 (5%) had hemophilia. Risk-factor information on the parents of the 13 (6%) remaining patients is incomplete.

The risk factors for pediatric HIV infection vary depending on the age group. Most children with AIDS are under 5 years of age. The primary risk factors are perinatal. Infants born to women who are intrave-

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1 Ammann 1985; Oleske et al. 1983; Shannon and Ammann 1985.
ous drug users or who have bisexual partners comprise the largest group. Clinical abnormalities are often present by age 3 months but may also be a late manifestation of the syndrome. About a third of the infants weigh less than 2500 g at birth and are small for gestational age. Most of the cases occur in metropolitan areas in which HIV infection is prevalent among adults. Vertical transmission from mother to infant occurs most likely during gestation (Scott et al. 1985). In addition, children exposed to blood products donated by persons at risk for HIV infection (prior to HIV screening tests) and children receiving regular infusions of lyophilized concentrates are also at risk.9 In the 5- to 13-year-old age group, hemophilia poses the most significant risk.

The first clinical signs of HIV infection in infants and children may include 1 or more of the following: failure to thrive, hepatosplenomegaly, diarrhea, interstitial pneumonitis, lymphadenopathy, oral candidiasis, and recurrent infections. In addition, significant neurological disease has recently been reported in children with HIV infection.4 In childhood, a progressive encephalopathy with loss of motor and intellectual milestones and prominent cortical atrophy has been observed (Epstein et al. 1985). The impact that this neurotropic virus has on the developing nervous system of high risk infants is unknown.

A recent report (Marion et al. 1986) described an HIV embryopathy that includes prominent forehead, flat nasal bridge, short nose with flattened columna, hypertelorism, long palpebral fissures with an upward slant, prominent triangular filtrum, growth failure with microcephaly, and a prominent upper lip with a patulous vermilion border. Some of these features are very similar to those of the fetal alcohol syndrome and DiGeorge’s syndrome, both of which are thought to develop secondary to an insult early in pregnancy.

**Oral Features of Immune Deficiency Diseases**

In general, the oral consequences of immunodeficiency diseases appear to depend on the nature of the host defect. Primary immune disorders of the B-cell system, particularly selective IgA deficiency and hypogammaglobulinemia, have not been associated with oral or craniofacial pathology (Robertson et al. 1978; Robertson et al. 1980). In contrast, severe oral changes are common in patients with phagocytic cell defects, T-cell defects (muco-cutaneous candidiasis, DiGeorge’s syndrome), and combined immunodeficiency diseases (severe combined immunodeficiency, Nezelof’s syndrome, ataxia-telangiectasia, Wiskott-Aldrich syndrome). Phagocytic defects characteristic of chronic granulomatous disease may result in severe gingivostomatitis, and Van Dyke (1984) has reviewed a growing body of evidence which suggests that periodontal diseases, particularly juvenile periodontitis, are associated with a reduction in number or function of circulating neutrophils.

Oral changes in T-cell and combined immune disease include oral and esophageal candidiasis, herpes simplex virus (HSV) infection, severe periodontal pathology, and recurrent aphthous ulceration (RAU) (Ammann 1984). Robertson et al. (1978) observed severe mucosal erythema in a patient with chronic mucocutaneous candidiasis. Moyer et al. (1983) reported dental findings in 2 children with severe combined immunodeficiency. The first child developed extensive carious lesions. The second child had oral and gingival infections which, the authors suggest, ultimately led to the patient’s demise. Leggott et al. (1986) recently reported abnormal eruption patterns in 4 patients with combined immunodeficiency.

The oral changes associated with HIV infection in children are similar to those seen in patients with primary T-cell and phagocytic cell defects. In addition to candidiasis, RAU, and HSV, oral lesions seen in HIV patients or in members of the risk groups may include severe gingivitis and parotitis.9

**Candidiasis**

Candidiasis, usually associated with *C. albicans*, is the most common oral lesion affecting patients with immune deficiency diseases. The use of oral *Candida* culture is of questionable value in the diagnosis of the disease since the prevalence of the carrier state has not been firmly established, although estimates range from 30 to 50% (Hornstein et al. 1979). The organism may occur as a commensal in the mouth and in other parts of the respiratory, gastrointestinal, and genitourinary tracts and can be isolated from saliva or from mucosal scrapings. In the neonate, however, the presence of *Candida* in a smear is regarded as being suggestive or even diagnostic of candidiasis.

Oral candidiasis has been divided into 4 general types—pseudomembranous, atrophic, chronic hyperplastic, and angular cheilitis—based on clinical and immunological evidence (Wells 1970, 1972). Chronic oral candidiasis and chronic mucocutaneous candidiasis may be features of all primary disorders of cellular immunity. *Pseudomembranous candidiasis*...
(thrush) is characterized by the presence of creamy white or yellowish plaques on the oral mucosa, which may or may not appear fiery red. Upon scraping, the white plaques can be removed, leaving a bleeding surface. This type of candidiasis may involve any part of the oral mucosa, but most often affects the buccal and labial mucosa, tongue, and hard and soft palate. 

Atrophic candidiasis appears clinically as a red lesion only, and, when located on the tongue, is associated with the loss of papillae. The common locations are the palate and dorsum of the tongue. Atrophic candidiasis may be acute or chronic, but when associated with HIV infection it is usually chronic. Atrophic candidiasis of the palate may be confused with the erythema caused by fellatio. Chronic hyperplastic candidiasis shows both red and white areas and is usually bilateral. The white areas cannot be rubbed off. Angular cheilitis shows sore red and/or fissured areas at the angle of the mouth, and Candida may be present on smear. Chronic mucocutaneous candidiasis is a persistent, superficial candidal infection that may develop during the first months of life, producing granulomatous involvement of the mucous membranes, nailbeds, scalp, and skin.

Candidal infections must be treated promptly and vigorously in any patient with cellular immunodeficiency. If the infection is limited to the oral cavity, nystatin troches or, for small children, nystatin oral suspension has been effective in the authors' patients. If the candidiasis fails to respond to nystatin therapy, clotrimazole oral troches or systemic ketoconazole may be indicated. Hepatotoxicity may be a significant complication of ketoconazole therapy. Mycolog® ointment may be useful for perioral lesions. If systemic involvement is suspected, amphotericin B is indicated.

Kessel and Taylor (1980) reported successful management of chronic mucocutaneous candidiasis with a miconazole topical gel applied 4 times daily. Effective resolution of the infection by oral administration of ketoconazole also has been reported (Collins and Van Sickels 1983). Chronic mucocutaneous candidiasis is refractory to topical nystatin therapy, and amphotericin B and clotrimazole appear to have limited usefulness in treating these persistent candidal lesions.

**Recurrent Aphthous Ulceration**

Recurrent aphthous ulceration usually is limited to nonkeratinized mucous membranes. The lesions begin as small raised papules on the mucosa with central blanching that creates a white appearance. The papule expands and undergoes a central necrosis to form a shallow ulcer approximately 2–10 mm in diameter. The ulcers show a central, slightly depressed grayish fibrin border and surrounding halo. Recurrent aphthous ulcers usually occur singly and resolve within 10–14 days. RAU appears to affect about 20% of the population, while the prevalence within a random population has been reported as being about 2%. The authors have seen RAU far more frequently in immunodeficient children, particularly those with chronic granulomatous disease and severe combined immune deficiency disease. Treatment of RAU is symptomatic.

**Periodontal Diseases**

In general, periodontal diseases among younger patients have been associated with defects in neutrophil function (Van Dyke 1984). Clinical descriptions of severe periodontal disease, primarily juvenile periodontitis, have been reported in children and adolescents with agranulocytopenia (Lampert and Fessler 1975), Down's syndrome (Saxen et al. 1977), Papillon-Lefèvre syndrome (Baer 1974; Tinanoff et al. 1986), and Chédiak-Higashi syndrome (White and Clawson 1980). It is well established that most juvenile periodontitis patients with unusually severe bone loss confined to the permanent molars and incisors exhibit abnormalities in neutrophil function. The lesion has been linked by association to the Gram-negative organism *Haemophilus (Actinobacillus) actinomycescomitans*, because of its recovery in high numbers from affected sites of patients with juvenile periodontitis and the significantly higher levels of serum and gingival fluid antibodies to *H.a.* found in juvenile periodontitis patients as compared with periodontally healthy patients (Ebersole et al. 1982; Murray and Genco 1980). The role of other microorganisms in juvenile periodontitis is less clear (Eisenmann et al. 1983; Moore et al. 1982). Microbiological information on other disorders of the phagocytic system is limited. Defects in this system have been implicated in prepubertal and rapidly progressing periodontitis, but evidence similar to that for juvenile periodontitis is not available.

The oral implications of B-cell, T-cell, and combined immune defects for the health of the periodontium are less clear. The authors have observed severe periodontal lesions in several adolescent patients with combined immune defects, but not in patients with IgA deficiency or hypogammaglobulinemia (Leggott et al. 1986). This observation is consistent with clinical studies by Robertson et al. (1978) and Robertson et al. (1980), who compared the oral status of pri-
marily young patients with B-lymphocyte immunodeficiencies and immunocompetent patients matched in age and oral hygiene. Although the immune system abnormalities had major consequences in other organ systems, the immunodeficient patients did not demonstrate oral developmental abnormalities, loss of periodontal structure, or severe caries. On the contrary, these immunodeficient patients showed consistently less gingival disease and caries than immunocompetent patients of similar age and oral hygiene. Moreover, the clinical response to dental treatment was similar in both groups.

There are few reports describing the periodontal status of children with HIV infection. The authors have observed an unusual gingivitis with diffuse erythema in 2 hemophiliac patients, aged 11 and 13 years, both of whom are HIV culture-positive. The gingival lesion is similar to an atypical form of necrotizing ulcerative gingivitis recently described by Silverman et al. (1986) and Winkler et al. (1986).

**Herpes Simplex Virus Infections**

Primary herpetic gingivostomatitis causes both oral lesions and systemic manifestations. It is an acute illness with varying degrees of fever and malaise, cervical lymphadenopathy, and perioral and oral lesions. The lesions start as vesicles that rupture to become painful, irregular ulcers on the gingiva, and may occur elsewhere on the oral mucosa as well as the vermillion border of the lips. Cytology (with staining using monoclonal antibodies and immunofluorescence) or culture confirms the diagnosis. Recurrent HSV infections result from reactivation of HSV latent in nerve tissue of patients with prior immunity and classically cause clusters of small, irregular vesicles without systemic manifestations. These vesicles normally are found on the hard palate and occasionally on the gingiva. The lesions subside rapidly and usually heal without scarring. In contrast, immunocompromised patients have been reported to suffer from severe, chronic, painful, recurrent HSV lesions (Cohen and Greenberg 1985) that occur on all mucous membranes and may be concurrent with lesions of the finger, eye, and chest. These intraoral lesions appear as crateriform ulcers with well-defined, raised white borders. They may be covered by a gray-white pseudomembrane or have a raw, red central area. On the skin of the face, nose, and lips the lesions begin as vesicles which rapidly become necrotic and crust over. Both the mucosal and the skin lesions will continue to enlarge until treated with anti-viral agents. Recurrent herpes labialis may be seen alone or associated with the intraoral lesions and is characterized by vesicles on the vermillion border and, in some cases, adjacent skin, which rupture and crust over.

In general, HSV infections in otherwise healthy children resolve within 10–14 days and require only palliative treatment. However, in children with a compromised immune response, HSV lesions progress rapidly and involve large areas of the oral mucosa. The lesions are extremely painful and many children refuse to eat and drink. Early diagnosis and treatment with anti-viral agents, such as acyclovir, are critical in the management of these HSV infections in immunodeficient patients.

**Salivary Gland Disease**

There is preliminary evidence suggesting the occurrence of parotid enlargement with partial xerostomia in pediatric HIV infection (Ammann 1985). Rubenstein et al. (1983) reported that 5 of 7 children with AIDS had parotid swelling. In 1 case parotitis was intermittently present, accompanied by elevations of serum amylase values. The pathologic and microbiologic features of this condition have not been reported. It has been shown that cytomegalovirus is present in whole and parotid saliva from adult AIDS patients (Marder et al. 1985). However, recent evidence suggests that the human immunodeficiency virus is infrequently found in whole saliva of patients with AIDS or AIDS-related complex (Groopman et al. 1984; Ho et al. 1985).

In summary, T-cell and combined immunodeficiencies, phagocytic dysfunction and human immunodeficiency virus infection have profound effects on the oral tissues of children. Oral infections, often caused by organisms that are either normally non-pathogenic or are a minor component of the oral microflora, are a common feature of these diseases. Since septicemia from an oral focus can cause a life-threatening infection in the immunocompromised host, careful evaluation of the oral tissues in children is an essential part of the pediatric dental examination. When possible, in children with known immunodeficiency, appropriate antibiotics should be administered 24 hr before and after dental examination and/or dental procedures which may result in systemic spread of infection.

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Dentists face little AIDS risk from patients

Dentists face little, if any, risk of contracting AIDS from patients according to 2 recent studies conducted in New York and San Francisco. Dentists are considered excellent subjects for studies on methods of contracting AIDS because of their constant on-the-job exposure to saliva and blood, both of which carry the AIDS virus.

In New York, 220 dental professionals were tested and in San Francisco 285 dentists and hygienists were tested. In both instances, some of those studied knowingly had treated persons with AIDS.

Both studies concluded that because there was no apparent infection in this greatly exposed group, AIDS "is not a highly contagious disease in an occupational environment."

Although no AIDS virus was detected, the San Francisco study did show that 20% of the dentists had been infected with hepatitis B, supporting researchers' recommendations that dental personnel improve their infection control efforts by receiving hepatitis B vaccine and by wearing protective items such as gloves, masks, and eyewear.