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# The Oral manifestations of Autoimmune diseases in children treatment: A Clinical Study.

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**Abstract**

As well as increased susceptibility to infections, autoimmune and inflammatory manifestations also eventuate due to dysregulation of immune system in a substantial proportion of patients with primary immunodeficiency (PID). Autoimmune and inflammatory manifestations can occur prior or after diagnosis of PID. This study aimed to evaluate autoimmune and inflammatory complications among all types of PID patients in childhood and to emphasize the importance of these findings as a warning sign to diagnose PIDs.

In children, there are several autoimmune diseases reported; some of which have characteristic manifestations while others may go undiagnosed due to vague or mild initial clinical features. So, in order to make an early diagnosis and treatment plan, it is required. This may even improve the prognosis of these diseases to a large extent. Therefore, this review aims to pool and compile the oral and systemic signs and symptoms of major autoimmune diseases in children.

**Keywords**: PID, Dysregulation, Children.

## Introduction

Increasing evidence is emerging for a steady rise of autoimmune diseases in the last decades. Indeed, the growth in autoimmune diseases equals the surge in allergic and cancer pathology; on the other hand, infections are shown to be less frequent in the Western societies. Oral manifestations of autoimmune disease are frequently the primary sign of autoimmune diseases.

Autoimmune disease occurs when the immune system fails to recognize self-cells and produce antibodies against them leading to their destruction. The etiology of these diseases is usually unknown, however, genetic predisposition in certain cases, environmental factors

like viral, bacterial or fungal infections and deleterious habits and lifestyle may act as triggering agents. In children, there have been several autoimmune diseases documented so far. Few have localized manifestations or organ specific while most of them have diverse and widespread effects involving multi organ system. In some of these auto immune diseases, oral symptoms become the first line of diagnosis. It is pertinent for the oral health care providers to have knowledge about these oral signs and symptoms. Therefore, this literature review aims to compile the evidence on oral manifestations along with major general findings in commoner auto immune diseases in children.

**Sjogren's Syndrome**

It is an autoimmune rheumatic disease which is often associated with other autoimmune diseases. It destructs exocrine glands of the body.

Generalized symptoms: Dryness of eyes (kerato-conjunctivitis), extreme fatigue, sensation of presence of in eyes are common findings.

Oral Findings*:* Xerostomia resulting in difficulty in swallowing, oral infections, gingivitis and tooth decay, tooth loss, swelling of salivary glands.

**Scleroderma**

It is an autoimmune disease of connective tissue where excessive collagen formation leads to fibrosis of tissues and organs systems. It is found to be more common in females. Generalized symptoms: Localized form is mostly limited to skin and presented as morphea, blanching and cyanosis of digits (Raynaud's phenomenon). Skin becomes thick, firm, and tight. Pulmonary, gastrointestinal, cardiac and renal are other organ systems involved.

Oral Findings*:* Fibrosis of oral mucosa resulting in limited mouth opening, telangiectasias of oral mucosa, gingival recession, loss of attachment, generalized paleness intra oral mucosa, stiffness of tongue, thickening of lamina dura and periodontal ligament, tooth root resorptions, pulp calcification, decreased salivary and lacrimal glands secretions, condylar alterations leading to crepitus or clicking sound on mouth opening.

**Systemic Lupus Erythematosus (SLE)**

It is basically exhibited as vasculopathy and presence of antinuclear antibodies forming immune complexes. It is more commonly seen in black females.

Generalized symptoms: Fever, tiredness, weight loss are general features. Dermatological symptoms include dry skin, malar rash, pruritis, discoid lesions and photo sensitivity. Arthritis of knee or wrist joints, muscle spasms, gastrointestinal disturbances, neurological disorders, renal diseases and hematological disorders like leukopenia, lymphopenia and throm Bo cytopenia may be seen in patients of SLE.

**Oral Findings**

Intraoral lesions are in the form of white plaques with purple-colored margins. petechiae, hyperemia, edema and ulcerations, depopulation and burning of tongue, mobile teeth, angular cheilitis, dental caries, dysgeusia, periodontitis, glossodynia and dysphagia.

**Addison's disease**

It is a rare endocrinal disorder which may have life threatening manifestations. It occurs due to the glucocorticoids and mineralocorticoids insufficiency disrupting water and electrolyte balance in the body.

Generalized symptoms: weakness, anorexia, weight loss, hyperpigmentation, hypotension, salt craving, nausea, vomiting. In extreme case, it may lead to Addisonian crisis which is characterized by penetrating pain abdomen, lower back and legs; severe vomiting, diarrhea, dehydration and loss of consciousness.

Oral Findings*:* Brownish hyper-pigmentation in the perioral and intra oral regions including buccal mucosa, alveolar mucosa, palate and gingiva. There could be loss of papilla with pigmentation on tongue as well.

**Alport's syndrome**

It is a progressive renal disease which is hereditary in origin. Type IV collagen forms an integral part of glomerular basement membrane by facilitating the cell attachment to the membrane. Type IV collagen constitute of six different alpha chains (α1 to α6) forming triple helix structure each corresponding to specific organ basement membranes i.e., glomerular, cochlea and ocular lens. In extreme cases, kidney failure deranges vitamin D production and the subsequent calcium absorption from the intestine. Further, decrease in excretion of phosphate from the kidney results in secondary hyperparathyroidism resulting in various craniofacial manifestations.

**Generalized symptoms**

Persistent hematuria progressing to proteinuria and renal insufficiency is the chief finding. Ocular manifestations include maculopathy, corneal endothelial vesicles, anterior lenticonus and recurrent corneal corrosion.

**Oral Findings**

Gingival hyperplasia and few craniofacial manifestations may be associated indirectly with this syndrome.

**Acquired immune deficiency syndrome (AIDS)**

It is caused by human immunodeficiency virus (HIV) leading to destruction of CD4 T- lymphocytes. It has wide spectrum of signs and symptoms because of the capacity of this virus to invade almost every organ system of the body.

Generalized symptoms: Dermatological pathology varies from mild pruritus to mucocutaneous rashes, hyperkeratosis of skin due to candida albicans, anal warts, generalized mycoses and dermatitis. Chronic diarrhea, weight loss and metabolic disturbances are often seen in patients of HIV. Toxoplasmosis infection involving respiratory, gastrointestinal and central nervous systems is also common. Progressing disease may also lead to Hepatitis, persistent generalized lymphadenopathy, peripheral neuronitis and upper respiratory tract infections such as pneumonia.

**Oral Findings**

These findings can be further categorized on the basis microbial infection.

Fungal infections: Candidiasis, angular cheilitis and intra oral ulcers and nodules formation associated with histoplasmosis, cryptococcosis and aspergill.

**Bacterial infections**

Linear gingival erythema (LGE), necrotizing ulcerative gingivitis (NUG) and necrotizing ulcerative periodontitis (NUP) are the most common bacterial infections in the patients suffering from AIDS. Tuberculosis exhibiting painful granulomatous ulcerations on the tongue and palate are also reported. Syphilis with clinical presentation as cankers, ulcers and plates often seen on lips, oral mucosa, palate, tongue and posterior pharyngeal wall may also be seen. Necrotizing stomatitis, recurrent Aphthous ulcers and xerostomia are other commonly associated infections.

**Autoimmune hepatitis (AIH)**

It is a progressive inflammatory disease of liver which has usually more aggressive course in children than adults. Elevated transaminase and positive autoantibodies (IgG) are the chief diagnostic criteria autoimmune hepatitis in the childhood. [32,33]

Generalized symptoms: malaise, nausea, vomiting, abdominal pain, loss of appetite and is often followed by jaundice; ultimately leading to fulminant liver failure. It is usually associated with other auto immune diseases like nephrotic syndrome, Bechet's syndrome, ulcerative

colitis, vitiligo, urticarial pigmentosa and autoimmune thyroiditis.

**Autoimmune thyroid disease**

It is one of the most common autoimmune diseases in children. Its prevalence is found more amongst females in early and mid-puberty. Evidence is documented regarding genetic risk factors involvement. Thyroid gland is essential for neurodevelopment and overall growth in children. It may be chronic (Hashimoto's disease and atrophic thyroiditis) or transient in nature. However, there is intra-thyroidal lymphocytic infiltration in both the types leading to hypothyroidism. [36,37]

**Generalized symptoms**

Behavioral disturbances such as decreased concentration span, nervousness, difficulty in sound sleep, hyperactivity, persistent tachycardia, proximal muscle weakness, goiter, fatigue, constipation, cold into lerancehypothermia, puffiness of face, dry skin, increased body hair, fluid retention, weight gain, delayed bone maturation and irregular menstrual periods.

Oral Findings*:* Autoimmune thyroid disease is usually associated with salivary glands leading to dry eyes and mouth.

Oral Findings*:* Soft tissue defects: It includes recurrent aphthous ulcers and stomatitis, angular cheilitis, atrophic glossitis, oral lichen planus, geographic tongue and burning tongue.

Hard tissue defects: Enamel defects are seen such as yellow opacities, shallow pits or deep grooves or even change in shape of enamel in extreme cases. Prolonged malnutrition may lead to delayed tooth eruption. Prevalence of dental caries may vary as hypo-mineralization of hard tissues act as caries promoter while strict gluten free diet may act as caries inhibiting factor.

**Churg Strauss syndrome**

It is a multi-organ disease typically presenting eosinophilia, asthma and vasculitis. It is a rare disease but if not diagnosed at initial stages, it may lead to severe multi-organ failure.

Generalized symptoms: It majorly includes pulmonary manifestations like allergic rhinitis and asthma and paranasal sinus abnormalities with characteristic histological findings like eosinophilia and non-fixed pulmonary infiltrates. Elevated skin lesions, sub cutaneous nodules, cardiac (pericarditis, myocarditis), musculoskeletal, gastrointestinal, neurological and renal involvement are seen as extra-pulmonary manifestations.

Oral Findings*:* Oral ulceration is the only possible oral fining reported. In rare situation, vasculitis of lips maybe seen.

**Diabetes mellitus type 1 (DM)**

It is a metabolic disorder having effect on all body functions due to abnormal protein, carbohydrate and fat metabolism. Its estimated prevalence in 2021 was 8.4 million people with 1.5 million youngers than 20 years. It is characterized by hyperglycemia or an increased blood glucose level.

Oral Findings*:* Altered dental development, delayed tooth eruption, increased dental caries, gingival inflammation and periodontal diseases are the common oral findings.

**Wegener's glomerulitis**

It refers to a triad of necrotizing granuloma of respiratory tract, generalized necrotizing vasculitis and glomerulonephritis. It is usually considered as hypersensitivity disease but the exact etiology is still unknown. Its prognosis has improved markedly after the introduction of immunosuppressive drugs.

**Discussion**

The type of autoimmunity varies according to the spectrum of immune deficiencies. Data from the US Immunodeficiency Network (USIDNET) have revealed that 1–11% of patients with PIDs have one or more of three autoimmune manifestations: autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, or inflammatory bowel disease. A study based on the French CEREDIH PID registry revealed that autoimmune cytopenia was the most common autoimmune disease (31.4%) followed by 24.4% gastrointestinal system findings, 14.1% dermatologic findings, 12.8% rheumatologic findings, 8.1% endocrinologic findings and 3.5% respiratory system findings. Autoimmune thyroiditis is the most common autoimmune disorder in the general population and its incidence rate is even higher in certain types of PIDs, including APECED, CVID and IPEX syndrome. Autoimmune cytopenia like ITP, autoimmune neutropenia, autoimmune hemolytic anemia and Evans syndrome are common in PID patients and may be the first sign of immune dysregulation, preceding the classical presentation of PID with recurrent infections. A wide spectrum of additional systemic and organ-specific autoimmune diseases has been documented in PID, including diabetes mellitus, non-infectious gastrointestinal diseases (pernicious anemia, celiac disease, autoimmune enteropathy, inflammatory bowel disease), rheumatologic diseases (juvenile rheumatoid arthritis, systemic lupus erythematosus, antiphospholipid syndrome, vasculitis), uveitis, multiple sclerosis, lichen planus, vitiligo, and psoriasis. In our study, autoimmune thyroiditis was the most common involvement (25.3%). This high prevalence may be due to the high level of awareness on this subject and the fact that it is examined during diagnosis and follow-up. Immune thrombocytopenic purpura was the second most common autoimmune manifestation (21.69%) followed by autoimmune hemolytic anemia (19.28%) and neutropenia (12.05%). It is considered that the difference between results may arise from the difference of age and diagnostic groups.

**Conclusion**

There are significant oral findings in Juvenile rheumatoid arthritis, Sjogren's Syndrome, Scleroderma, Systemic Lupus Erythematosus (SLE), Myasthenia gravis, Idiopathic thrombocytopenic purpura (ITP), Autoimmune Pernicious Anemia, Acquired immune deficiency syndrome (AIDS), Celiac disease, Diabetes mellitus type 1 (DM) and Wegener's glomerulitis. Though in majority of cases, these manifestations are similar to that found in adults, however, in few diseases like autoimmune hepatitis, it has more aggressive in children than adults. Similarly, it is easier to diagnose celiac disease and myasthenia gravis in childhood than in later stages of life. Therefore, the knowledge of chief oral and systemic findings of major autoimmune diseases in children will help the dental practitioners to make an early diagnosis of these diseases and refer to the pediatricians in time.

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