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# Oral Manifestations of Autoimmune Diseases in Neonates – A Narrative Review

[1]Mallayya C. Hiremath, Associate Professor, Department of Pediatric and Preventive Dentistry, Government Dental College and Research Institute, Fort, Bengaluru-560002. Karnataka, India.

[2]SK. Srinath, Professor and Head, Department of Pediatric and Preventive Dentistry, Government Dental College and Research Institute, Fort, Bengaluru-560002. Karnataka, India.

[3]Pushpalatha Shivashankar, Post-Graduates, Department of Pediatric and Preventive Dentistry, Government Dental College and Research Institute, Fort, Bengaluru-560002. Karnataka, India.

[4]Raja Jayadeva Nayak, Post-Graduates, Department of Pediatric and Preventive Dentistry, Government Dental College and Research Institute, Fort, Bengaluru-560002. Karnataka, India.

[5]Aarcha S. Kumar, Post-Graduates, Department of Pediatric and Preventive Dentistry, Government Dental College and Research Institute, Fort, Bengaluru-560002. Karnataka, India.

**Corresponding Author:** Mallayya C. Hiremath, Associate Professor, Department of Pediatric and Preventive Dentistry, Government Dental College and Research Institute, Fort, Bengaluru-560002. Karnataka, India.

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**Abstract**

Neonatal autoimmune diseases are rare but they should be considered for early diagnosis and prevention of complications. Oral manifestations of such conditions are especially helpful for early diagnosis, as oral lesions appear first in such conditions due to the high turnover rate of the oral mucosa. This can therefore provide an upper hand to paediatric dentists who can alert the paediatrician about neonatal autoimmune diseases. In this review we try to navigate through the oral manifestations of rare autoimmune diseases that can appear in neonates.

**Keywords:** Autoimmune, lupus erythematosus, neonate, oral manifestation.

## Introduction

The immune system is a tightly regulated network that is able to maintain a balance of immune homeostasis under normal physiological conditions. Normally, when challenged with a foreign antigen, specific responses are initiated that are aimed at restoring homeostasis. However, under particular circumstances, this balance is not maintained and immune responses either under or over react. Systemic autoimmune disorders in expectant mothers may induce passive autoimmunity in fetus and

neonates. If the disease is IgG auto antibody mediated, it can cross placenta and induce immune reactions in fetus and neonates.[1] Autoimmune diseases are distinctly rare in neonates, because of the immature immune system. Relative immunodeficiency and expression of inhibitory receptors in neonatal immune cells make it incapable of becoming over-reactive to self-tissues.[1,2]

Systemic autoimmune diseases often manifest as oral lesions in their earliest stages because of faster turnover rate of the oral mucosa, any changes in the body will be reflected in the oral cavity at the earliest. Therefore, early oral examination and diagnosis is the key for improved outcomes. Thus, early recognition of signs is important in diagnosis and management. This also helps in decreasing morbidity and mortality rates and also improving the quality of oral health.[2] Paediatric dentists play an important role in detecting oral lesions and also during multidisciplinary management of these autoimmune diseases. The purpose of this review article is to discuss oral manifestations of rarely seen neonatal autoimmune diseases.

**Discussion**

Neonatal autoimmunity is defined as an aberrant immune response to self-tissues in the first few months of life, leading to diseases that are closely related to autoimmune diseases in children and adults.[2,3] Neonatal autoimmunity is a relatively rare event, mostly related to maternal antibodies. Transplacental neonatal autoimmune diseases that target fetal or neonatal antigens are the most common type seen in neonates. Primary neonatal autoimmunity has almost never been described. Other classifications based on damage to organs can be single organ involvement or multiple organs targeting autoimmune diseases.

**Pathophysiology of Neonatal Autoimmune Diseases**

The exact mechanism of pathophysiology of neonatal autoimmune diseases is unknown. It is considered to be multifactorial, with genetic, environmental, epigenetic and hormonal factors all play role.[2,3]

- **Defective Apoptosis:** Ro and La antigens are densely present in the nucleus of the cell during the s and g phase of cell division. These antigens will be expressed on the cell surface during the early apoptotic and late apoptotic phases. These antigens become accessible to maternal antibodies that have crossed the placenta after week 12 of gestation. While binding of the antibody to the antigen on apoptotic cells may not in itself be pathologic, the authors proposed that this process elicits a strong inflammatory response resulting in tissue damage.[2,3]
- **Micro chimerism:** It is defined as the presence of low concentrations of two genetically distinct cell populations in the same individual. During pregnancy, small amounts of maternal cells can travel across the placenta into the fetal circulation. These maternal cells can co-exist in the fetal environment and can even cause the pathogenesis of neonatal lupus. In general, this does not pose a threat to the foetus or neonate. However, it is possible that these maternal cells, under the right conditions, could become allogeneic and induce an immune response in the foetus or neonate.[2,3]
- **Defects in T-cell mechanism and inhibitory receptors:** Regulatory T cells control immune responses by suppressing various inflammatory cells. These cells in new born babies may play an important role in preventing excessive immune responses during their environmental change. In neonates, increased expression of inhibitory receptors is found on a number of immune cells, including neutrophils, monocytes, T-lymphocytes, and natural killer cells. These inhibitory receptors

regulate the immune system by setting a higher threshold for activation of immune responses and lead to the tolerogenic nature of neonatal immune cells. Any defect in regulatory T-cells and inhibitory receptors with a secondary event such as exposure to an environmental agent capable of eliciting autoimmunity in neonates.[2,3]

- **Genetic Predisposition:** Only 2% of neonates exposed to maternal antibodies to Ro and La develop neonatal lupus, it has been attempted to be explained by a genetic predisposition involving the major histocompatibility complex. In contrast to systemic lupus erythematosus, there are almost as many males as females with neonatal lupus, and while the presence of anti-Ro and anti-La antibodies in the mother is associated with DR3/DR2, there is no such association in the foetus and neonate. One study did show a possible link between HLACw3 and neonates with lupus, but this has not been confirmed. A genome-wide association study (GWAS) of 116 children and 3551 controls has identified two candidate loci at 6p21 and 21q22 to be risk alleles for neonatal lupus. The role of genetics in neonatal autoimmunity remains obscure and yet to be elucidated.[2,3]

**Neonatal Lupus Erythematosus (NLE)**

NLE is a disease that occurs annually in 1 of 20,000 live births in USA and in 0.6 of 100,000 births overall. It affects the offspring of women with anti-SSA/Ro or anti-SSB/ La antibodies. These antibodies are most likely to be found in patients with Sjogren's disease and SLE.[2,3]

Pathophysiology of NLE: There are three types of antibodies in the pathogenesis of NLE – anti-SSA/Ro, anti-SSB/La and anti-U1-RNP. These antibodies are directed against antigen present in the nucleus, nucleolus and cytoplasm. These antigens are displayed on the surface of the cells during the process of apoptosis in fetal development. In the second trimester, maternal autoantibodies (IgG) start to cross the placenta and form complexes with the antigens in foetal organs. These complexes are then opsonized and phagocytosed, which triggers proinflammatory process and subsequent tissue damage. The most common organs involved are skin, heart, hepatic and blood system.[2,3]

- Complications of NLE: In most cases cutaneous, hepatobiliary, haematological and neurological involvement is seen but the symptoms fade spontaneously within 6–8 months as maternal antibodies resolve. Further treatment is usually unnecessary and residual complications are uncommon. However, some neonates may manifest the symptoms of SLE when they grow older. So, the patients with NLE, their mothers and their siblings should be observed for prolonged duration for signs of active disease.[2,3]
- Oral manifestations: NLE presents with painless orolabial ulceration on lower and upper lip. Ulcers are discrete, painless, non-draining, well demarcated with surrounding erythema. Mucosal lesions are rare in NLE, but cohort study report conducted by Victor Martin *et al.* showed children with palatal ulcers as a manifestation of neonatal lupus erythematosus.[4,5] No specific treatment was required as the mucosal ulcers resolved spontaneously.[6,7,8]

**Neonatal Pemphigus Vulgaris (NPV)**

Neonatal pemphigus vulgaris (NPV) is a rare autoimmune disease that is caused by transplacental transfer of IgG antibodies. It is uncommon in the paediatric population, representing about 1.4 to 2.9% of all cases. Pemphigus vulgaris and pemphigus foliaceus are characterized by autoantibodies directed against desmoglein-3 and desmoglein-1 respectively, both these transmembrane glycoproteins of desmosomes belonging to the cadherin family. In patients with pemphigus vulgaris, autoantibodies against desmoglein-3 cause

blisters as a result of loss of cell–cell adhesion in the basal and supra-basal layers of the deeper epidermis, with keratinocytes in the more superficial layers of the epidermis maintaining their cell adhesion. It is expressed in children of pemphigus carriers after the occurrence of a transient event, which stops the maternal antibodies from disappearing. The clinical manifestation of neonatal pemphigus is less severe in comparison to the disease that caused it, as it is not a systemic disease. The signs and symptoms of neonatal pemphigus are restricted to skin lesions, and they have a good prognosis. It is expected for the symptoms to be resolved within three weeks.[9,10]

- Oral manifestations: Benign multiple ulcers on buccal mucosa, tongue and palate are commonly seen oral manifestations.
- Management: Lesions usually resolve spontaneously within 3-weeks. Hence, usage of corticosteroids is not supported in neonatal pemphigus because of its potent anti-inflammatory and immune-suppressive effect. Complications: Neonatal pemphigus has not been recorded as progressing to adult disease.[9,10]

**Neonatal Epidermolysis Bullosa Acquisita (NEBA)**

Very few cases have been reported worldwide for NEBA. EBA is an autoimmune bullous disorder that is caused by circulating autoantibodies directed against the 145-kDa NC1 domain of collagen VII which has been transmitted trans-placentally from a mother suffering from Epidermolysis Bullosa. Lesions mainly consists of multiple superficial and deep erosions of face, chest, abdomen and extremities of the neonate, with the most prominent involvement on the hands, ankles and feet. There is also the presence of scattered intact vesicles and bullae.[11]

Oral manifestations: Oral manifestations are mainly vesicles, erosions and crusting of the lips and the oral mucosa was clear in the reported cases. It is self-limiting and symptoms resolve with supportive therapy.[11]

**Neonatal Bechet's Disease (NBD)**

Bechet's disease (BD) is a recurrent systemic vasculitis of unknown aetiology, characterised by recurrent oral and genital ulcers and ocular inflammation. Other clinical manifestations include arthritis, skin lesions, neurological, gastrointestinal and vascular abnormalities. A transient form of BD may develop in a neonate of a mother with this disease.[12,13]

Oral manifestations: Multiple painful, non-scarring oral lesions, characterized by sharp circular shapes with erythematous borders and usually occur on the tongue or on the oropharyngeal and buccal mucosa. MA Lewis et al. reported a case of 8-days neonate presented with multiple mouth ulcers that progressed to severe destructive ulcers of lip, buccal mucosa and tongue which healed by scarring leading to cosmetic deformity.[12,13]

Management: Early diagnosis and effective treatment strategy by using prednisolone reduces the incidence of scarring.[12,13]

**Neonatal Kawasaki Disease (KD)**

Kawasaki Disease (KD) is a self-limiting and acute systemic vasculitis disease of childhood that leads to coronary artery abnormality in about 20% to 25% of untreated cases. It is frequent in children under 5-years age. It is the leading cause of acquired heart disease like coronary artery aneurysms in children in developed countries. The age of onset of KD is usually between 6-months and 5-years of age. It is much less common under 6-months of age and rare in children under 3-months of age. It is especially rare in the neonatal period, with only a few neonatal cases ever reported in the literature.[14,15]

Oral manifestations: These are caused by typical necrotizing microvasculitis with fibrinoid necrosis.

- Erythematous and oedematous lips with fissures and bleeding.
- Mucosa of oropharynx appears bright red, the tongue has typical strawberry tongue appearance (marked erythema to gustatory papilla).

Management: Timely intravenous immunoglobulin administration prevents cardiac complication and improves clinical condition of patient.[14,15]

**Celiac Disease (CD)**

This is one of the rare autoimmune disorders first seen around six months of age. 1.4% is the worldwide prevalence with girl predilection. It occurs in genetically predisposed individuals and is caused by gluten, which is a protein present in various grains.[16] It attacks the lining of small intestines and damages the villi, leading to malabsorption. Persistent diarrhea, steatorrhea, loss of appetite, weight loss, muscle wasting and stunted growth are the clinical features.[16]

Oral manifestations: Glossitis, recurrent aphthous ulcers, stomatitis, burning mouth syndrome. Management includes a strict life-long gluten-free diet, along with other supportive measures for celiac disease.[16]

Some of the other rare neonatal autoimmune disorders are as follows[2,3]:

- Neonatal anti-phospholipid syndrome.
- Neonatal autoimmune haemolytic anaemia.
- Neonatal dermatomyositis.
- Neonatal myasthenia gravis.
- Neonatal scleroderma.
- Neonatal type-I diabetes mellitus.

**Conclusion**

Maternal health status is an important cause for the development of autoimmune diseases in neonates. Neonatal autoimmune diseases require continued follow-up, especially prior to adolescence and if the mother herself has an autoimmune disease. Oral manifestations could be the earliest sign in diagnosing such autoimmune diseases. Early diagnosis can play a decisive role in improving the treatment strategies as well as the quality of life.

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