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ETIOLOGY, PATHOGENESIS, AND RISK FACTORS OF SCLERODERMA IN NEWBORNS

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Abstract

Scleroderma (Systemic Sclerosis, SSc) is a chronic autoimmune connective tissue disease characterized by progressive fibrosis of the skin and internal organs, vasculopathy, and immune system dysregulation. In neonates, this condition is exceedingly rare and diagnostically challenging, frequently being confused with similar entities — sclerema neonatorum, scleredema, and subcutaneous fat necrosis (SCFN). This article provides a detailed review of the etiological factors, pathogenetic mechanisms, and clinically relevant risk factors of neonatal scleroderma. In particular, the roles of genetic susceptibility, maternal-fetal immunological interactions (microchimerism), infectious agents, and environmental influences are analyzed.

Keywords: Neonatal scleroderma, sclerema neonatorum, fibrosis, autoimmune disease, microchimerism, pathogenesis, HLA genes.

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1. Introduction

Scleroderma is a disease of incompletely understood but multifactorial etiology. Its principal clinical features include skin thickening and hardening, Raynaud's phenomenon, excessive collagen accumulation in subcutaneous tissues, and fibrotic changes in internal organs. The disease occurs predominantly in women aged 30–55; its occurrence in children and particularly in newborns is considered a rare phenomenon.

At the same time, conditions presenting with skin hardening in the neonatal period (sclerema neonatorum, scleredema, SCFN) are frequently misclassified as "scleroderma." For this reason, distinguishing these conditions from one another and accurately understanding their pathogenetic mechanisms carries both scientific and practical importance for neonatologists, dermatologists, and pediatric rheumatologists.

The aim of this article is to elucidate, on the basis of current scientific evidence, the etiopathogenetic foundations, genetic-immunological mechanisms, and risk factors of scleroderma and related sclerotic conditions in newborns.

2. Etiology

The precise cause of systemic scleroderma remains unknown. From the perspective of modern medicine, the disease has a multifactorial etiology, and the following principal factors are involved in its development:

2.1. Genetic Factors

Contemporary research has demonstrated a significant role for genetic factors in the development of scleroderma. Variants in HLA class II genes — particularly HLA-DRB1 and HLA-DQB1 — play an important role in the pathogenesis of the disease. In addition, non-HLA loci — PTPN22, NLRP1, STAT4, and IRF5 — make independent contributions to disease etiology. These genes play a central

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role in regulating the immune response and ensuring the functional activity of T- and B-lymphocytes.

It should be emphasized that scleroderma is not a hereditary disease — it is not transmitted directly from parent to child. However, a family history of autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, autoimmune thyroid disease) increases the likelihood of disease development in the child. In localized pediatric scleroderma, the HLA-DRB1*04:04 allele demonstrates a shared genetic association with rheumatoid arthritis.

2.2. Immunological Factors

The central link in the pathogenesis of scleroderma is immune system dysregulation. Its principal mechanisms include:

- T-lymphocytes (particularly Th2-type CD4+ cells) become activated and synthesize profibrotic cytokines such as IL-4 and IL-13.
- B-cells produce anti-topoisomerase-I (anti-Scl-70), anti-centromere, and anti-RNA polymerase III antibodies.
- Polarization of macrophages toward the M2 phenotype leads to excessive accumulation of collagen and extracellular matrix in tissues.
- TGF-β (transforming growth factor-beta) signaling is pathologically activated and plays a decisive role in converting fibroblasts into myofibroblasts.

2.3. Maternal-Fetal Immunological Interaction (Microchimerism)

Research conducted over the past decade has identified an important role for fetal-maternal microchimerism in the pathogenesis of scleroderma. During pregnancy, maternal and fetal cells are exchanged bidirectionally across the placenta. Maternal cells retained in the child, or fetal cells retained in the mother, may subsequently be recognized as "foreign" antigens, eliciting an immune response directed against them. This process resembles graft-versus-host disease

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and is considered one of the potential initiating causes of fibrotic conditions such as scleroderma.
In newborns, this mechanism is of particular significance, since maternal cells may still be present in the infant's body and engage in complex interactions with its developing immune system.

2.4. Infectious Factors

A number of studies indicate that viruses and bacterial infections may serve as triggering factors in the development of scleroderma. The following pathogens are of particular importance:
- Cytomegalovirus (CMV) — may trigger vasculopathy through endothelial cell tropism.
- Epstein–Barr virus (EBV) — causes excessive activation of B-lymphocytes.
- Parvovirus B19 — directly affects fibroblasts and stimulates collagen synthesis.
- Helicobacter pylori, certain retroviruses — trigger autoimmune responses through molecular mimicry.

In newborns, infections (particularly neonatal sepsis) are among the principal triggers for the development of sclerema neonatorum.

2.5. Environmental and Chemical Factors

Environmental exposures during pregnancy may reach the fetus through the mother. Epidemiological studies have identified the following as contributing factors: silica dust, vinyl chloride, trichloroethylene, aromatic solvents, ketones, welding fumes, and certain medications (bleomycin, cocaine-type substances). Occupational or domestic exposure of the mother to such substances during pregnancy may induce epigenetic changes in the fetus.

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3. Pathogenesis

The pathogenesis of systemic sclerosis rests on three principal mechanisms: vascular injury, immune dysregulation, and tissue fibrosis. These mechanisms are intimately interconnected and form a mutually reinforcing cycle.

3.1. Stage One: Endothelial Injury and Vasculopathy

In the initial stage of the disease, injury to the endothelium of small blood vessels is observed. Apoptosis increases in endothelial cells, vessels narrow, and oxygen delivery to tissues is impaired. This state of hypoxia stimulates the release of additional cytokines (endothelin-1, VEGF) and paves the way for subsequent fibrotic processes.

3.2. Stage Two: Immune System Dysregulation

Following endothelial injury, immune cells (T-lymphocytes, B-lymphocytes, macrophages) infiltrate the tissue. Their activation results in the production of large quantities of profibrotic cytokines (TGF-β, IL-4, IL-6, IL-13, PDGF). Specific autoantibodies synthesized by B-cells carry diagnostic significance and assist in determining the clinical subtype of the disease.

3.3. Stage Three: Fibrosis

In the fibrotic stage, fibroblasts differentiate into myofibroblasts and begin producing excessive quantities of type I and type III collagen as well as other extracellular matrix proteins. As a result, rigid, scar-like changes develop in the skin, subcutaneous tissues, vessel walls, and internal organs (lung, heart, kidneys, gastrointestinal tract). At this stage, collagen degradation slows, as IL-6 and TGF-β inhibit breakdown of the extracellular matrix.

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3.4. Distinctive Features in Newborns

In the neonatal period, the pathogenesis of sclerotic changes differs substantially from that in adults. In newborns, the subcutaneous adipose tissue contains a higher proportion of saturated fatty acids (palmitic, stearic) relative to unsaturated ones (oleic acid). This is related to a deficiency of desaturase enzymes involved in fatty acid metabolism. During hypothermia, shock, or sepsis, this ratio deteriorates further, leading to fat crystallization and skin hardening — a hallmark of sclerema neonatorum.

True neonatal scleroderma, in contrast, develops primarily through an immunopathological mechanism and is thought to arise largely under the influence of antibodies transmitted transplacentally from the mother.

4. Risk Factors

The principal risk factors contributing to the development of scleroderma and related sclerotic conditions in newborns are summarized systematically in the table below:

Risk Factor Group	Details
Genetic factors	HLA-DRB1, HLA-DQB1 alleles; PTPN22, STAT4, IRF5, NLRP1 loci; family history of autoimmune diseases
Immunological factors	Bidirectional exchange of maternal and fetal cells (microchimerism); autoantibodies (anti-Scl-70, anti-centromere); predominance of Th2-type immune response
Infectious factors	CMV, EBV, parvovirus B19, neonatal sepsis, viral infections during pregnancy
Perinatal factors	Prematurity, hypothermia, hypoxia, respiratory insufficiency, dehydration
Environmental factors	Maternal exposure to silica dust, solvents, vinyl chloride during pregnancy; certain medications (bleomycin)
Metabolic factors	Elevated ratio of saturated to unsaturated fatty acids; deficiency of desaturase enzymes (characteristic of sclerema neonatorum)

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5. Differential Diagnosis

When skin hardening is detected in a newborn, several similar conditions must be distinguished from one another. Their principal distinguishing features are presented in the table below:

5.1. Sclerema Neonatorum

This is a rare form of panniculitis occurring in severely ill, predominantly premature newborns. The skin and subcutaneous adipose tissue become diffusely hardened, assume a waxy appearance, and adhere to the underlying tissues. The condition typically develops in the setting of sepsis, severe infections, hypothermia, and dehydration. The prognosis is extremely grave — mortality may reach 60–87%.

Feature	Sclerema Neonatorum	Neonatal Scleroderma	SCFN
Affected population	Premature or severely ill newborns	Newborns of varying gestational age, often post-infection	Post-term or healthy full-term newborns
Onset	First week of life	Variable, often after infection	1–4 weeks after birth
Skin presentation	Diffuse hardening, waxy, immobile	Progressive edema, later hardening	Localized firm nodules
Prognosis	Very severe; mortality 61–87%	Generally favorable; may resolve spontaneously	Good; resolves spontaneously
Histology	Needle-shaped crystals in adipocytes; no infiltrate	Increased collagen; lymphocytic infiltrate	Granulomatous inflammation; fat necrosis

5.2. Subcutaneous Fat Necrosis (SCFN)

This condition occurs in healthy post-term newborns and manifests within 1–4 weeks after birth. Localized firm nodules develop, but they are mobile and

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resolve spontaneously. SCFN frequently occurs in the context of perinatal hypoxia, hypothermia, or large-for-gestational-age infants.

5.3. True Neonatal Scleroderma

This is a very rare condition beginning with progressive edema of the extremities that gradually evolves into hardening. It most often develops following gastrointestinal or respiratory tract infections. The prognosis is relatively favorable, but early diagnosis and appropriate management are critically important.

6. Clinical Significance

When skin hardening is detected in a newborn, the clinician's principal responsibilities include:

- Perform differential diagnosis promptly and accurately — the therapeutic approach depends entirely on the type of condition.
- Assess the infant's overall status — exclude sepsis, hypothermia, dehydration, or congenital malformations.
- Conduct laboratory investigations: complete blood count, biochemistry, blood gas analysis, and testing for autoantibodies (anti-Scl-70, anti-centromere).
- Perform skin biopsy and histological examination where indicated.
- Ensure an integrative approach through collaboration among a pediatric rheumatologist, neonatologist, and dermatologist.

7. Conclusion

Scleroderma in newborns is a rare condition with highly complex etiopathogenetic mechanisms. Genetic predisposition, maternal-fetal immunological interaction (microchimerism), infectious triggers, environmental exposures, and metabolic alterations all play important roles in its development. Moreover, distinguishing neonatal scleroderma from other sclerotic conditions

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such as sclerema neonatorum and subcutaneous fat necrosis is of vital importance, as their prognoses and treatment strategies differ substantially.

Contemporary molecular-genetic and immunological research continues to deepen our understanding of scleroderma pathogenesis. Investigation of microchimerism theory, epigenetic alterations, and novel pathogenic mechanisms forms the foundation for future personalized therapeutic approaches. For this reason, clinical and experimental research in this area remains one of the priority tasks of the field of pediatric rheumatology.

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