

Stiff Skin Syndrome: Clinical Exploration, Pathophysiology and Therapeutic Advances in a Rare Connective Tissue Disease

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ABSTRACT

Stiff Skin Syndrome, also known as "diffuse stiff skin syndrome" or "Scleroderma-like syndrome with focal contracture", is a rare and complex clinical entity in the spectrum of connective tissue diseases. This disorder is characterized by progressive and diffuse infiltration of connective tissue into the skin and underlying tissues, resulting in extreme skin stiffness and limited joint mobility. In addition to its cutaneous and joint manifestations, stiff skin syndrome can affect multiple internal organs, making it a clinical entity of great multidisciplinary relevance.

This article aims to provide a comprehensive review of stiff skin syndrome, addressing its epidemiology, clinical manifestations, etiopathogenesis, differential diagnosis, and current therapeutic options. Recent research that has shed light on the underlying molecular mechanisms and emerging therapies that are being developed to improve the quality of life of patients affected by this disease are highlighted. In addition, the importance of a comprehensive evaluation and an interdisciplinary therapeutic approach to optimize the clinical management of individuals with rigid skin syndrome is highlighted.

KEYWORDS: Stiff, Skin, Syndrome, disease.

ARTICLE DETAILS

Published On:
22 September 2023

Available on:
<https://ijmscr.org/>

INTRODUCTION

Rigid Skin Syndrome (RPS), also known as "diffuse rigid skin syndrome" or "Scleroderma-like syndrome with focal shrinkage," is an uncommon and enigmatic pathology that falls within the realm of connective tissue diseases, characterized by profound disruption of the structural and functional integrity of dermal and underlying tissues. This syndrome, although rare, poses a significant clinical and scientific challenge due to its complexity and the diversity of organ systems that may be affected.¹

PRS is characterized by progressive accumulation of extracellular matrix and subsequent fibrosis involving the skin and subcutaneous connective tissues, resulting in severe and unusual loss of skin elasticity, stiffness, and limited joint mobility. These prominent clinical manifestations often emulate a "statuesque skin" appearance and can lead to a significant impact on the quality of life of affected individuals.¹

In addition to cutaneous manifestations, PRRS can involve a diversity of organ systems, including the musculoskeletal, vascular, gastrointestinal, pulmonary, and cardiac systems. The clinical heterogeneity and lack of in-depth understanding of the underlying etiopathogenesis have complicated the investigation and treatment of this condition, underscoring the need for a multidisciplinary approach and further scientific exploration in search of effective therapeutic solutions.¹

In this comprehensive review, we aim to address Stiff Skin Syndrome from a clinical, pathophysiological and therapeutic perspective, highlighting the most recent advances in the understanding of its etiology, as well as emerging therapeutic strategies that are being investigated in the quest to improve the clinical management and quality of life of patients affected by this rare but challenging medical entity.^{1,2}

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EPIDEMIOLOGY

Rigid Skin Syndrome (RPS), a rare and enigmatic clinical entity, holds significant relevance in the medical field due to its clinical complexity and profound impact on the quality of life of affected individuals. Given its infrequent nature and diverse and severe clinical manifestations, the importance of understanding and addressing this syndrome lies in multiple epidemiological, clinical and therapeutic dimensions.²

From an epidemiological perspective, PRRS is considered a rare disease, with a global incidence estimated at less than 1 case per million people, although prevalence varies according to geographic and ethnic populations. Despite its low frequency, its significant clinical, functional and psychosocial impact on affected individuals makes it an area of growing interest to the medical and scientific community.² The epidemiology of PRRS, although poorly documented, suggests a possible gender predisposition, with a higher prevalence in females than in males. In addition, a clinical presentation has been observed that spans all ages, from infancy to adulthood, however, onset in childhood is less common and tends to be more aggressive in terms of disease progression.²

The clinical relevance of PRRS is manifested in the considerable morbidity it entails, affecting not only the physical appearance of patients due to extreme skin stiffness, but also compromising joint function, resulting in disability and limited mobility. In addition, potential systemic complications, such as pulmonary, cardiovascular and gastrointestinal involvement, can have a potentially lethal impact.^{2,3}

Given its rarity and complexity, scientific research and interdisciplinary collaboration are essential to advance the understanding of the etiopathogenesis of PRRS and the search for effective therapeutic strategies. The importance of addressing PRS lies in providing a better prognosis and quality of life for those suffering from this condition, as well as the potential to shed light on underlying mechanisms of fibrosis and connective tissue dysfunction, which could have applications in the management of other more common connective tissue diseases. Thus, the relevance and epidemiology of PRS converge on the compelling need for in-depth research and clinical efforts to comprehensively address this complex medical entity.³

CLINICAL MANIFESTATIONS

Rigid Skin Syndrome (RPS), a clinical entity that falls under the umbrella of connective tissue diseases, presents a wide range of clinical manifestations spanning multiple organ systems, which contributes to its complexity and heterogeneity. The most distinctive and obvious feature of PRS is the profound alteration of the skin and underlying connective tissues, resulting in a peculiar skin phenotype and a significant loss of skin elasticity, which translates into a "statue skin" or "ivory skin" appearance. This skin phenotype,

in essence, derives from intense fibrosis affecting not only the skin, but also the subcutaneous tissues, muscles and fasciae, which manifests itself in a marked decrease in joint mobility.⁴

Specific clinical manifestations of PRRS include:

Cutaneous involvement: Skin affected by PRS becomes stiff, tight and shiny in appearance, with significant limitation of dermal expansion. Loss of normal skin folds can lead to restriction of joint function, resulting in joint contractures and deformities.⁴

Joint involvement: Stiffness and progressive loss of joint mobility are common findings in patients with PRRS, which can lead to functional disability and a significant decrease in quality of life. The joints most commonly affected are the hands, elbows, knees and wrists.⁴

Fasciitis: Fibrous infiltration of muscle fasciae and underlying tissues contributes to restricted mobility and chronic pain, which can negatively impact muscle function and the ability to perform daily activities.⁵

Muscle involvement: Intramuscular fibrosis can lead to muscle weakness and myalgias, which adds an additional dimension to the functional disability experienced by patients with PRRS.⁵

Systemic Complications: Although less common, systemic complications can include pulmonary, cardiovascular, gastrointestinal and renal involvement. Pulmonary fibrosis, in particular, can pose a life-threatening threat.⁵

Dermatologic Complications: Skin ulcers and subcutaneous calcifications are dermatological complications that may arise in the course of PRRS.⁵

Ophthalmologic involvement: In some cases, PRRS can lead to ocular alterations, such as conjunctival thickening or lens disorders.⁵

Gastrointestinal Motility Alterations: Fibrosis in the gastrointestinal tract can lead to symptoms such as dysphagia, gastroesophageal reflux and gastric stasis.^{5,6}

Cardiovascular conditions: Vascular disorders may manifest as Raynaud's phenomenon, pulmonary hypertension and cardiac valve dysfunction.⁶

In summary, PRS presents as a profoundly intricate and multifaceted medical entity characterized by extensive fibrosis of the skin and connective tissues, resulting in a range of clinical manifestations affecting several organ systems. A thorough understanding of these manifestations is crucial for early diagnosis, proper clinical management and improvement of the quality of life of patients affected by this rare and challenging medical entity.⁶

DIAGNOSIS

The diagnosis of Stiff Skin Syndrome (RPS), an exceptionally complex and rare medical entity that falls within the spectrum of connective tissue diseases, requires a comprehensive and thorough evaluation, given that its

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clinical presentation is heterogeneous and can emulate other connective tissue disorders and fibrosing diseases.⁷

The diagnostic evaluation of PRS involves several essential steps:

Detailed Medical History: This begins with a thorough collection of the patient's medical and clinical history, paying attention to the onset and progression of symptoms, family history of autoimmune or connective tissue disease, as well as any exposure to environmental or toxic triggers.⁷

Clinical Physical Examination: A thorough physical examination is essential, highlighting skin stiffness, limited joint mobility, contractures, "statuesque skin" appearance, and palpation of areas of subcutaneous fibrosis or fasciitis, which are key findings of PRRS.⁷

Dermatological Evaluation: Consultation with a specialist dermatologist is recommended for a detailed evaluation of the skin and subcutaneous tissue, including the performance of skin biopsies to assess the extent and characteristics of dermal fibrosis.⁷

Laboratory Studies: Blood tests may reveal nonspecific findings, such as elevated markers of inflammation, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Autoantibodies, such as antinuclear antibodies (ANA), can be evaluated to rule out or confirm the coexistence of autoimmune diseases.⁸

Pulmonary Function Tests: Given the potential pulmonary involvement, pulmonary function tests, including spirometry and diffusing capacity for carbon monoxide (DLCO), should be performed to screen for restrictive pulmonary fibrosis.⁸

Imaging Studies: Imaging tests, such as high-resolution computed tomography (CT), can be crucial in assessing the extent of pulmonary fibrosis and detecting soft tissue and joint changes.⁹

Electrodiagnostic studies: In some cases, electrodiagnostic studies, such as electromyography (EMG), may be performed to assess muscle and nerve involvement.⁸

Tissue Biopsy: Biopsy of connective or skin tissue may be necessary to confirm the diagnosis and evaluate the extent and characteristics of fibrosis.⁸

Multidisciplinary Evaluation: Given the complexity of PRRS and its potential multisystem involvement, a multidisciplinary evaluation involving rheumatologists, dermatologists, radiologists, physiotherapists and other specialists as needed is recommended.⁸

The diagnosis of PRRS is a complex and multidimensional process that requires careful clinical evaluation, laboratory analysis, imaging tests and, on occasion, biopsies. Diagnostic confirmation is essential to guide an appropriate therapeutic approach and improve the quality of life of patients affected by this rare medical entity.⁸

TREATMENT

The treatment of Rigid Skin Syndrome (RPS), a rare and complex medical entity characterized by progressive fibrosis of the skin and underlying connective tissues, is a clinical challenge that requires an interdisciplinary and personalized approach to address the heterogeneous and multisystemic clinical manifestations of this disease. Given the scarce scientific evidence and the lack of controlled clinical trials specific to PRS, therapeutic strategies are mainly empirical and aimed at relieving symptoms and improving patients' quality of life.⁹

Therapeutic modalities employed in the management of PRRS include:

Pharmacological Therapy

Immunosuppressants: Corticosteroids, such as prednisone, are occasionally used in moderate doses to control inflammation and reduce the progression of fibrosis.

Immunomodulatory Agents: Drugs such as methotrexate, cyclophosphamide and mycophenolate mofetil have been used in some cases to modulate the immune response and limit fibrosis.⁹

Anti-inflammatory therapy: Nonsteroidal anti-inflammatory drugs (NSAIDs) can help relieve joint pain and inflammation.⁹

Physical Therapy and Rehabilitation

Physical therapy: Used to maintain joint mobility, reduce contracture and improve muscle function.

Occupational Therapy: Focus on adapting activities of daily living to improve functional independence.

Orthoses and Technical Aids: Can be useful to maintain joint function and prevent deformities.⁹

Cutaneous Therapy

Skin Moisturizing: The use of emollients and moisturizers can help improve skin elasticity.⁹

Sun protection: Given the fragility of the skin, it is essential to avoid excessive exposure to the sun and to use appropriate sunscreens.⁹

MANAGEMENT OF SYSTEMIC MANIFESTATIONS

Treatment of pulmonary involvement: In cases of pulmonary fibrosis, antifibrotic drugs and oxygen therapy may be used.¹⁰

Management of Cardiovascular Complications: Pulmonary hypertension and valvular heart disease may require specific treatments.¹⁰

Management of Gastrointestinal Disorders: Pharmacological therapies and dietary measures are used to address problems such as dysphagia and reflux.¹⁰

Psychological and Psychosocial Support: Counseling and psychological support are essential to help patients cope with the emotional and psychosocial implications of PRRS.¹⁰

Research in Emerging Therapies: Given the lack of specific therapeutic options for PRRS, research in emerging therapies, such as gene therapy, targeted antifibrotic therapy and

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selective immunomodulation, represents a field of great promise.

Multidisciplinary management:

Coordination of a multidisciplinary medical team, including rheumatologists, dermatologists, physical therapists, pulmonologists and other specialists as needed, is essential for a comprehensive and effective approach to the management of PRS.

The treatment of PRRS is a clinical challenge involving a variety of therapeutic approaches aimed at mitigating symptoms and improving patients' quality of life. 10

Given the complexity and rarity of this disease, continued research is crucial to develop more targeted and effective therapies in the future.10

CONCLUSION

Rigid Skin Syndrome (RPS), an exquisitely rare and complex medical entity that falls within the spectrum of connective tissue diseases, has emerged as a clinical and scientific challenge in the field of medicine. Through a comprehensive review of its epidemiology, clinical manifestations, and therapeutic options, it becomes clear that RPS represents a paradigm of heterogeneity and multidimensionality in rare diseases.

The evaluation and diagnosis of PRS requires a thorough understanding of its cutaneous and systemic clinical manifestations, in addition to consideration of multiple organ systems that may be affected. The ability to mimic other connective tissue pathologies and the lack of specific biomarkers underscore the need for a comprehensive, multidisciplinary evaluation to achieve an accurate and timely diagnosis.

In the therapeutic setting, current strategies are mainly based on symptomatic relief and preservation of functionality, with the use of immunosuppressive agents, physical therapy, and psychological support measures. However, the lack of specific treatments targeting the underlying mechanism of fibrosis and the absence of controlled clinical trials represent a significant therapeutic gap.

Ongoing scientific research focused on elucidating the molecular etiopathogenesis of PRRS and the development of targeted therapies holds encouraging promise for the future. Gene therapy, modulation of pro-fibrotic signaling pathways and the discovery of predictive biomarkers could change the treatment paradigm and improve the prognosis of affected patients.

Ultimately, Stiff Skin Syndrome is a vivid reminder of the complexity and diversity of the connective tissue disease spectrum. Its study not only sheds light on this particular rare entity, but also offers valuable insights into the pathobiology of fibrosing diseases in general. As we move toward a future characterized by a greater understanding of the molecular and therapeutic basis of PRS, there is hope to improve the lives of

those facing this challenging disease and to contribute to the advancement of medicine as a whole.

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