Review Article **www.ijcps.com**

International Journal of
Chemical and Pharmaceutical Sciences
2024, Dec, Vol. 15 (4)

ISSN: 0976-9390
IJCPS

Distinct Yet Connected: Exploring the Genetic and Clinical Landscapes of Haim-Munk and Papillon-Lefèvre Syndrome

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Received: 15th Nov 2024, Revised and Accepted: 23rd Dec 2024

ABSTRACT

Haim-Munk Syndrome (HMS) and Papillon-Lefèvre Syndrome (PLS) are rare autosomal recessive conditions characterized by shared dermatological and periodontal symptoms resulting from mutations in the cathepsin C (CTSC) gene. Both syndromes display palmoplantar hyperkeratosis and severe early-onset periodontitis but have unique features. HMS is distinguished by arachnodactyly, acro-osteolysis, pes planus, and onychogryphosis, whereas PLS is associated with neurological issues, calcification of the dura mater, excessive sweating, and increased infection susceptibility. Despite sharing the same genetic mutation, the phenotypic differences between these conditions are considerable, making diagnosis and treatment challenging. The estimated incidence of HMS is about one case per million individuals, with fewer than one hundred cases documented. PLS has approximately 300 reported cases, primarily identified in populations with high consanguinity. This review aims to shed light on the genetic and clinical aspects of HMS and PLS, providing insights into their pathophysiology and potential therapeutic approaches to improve our understanding and management of these intriguing genetic disorders.

Methods: This literature review involved a comprehensive search from April to June 2024 using PubMed and Google Scholar. Keywords included "Haim-Munk Syndrome" OR "Papillon-Lefèvre Syndrome") AND ("CTSC gene mutations" OR "palmoplantar hyperkeratosis" OR "early-onset periodontitis"). The review encompasses studies from 1964 to 2023.

Conclusion: Haim-Munk syndrome (HMS) and Papillon-Lefèvre syndrome (PLS) are rare autosomal recessive disorders due to mutations in the CTSC gene. Both are characterized by palmoplantar hyperkeratosis and periodontitis. Understanding the genetic basis, clinical features, and management strategies of these syndromes is crucial due to their impact on patients' lives and their low incidence globally.

Keywords: Haim-Munk Syndrome, Papillon-Lefèvre Syndrome, CTSC, palmoplantar hyperkeratosis, early-onset periodontitis.

1. INTRODUCTION

Haim-Munk syndrome is an exceptionally rare autosomal recessive disorder of keratinization. Clinically, it presents with palmoplantar hyperkeratosis, severe early-onset periodontitis, onychogryphosis, pes planus, arachnodactyly, and acro-osteolysis. Recent genetic research has

identified germ-line mutations in the lysosomal protease cathepsin C gene as the cause of the underlying genetic defect in Haim-Munk syndrome. These mutations are also implicated in other related disorders, including Papillon-Lefèvre syndrome and prepubertal periodontitis. Papillon-Lefèvre syndrome (PLS) was first identified by French physicians Papillon and Lefèvre. This inherited autosomal recessive disease is characterized by abnormalities in keratinization, which manifest as redness and thickening of the skin on the soles and palms. In addition to these skin symptoms, PLS results in severe and destructive periodontal disease, affecting both primary and permanent teeth. The underlying cause of PLS is mutations in the cathepsin C (CTSC) gene, which plays a critical role in the development and function of the immune system. Given the shared genetic foundation and overlapping scientific capabilities of these syndromes, the objective of this literature review is to examine and compare Papillon-Lefèvre syndrome and Haim-Munk syndrome. This review will uncover their epidemiology, genetics, pathophysiology, diagnosis, management, and prognosis. By examining these similarities and differences, the goal is to gain a deeper understanding of the underlying biology and identify more effective strategies for addressing these rare genetic disorders. This literature review is important because it synthesizes current knowledge, highlights gaps in understanding, and provides a comprehensive overview that can inform future research and clinical practices. Increased awareness and understanding of these conditions can lead to improved diagnosis, management, and potentially new therapeutic approaches, ultimately enhancing patient outcomes.

2. METHODS

A comprehensive search was conducted from April to June 2024 using the databases PubMed and Google Scholar. Keywords included: ("Haim-Munk Syndrome" OR "Papillon-Lefèvre Syndrome") AND ("CTSC gene mutations" OR "palmoplantar hyperkeratosis" OR "early-onset periodontitis. Studies not involving human subjects were excluded. The inclusion criteria were peer-reviewed articles, studies with confirmed diagnoses of Haim-Munk Syndrome or Papillon-Lefèvre Syndrome, and research focusing on the CTSC gene mutations, clinical manifestations, and management of these conditions. The range of studies used for this review spans from 1964 to 2023, providing both historical and recent perspectives on these syndromes.

2.2. EPIDEMIOLOGY

Haim-Munk syndrome (HMS) has an estimated incidence of about one case per million individuals, with the majority of reported cases stemming from a few consanguineous families. To date, fewer than one hundred HMS cases have been documented in scientific literature. The ratio of affected males to females is equal for both HMS and Papillon-Lefèvre syndrome (PLS). Consanguinity, which is more common in certain socioeconomic and cultural contexts, plays a significant role in the prevalence of HMS. Further studies are needed to explicitly define the relationship between socioeconomic status and the prevalence or management of HMS.

An evaluation of the literature suggested approximately 200 cases of Papillon-Lefèvre syndrome (PLS). This number has since increased to about 250, predominantly reported by dentists. Over the last few decades, more than half of the global PLS cases have been reported. Notable initial cases were identified among Arab-Iraqi, Saudi, Egyptian, Arab-Jordanian, Qatari, Nigerian, and Yemeni populations. Multiple cases have been documented in families from Egypt, Saudi Arabia, Iran, Yemen, Turkey, and India, frequently involving siblings from consanguineous unions. Currently, over 300 PLS cases have been reported in both dental and medical literature.

2.2. GENETICS

Both HMS and PLS are autosomal recessive disorders resulting from mutations in the cathepsin C (CTSC) gene located on chromosome 11q14. This gene encodes cysteine-lysosomal protease, also known as dipeptidyl-peptidase I, which plays a crucial role in cleaving dipeptides from protein substrates and displaying endopeptidase activity. Currently, 89 mutations within the CTSC gene have been identified, with the bulk located in patients with PLS. Only 4% of those mutations are related to HMS. Both are characterized by palmoplantar keratoderma (PPK) and gum inflammation. HMS is distinguished by unique features such as flat feet, finger deformities evident on X-rays, narrow fingers, bone resorption in the extremities, and abnormal nail growth. In contrast, PLS can present additional symptoms including neurological issues, dura mater calcification, excessive sweating, and increased susceptibility to infections.

Next-generation sequencing has revealed a homozygous variant c.901G>A (p.Gly301Ser) in the CTSC gene. Although 89 mutations in this gene have been documented across various ethnic groups, the majority (75 mutations) are linked to PLS. The presence of this variant (previously associated with PLS in a patient with HMS) is to

the best of our knowledge, a unique finding. Due to the rarity of both PLS and HMS, establishing clear genotype–phenotype correlations has posed challenges in medical research. Notably, CTSC gene expression is prominent in epithelial regions commonly affected by PLS, including the palms, soles, knees, and keratinized oral gingiva. Moreover, it exhibits significant expression levels in various immune cells, such as polymorphonuclear leukocytes (PMNs), macrophages, and their precursors. A diverse array of mutations in the CTSC gene have been identified across individuals from various ethnic backgrounds.

2.3. PATHOPHYSIOLOGY

Haim-Munk Syndrome (HMS)

HMS is a rare genetic disorder associated with mutations in the CTSC gene, which encodes for cathepsin C (Table 1). This condition presents with distinct clinical features including arachnodactyly, acro-osteolysis, pes planus, and nail abnormalities. These manifestations, particularly those related to bone, may arise from specific CTSC mutations or genetic alterations. The pathophysiology of HMS involves disruptions in various biological processes, primarily related to the function of cathepsin C. Cathepsin C, also known as dipeptidyl-peptidase I, plays a crucial role as a lysosomal cysteine proteinase responsible for protein breakdown within cells and activation of numerous serine proteinases in immune-inflammatory cells. It is highly expressed in tissues commonly affected by HMS, including the palmar, plantar, and gingival epithelium, as well as in osteoclasts crucial for bone resorption, modeling, and remodeling.

Impact of Dysregulated Immune System on Bone Metabolism

Osteoclasts, derived from hematopoietic stem cells, play a pivotal role in bone metabolism by resorbing bone tissue, which is essential for remodeling and maintenance of skeletal integrity. Their function is intricately regulated by cytokines, influencing differentiation, fusion into multinucleated cells, and bone-resorbing capacity. Conditions such as HMS and PLS disrupt this balance by altering cytokine levels, which significantly impact osteoclast activity.

Mutations in the CTSC gene impair the function of Cathepsin C, a crucial lysosomal protease involved in activating other proteases necessary for osteoclast activity and bone remodelling. This disruption leads to skeletal abnormalities. The dysregulated immune responses characteristic of HMS and PLS contribute to an inflammatory environment that further exacerbates bone metabolism abnormalities. Imbalances in pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) promote osteoclastogenesis and enhance osteoclast activity.

Papillon-Lefèvre Syndrome (PLS)

Papillon-Lefèvre Syndrome (PLS) shares a genetic foundation with HMS but presents with unique challenges, particularly evident in its dermatological and severe periodontal symptoms. While the precise biological mechanisms at play remain somewhat mysterious, the role of the CTSC gene is critical in maintaining the integrity of tissues, especially around the teeth and in the extremities.

In PLS, periodontitis is not just a matter of bacterial infection - it is a complex condition involving molecules such as free radicals and reactive oxygen species (ROS). These molecules, when overproduced, create oxidative stress, which damages cells and tissues. Neutrophils, essential defenders against microbial invaders, lose their effectiveness when the CTSC gene malfunctions in PLS. This leads to severe periodontitis because the proteases needed to defend against bacteria are impaired.

Impact on the Immune System in PLS

PLS triggers a heightened immune response where neutrophils become hyperactive, releasing more pro-inflammatory cytokines due to ongoing inflammation. However, despite this heightened activity, these same neutrophils paradoxically lose their ability to effectively combat microbes, which worsens oxidative stress in the gums. While overall immune deficiencies in PLS are relatively mild, the localized effects on the gums are profound, highlighting the critical role of neutrophil dysfunction and bacterial infections in driving the disease process.

Understanding these intricate interactions between neutrophil dysfunction, inflammation, and oxidative stress in PLS is crucial for developing treatments that can effectively manage its unique challenges. Further research into these mechanisms holds promise for developing new therapies that can improve the quality of life for individuals affected by this rare genetic disorder.

Table 1: Comparison of Features between Haim-Munk Syndrome (HMS) and Papillon-Lefèvre Syndrome (PLS)

Feature	Haim-Munk Syndrome (HMS)	Papillon-Lefèvre Syndrome (PLS)
Genetic Mutation	CTSC gene on chromosome 11q14	CTSC gene on chromosome 11q14
Inheritance Pattern	Autosomal recessive	Autosomal recessive
Key Symptoms	Palmoplantar hyperkeratosis	Palmoplantar hyperkeratosis
	Severe early-onset periodontitis	Severe early-onset periodontitis
-	Onychogryphosis (thickened, curved nails)	Absence of nail abnormalities
	Arachnodactyly (long, narrow fingers)	No finger abnormalities
-	Acro-osteolysis (bone resorption in phalanges)	No bone resorption
	Pes planus (flat feet)	No flat feet
Periodontitis Severity	Less severe, better tooth retention with early intervention	More severe, early loss of primary and permanent teeth
Skeletal Abnormalities	Present (finger deformities, pes planus)	Absent
Nail Abnormalities	Present (onychodystrophy)	Absent
Other Features	Bone resorption in extremities	Neurological issues
	Abnormal nail growth	Dura mater calcification
		Excessive sweating
-	-	Increased susceptibility to infections
Consanguinity	Often found in consanguineous families	Often found in consanguineous families
Prevalence	Extremely rare, fewer than 100 cases documented	Rare, over 300 cases reported globally

2.4. DIAGNOSIS

HMS and PLS are rare autosomal recessive disorders characterized by overlapping dermatological and periodontal manifestations (Figure 1). Both syndromes typically present with palmoplantar hyperkeratosis, causing significant thickening of the skin on the palms and soles, often leading to painful fissures. The periodontitis associated with these syndromes is aggressive, resulting in early loss of both primary and permanent teeth due to severe gingival inflammation and destruction of the alveolar bone. Despite these similarities, HMS and PLS can be clinically differentiated by their unique features. HMS is distinguished by additional skeletal abnormalities, including onychogryphosis, arachnodactyly, acro-osteolysis, and pes planus. While periodontal involvement in HMS is significant, it is generally considered less severe compared to PLS, which may allow for better retention of teeth with early intervention.

Genetic Basis, Testing, and Differential Diagnosis

Both HMS and PLS are caused by mutations in the Cathepsin C gene located on chromosome 11q14.1-q14.3. This gene is crucial for the normal functioning of epithelial tissues in areas such as the palms, soles, and gingiva. Consanguinity is frequently observed, reflecting the autosomal recessive inheritance pattern of these syndromes.

Laboratory assessments in patients with HMS and PLS often yield normal results but are crucial for ruling out other conditions with similar symptoms, such as leukocyte disorders, mercury or radiation toxicities, and achalasia. Genetic testing for CTSC mutations is essential for a definitive diagnosis and to differentiate between these syndromes and other similar disorders.

COMORBIDITIES

Periodontitis Management, Prosthetic Rehabilitation, Challenges, and Considerations

In PLS, periodontitis is closely associated with high levels of Actinobacillus actinomycetemcomitans, necessitating targeted antibiotic therapy. Managing PLS-related periodontitis is particularly challenging, especially during the mixed dentition stage or later. Despite comprehensive periodontal treatment and antibiotic regimens, the prognosis for controlling periodontal breakdown and minimizing tooth loss remains guarded. Prosthetic rehabilitation is essential for restoring function and aesthetics in patients with HMS and PLS who have suffered extensive tooth loss. Treatment options include complete or partial dentures and consideration for implant-supported prostheses in the future.

While HMS and PLS share many clinical features, the presence of distinct skeletal abnormalities in HMS, coupled with the severity of periodontitis in PLS, aids in their differentiation. Effective management requires a multidisciplinary approach involving dermatologists, periodontists, geneticists, and prosthodontists to address both the dermatological and oral health aspects comprehensively.

2.4. MANAGEMENT

A multidisciplinary approach is essential for managing patients with HMS and PLS, given the complex and multifaceted nature of these conditions.

Skin Manifestations

The management of hyperkeratotic skin lesions HMS and PLS relies significantly on topical treatments and systemic retinoids. Emollients and keratolytics such as salicylic acid and urea play a fundamental role in reducing the thickness of the skin and alleviating discomfort associated with palmoplantar hyperkeratosis. These agents work by softening the keratinized skin and promoting its exfoliation, thereby improving the condition of the palms and soles affected by these syndromes.

In addition to topical therapies, systemic retinoids are essential for managing both keratoderma and aggressive periodontitis in patients with HMS and PLS. Medications such as acitretin, etretinate, and isotretinoin are mainstays in treatment, as they effectively reduce keratin production and inflammation. This dual action not only helps in controlling the skin symptoms but also contributes to improving periodontal health by mitigating the underlying inflammatory processes in the gums and bone. However, the use of long-term retinoid therapy in these syndromes requires careful consideration due to potential side effects, especially in younger patients. While retinoids are generally safe and effective, prolonged use can lead to skeletal abnormalities such as osteoporosis, periosteal thickening, slender long bones, and premature epiphyseal closure. Therefore, close monitoring and regular assessment of bone health are crucial aspects of managing patients on retinoid therapy, particularly children and adolescents with inherited keratinization disorders like HMS and PLS. A multidisciplinary approach involving dermatologists, paediatricians, and dentists is essential to optimize treatment outcomes while minimizing adverse effects associated with systemic retinoid use.

Periodontal Disease

Patients with HMS and PLS often present with severe periodontal disease that proves challenging to manage with standard treatments alone. The aggressive nature of periodontitis in these syndromes necessitates a collaborative approach for effective therapeutic strategies. Primary teeth extraction is frequently required to halt the progression of periodontal damage and prevent further infection spread, which can compromise overall oral health. Additionally, oral antibiotics play a crucial role in controlling bacterial infections associated with periodontitis in HMS and PLS, contributing significantly to treatment efficacy.

Regular and professional dental cleanings are essential components of management, helping to mitigate the impact of periodontal disease and maintain optimal oral hygiene. Given the complex nature of these conditions, collaborative care involving dermatologists, dentists, periodontists, and other healthcare professionals is indispensable. This approach ensures comprehensive evaluation, tailored treatment plans, and ongoing monitoring to enhance the quality of life and oral health outcomes for individuals affected by HMS and PLS.

2.5. PROGNOSIS

PLS patients with partial edentulism and implant-supported prostheses who do not adhere to a regular maintenance program are at a significantly higher risk of developing peri-implantitis and experiencing implant loss.

It is crucial to recognize that environmental and lifestyle factors may also contribute to these phenotypic differences in addition to genetic factors. Further functional studies are needed to confirm the clinical relevance of the identified phenotype-modifying genetic factors and to elucidate the mechanisms underlying their effects. Our literature review adds to the growing body of evidence emphasizing the clinical importance of phenotype-modifying genetic factors and their potential to enhance the understanding of genotype-phenotype correlations and disease prognosis.

2.6. FUTURE DIRECTIONS

To determine whether PLS and HMS are the same syndrome or distinct entities, mutational genetic analysis is necessary. Special attention should be given to the early management of skeletal manifestations in HMS. Our literature review provides additional evidence that HMS and PLS are allelic variants resulting from mutations in the cathepsin C gene. It also suggests that other genetic or environmental factors may significantly influence the clinical presentation of these conditions, highlighting the need for further research.

3. CONCLUSION

HMS and PLS are rare autosomal recessive disorders characterized by palmoplantar hyperkeratosis and severe periodontitis, with mutations in the CTSC gene. While HMS presents with additional skeletal abnormalities, PLS primarily manifests with aggressive periodontitis. Understanding the genetic basis, clinical features, and management strategies of these syndromes is essential due to their rarity and significant impact on patients lives. Both have exceptionally low incidences globally, often found in consanguineous families. Genetic analysis has identified various mutations in the CTSC gene associated with both syndromes, contributing to our understanding of their genetic etiology. Despite their rarity, these syndromes highlight the importance of genetic factors in dermatological and periodontal health and underscore the need for further research into their pathophysiological mechanisms.

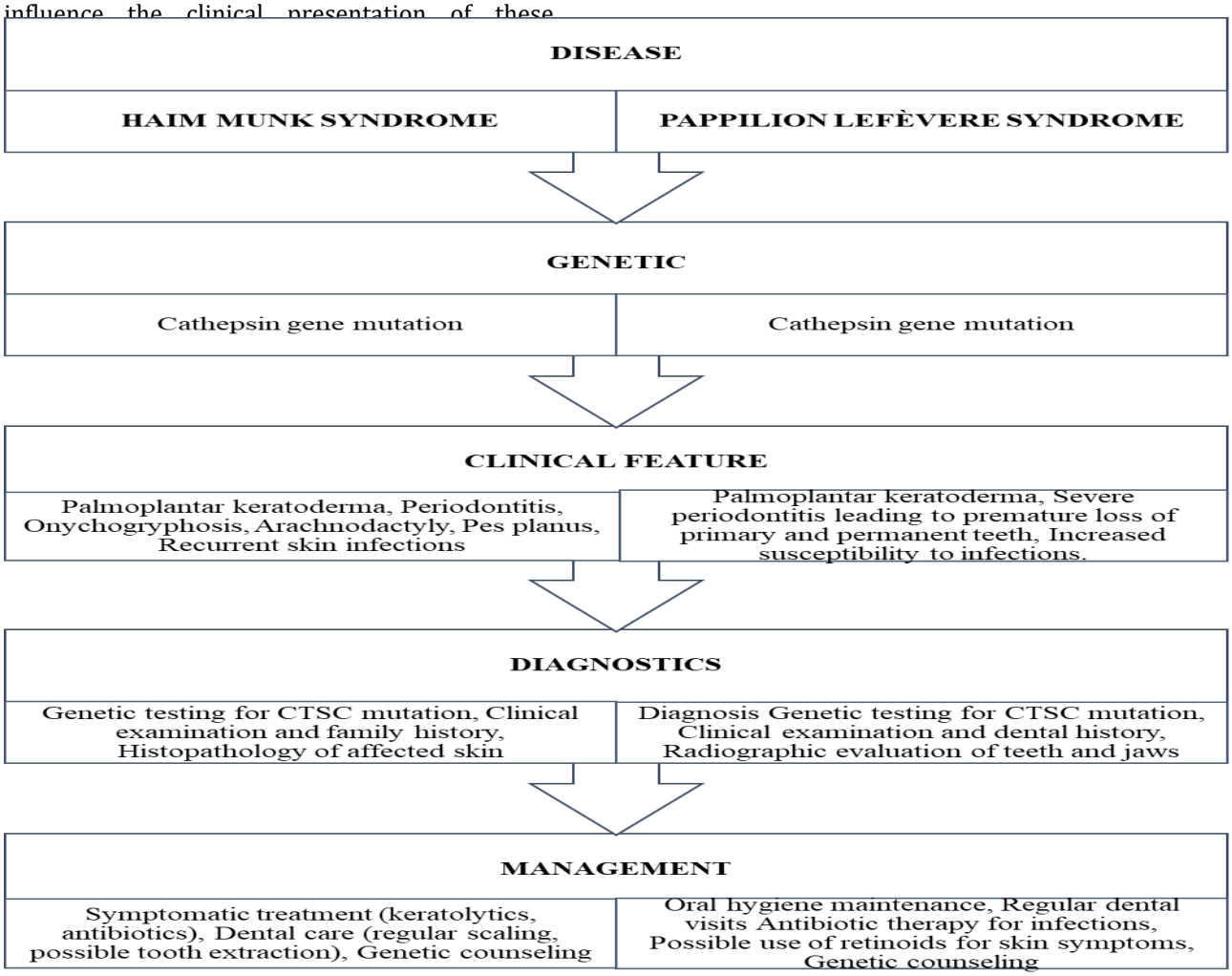

Figure 1: Comparison between Haim Munk Syndrome and Papillion Lefèvre Syndrome

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