International Medicine
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Research Article

Section: Dermatology and Venereology

H SYNDROME: An Exceptional Case of Non-Langerhans Histiocytosis with Clinical and Genetic Insights

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ARTICLE INFO

Article History:

Received: 11-10-2024

Accepted: 12-11-2024

Keywords:

H syndrome

Genodermatosis

Histiocytosis

Hyperpigmentation

Hypertrichosis.

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ABSTRACT

H syndrome is a rare autosomal recessive genodermatosis characterized by a unique form of non-Langerhans histiocytosis caused by mutations in the SLC29A3 gene, which encodes the nucleoside transporter hENT3. This condition leads to impaired nucleoside transport, resulting in exaggerated inflammatory responses and abnormal histiocytic proliferation. We report a 28-year-old Moroccan man presenting with hyperpigmentation and hypertrichosis of the lower limbs for over 20 years, accompanied by hearing loss, cardiac anomalies, and spinal deformities. Genetic analysis revealed compound heterozygosity for pathogenic variants in the SLC29A3 gene, confirming the diagnosis of H syndrome. H syndrome typically manifests with cutaneous symptoms such as hyperpigmentation and hypertrichosis, as well as systemic issues including hearing loss, cardiac anomalies, short stature, and diabetes. The wide phenotypic variability complicates diagnosis and management. Recognizing the genetic basis of H syndrome is essential for accurate diagnosis and appropriate management. While systemic corticosteroids have shown some effectiveness, no consensus on optimal treatment exists due to the condition's complexity and rarity. Early identification and genetic counseling are critical for affected families. H syndrome is an exceptionally rare condition with diverse clinical manifestations, highlighting the need for awareness and accurate diagnosis to prevent unnecessary interventions.

INTRODUCTION

H syndrome is a rare autosomal recessive genodermatosis; characterized by a novel form of non-Langerhans histiocytosis resulting from a mutation in the SLC29A3 gene, which encodes the nucleoside transport protein hENT3 [1]. hENT3 is essential for the intracellular transport of nucleosides, including adenosine, and plays a crucial role in regulating the salvage pathway of DNA synthesis and histiocyte-mediated apoptotic cell clearance. Mutations in SLC29A3 gene, which encodes hENT3, disrupt this function, leading to impaired phagocytosis. As a result, this leads to exaggerated inflammatory responses and abnormal histiocytic proliferation, presenting as skin sclerosis and hypertrichosis [2] [3]. The interaction between histiocytes and fibroblasts following tissue injury is vital in the development of fibrosis [4]. Hypertrichosis may result from the disruption of the unique dermal sheath cell population caused by infiltrating histiocytes [5].

H syndrome presents with a range of cutaneous and systemic features, many of which begin with the letter "H". Symmetrical cutaneous Hyperpigmentation and Hypertrichosis of the inner tight accompanied by sclerodermatous induration, Hearing loss, Heart anomalies, low Height, Hypogonadism and Hepatosplenomegaly. Systemic features of H syndrome include arthritis, joint deformity, gynecomastia, anemia, hyperglycemia and hypertriglyceridemia [1].

To date, a total of 79 cases were reported by Molho et al [1] and approximately 124 cases have been identified through a PubMed database search until September 2024.

CASE REPORT

A 28-year-old Moroccan man; presented to the outpatient department with hyperpigmentation and hypertrichosis of the lower limbs for over 20 years. The patient also had hearing loss for more than 6 years, for which he was using a hearing aid. Additionally, he was followed up for cardiac anomalies and spinal deformities. The patient was born after a normal pregnancy to unrelated parents, and the siblings were reported to be in good health.

On physical examination, a well-defined hyperpigmented and sclerotic patches with localized hypertrichosis were observed, bilaterally and symmetrically distributed on the inner thighs extending up to the pubis, sparing the knees (Figure 1). Additionally, scrotal masses were also noted. The patient exhibited a height below the normal range for their age.

Laboratory test results indicated that the fasting blood glucose and HbA1c levels were within normal ranges. However, C-reactive protein (CRP) level was elevated at 26 mg/L (normal < 5 mg/L), suggesting inflammation. Cytopenia was not observed.

Following informed consent and approval from the Institutional Ethics Committee, a genetic study was performed, revealing compound heterozygosity for two pathogenic variants in the SLC29A3 gene through whole exome sequencing and analysis under a rare recessive disease model. Segregation analysis using Sanger sequencing in available family members demonstrated a pattern of recessive inheritance. This mutation substitutes Gly427 with Ser at the C-terminus of hENT3, leading to a partial loss of nucleoside transport and decreased stability.

To date, only 20 mutations related to H syndrome have been identified [6]. The range of phenotypes associated with SLC29A3 mutations is notably diverse, varying from severe manifestations, as observed in our patient, to milder clinical presentation. Currently, no link has been established between specific mutations and distinct clinical features. Interestingly, individuals exhibiting mild symptoms have been discovered through mutation screening in families with members who have severe forms of the syndrome [1].

DISCUSSION

H Syndrome, a rare form of non-Langerhans histiocytosis, is characterized by a spectrum of clinical manifestations that can complicate diagnosis and management. The protean nature of this syndrome often leads to misdiagnosis, as affected individuals may present with various symptoms that do not immediately suggest a systemic disorder. The patient presented with multiple visceral pathologies; however, no specialist had managed to establish a systemic association between these conditions. During his consultation with our dermatology team, we reassessed his condition and refined the diagnosis. Through thorough analysis and additional examinations, we confirmed the diagnosis of H syndrome.

The clinical features of H Syndrome (Table 1) typically include skin changes found in 68% of cases, such as pigmented and sclerodermatous plaques (91%), and hypertrichosis (68%) of the inner thighs, which typically spare the knees. Telangiectasias and hypopigmentation can also be observed in some cases. In addition to the classic cutaneous features, H Syndrome presents with a wide range of systemic manifestations, including flexion contractures of the proximal interphalangeal joints (56%), short stature (49%), diabetes, hepatosplenomegaly (40%), hallux valgus (25%), hearing loss, hyperglycemia, and various cardiac anomalies, which constitute a major prognostic factor. Diffuse lymphadenopathy may be present in 24% of cases. Furthermore, this syndrome is classified within the spectrum of monogenic autoinflammatory diseases, with 25% of patients experiencing autoinflammatory complications such as recurrent febrile episodes, persistently elevated acute phase reactants, or fibrosis. In our patient, hearing loss, a cardiac anomaly, skeletal deformity of the spine, and scrotal masses were found.

Table 1: Comparison of Clinical and Biological Findings in H Syndrome: Our Patient Vs. Literature Reports

Clinical and Biological Findings Reported in the Literature	Patient's Case
Skin Manifestations	Yes
Hearing Loss	Yes
Cardiac anomaly	Yes
Joint Stiffness	No
Arthritis	No
Short Stature	Yes
Hepatosplenomegaly	No
Lymphadenopathy	No
Scrotal masses	Yes
Micropenis	No
Agenesis of the inferior vena cava	No
Proptosis or Exophthalmos	No
Recurrent febrile episodes	No
Diabetes	No
Anemia	No
Hypertriglyceridemia	No
Mutations in SLC29A3	Yes

Histological examination normally reveals dermal and subcutaneous fibrosis accompanied by a lymphohistiocytic infiltrate that expresses CD68, CD34, and factor XIIIa. These histopathological characteristics, similar to those of Rosai-Dorfman syndrome, may suggest a common pathogenic mechanism for these two entities. However, histological analyses have limitations. Biopsies of lymph nodes or infiltrated tissues may assist clinicians in identifying histopathological characteristics (such as CD163, CD68, CD1a, PS100, and Langerin); nonetheless, there are no specific features that define H syndrome.'[7]

Recognizing the genetic basis of H syndrome is essential for accurate diagnosis and effective management. Genetic testing can confirm the presence of mutations in the SLC29A3 gene [8], as observed in our patient. This confirmation facilitates early identification and ensures that affected families receive appropriate genetic counseling. Understanding the hereditary nature of the disorder empowers families to make informed decisions regarding reproduction and the potential risks for future offspring.

Given the complexities associated with H syndrome, no consensus exists on the optimal treatment approach. Systemic corticosteroids have shown positive results in managing H syndrome, although they can lead to significant long-term side effects, particularly in diabetic patients[9]. In contrast, colchicine, anti-IL1 agents, and Tumor Necrosis Factor (TNF)-alpha therapies appear to be ineffective [10]. Some patients have experienced partial improvement with methotrexate, resulting in notable enhancements in hyperpigmentation, joint stiffness, and arthritis [11]. Methotrexate can be combined with Tocilizumab or Ciclosporine to improve disease management [12], [13]. While Ciclosporine has generally alleviated symptoms, it has not effectively addressed arthritis and persistent inflammation[12]. Additionally, mycophenolate mofetil has shown promising results in reducing hyperpigmentation and joint stiffness [14]. Notably, Tocilizumab demonstrates greater efficacy in treating inflammatory manifestations such as arthritis and organ infiltration[9].

CONCLUSION

H syndrome is an exceptionally rare condition, with approximately 124 cases reported to date. This report highlights that H syndrome, resulting from mutations in the SLC29A3 gene, is associated with a diverse array of intricate clinical manifestations. Given the absence of a definitive treatment for this rare disorder, recognizing this condition is crucial to avoid unnecessary interventions aimed at addressing cutaneous manifestations.

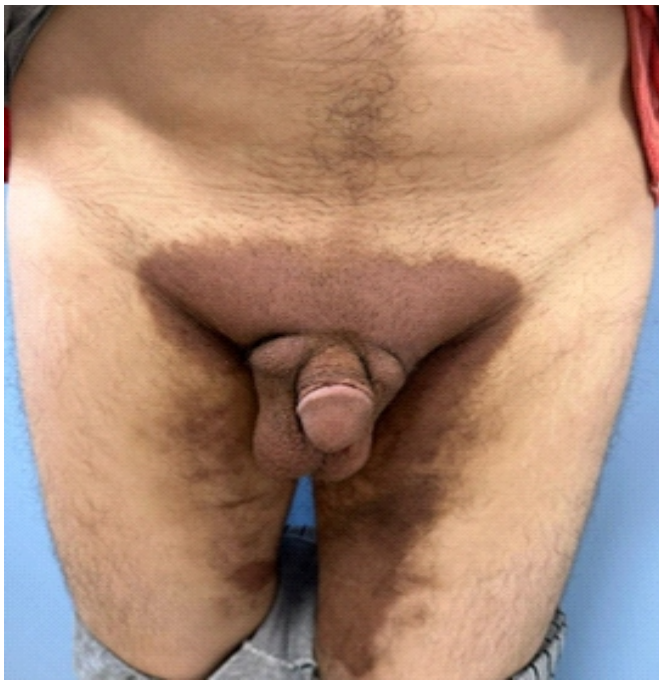

Figure 1: Hyperpigmented, Indurated Plaques with Marked Hypertrichosis Arranged Symmetrically Over Inner Thighs

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How to cite: El Haddad Meriem, El Jouari Ouiame, Rkiek Yasmine, Gallouj Salim. H SYNDROME: An Exceptional Case of Non-Langerhans Histiocytosis with Clinical and Genetic Insights. *International Medicine, 2024;10(2):1-4..*