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ORIGINAL RESEARCH

# Cases with the H syndrome presenting with skin and bone findings

**Hulya Kose MD** | **Merve Deniz Baskaya MD** | **Sara Sebnem Kilic MD**

Department of Pediatric Immunology and Rheumatology, Uludag University Faculty of Medicine, Bursa, Turkey

**Correspondence**
Sara Sebnem Kilic, Department of Pediatric Immunology and Rheumatology, Uludag University School of Medicine, Görükle-Bursa 16059, Turkey.
Email: sebnemkl@uludag.edu.tr

**Abstract**

**Background:** The H syndrome is an autosomal recessive disease characterized by hyperpigmentation, hypertrichosis and sensorineural hearing loss.

**Methods:** A mutation in the coding of the human equilibrative nucleoside transporter 3 (hENT3) within the SLC29A3 gene on chromosome 10q22 leads to the manifestation of this disease. In this report, we present two cases of H syndrome.

**Results:** The first patient exhibits hyperpigmentation, hypogonadism, Type 1 diabetes mellitus, arthritis and osteoporosis. The second patient experiences hyperpigmentation, hypertrichosis, osteopenia and hypogonadism.

**Conclusion:** Our objective is to broaden the clinical spectrum of H syndrome, highlighting the involvement of arthritis, hyperinflammation and low bone mineral density in individuals with this disorder.

KEYWORDS

H syndrome, hENT3, hyperpigmentation, hypertricosis, osteoporosis

## INTRODUCTION

The H syndrome, an autosomal recessive disease, causes skin findings (hyperpigmentation and hypertrichosis) and has characteristic features such as sensorineural hearing loss and deformities.[1] Patients commonly with hepatosplenomegaly, heart anomalies, growth retardation, hyperglycemia, hemolytic anemia and hypogonadism.[2-4] The etiology of this disease is attributed to mutations within the SLC29A3 gene, encoding the human equilibrative nucleoside transporter 3 (hENT3), located on chromosome 10q22, either in a homozygous or compound heterozygous form.[5] These mutations likely impact nucleoside pools in the membranes of mitochondria and lysosomes, disrupting the homeostatic functions of these organelles, which are dependent on hENT3 substrates. Consequently, cell proliferation may be affected, and apoptosis may not be initiated.[5]

Clinical studies have revealed a range of manifestations, with some patients experiencing joint swelling, recurrent fever, hyperinflammation, and osteopenia.[5,6] Previous research indicates that hENT3 is crucial in facilitating mitochondrial and lysosomal functions, affecting cell proliferation and apoptosis. Elevated acute phase reactant values, similar to hyperinflammatory periodic fever syndrome, can be observed in patients with H syndrome.[7]

This report presents two cases of H syndrome, with one exhibiting hyperinflammation and osteopenia and the other presenting with arthritis and osteoporosis. This report aims to provide an overview of the symptoms and conditions observed in these cases, contributing to a better understanding of H syndrome and improving treatment options for affected individuals. Informed consent was taken from both patients.

## CASE PRESENTATIONS

### Case 1

A 17-year-old male patient with relative parents was referred to us due to contractures in his fingers, hallux

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valgus and swelling in the left elbow. His medical history includes growth retardation, type 1 diabetes mellitus, and congenital heart anomalies. He underwent growth hormone replacement therapy for 2 years due to growth hormone deficiency. At the age of 16, he developed autoimmune hemolytic anaemia and hepatosteatosis. Due to gonadal insufficiency, he is currently undergoing treatment for testosterone deficiency.

During the physical examination, deformities were observed in the patient's hands. Additionally, there were hallux valgus, hyperpigmentation and hypertrichosis in the bilateral thigh areas. Furthermore, the right elbow region displayed signs of swelling and redness, as depicted in Figure 1. Based on the laboratory findings, the acute phase reactants have been elevated beyond the normal range (Table 1).

Anti-nuclear antibody (ANA), rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) were negative. Genetic analysis detected a homozygous mutation in the SLC29A3 gene (c.1A > GT; T).

His calcium, phosphorus and ALP levels were within the normal range. However, his parathormone level was high at 140 pg/mL (normal range: 21.8–87.5), and his 25 OH vitamin D level was low at 5 ng/mL (normal range: 20–50). A dual-energy X-ray absorptiometry scan (DEXA scan) demonstrated osteoporosis (z score was – 3.1). An MRI scan of the left elbow revealed synovitis and effusion at the olecranon level. Consequently, the patient was put on methotrexate treatment due to arthritis and systemic inflammatory symptoms. Two months later, the symptoms of arthritis had significantly reduced. About a month ago, he started experiencing pain and inflammation in his right ankle, which was later diagnosed as arthritis. Consequently, he began taking etanercept medication to alleviate the symptoms.

## Case 2

A 20-year-old male patient from a family with a history of consanguinity developed hypertrichosis and hyperpigmentation in the groin, abdomen, waist and upper inner thigh areas at the age of 1. Sensorineural hearing loss was diagnosed at the age of 1.5, and he underwent cochlear implant surgery at 6 years of age.

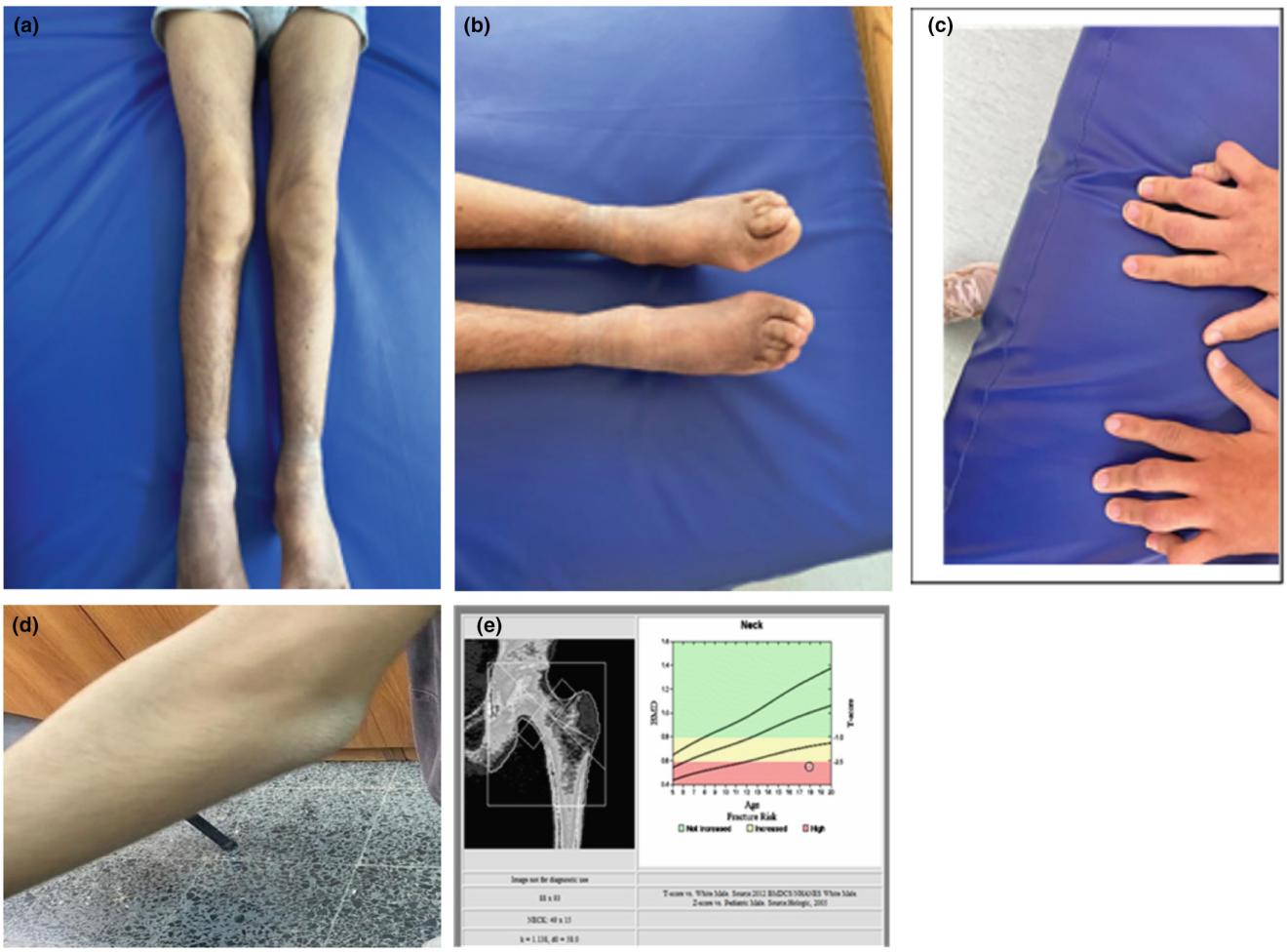



FIGURE 1 (a) Hyperpigmentation, (b) hypertricosis, (c) deformities, (d) arthritis in the left elbow joint and (e) the DEXA scan report.

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The physical examination assessed hypertrichosis in the inguinal, thigh, axillary and lower extremities. A hallux valgus deformity of the toe fingers was noticed (Figure 2).

Laboratory investigations revealed hyperinflammation, with inflammatory markers provided in Table 1. Immunoglobulin levels were IgA 247 mg/dL (139-373), IgM 31 mg/dL (88–322) and IgG 1290 mg/dL (913–288). Hormonal analysis showed follicle-stimulating hormone (FSH) at 39.2 (0.9–11.5 IU/L), luteinizing hormone (LH) at 16.4 (0.57–12.07 IU/L), total testosterone at 731 (240–870 ng/dL) and dihydroepiandrostenodion sulfate (DHEA-Sulfate) at 196.1 (238.4–539.3). The parathormone level was elevated at 107 pg/mL (normal range: 15.8–60). The 25 OH vitamin D level was low at 8.1 ng/mL (normal range: 20–50), while calcium and phosphorus levels were within normal limits. The results of a bone density scan (DEXA, dual-energy X-ray absorptiometry scan) showed that the patient had osteopenia (z score was – 1.2).

The SLC29A3 gene was found to have a homozygous mutation (p.Glu447Lys) using Sanger sequencing. After performing the skin biopsy, immunohistochemical staining confirmed the presence of PAS, CD68, CD1a, CD117 and S100. Our patients' detailed clinical and laboratory findings are given in Table 2.

## DISCUSSION

The disease known as H syndrome or SLC29A spectrum disorder is caused by a defect in the gene that encodes the human equilibrative nucleoside transporter 3 (hENT3). First described by Molho-Pessach in 2008,[1] the transport mechanism involves the movement of free nucleotides from endosomes, lysosomes, and cytoplasm to the inner mitochondrial membrane. Human ENT3 (hENT3) is located in the cell's late endosomes/lysosomes/mitochondria and may impact macrophage homeostasis and function.[8] It is likely to transport nucleotides from the lysosomal and mitochondrial membranes to the cytoplasm, maintaining a cytoplasmic nucleotide pool for various cellular pathways.[9] A defective SLC29A3 gene can lead to abnormal trafficking of lysosomal nucleotides, causing a change in the cytoplasmic pool, which, in turn, increases lysosomal pH and blocks some cellular pathways.

On the other hand, the deficiency of ENT3 results in a loss of lysosome integrity, leading to the accumulation of mitochondria and an increase in cellular reactive oxygen species (ROS).[9] However, the exact relationship between hENT3 and the pathophysiology of these disorders has yet to be clearly defined. Patients may experience a variety of symptoms, including hypertrichosis, hyperpigmentation, hypogonadism, hyperglycemia, hearing loss, hallux valgus and foot anomalies. Additionally, hepatosplenomegaly and direct Coombs-positive hemolytic anemia are commonly observed. According to Molho-Pessach et al.,[1] hypogonadism was found in 16% of their series, and we also identified hypogonadism in both of our patients.

Bloom et al. were the first to publish about immunodeficiencies, such as low levels of IgG2, IgG4, and B memory cells.[10] Our first patient has deficiencies in IgM, IgG2, IgG4, and memory B cells. Both of our patients have

**TABLE 1** Inflammatory markers and immunological values of the patients.

| | CRP (mg/dL) | Sedimentation rate (mm/h) | Fibrinogen | Serum amyloid A | IgM | IgG2 | IgG4 |
|---|---|---|---|---|---|---|---|
| | Reference level (0–5) | Reference level (2–20) | Reference level (180–350) | Reference level (0,8–6,8) | 84–230 | 81–472 | 5–198 |
| Patient 1 | 81,5 | 120 | 595 | 457 | 35 | 71 | <4 |
| Patient 2 | 27,6 | 20 | 358 | 86 | 31 | 182 | 9 |

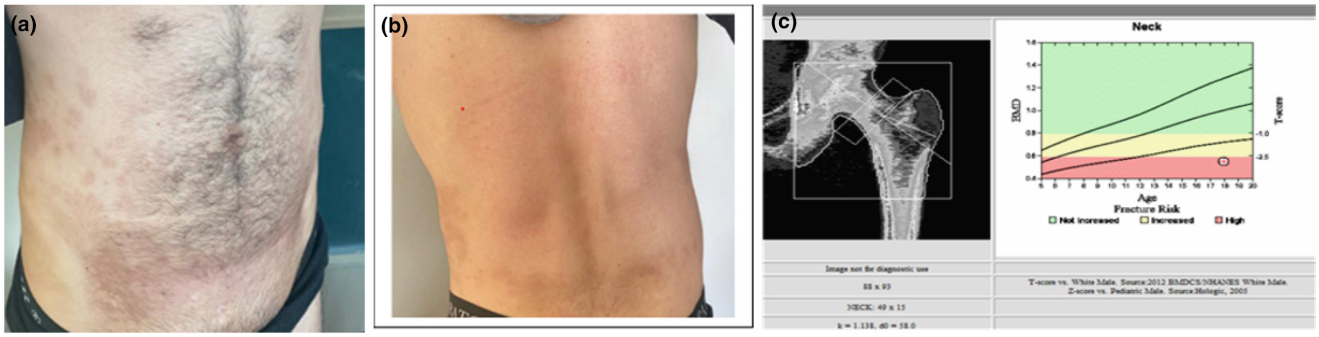



**FIGURE 2** (a) Hypertricosis, (b) hyperpigmentation and (c) dexa scan of the second patient.

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**TABLE 2** Clinical findings of the patients.

| | Patient 1 | Patient 2 |
|---|---|---|
| Hyperpigmentation | + | + |
| Hypertrichosis | + | + |
| Hyperglycemia | + | − |
| Heart defects | + | − |
| Hearing loss | + | + |
| Osteopenia or osteoporosis | + | + |
| Histopathology: a dense infiltration of histiocytes in the dermal and subcutaneous layers, progressing to fibrosis | N/A | + |
| Flexion deformities | + | − |
| Arthritis | + | − |
| Growth retardation | + | + |
| Hypogonadism | + | + |
| Autoimmune hemolytic anemia | + | − |
| Immune abnormalities (selective IgM deficiency) | + | + |

selective IgM deficiency and memory B-cell deficiency. The precise etiology underlying the immunodeficiency manifested in these patients remains unclear and requires further investigation.

There have been a few reports of patients with recurrent fever, some of which are accompanied by joint inflammation.[10,11] Our first patient had arthritis and hyperinflammation. Upon examination of the blood monocyte subgroups, an increased ratio of proinflammatory CD14+CD16 cells and CD14+CD16+ non-classical monocytes was found compared to the healthy control. Laboratory results often reveal chronic elevation of inflammatory markers. Methotrexate treatment was started, and clinical regression was observed in both skin findings and arthritis, but right ankle arthritis developed, and etanercept was added to the treatment. In the literature, various therapies, including steroids, IL-6, IL-1, TNF alpha-blockers, and methotrexate, have been utilized.[10,11]

The skin biopsy of Patient 2 revealed that CD1a was present in CD68 and S-100 histiocytes, which are cells originating from monocytes, histocytes, and dendrites. People with Rosai Dorfman syndrome[13] can exhibit symptoms such as epidermal hyperplasia, dermal infiltration of histiocytes (with CD68 and S100 staining in tissues), lymphocytes, and plasma cells, and sometimes hemosiderin and calcification, according to published cases. H syndrome patients have primary cells in their dermis with antigenic signatures similar to monocyte-derived cells. The infiltrating cells have CD68 and S-100 immunophenotypes identical to RDD, but their CD1a positivity different. The activation of M1-type monocytes may be responsible for the skin findings and systemic hyperinflammation.

Both patients have low vitamin D secondary hyperparathyroidism and inadequate bone mineral density, possibly due to malabsorption, which can be seen in these patients,[1] insufficient sunlight, and chronic inflammation. Chronic inflammation has a negative impact on bone metabolism and is commonly linked to osteoporosis.[13] Various immune system mediators, including the proinflammatory cytokines TNF-a, IL-1β, IL-6 or interferon-gamma, govern bone loss. The development of osteoporosis is facilitated by a complex group of mediators, including TNF-α, IL-1, IL-6, IFN-γ, RANK, RANKL or osteoprotegerin, that regulate bone remodeling and activate osteoclasts.[14]

## CONCLUSION

Our findings have shown that patients diagnosed with H syndrome demonstrate significant cases of systemic hyperinflammation and are at risk of developing osteoporosis or osteopenia. It is essential to maintain close monitoring of the bone health of these patients to facilitate early intervention if necessary.

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### CONFLICT OF INTEREST STATEMENT
We declared that we have no commercial, financial and other relationships in any way related to the subject of this article all that might create any potential conflict of interest.

### DATA AVAILABILITY STATEMENT
The authors confirm that the data supporting the findings in the study are available within the article.

### ETHICAL APPROVAL
The ethics committee concluded that patient consent was sufficient for a case report since it was not a clinical trial, so ethics committee approval was unnecessary.

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## ORCID

*Hulya Kose* https://orcid.org/0000-0002-5727-4075
*Merve Deniz Baskaya* https://orcid.org/0009-0003-9406-7889
*Sara Sebnem Kilic* https://orcid.org/0000-0001-8571-2581

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