H Syndrome: A Case Report and Review of Literature
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Abstract

H syndrome is a rare autosomal recessive syndrome characterised by constellation of clinical features and systemic manifestations including cutaneous hyperpigmentation, hypertrichosis, hepatosplenomegaly, hearing loss, heart anomalies, hypogonadism, hyperglycaemia, low height, and hallux valgus. We report a case of this syndrome with typical clinical findings. We report this case citing the rarity of this uncommon entity.

Key Words: Genodermatosis, H syndrome, histiocytosis

Introduction

H syndrome is an autosomal recessive genodermatosis caused by the mutations in the SLC29A3 gene which encodes the human equilibrative nucleoside transporter 3 (hENT3), a protein found in endosomes, lysosomes, and mitochondria. It was first described by Molho-Pessach et al in 2008, also naming it H syndrome considering the fact most of the clinical features start with the letter “H.” Thereafter, about 100 patients of H syndrome have been described worldwide. It is now considered a novel form of histiocytosis.

Symmetrical cutaneous hyperpigmentation involving inner thighs accompanied by hypertrichosis and sclerodermatous induration are the most common features observed and considered hallmark of the disease.

Case Report

A 13-year-old boy born out of a consanguineous marriage presented to the outpatient department with hyperpigmentation and hypertrichosis of lower extremities and trunk for last 4 years. The patient also had hearing loss for more than 5 years which was progressive and was using hearing aid for the same. There was no family history of similar skin changes.

On mucocutaneous examination well defined, bilaterally symmetrical hyperpigmented, indurated plaques with marked hypertrichosis were present over medial aspect of thighs and legs [Figure 1a-c]. Knees and feet were spared. Similar lesions were present over sacral area and lower back bilaterally [Figure 1d]. General physical examinations showed mild hepatomegaly and pallor. He had short stature for his age (131 vs. 154 cm). Hallux valgus was also present [Figure 2].

Routine laboratory investigations revealed haemoglobin to be 6.7 g/dl. Liver function tests, thyroid profile, serum cortisol (15.25 µg/dL), and blood sugar were normal. Chest X-ray was normal. Antinuclear antibody was negative. Growth hormone level was reduced to 0.77 ng/ml (normal range 1–14.4 ng/ml). Serum Vitamin D3 level (51.88 vs. 81–250 nmol/L) was found to be low. No “M” spike was seen in serum protein electrophoresis.

Ultrasonography (USG) abdomen revealed mild hepatomegaly. USG of scrotum was normal. Contrast enhanced computed tomography head, and orbit revealed bilateral mild axial proptosis.

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Skin biopsy was taken from the hyperpigmented plaque on the thigh and revealed mild irregular acanthosis, and increased melanin deposition in basal keratinocytes. Significant thickening of collagen bundles in upper and mid-dermis was seen along with perivascular infiltrate of histiocytes. Immunohistochemistry was positive for CD68 and CD45 in dermal perivascular histiocytic infiltrate and for CD34+ in vessel endothelium [Figure 3].

The final diagnosis of H syndrome was made based on the characteristic clinical and histopathological findings.

**Discussion**

H syndrome is a novel form of histiocytosis which involves multiple systems. The characteristic cutaneous features of the disorder are cutaneous hyperpigmentation, overlying hypertrichosis, and sclerodermatous thickening.[4] Genetic mutational analysis aids in confirmation of the diagnosis when characteristic cutaneous changes are absent. Mutations in SLC29A3 gene which encodes for the hENT3 resulting in this disorder.[2] Besides the classical cutaneous features, a plethora of other systemic manifestations can be seen in H syndrome including low height, hearing loss, hyperglycaemia, flexion contractures, hallux valgus, hepatosplenomegaly, and various heart anomalies.[3] Among the various cardiac anomalies, pericardial involvement is seen to be the most common which was ruled out in our patient by a normal echocardiogram. Various haematologic abnormalities have been described in H syndrome including severe anaemia with reticulocytopenia, pancytopenia, red cell aplasia, and myelofibrosis.[5] Severe anaemia was present in the present case. Although not present in our patient, insulin-dependent diabetes mellitus may be the sole presentation in a few patients.[4] Other novel clinical features that have been described are pancreatic exocrine deficiency,[7] recurrent febrile episodes,[1] and complete agenesis of the inferior vena cava with varicose veins.[6] Proptosis or exophthalmos has been described as a feature of H syndrome which was also seen in the present case.[9]

In one case series, lymphadenopathy was present in 24% of patients. Inguinal, cervical, and axillary nodes are usually the most commonly affected lymph nodes.[3] Lymphadenopathy may be generalised or localised. Massive lymphadenopathy as noted in Rosai-Dorfman disease (RDD) can also be seen.

H syndrome might have histopathological features similar to RDD, including CD68+ S100+ CD1a – histiocytes with emperiploesis.[1] The histopathologic similarity to RDD suggests a common pathogenesis.

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome were considered for the differential diagnosis in the present case, but the absence of M protein, endocrinopathy, angiomas, and leg oedema helped in ruling it out. Approximately 100 cases of H syndrome have been reported till date, with a total of 10 cases from the Indian subcontinent.[10] No definitive treatment of this rare disorder exists which makes it important to recognise this entity; thus, avoiding unnecessary interventions for treating cutaneous manifestations. Genetic counselling may play an important role in the management.

Given the rarity of this condition, the diagnosis might be missed which could be detrimental to the patient considering the involvement of various systems such as heart, blood, kidneys, endocrine, and eye.
Conclusion

H syndrome is an extremely rarely reported entity more so in the Indian subcontinent with only 10 cases reported from India till now in the literature. We present this case to increase the awareness of this extremely rare and unique entity.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient had given his consent for his images and other clinical information to be reported in the journal. The patient understood that his name and initial would not be published and due efforts would be given to conceal his identity, but anonymity could not be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

What is new?

- H syndrome is an extremely rarely reported entity with only 10 cases reported from India till now
- Presence of symmetrical/hyperpigmentation with hypertrichosis in characteristic areas should raise suspicion

References

1. Molho-Pessach V, Agha Z, Aamar S, Glaser B, Doviner V, Hiller N, et al. The H syndrome: A genodermatosis characterized by indurated, hyperpigmented, and hypertrichotic skin with systemic manifestations. J Am Acad Dermatol 2008;59:79-85.
2. Molho-Pessach V, Lerer I, Abeliovich D, Agha Z, Abu Libdeh A, Broshtilova V, et al. The H syndrome is caused by mutations in the nucleoside transporter hENT3. Am J Hum Genet 2008;83:529-34.
3. Molho-Pessach V, Ramot Y, Camille F, Doviner V, Babay S, Luis SJ, et al. H syndrome: The first 79 patients. J Am Acad Dermatol 2014;70:80-8.
4. Tekin B, Atay Z, Ergun T, Can M, Tuney D, Babay S, et al. H syndrome: A multifaceted histiocytic disorder with hyperpigmentation and hypertrichosis. Acta Derm Venereol 2015;95:1021-3.
5. Avitan-Hersh E, Mandel H, Indelman M, Bar-Joseph G, Zlotogorski A, Bergman R, et al. A case of H syndrome showing immunophenotype similarities to Rosai-Dorfman disease. Am J Dermatopathol 2011;33:47-51.
6. Broshtilova V, Ramot Y, Molho-Pessach V, Zlotogorski A. Diabetes mellitus may be the earliest and sole manifestation of the H syndrome. Diabet Med 2009;26:1179-80.
7. Hussain K, Padidela R, Kapoor RR, James C, Banerjee K, Harper J, et al. Diabetes mellitus, exocrine pancreatic deficiency, hypertrichosis, hyperpigmentation, and chronic inflammation: Confirmation of a syndrome. Pediatr Diabetes 2009;10:193-7.
8. Mutlu GY, Ramot Y, Babaoglu K, Altun G, Zlotogorski A, Molho-Pessach V, et al. Agenesis of the inferior vena cava in H syndrome due to a novel SLC29A3 mutation. Pediatr Dermatol 2013;30:e70-3.
9. Molho-Pessach V, Mechoulam H, Siam R, Babay S, Ramot Y, Zlotogorski A, et al. Ophthalmologic findings in H syndrome: A unique diagnostic clue. Ophthalmic Genet 2015;36:365-8.
10. Mehta S, Masatkar V, Mittal A, Khare AK, Gupta LK. The H syndrome. Indian J Paediatr Dermatol 2015;16:102-4.