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Case Report

H syndrome: a genodermatosis characterised by hyperpigmented, and hypertrichotic skin

H綜合徵：一種以皮膚色素沉著和多毛為特徵的遺傳性皮膚病

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H syndrome is an autosomal recessive genodermatosis caused by *SLC29A3* gene mutation. An important feature of the H syndrome is the hyperpigmented patchs and plaques, usually accompanied by hypertrichosis, seen in the inner thigh. Cardiac anomalies, hepatosplenomegaly, sensorineural hearing loss, short stature, hallux valgus and hypergonadotropic hypogonadism are other common findings of the syndrome. Herein, we report a case of H syndrome with hyperpigmented patches and plaques accompanied by hypertrichosis in inner thighs and had homozygous c.1339G> A (p.Glu447Lys) mutation in exon 6 of the *SLC29A3* gene.

H綜合徵是由 *SLC29A3* 基因突變引起的常染色體隱性遺傳性皮膚病。H綜合徵的一個重要特徵是在大腿內側有著色素沉著的斑和斑塊，並常伴有多毛症。心臟結構異常、肝脾腫大、感音神經性聽力損失、身材矮小，拇趾外翻和高促性腺激素性性腺功能減退症是該綜合徵的其他常見表現。在本文中，我們報導了一例H綜合徵伴有色素沉著的斑和斑塊，伴有大腿內側多毛症，並且在 *SLC29A3* 基因的外顯子6中具有純合的c.1339G> A（p.Glu447Lys）突變。

Keywords: H syndrome, Homozygous mutation, *SLC29A3*

關鍵詞：H綜合徵、純合突變、 *SLC29A3*

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Introduction

H syndrome (OMIM 602782) is a rare autosomal recessive genodermatosis caused by *SLC29A3* gene mutation. H syndrome forms part of the spectrum of disorders termed "Histiocytosis Lymphadenopathy Plus Syndrome" the others of which are: Faisalabad histiocytosis, pigmented hypertrichosis with insulin-dependent diabetes mellitus syndrome and sinus histiocytosis with massive lymphadenopathy.[1-3] The characteristics of the disease are hyperpigmentation, hypertrichosis, cardiovascular anomalies, hearing loss, hepatosplenomegaly, flexion contractures in the joints and histiocyte infiltration. To date, approximately 100 patients have been described in the literature.[2-8] Herein, we report a case of H syndrome with hyperpigmented patches and plaques accompanied by hypertrichosis in the inner thighs and had homozygous c.1339G> A (p.Glu447Lys) mutation in exon 6 of the *SLC29A3* gene.

Case report

A 26-year-old male patient presented to our clinic with a four-year history of hyperpigmented lesions on the inner thigh and deformity of the hand fingers. Dermatological examination revealed symmetrical hyperpigmented and hypertrichotic patches of approximately 25x10 cm, extending from the inner thighs to the scrotum (Figure 1). There was flexion deformity in both proximal interphalangeal joints (Figure 2), multiple cervical lymphadenopathy and hepatosplenomegaly on examination. Arthritis was detected in both wrist and knee joints of the patient. Investigations showed microcytic anaemia and histopathological examination of the lesion revealed histiocyte infiltrations in the dermis, lymphocytes and plasma cell accumulations in the form of foci. Immunohistochemical examination revealed CD68 (+), S100 (+) and CD1a (-). These findings were suggestive of a diagnosis of H syndrome. The *SLC29A3* gene was sequenced together with all exons and exon-intron junction regions. Homozygous c1339G> A (p.Glu447Lys) mutation was detected in 6th exon (Figure 3), confirming the diagnosis.

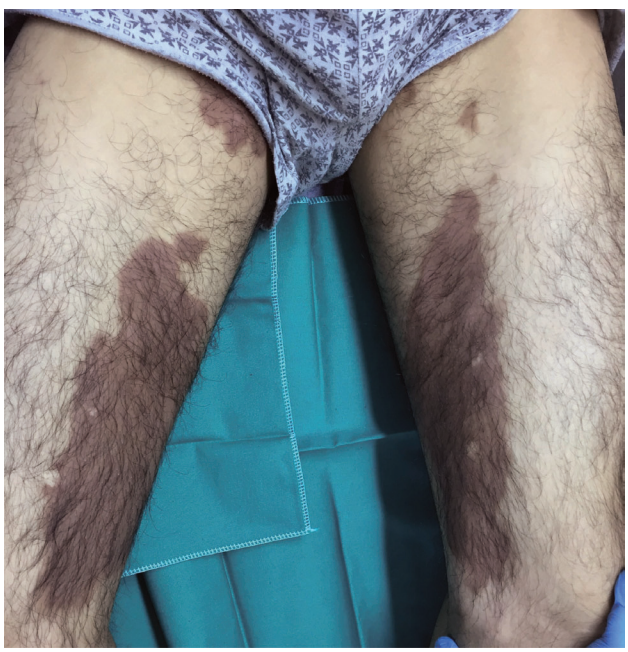

Figure 1. Symmetrical hyperpigmented and hypertrichotic patches extending from the inner thighs to the scrotum.

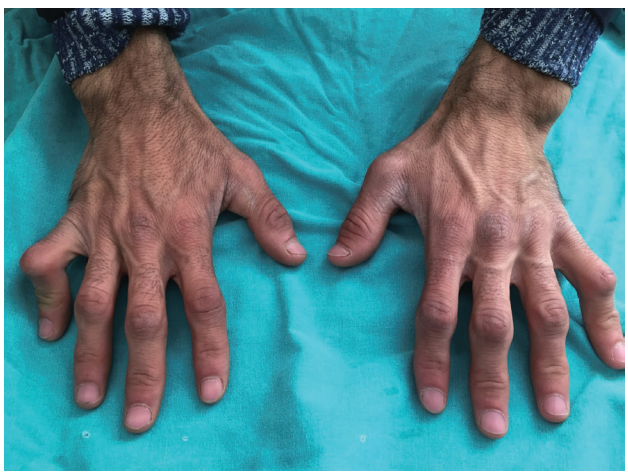

Figure 2. Flexion deformity is observed in the proximal interphalangeal joints of both hands.

Discussion

H syndrome is caused by a mutation in the *SLC29A3* gene encoding the human equilibrative nucleoside transporter (hENT3) protein. ENT3 is mainly found on mitochondrial and lysosomal membranes and has important effects on the structure and function of these organelles. When the function of this protein is impaired, it results in histiocytic infiltration of many organs such as skin and heart.[4-6]

The H syndrome is characterised by hyperpigmented patches and plaques with hypertrichosis, usually seen in the inner thigh. In the later stages of the disease, hyperpigmented patches and plaques can be seen throughout the body including the trunk and neck.[1-3] In our patient, hypertrichosis and hyperpigmentation were present only on the medial aspects of the thighs.

Cardiac anomalies, hepatosplenomegaly, sensorineural hearing loss, short stature, facial dysmorphism, hallux valgus, orbital involvement and hypergonadotropic hypogonadism are other common findings of the syndrome. In H syndrome, mild microcytic anaemia, high erythrocyte sedimentation rate and elevated liver enzymes can be found.[1-4,7]

Melki et al reported a *SLC29A3* mutation in an 11-month-old boy with fever, pericardial effusion, diarrhoea and abdominal pain.[6] In H syndrome, cardiac anomalies such as interseptal defects and vena cava inferior agenesis can be seen.[1,2] No cardiac anomalies were found in our patient.

In the differential diagnosis of H syndrome, Winchester syndrome and POEMS syndrome are included.[9,10] Winchester syndrome is an autosomal recessive disease characterised by short stature, osteoporosis, joint contractures,

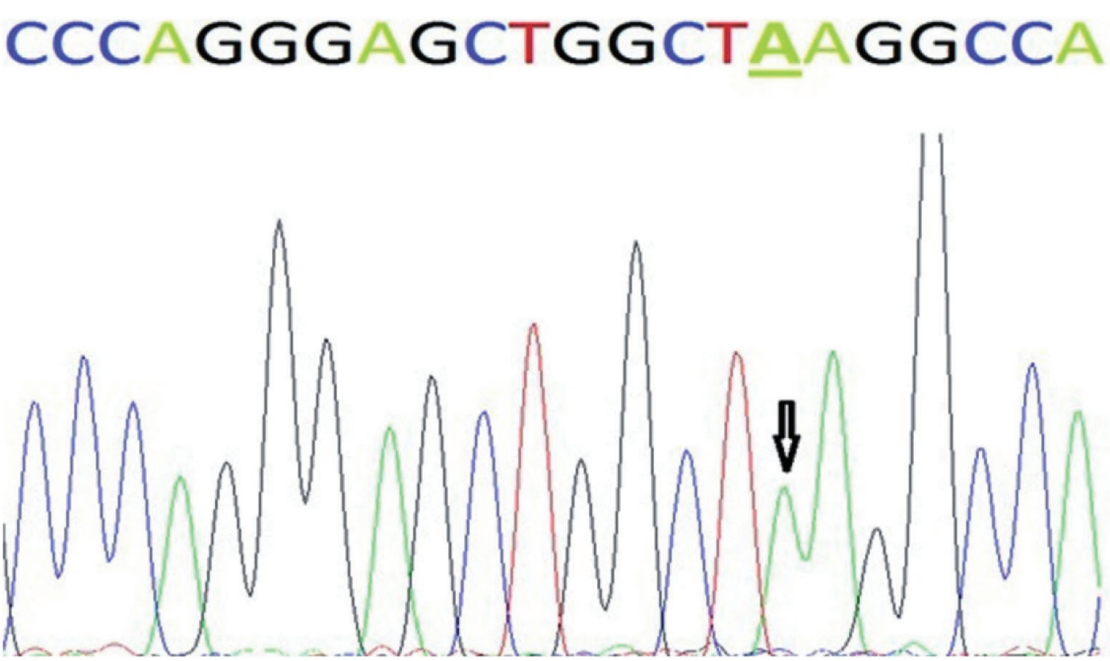

Figure 3. Homozygous c.1339G> A (p.Glu447Lys) mutation was detected in the 6th exon of the *SLC29A3* gene.

corneal opacities, gingival hypertrophy, hyperpigmented and hypertrichotic skin. Cardiac anomalies, hepatosplenomegaly, azoospermia and hearing loss in H syndrome are not seen in Winchester syndrome.[9] In our patient, there were no signs of osteoporosis, corneal opacities and gingival hypertrophy.

POEMS syndrome is a rare plasma cell dyscrasia characterised by polyneuropathy, organomegaly, endocrinopathies, M protein and skin changes such as hyperpigmentation, hypertrichosis, hyperhidrosis, skin thickening such as scleroderma and capillary angiomas. Paraproteinaemia and the presence of neurological findings are helpful clinical features in distinguishing POEMS syndrome from H syndrome.[10] Paraproteinaemia and neurological findings were not seen in our patient.

In H syndrome, immunohistochemically, CD68 (+), S100 (+) and CD1a (-) are detected. These findings support the diagnosis of H syndrome, but the definitive diagnosis is made by showing the *SLC29A3* gene mutation. The diagnosis of our case was confirmed by *SLC29A3* gene mutation.[1,2] Treatment of H syndrome is generally supportive. Oral steroids may temporarily improve skin changes in some patients, but are not suitable for long-term use due to side effects. An early screening for sensorineural hearing loss and diabetes mellitus should be performed. The disease is usually variable but progressive course may be observed and in some cases early death has been reported.[2,3,6,7]

As a result, the diagnosis of H syndrome should be considered in the presence of hyperpigmented patches and plaques accompanied by hypertrichosis on the medial aspects of the thighs and it should be borne in mind that genetic analysis is required for diagnosis.

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