H syndrome with possible new phenotypes

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Key words: genetic; genodermatosis; H syndrome; hallux valgus; hyperpigmentation; hypertrichosis; SLC29A3.

INTRODUCTION

H syndrome is an autosomal recessive syndrome affecting multiple organ systems with a characteristic skin lesion. It occurs because of a mutation in the *SLC29A3* gene.[1] The first cases of this extremely rare syndrome were reported in consanguineous families of Arab and Bulgarian descent and described in 2008 by Molho-Pessach et al.[2,3] Approximately 100 cases of H syndrome have been reported worldwide.[4] Currently, H syndrome is considered a novel form of histiocytosis.[5] The hallmark of this syndrome is the presence of bilateral symmetrical hyperpigmented indurated patches with overlying hypertrichosis, mainly involving the medial aspects of the thighs. Other commonly observed features are sensory neural hearing loss, hypogonadism, heart anomalies, hepatosplenomegaly, insulin-dependent diabetes, short stature, and lymphadenopathy.[6] Here we report a case of H syndrome, possibly with new phenotypes not described in previous studies.

CASE REPORT

A 16-year-old Iraqi boy, born of first-cousin parents, presented to our outpatient clinic at Al-Sadr Teaching Hospital with hyperpigmented patches symmetrically overlying with hypertrichosis involving the inner aspects of his thighs. These lesions progressed slowly over 6 years, starting first as hypertrichosis and then with indurated hyperpigmented patches gradually developing. He also had hearing loss, speaking difficulties, premature graying of the hair, gynecomastia, corneal arcus, hypospadias, and finger and toe deformities (hallux valgus). These features started at age 10, except for the hypospadias, which was present since birth, and the hearing loss and speaking difficulties, which were diagnosed in early childhood. The mother stated that the child delayed walking until the age of 2 years, and she reported that he had a severe ear infection by the age of 6. The patient has 3 brothers and 2 sisters; his older brother has bilateral swelling of the feet and deformities of the toes, but the patient's other siblings are all healthy. See Table I for clinical examination findings (Figs 1-3).

Laboratory test results showed elevated erythrocyte sedimentation rate of 93 (normal range, 0−15 mm/h), elevated serum cortisol of 1030 nmol/L (normal range at morning, 171-536 nmol/L), and decreased serum testosterone level of 2.63 ng/mL (normal range, 2.8-8 ng/mL). Complete blood count showed mild microcytic anemia.

Thyroid function tests, liver function tests, renal function tests, serum electrolytes, vitamin B12, serum ferritin, serum iron, antinuclear antibodies, anti−double-stranded DNA, anti-cyclic citrullinated peptide, and lipid profile all were normal. Echocardiography and electrocardiogram were normal, abdominal ultrasound scan found mild hepatosplenomegaly, brain magnetic resonance imaging was normal, and pure tone audiometry found bilateral profound mixed hearing loss.

Histopathology findings showed widespread fibrosis and thickened collagen bundles in the papillary and mid dermis and striking infiltrates of $CD68^+$ histiocytes (see Fig 4). The biopsy was taken from the hyperpigmented patch on the medial aspect of the right thigh.

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Funding sources: None.
Conflicts of interest: None disclosed.
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JAAD Case Reports 2019;5:355-7.
2352-5126

https://doi.org/10.1016/j.jdcr.2019.02.003

Table I. Findings on examination

Examination	Findings
Vital signs	Pulse rate, 83 beats per minute; blood pressure, 100/70 mmHg; respiratory rate, 13 breaths per minute; and temperature, 37°C
Anthropometric parameters	Weight, 47.1 kg; height, 160 cm; MUAC, 19.3; BMI, 18.4; height/age, -1.7 SD; BMI/age, -0.9 SD
Skin	Large hyperpigmented indurated patches overlying with hypertrichosis, symmetrically involving the medial aspects of the thighs and extending to the posterior aspects of the legs. The dorsa of the feet are also involved with well-demarcated, large, hyperpigmented patches. However, the pigmented patches spare the buttocks and knees (see Fig 1). There are both hypo- and hyperpigmented lesions on the face, neck, and upper chest.
Hair	Shows salt-and-pepper gray hair (see Fig 2)
Head	OFC, 51 cm (-2.8 SD, $<1^{st}$ percentile); face looks flat; ears are of abnormal shape and size.
Eyes	Bilateral corneal arcus; moderate exophthalmos; asymmetrical corneal light reflex. Ophthalmoscopic examination showed bilateral swelling of the optic disc. Visual acuity is normal.
Hearing assessment	Severe hearing loss
Breast	Bilateral gynecomastia
Heart	Normal
Abdomen	Mild hepatosplenomegaly
Lymph nodes	Severely enlarged inguinal lymph nodes, with tenderness on palpation
Genitourinary	Hypospadias; pubic hair presents in normal distribution; scrotal examination is normal.
Musculoskeletal	Bilateral hallux valgus deformity, with fixed flexion contractures, in the interphalangeal joints of the toes and the little fingers (see Fig 3). There is also a nonpitting edema of the ankles.

BMI, Body mass index; *MUAC*, mid-upper arm circumference; *OFC*, occipitofrontal circumference.

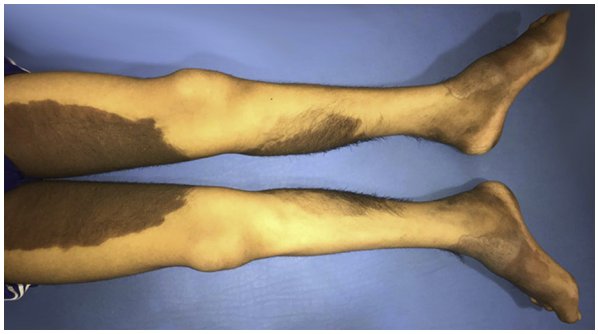

Fig 1. Large, hyperpigmented patches overlying symmetrically with hypertrichosis involving the inner aspect of the thighs, both calves, and the dorsa of the feet, while sparing the knees.

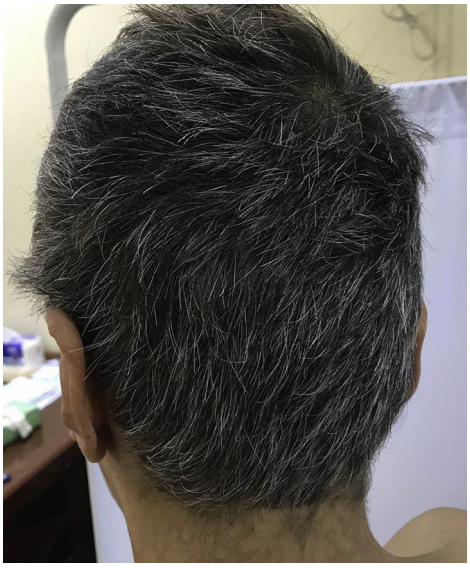

Fig 2. Posterior view of the patient's head shows salt-and-pepper gray hair.

DISCUSSION

Here we report on a 16-year-old Iraqi boy who had classic features of H syndrome.[2] In our case, cardiac abnormalities and insulin-dependent diabetes were absent. This is not an issue, as not all patients with H syndrome have these findings; only 34% of patients with H syndrome are reported to have cardiac anomalies, and only 20% have insulin-dependent diabetes.[5] Our patient's parents refused genetic testing; therefore, we diagnosed the condition clinically, as the hyperpigmented indurated lesions, coupled with hypertrichosis, are pathognomonic for H syndrome.[5,7] These findings are supported by the typical histopathology of the condition. On the other hand, 3 additional clinical features were noticed: premature graying of the hair, bilateral optic disc swelling, and hypospadias. Graying of hair is rare before the age of 25 years; many causes have been postulated to explain premature graying of hair, such as genetics, thyroid disorders, vitamin B12 deficiency, low serum

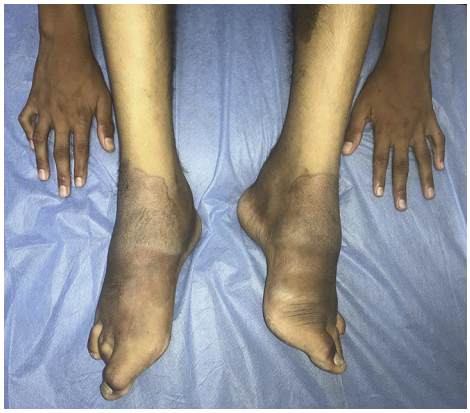

Fig 3. Hallux valgus deformity, with flexion contractures of the toes and little fingers.

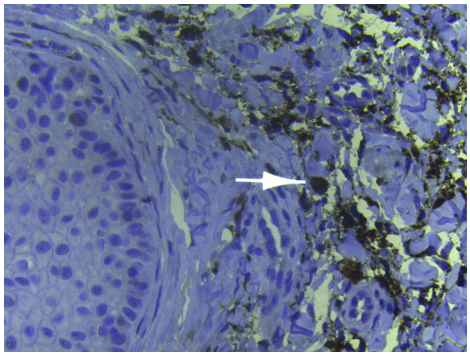

Fig 4. Immunohistochemistry stain shows diffuse infiltration of histiocytes. ($CD68^+$; original magnification: ×400.)

ferritin, and low serum calcium.[8] We did not find any reasonable explanation for this finding in our patient. Based on these findings, and on previous studies that described different clinical features of H syndrome, we suppose that premature graying of the hair may be a novel phenotype of this genodermatosis. Bilateral optic disc swelling is also an unexplained finding in our patient. The result of brain magnetic resonance imaging was normal, and a careful ophthalmologic examination has been performed by the ophthalmologist; however, no cause has been found to explain the presence of this finding in our patient, so it may also be a novel clinical feature of H syndrome. Genital findings are reported in some patients with H syndrome; for example, scrotal masses with a swollen and retracted penis.[9] In our case, hypospadias may be a novel genital feature of this syndrome; however, it can be a coincidental finding, as its prevalence rate in Asia is 0.6 to 69 per 10,000 live births.[10] Correlation with future reported cases will, therefore, be required.

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