Acta Derm Venereol 2015; 95: 1021–1023

SHORT COMMUNICATION

H Syndrome: A Multifaceted Histiocytic Disorder with Hyperpigmentation and Hypertrichosis

Burak Tekin[1], Zeynep Atay[2], Tulin Ergun[1], Meryem Can[3], Davut Tuney[4], Sofia Babay[5], Serap Turan[2], Abdullah Bereket[2], Abraham Zlotogorski[5] and Vered Molho-Pessach[5]

Departments of [1]Dermatology, [2]Pediatric Endocrinology, and [4]Radiology, School of Medicine, Marmara University, Mimar Sinan Cad. No:41, TR-34899 Pendik, Istanbul, [3]Department of Rheumatology, Fatih Sultan Mehmet Research and Training Hospital, Istanbul, Turkey, and [5]Department of Dermatology, and The Center for Genetic Diseases of the Skin and Hair, Hadassah - Hebrew University Medical Center, Jerusalem, Israel. E-mail: burak.tekin@marmara.edu.tr

Accepted May 11, 2015; Epub ahead of print May 27, 2015

H syndrome (OMIM #602783) is an autosomal recessive genodermatosis, first described in 2008 (1). It has multisystemic involvement and is characterized by numerous clinical features, including cutaneous *h*yperpigmentation and *h*ypertrichosis, *h*epatosplenomegaly, *h*earing loss, *h*eart anomalies, *h*ypogonadism, low *h*eight (short stature), *h*yperglycaemia (insulin-dependent diabetes mellitus), and *h*allux valgus/flexion contractures. Cutaneous hyperpigmentation, commonly accompanied by hypertrichosis and progressive sclerodermatous induration, typically affecting initially the medial thighs with sparing of the knees, is the hallmark of the disorder and is considered pathognomonic (1–3). Causative mutations have been identified in the *SLC29A3* gene encoding the human equilibrative nucleoside transporter 3 (hENT3), which serves as a transporter of nucleosides in the late endosome/lysosomes, and across the inner mitochondrial membrane (4). Although numerous mutations have been reported since the initial description (3, 5–8), a solid genotype–phenotype correlation is lacking (3).

Increased recognition of the disorder has led to the identification of approximately 100 patients with H syndrome worldwide (9). Novel clinical features have been associated with this condition, such as lymphadenopathy, pancreatic exocrine deficiency, and recurrent febrile episodes (3). Recently, complete agenesis of the inferior vena cava (IVC) was reported in a patient from Turkey who also had striking varicose veins (8). Oligosymptomatic patients with a very mild phenotype have also been described (2, 3, 7). Interestingly, patients with variable degrees of involvement have been described from the same family or geographical region with similar or even identical genetic mutations, reflecting the pleiotropic nature of this unique disorder (3, 6, 7).

Histopathologically, H syndrome may simulate Rosai-Dorfman disease, displaying $CD68^+$ $S100^+$ $CD1a^-$ histiocytes with emperipolesis (3, 10, 11). Overall, H syndrome may be regarded as an inherited histiocytic disorder based on demonstration of increased $CD68^+$ histiocytes in the skin and lymph nodes, suggesting a possible role of hENT3 in histiocyte turnover.

This paper highlights the pleiotropic nature of H syndrome by reporting 2 unrelated Turkish patients from a single institution who share a common mutation in the *SLC29A3* gene but demonstrate different phenotypes.

CASE REPORTS

Patient 1. A 29-year-old man of Caucasian origin born to non-consanguineous parents. He had progressive sclerodermatous induration of the upper and lower extremities beginning at the age of 21 years. In addition, he had had sensorineural hearing loss

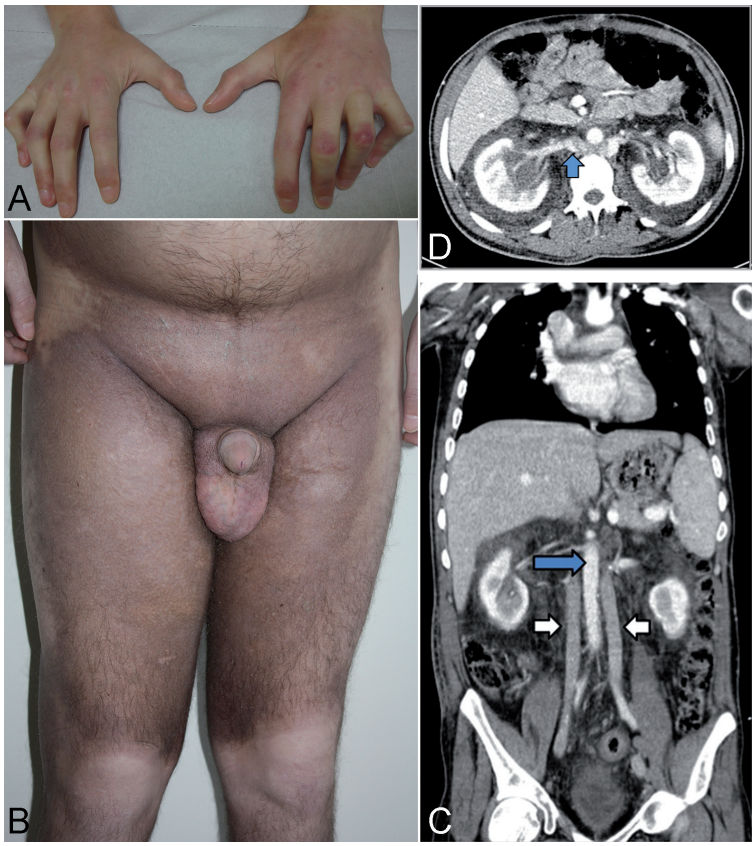

Fig. 1. (A) Fixed flexion contractures of the proximal interphalangeal joints. (B) Diffuse hyperpigmented and hypertrichotic patches over the lower abdomen, groin and thighs, sparing the knees. (C) Coronal maximum intensity projection computed tomography (CT) image showing right and left inferior vena cava (IVC) (*white arrows*). *Blue arrow* indicates abdominal aorta. (D) Axial image showing right renal vein and right IVC meet (*blue arrow*) and cross posterior to the aorta to join the left IVC. A permission from the patient is given to publish this figure.

 doi: 10.2340/00015555-2145
 ISSN 0001-5555

since the age of 7 years and insulin-dependent diabetes mellitus (IDDM) since the age of 10 years, as well as recurrent febrile episodes. On physical examination he was noted to have inguinal and scrotal swelling, hepatosplenomegaly and induration of the skin on the hands and forearms with fixed flexion contractures of the proximal interphalangeal joints (Fig. 1A), sclerotic patches with hyperpigmentation and hypertrichosis of the lower part of the trunk and lower extremities (Fig. 1B). Prominent varicosities were noted on the abdomen, pubis, genitalia and thighs. In addition, the patient had bilateral gynecomastia, micropenis, mild scoliosis, lateral tibial torsion, hallux valgus, facial telangiectasias, dilated lateral scleral vessels, exophthalmos, and arcus senilis. Skin biopsy from a hyperpigmented lesion on the lower extremity demonstrated a lymphoplasmocytic infiltrate in the dermis, atrophy of skin appendages and coarse collagen fibres in the subcutaneous fat. Laboratory work-up showed microcytic anaemia (haemoglobin 9.6 g/dl, mean corpuscular volume 68 fl), hypovitaminosis D (3 ng/ml; normal >30 ng/ml) and increased fasting glucose (330 mg/dl; normal 74–106 mg/dl) and haemoglobin A_{1c} (10.4%; normal 4.5–5.7%) levels. Erythrocyte sedimentation rate (71 mm/h) and C-reactive protein (77 mg/l; normal 0–8 mg/l) were elevated. Thyroid-stimulating hormone (7.84 µIU/ml; normal 0.4–4.2 µIU/ml), follicle stimulating hormone (16.3 mIU/ml; normal 1.5–12.4 mIU/ml), luteinizing hormone (26.73 mIU/ml; normal 1.7–8.6 mIU/ml) and prolactin levels (24 ng/ml; normal 4.04–15.2 ng/ml) were increased. Computed tomography (CT) scans revealed enlarged cervical, axillary, inguinal and intra-abdominal lymph nodes and hepatosplenomegaly. Furthermore, thoracoabdominal CT scan demonstrated double IVC with retro-aortic right renal vein and hemi-azygous continuation of the IVC (Fig. 1C and D).

Patient 2. A 7-year-old boy, born to non-consanguineous parents, who had IDDM since the age of 1.5 years. He developed bilateral cervical masses at the age of 6 years. Physical examination was unremarkable, with the exception of coarse facial features, depressed nasal bridge, multiple enlarged cervical lymph nodes and approximately 70 naevi at various body sites. Abdominal ultrasonography, echocardiography, bone X-rays and audiometry were normal. Histopathological examination of a cervical lymph node demonstrated massive sinus dilatation, histiocytic proliferation, which was stained densely with S100 and CD68, capsular and pericapsular fibrosis in the adipose tissue and emperipolesis, which were consistent with Rosai-Dorfman disease. The presence of lymphadenopathy characteristic of Rosai-Dorfman disease and IDDM suggested the diagnosis of H syndrome.

Genetic analysis

After informed consent was obtained, blood samples were collected from both patients and DNA was extracted. Direct sequencing of the complete coding region of the *SLC29A3* gene revealed 2 novel missense mutations, p.A367T ((c.1099G>A) in both patients, in a homozygous state in patient 2 and heterozygously in patient 1. A p.G2098R c.625G>A) mutation was found in a heterozygous state in patient 1. Neither mutation is listed in dbSNP (www.ncbi.nlm.nih.gov/SNP), 1000 Genomes (www.1000genomes.org), or the Exome Variant Server (evs.gs.washington.edu). The Mutationtaster software tool (http://www.mutationtaster.org), as well as Polyphen-2 (http://genetics.bwh.harvard.edu/pph2/) predicts that these mutations are disease causing, with scores of 0.999/0.99 for the p.A367T mutation and 0.999/1 for the p.G2098R mutation, respectively.

DISCUSSION

Patient 1 has numerous typical features of H syndrome, whereas patient 2 has a limited phenotype consisting only of IDDM and cervical lymphadenopathy. Both patients share the same *SLC29A3* mutation, although this mutation is present in a heterozygous state in patient 1, as part of compound heterozygosity. The relatively restricted phenotype of patient 2 may be explained by his young age, due to the progressive nature of H syndrome (3). It should be noted that patient 1 had been followed-up and treated with a presumed diagnosis of scleroderma for 8 years before the diagnosis of H syndrome. The presence of multiple naevi, as seen in patient 2, has not previously been regarded as a feature of H syndrome. However, multiple naevi may be more than just an incidental finding, as another patient with multiple halo naevi has been observed (5). The mechanism behind this melanocytic proliferation is still obscure.

Several clinical features of H syndrome deserve further mention. Early-onset IDDM, seen in both of our patients, is an important clinical finding. IDDM may even be the sole manifestation of H syndrome, presenting a diagnostic challenge (7). Agenesis of IVC with azygous continuation was reported only once within the context of H syndrome in a Turkish patient (8). Our patient's complex venous anomaly, double IVC with retro-aortic right renal vein and hemi-azygous continuation of the IVC, is embryologically explained by persistence of the left lumbar and thoracic supracardinal veins and the left suprasubcardinal anastomosis, accompanied by failure of formation of the right subcardinal-hepatic anastomosis (12). Interestingly, even major aberrations from the normal IVC anatomy may be asymptomatic and detected incidentally during radiological evaluation, as was the case in patient 1. Similar to the aforementioned report (8), patient 1 had prominent varicosities, possibly linked to the underlying IVC anomaly. Intriguingly, varicose veins have been described within the clinical spectrum of H syndrome, even without coexistent IVC anomaly (1–3, 5). Considering that there are many other cardiovascular anomalies reported in H syndrome, it may be speculated that hENT3 somehow contributes to cardiovascular morphogenesis (8). Similar to many other aspects of H syndrome, vascular involvement also seems to have a pleomorphic expression, with facial telangiectasias, dilated lateral scleral vessels and mild varicosities representing one end of a spectrum, and various cardiac and IVC anomalies representing the other end.

ACKNOWLEDGEMENTS

We thank the patients and family members for their participation in this study.

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: 529–534.
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: 80–88.
4. Kang N, Jun AH, Bhutia YD, Kannan N, Unadkat JD, Govindarajan R. Human equilibrative nucleoside transporter-3 (hENT3) spectrum disorder mutations impair nucleoside transport, protein localization, and stability. J Biol Chem 2010; 285: 28343–28352.
5. Molho-Pessach V, Suarez J, Perrin C, Chiaverini C, Doviner V, Tristan-Clavijo E, et al. The H syndrome: two novel mutations affecting the same amino acid residue of hENT3. J Dermatol Sci 2010; 57: 59–61.
6. Priya TP, Philip N, Molho-Pessach V, Busa T, Dalal A, Zlotogorski A. H syndrome: novel and recurrent mutations in SLC29A3. Br J Dermatol 2010; 162: 1132–1134.
7. 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: 1179–1180.
8. Mutlu GY, Ramot Y, Babaoglu K, Altun G, Zlotogorski A, Molho-Pessach V. Agenesis of the inferior vena cava in H syndrome due to a novel SLC29A3 mutation. Pediatr Dermatol 2013; 30: e70–73.
9. Molho-Pessach V, Varma M, Godbole K, Kamath N, Zlotogorski A. H syndrome – four new patients from India. Indian J Dermatol Venereol Leprol 2014; 80: 579.
10. Rossbach HC, Dalence C, Wynn T, Tebbi C. Faisalabad histiocytosis mimics Rosai-Dorfman disease: brothers with lymphadenopathy, intrauterine fractures, short stature, and sensorineural deafness. Pediatr Blood Cancer 2006; 47: 629–632.
11. Avitan-Hersh E, Mandel H, Indelman M, Bar-Joseph G, Zlotogorski A, Bergman R. A case of H syndrome showing immunophenotye similarities to Rosai-Dorfman disease. Am J Dermatopathol 2011; 33: 47–51.
12. Bass JE, Redwine MD, Kramer LA, Huynh PT, Harris JH Jr. Spectrum of congenital anomalies of the inferior vena cava: cross-sectional imaging findings. Radiographics 2000; 20: 639–652.