

## Generalized Lipoatrophy: A New Phenotype of H-Syndrome

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### Abstract

The H-syndrome is a recently known autosomal recessive genodermatosis caused by mutations in the SLC29A3 gene, which encodes the nucleoside transporter hENT3. Cutaneous changes including Hyper pigmentation, hypertrichosis is characteristic for this syndrome but herein, we newly describe this syndrome in a 16 years old boy associated with generalized lipoatrophy and a novel mutation in exon 3 G155>A mutation in SLC29A3 gene. It seems that the clinical spectrum of this syndrome is much broader than the symptoms which were described in the first reported patients.

**Keywords:** H-syndrome; Generalized lipoatrophy; Hyper pigmentation; Mutations

### Introduction

Mutations in the SLC29A3 gene, which encodes the nucleoside transporter hENT3 is associated with various clinical manifestations, recently described as H-syndrome [1]. Hyperpigmentation, hypertrichosis, hepatosplenomegaly, hearing loss, heart anomalies, hypogonadism, low height (short stature), hyperglycemia/diabetes mellitus, and hallux valgus/flexion contractures compose the most common features of this autosomal recessive genodermatosis [1-3]. Herein, we describe a patient with generalized lipoatrophy who fulfilled the phenotype and genotype characteristics of H-syndrome. To the best of our knowledge, generalized lipoatrophy has not been explained as a clinical feature of H-syndrome in the reported cases. It seems that clinical spectrum of this newly defined syndrome is much broader than was described in the first cases.

### Case Report

A 16-years-old boy referred to our hospital for assessment of prolonged abdominal pain and occasional nausea during the 2 past months. There was no history of vomiting, change in bowel habit, jaundice, chills and/or fever but he lost 4 kg weight during this time. At birth he had 2 kg weight and the growth process was normal apparently during the first 2 years of life. Thereafter, he experienced declining the growth rate and failure to thrive was labeled by his pediatrician without a confirmed cause. Intellectual development was normal during pre-school and school period as he was able to finish the elementary (school) learning level. In family history, he was born from a consanguineous marriage. His parents appeared normal phenotypically. His family had 6 siblings; 4 boys and 2 daughters. Two of his brothers died in childhood for unknown cause but now he had two healthy sisters and one brother with normal developmental status. Otherwise the history was unremarkable even in the secondary degree relatives. There was no family history of diabetes mellitus in the first and the second degree relatives. On physical examination, the vital signs were normal, as the blood pressure was 120/70 mm /Hg, the pulse rate was 72/minute, the oral temperature was 36.9°C, and the respiratory rate was 12/minute. His weight and height were 25 kg and 130 cm respectively with a body mass index (BMI) equal to 14.8. The cutaneous examination revealed

hyperpigmentation, hypertrichosis and a few indurated lesions in different body areas. The non-tender well demarcated hyperpigmented patches were located on the trunk, extremities, axillae, forehead and periorbital areas. There was a mild hypertrichosis on forehead, upper extremities and lower back. A few indurated lesions were noticed on buttock, scapula and elbow areas. Enormous loss of subcutaneous fat tissue in almost all parts of his body was seen. A remarkable reduction in muscle mass was detected. Additional cutaneous features such as coarse facies, short stature and acanthosis nigricans in axillae and nape, were also observed. Nails and mucous membranes were normal. No hair shaft abnormalities or hair loss were found (Figure 1).

The liver and spleen were palpable about 4 cm below the costal margins. Skeletal examination revealed poorly developed muscular bulk. Male genital organs were smaller than the size for patient's age. Neurological examinations including the mental status, cranial and peripheral nerves were normal. The remainder of the general examinations including the thyroid, lungs and heart were also normal.

Laboratory test results revealed mild normochromic normocytic anemia, low platelet, high erythrocyte sedimentation rate (ESR), hyperglycemia and low sex hormone levels. Oxygen saturation was 93% while on ambient room air. Iron profile, thyroid function test, serum level of growth hormone, cortisol at 8 AM, amylase, lipase, CRP, serum protein electrophoresis and stool exam were normal. Anti- nuclear antibody (ANA), anti-double stranded nuclear antibody (anti- DNA) tests, serology for hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) were also negative (Table 1). Bone marrow aspiration and biopsy displayed hypercellular marrow with increased megakaryocytes.

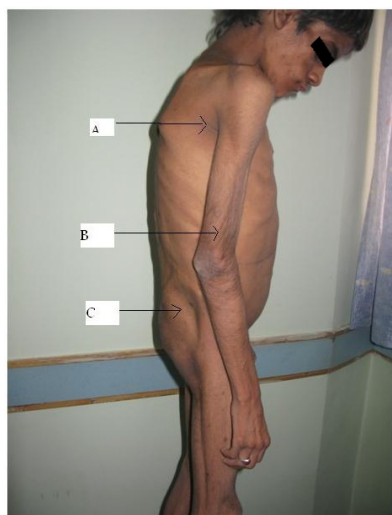
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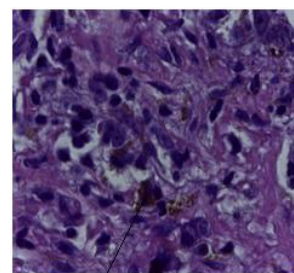
In skin biopsy which was taken from different areas of skin, epidermal changes including hyperkeratosis, acanthosis, increased melanin deposits in basal keratinocytes and widespread dermal fibrosis were observed (Figures 2 and 3). In dermis a dense



**Figure 1 A:** Acanthosis nigricans, B: Hypertrichosis, C: Massive lipoatrophy.

	Results	Normal Range
WBC	4800(per mm <sup>3</sup> )	4000-11000
HGB	9/4 g/dl	14-16.5 (men)
Plat	64000 (per mm <sup>3</sup> )	150,000-450,000
FBS	566 (mg/dl)	65-95
Triglyceride	99 (mg/dl)	30-200
Total Cholesterol	157 (mg/dl)	<200
BUN	23 (mg/dl)	7-20
Cr	0.7 (mg/ dl)	0.5 -1
AST	132 IU/ L	18-34
ALT	114 IU /L	12-30
Alk.P	459 IU/L	33-96
Bill Total	1.5 mg/ dl	0-1
Bill Direct	0.5 mg/ dl	0-0.4
PT T	35 sec	35-45
PT	13 sec	12-13
INR	1	1
Amylase	71 IU/ L	20-96
LDH	795 IU/ L	150-230
Albumin	3.2 g/dl	3.5-4.5
Total protein	7.4 g/dl	6.7-8.6
Serum Iron	55 µg/ dl	41-141
TIBC	283µg/ dl	251-406
Ferritin	33 ng/ml	30-250
ESR	89 (mm/hrs)	<20
TSH	1.1 µIU/ml	0.4-4.3
T3,total	90 ng/dl	77-135
T4 ,total	8 µg/dl	5.4-11.7
Cortisol 8:AM	20 µg/dl	5-25
FSH	0.83 mIU/ml	1-12
LH	0.1 mIU/ml	2-12
Testosterone	0.5 nmol/l	9.2-37
Free Testosterone	111pmol/l	312-1021
Anti-tissue transglutaminase Antibody (Ig A)	<10 IU/ml	Neg

**Figure 1A:** Acanthosis nigricans, B: Hypertrichosis, C: Massive lipoatrophy.



emperipolesis: the presence of an intact cell within the cytoplasm of another cell

increased melanin deposits

**Figure 2:** Epidermal changes including hyperkeratosis, acanthosis, increased melanin deposits in basal keratinocytes and widespread dermal fibrosis are observed.



Hyperkeratosis

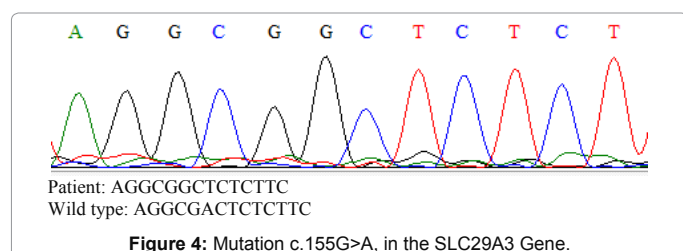
Acanthosis

widespread dermal fibrosis

**Figure 3:** In dermis a dense infiltrate of mononuclear cells including histiocytes, papillary dermal melanophages and intracytoplasmic inflammatory cells (Emperipolesis: the presence of an intact cell within the cytoplasm of another cell) are found.

infiltrate of mononuclear cells including histiocytes, papillary dermal melanophages and intracytoplasmic inflammatory cells (emperipolesis) were found, and the content of fat tissue in subdermis has decreased remarkably (Figure 3). In the abdomen and pelvis imaging, by both ultrasound and contrast enhanced CT scan, diffuse hepatosplenomegaly observed. Biliary tree was normal and portal vein diameter was 13.8 mm. Both kidneys as well as other organs were normal in size and parenchymal density. No lymphadenopathy was detected. In esophagogastroduodenoscopy no esophageal varices or other abnormality were observed. Ophthalmology examination revealed mild corneal opacity in both eyes, but visual acuity and funduscopy were normal. In Audiologic assessment no sensorineural or conducting hearing loss were found. Speech was normal but his voice was trebled (high pitched) for the age. In cardiac examination; electrocardiogram was normal, but echocardiogram disclosed early diastolic dysfunction with an ejection fraction of 45%. No valvular abnormality was detected.

Peripheral vein blood sample was obtained and mixed with EDTA as anticoagulant. To avoid any nuclease activity, the sample was frozen at -20°C until DNA extraction. DNA was extracted from the whole blood using CinnaPure DNA kit (Cat. No. PR881612) according to the manufacturer's protocol. In brief, it was done using lysis buffer, precipitation solution, wash buffer I, wash buffer II and elution buffer which was provided by the manufacture. The selected primers were amplified using CinnaGen PCR Master Kit according to the instruction



by the supplier (CinnaGen Co., Iran). The PCR reactions were carried out under the same conditions as Molho-Pessach et al. [1]. Sequence analysis of SLC29A3 indicated a heterozygous point mutations in exon 6, which was a nucleotide transition c.1309G>A resulting in the missense amino acid substitution p.Glycin 437Arginin. There was also a mutation in exon 3 G155>A mutation, changing Threonine to Alanine (Figure 4).

## Discussion

Here, we report a 16 years old boy with hyperpigmentation, hypertrichosis, hepatosplenomegaly, hypogonadism, low height, hyperglycemia, generalized lipoatrophy and high ESR associated with mutations in the SLC29A3 gene. These distinctive clinical features on a specific genetic background were compatible with H-syndrome.

Firstly in 2008 Vered Molho-Pessach described combination of hyperpigmentation and hypertrichosis with systemic manifestations as a new disease entity, in 10 Arab patients [2]. In 2013, symptoms of the first 79 patients were described, so the hyperpigmentation, phalangeal flexion contractures, hearing loss, and short stature were the most common clinical features of H-syndrome [4].

As in our case, cutaneous hyperpigmentation was the hallmark of H syndrome and it was seen in about 68% of affected patients. In patients with lacking characteristic cutaneous hyperpigmentation the clinical diagnosis may be more challenging, but mutation analysis can confirm the diagnosis.

Less than 15% of cases show additional systemic features. In addition to other common clinical features in the present case, generalized lipoatrophy was a prominent clinical finding. As noted above generalized lipoatrophy has not been reported in H syndrome but gluteal lipodystrophy was reported in about 5% of patients [4]. Based on previous studies which have found various clinical manifestations in mutations of the SLC29A3 gene, we suppose that generalized lipoatrophy may be a new phenotype of this genetic syndrome.

In previous studies twenty mutations have been identified so far in the SLC29A3 gene in affected individuals [1,5-12]. We report here a novel mutation in exon 3 G155>A mutation, changing Threonine (which is classified as polar essential amino acid) to Alanine (which is classified as a non-polar amino acid). The SLC29A3 gene is widely expressed and is believed to play a role in nucleotide salvage because it encodes a pH-dependent equilibrate nucleoside transporter protein (hENT3). The hENT3 protein is an integral membrane protein of mitochondria [13], where it joins hENT1 as one of the two known nucleoside/nucleobase transporters of mitochondria. Multiple tissues are involved in disorders of hENT3 because of its role in nucleotide salvage. Although at this time there is no data to explain why some symptoms appear explicable on the basis of loss of SLC29A3 function but paradoxical autoimmunity may be a rule [14].

On initial evaluation, the below mentioned conditions were considered in the differential diagnosis: congenital generalized

lipoatrophy (CGL), namely CGL type 1 and 2, SHORT syndrome and Werner syndrome.

CGL type 1 (Berardinelli-Seip syndrome) is a rare autosomal recessive syndrome and compose about 95 percent of all cases with generalized lipoatrophy. Total or near total absence of subcutaneous fat tissue at birth or during the first years of life along with muscular hypertrophy gives the distinct appearance to this children. Hypertriglyceridemia leading to acute pancreatitis, diabetes mellitus and hepatomegaly due to fatty deposition is common. Initial growth pattern is accelerated, but the final height is usually within normal limit [15,16].

SHORT syndrome is an autosomal dominant disorder with multiple abnormalities in different parts of the body including: short stature; hyperextensibility of joints and/or inguinal hernia; ocular depression; Rieger anomaly (impaired defect in ophtalmic anterior chamber that may lead to glaucoma); and teething delay. Lipodystrophy and glucose intolerance are commonly present [17,18].

Werner syndrome is the most common premature aging disorder that is inherited in autosomal recessive manner and characterized by growth retardation, short stature, early graying of hair, prematurely aged faces, scleroderma like skin and partially lipoatrophy especially in legs and arms [19,20].

All of these syndromes were excluded by non-compatible clinical features, and finally by genetic background analysis. In conclusion, the H-syndrome is a rare and recently described syndrome with a wide spectrum of manifestations and generalized lipoatrophy may be a new phenotype of this syndrome.

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