Case Report H Syndrome

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Abstract: Background: H syndrome is a monogenic systemic inherited form of histiocytosis, with characteristic cutaneous findings accompanying systemic manifestations. The major common endocrine manifestations like hypogonadism, short stature and diabetes mellitus with characteristic genodermatosis lead to the diagnosis. **Objective:** To report a rare case of H syndrome, an autosomal non autoimmune disorder in a three years old Syrian boy who was presented with diabetes mellitus type one, hyperpigmented hypertrichosis, hepatosplenomegaly, aortic stenosis. **Method**: We described the clinical spectrum of H syndrome with multisystem spectrum involvement, the solute carrier family 29(nucleoside transporters), member 3(SLC29A3) gene was screened for molecular diagnosis utilizing the NGS based mutational analysis. **Results**: H-syndrome is caused by a mutation in SLC29A3 gene which encodes for the human equilibrative nucleoside transporter-3(hENT3). a 3 years old boy who was diagnosed to have diabetes mellitus, his clinical phenotype included hyperpigmented hypertrichosis, hepatosplenomegaly, short stature, cardiac involvement, a clinical diagnosis of H SYNDROME were suspected, and we identified a reported homozygous pathogenic variant c.1279G^A(p. Gly427ser)in the SLC29A3 gene by sequencing. **Conclusion**: The characteristic pigmentary hypertrichosis and cardiac involvement in diabetes mellitus patient raised the suspicion of H syndrome. NGS with its multiplexing option offers a rapid and robust platform for molecular diagnosis at an affordable cost.

[Abdullah Alshaya, Sultan Alkhonaizan, Majed Alfadhl, Fatemah Altamimi, Ali Almajhad, Maher Alshami and Mosleh Jabari. **Case Report H Syndrome.** *J Am Sci* 2016;12(11):104-105]. ISSN 1545-1003 (print); ISSN 2375-7264 (online). http://www.jofamericanscience.org. 10. doi:10.7537/marsjas121116.10.

Keyword: Syndrome

Abbreviation: **NGS** = Next generation sequencing; **SLC29A3** = Solute Carrier family 29(nucleoside transporters), member 3; **hENT3** = human Equilibrative Nucleoside Transporter-3; **HbA1c** = Glycosylated haemoglobin, **GAD** = Glutamic Acid Decarboxylase antibodies; **TSH** = Thyroid Stimulating Hormone; **IGF** = Insulin like Growth Factor; FSH = Follicular Stimulating Hormone; **CRP** = C-Reactive Peptide; ESR = Erythrocyte sedimentation rate; **CD** = cluster of differentiation.

Introduction:

H-syndrome is a monogenic autosomal recessive disorder characterized by little or no evidence of autoimmunity. Mutated proteins are involved in the regulation of inflammation. This rare genodermatosisis caused by a mutation in the solute carrier family 29 (nucleoside transporters) member 3gene (SLC29A3) which encodes for the human equilibrative nucleoside transporter-3 (hENT3, Q9BZD2.3). This report covers the case of a 3 year old male patient with H syndrome due to SLC29A3 mutation identifiedutilizing a NGS approach.

Case details:

Currently the patient is 3 years old Syrian boy, came initially at age of 8 month with c/o polyuria, and polydipsia and diagnosed to have diabetic ketoacidosis and then started on insulin regimen for DM type 1, he was diagnosed previously to have aortic stenosis and pure red cell aplasia at age of 3 month when he had pallor and bone marrow aspiration confirmed the diagnosis, he has also caw milk allergy at age of 20 month, developmentally walked at 22 month and speak at 30 month of age and has good social contact, He is the second boy for first causin consequent healthy parent who has other healthy boy with history of three abortion.

By examination:

He has short stature (height 71 cm below 3rd centile) weight 13 kg on the 50th centile, no midline face defect, cutaneous features included symmetrical large hyperpigmented plaques with hypertrichosis on the upper and lower arms and face and trunk

(fig.1&2), systolic ejection murmur best heard at the aortic area, with normal blood pressure reading and no femoral delay, hepatomegaly 4 cm below costal margine and splenomegaly 3 cm below costal margine.

Laboratory:

HGB, WBC, PLT all are within normal levels, ESR, CRP: IGF1: kidney and liver function within normal range. With this finding we suspect H syndrome so genetic analysis for the gene SLC29A3 was done and the result came as follow: homozygous pathogenic variant in axon 6 of the SLC29A3 gene, c.1279G>A(p. Gly427Ser).

Discussion:

H-syndrome is a monogenic autosomal-recessive-autoimmune syndrome. This multisystem disorder is caused by mutations in the SLC29A3 gene which encodes nucleoside transporter hENT3**(1)**. Patients with this syndrome were initially described in families of Arab and Bulgarian origin, having a consanguineous parents**(1,2).** A few patients have been reported from India**(3,4)**. The H-syndrome is characterized by major clinical findings of pigmentary hypertrichosis, hyperglycemia (non-autoimmune diabetes mellitus), hepatosplenomegaly, heart anomalies, sensor neural hearing loss, hypogonadotrophichypogonadism and growth hormone deficiency manifesting with short stature**(1).** Male subjects have been reported to have scrotal masses, gynecomastia and azoospermia**(3)**. Other features that are described include varicose veins and joint deformities (hallux valgus and fixed flexion contractures of interphalangeal joints). The most common clinical features (>45% of patients) were hyperpigmentation, phalangeal flexion contractures, hearing loss, and short stature. Insulin-dependent diabetes mellitus and lymphadenopathy were found in around 20% of these patients**(4)**. These patientsdevelop progressive cutaneous hyper pigmented, hypertrichotic and induratedplaques over the lower limbs and lower abdomen during the first or second decade of life which is the hallmark for the diagnosis. Histopathological examination of the involved skin is characterized by inflammation with the basal layer showing seborrheic keratosis-like acanthosis, infiltration of histiocytes, and a perivascular mononuclear infiltrate with plasma cells and mast cells throughout the dermis and subcutaneous fat**(1-4).**

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11/6/2016