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Trichohepatoenteric Syndrome: A Rare Cause of Congenital Diarrhea

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Abstract

Trichohepatoenteric syndrome (THES) is inherited syndrome that characterized by early onset chronic diarrhea, hair abnormalities, dysmorphic features, and liver disease. THES is caused by pathogenic variant mutation within TTC37 or SKIV2L genes. We, herein, describe a case of 1-month-old girl with no dysmorphic features, unexplained chronic diarrhea, and loss of weight, diffuse fragile hair and skin abnormalities.

Keywords: ***Trichohepatoenteric syndrome; TTC37 gene; SKIV2L gene***

1. Introduction

Trichohepatoenteric syndrome (THES) [OMIM: 600478] is a rare autosomal recessive (AR) disorder characterized by a triad of severe intractable diarrhea, hair abnormalities, and hepatic derangement [1]. It's caused by a genetic mutation of the human SKI complex in either of tetratricopeptide repeat domain-containing protein 37 gene (TTC37) or SKI2-Like RNA Helicase (SKIV2L) genes [2]. Worldwide, THES prevalence is estimated to be 1:1,000,000, with high mortality rate in infancy attributed to severe infections, diarrhea, and liver cirrhosis [3]. Here we describe a Saudi child with THES to increase awareness of this rare syndrome and hopefully optimize early recognition and better management.

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2. Case Presentation

A Saudi newborn girl presented at the age of 28 days with failure to thrive, decreased activity and unexplained chronic non-foul-smelling watery diarrhea since birth, with frequency of 7 times per day. There were no blood or mucus in the stool and no history of projectile vomiting. She was admitted to pediatric intensive care unit (PICU) and started on total parenteral nutrition (TPN) pending work up. She was born to a healthy non-consanguineous couple by cesarean section due to symmetrical intrauterine growth retardation. Her birth weight was 3.5 kg (50^{th} centile) but dropped to 2.86 Kg on admission. Her length was 45 centimeters ($<5^{th}$ centile). She had 2 healthy siblings, and her immunization history was up to date. On examination, she looked sick and dehydrated with no cyanosis, jaundice fever or dysmorphism. Her heart rate was 140, blood pressure 100/52 mmHg, respiratory rate 40 per minute, and Oxygen saturation 99%. Her Sodium was 135 (136 to 145 mmol/l), Chloride 117 (95 to 110 mmol/l), blood urea nitrogen 12.1 (1.8 - 8 mmol/l), Creatinine 44 (5 to 130 mmol/l), CO2 27 (20 to 28 mmol/l), AGAP 19 (7 to 15 mmol/l), and AST 28 (22 to 71 units/l). Serum Zinc, Copper and Ammonia were normal. Blood immunoglobulin levels were low, specifically: IgG 4.49, IgM 0.22 and IgA 0.14 (normal 7.5-15.6 g/l, 0.46-3.04 g/l and 0.82-4.53 g/l) respectively.

Skin examination revealed multiple sharply demarcated tan, brown café-au-lait macules (CALM) and patches of different sizes and tones located on the groin and waist area. These CALMs were variegated in color, arranged in linear pattern, and admixed with hypopigmented macules (FIG. 1A). There were no axillary freckles or neurofibromas. Hair examination revealed diffuse hypotrichosis with fragile brittle lightly pigmented hair (FIG. 1B). Hair shaft microscopy revealed fragmentation and breakage points consistent with trichorrhexis nodosa (FIG. 1C). THES syndrome was suspected and later confirmed by genetic testing.

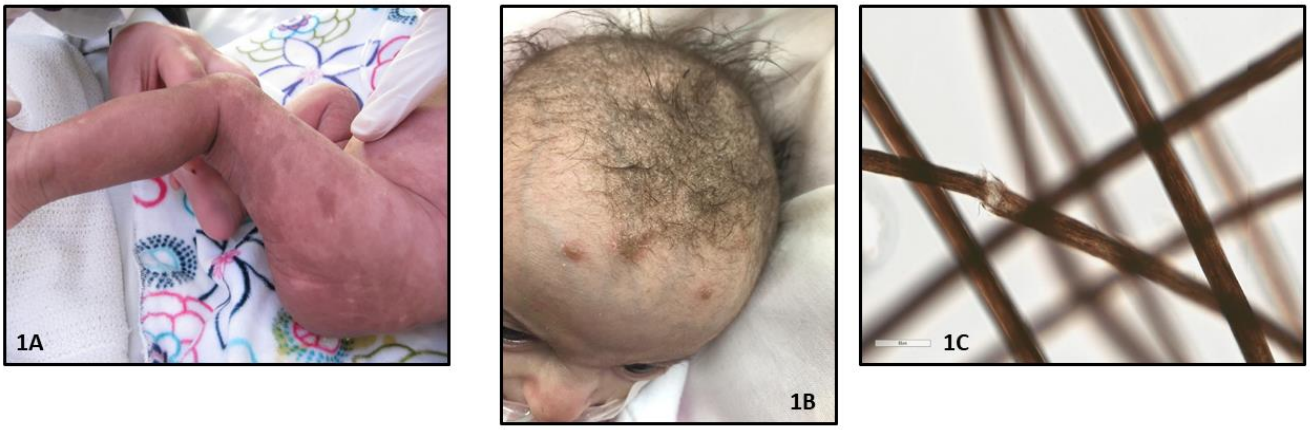

FIG. 1. **Patient's dermatological presentations. A) Photograph of the waist area and left thigh showing CALM with hypopigmented macules; B) Photograph showing hypotrichosis of the hair; C) Hair shaft microscopy revealed fragmentation and breakage points consistent with trichorrhexis nodosa.**

Whole exome sequencing (WES) was performed on patient genomic DNA focusing on genes that associated with congenital diarrhea such as *ADAM17, CYP27A1, DGAT1, EPCAM, FOXP3, GUCY2C, IL10, IL10RA, IL10RB, IL21, LCT, LIPA, MVK, MYO5B, NCF2, NEUROG3, SAR1B, SI, SKIV2L, SLC5A1, SLC9A3, SLC10A2, SLC26A3, SPINT2, TTC7A, TTC37* and *XIAP*. The proband was proven to carry a homozygous pathogenic inframe deletion variant c.3561_3581del, p.(Ser1189_Leu1195del)

in the *SKIV2L* gene with parents heterozygous for the same variant by sanger sequencing. The patient was managed by and maintained on home TPN with improvement in growth parameters. She was later lost to follow up.

3. Discussion

Trichohepatoenteric syndrome is a rare AR that was first described by Stankler in 1982 [1]. It is characterized by a chronic intractable diarrhea, hair loss and liver cirrhosis. Other variable features include immunodeficiency mostly due to hypogammaglobulinemia [4]. Many authors described facial dysmorphism features in THES including large ears, broad flat nose, prominent forehead and hypertelorism [4]. Infrequent findings include congenital heart defects and platelet abnormalities [4].

Hair abnormalities described in THES include easily removable, brittle hair leading to hypotrichosis [4]. Hair shaft abnormalities reported in THES include wooly hair and trichorrhexis nodosa as seen in our patient. Skin findings described in THES include CALMs extending from the waist area to knees [5]. We noticed many peculiarities in the CALM seen in our THES patients that are worthy of mentioning. They followed linear or semi linear configuration, were variegated in color with different shades of brown tent and admixed with white hypopigmented macules.

Gastrointestinal features of THES include persistent severe diarrhea leading to malnutrition and failure to thrive usually requiring long term TPN [2]. Histopathologic features of small intestine biopsy are nonspecific with villous atrophy, with or without mixed inflammatory infiltrate [2]. Fabre et al reported that 12 of 22 (55%) patients with THES had liver disease, 9 of 18(50%) had hepatic cirrhosis, and 4 of 17(24%) had hepatic hemosiderosis, indicating that iron overload may contribute to liver pathogenesis in THES [4]. Recently, Alsaleem et al estimated a much higher incidence of THES in Saudi Arabia of around 1:200,000 births, which they attributed to the high rate of consanguineous marriages in Saudi Arabia [6].

The cause of THES is homozygous or compound heterozygous mutations in either of SKIV2L gene on chromosome 6p21.3 or TTC37 on chromosome 5q15. [4,7,8]. TTC37 (MIM 614589) and (2) SKI2-Like RNA Helicase (SKIV2L) (MIM 600478) [6]. Fabre et al. in his review, found 40 out of 80 THES patients had a mutation in TTC37, 14 patients had mutation in SKIV2L, one patient without mutation of SKIV2L or TTC37, and 25 patients were not tested. This study showed that SKIV2L gene mutation is less common than TTC37 [4]. The described *SKIV2L* variant c.3561_3581del, p.(Ser1189_Leu1195del) in our patient was previously reported in dbSNP (rs1582192007) and in the gnomAD database, resulting in loss of 7 residues leading to pathological effect on SKI complex and subsequence effect on RNA decay. The two genes encode cofactors of the human SKI complex involved in RNA degradation [7]. The function of these gene products in humans is not yet fully elucidated. SKIV2L and TTC37 encode orthologs of the yeast proteins SKI2 and SKI3, respectively, which form the superkiller complex, together with 2 copies of SKI8. The superkiller complex is a cofactor of the cytosolic exosome, which is involved in the degradation of aberrant mRNA molecules. The mechanism by which a defect in the mRNA degradation system leads to the specific symptoms associated with THES remains unclear. Most patients with SKIV2L or TTC37 mutations have absent or significantly reduced expression levels of SKIV2L or TTC37 proteins [5].

The primary management of THES involves TPN, enteral feeding, and supportive management for other involved organs. In some cases, corticosteroids, immunosuppressant medications, and immunoglobulin can be used [8,9]. The prognosis of THES is generally poor with death early in life usually resulting from liver failure, recurrent infection, or complications associated with long-term TPN with few patients now surviving to the third decade. A recent study demonstrated better survival rates in THES patients with TTC37 over SKIV2L mutations [5].

4. Conclusion

In conclusion, we presented a new patient with THES and delineate the clinical features with particular emphasis on the skin findings that may facilitate early recognition of this rare syndrome.

5. Conflict of Interest

None

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