# Tricho-Hepato-Eenteric Syndrome: Same Genotype but Different Phenotypes in Two Pakistani Children

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## ABSTRACT

Tricho-hepato-enteric syndrome (THES) is characterised by infantile diarrhea with characteristic facies, trichorrhexis nodosa and hepatic involvement. The underlying genetic mutation is in tetratricopeptide repeat domain 37 (TTC37) gene. It is a very rare syndrome and only 44 cases have been reported so far in the medical literature. We recently diagnosed two children with THES on genetic analysis, who had same genotype but different phenotypes. Using these cases as a precedent, we reviewed what is known about this rare syndrome, as well as the novelties in our cases and treatment options.

**Key Words:** *Chronic diarrhea, Liver disease, Genetic mutation, TTC37.*

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## INTRODUCTION

Tricho-hepato-enteric syndrome (THES) is a rare condition that affects the hair, liver, and intestines. It is manifested by intractable diarrhea that usually begins during the first six months after birth and leads to failure to thrive. The liver involvement in the affected individuals is variable ranging from cirrhosis to mild hepatomegaly with or without liver dysfunction. The syndromic children usually have characteristic hairs, trichorrhexis nodosa and typical facies as broad forehead, small mouth, low-set ears and uplifted tip of nose.[1]

THES is an autosomal recessive disorder, caused by mutations in TTC37 gene, located on chromosome 5q15.[2] Other names given to this condition are phenotypic diarrhea, syndromic diarrhea, and THE syndrome. Intractable diarrhea is managed with parenteral nutrition, despite of which, affected individuals are shorter than their peers. Generally, hepatic involvement contributes to the poor prognosis.[3]

We present two cases diagnosed as THES on genetic analysis, having different phenotypes but same genotype.

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**CASE 1:**

An 11-year boy was referred to Pediatric Gastroenterology and Hepatology Unit, for his relentless chronic diarrhea. His symptoms started with persistent diarrhea at three years of life with frequency of 5-6 stools/day of grade III-IV consistency that were bulky and foul smelling without any blood and mucus. He described abdominal distension and failure to thrive along with these symptoms. There was also history of recurrent chest infections (3-4 episodes per year) in the form of fever, cough and respiratory distress. There was no history of vomiting, abdominal pain, skin or nail infection and recurrent ear discharge.

For two years, he had visited local private clinics for diarrhea and was advised antiprotozoals without any improvement. He was diagnosed as celiac disease at six years of age on the basis of elevated anti-tissue transglutaminase antibodies (TTG-IgA, 167 IU/L (Normal <9 IU/L); and advised gluten-free diet. Frequent chest infections were being managed with nebulisation, antibiotics in addition to anti-tuberculosis therapy for six months with temporary improvement. He had blood transfusions over this period.

He was born full-term with low birth weight to a consanguineous couple with three other healthy siblings. He was exclusively breast fed till six months of life and complementary diet was introduced at six months. There was no history of food allergies, tuberculosis and immunodeficiency in the family. He achieved all of his developmental milestones accordingly; but he never attended school because of his chronic illness. He was fully vaccinated according to local EPI schedule.

His examination revealed a thin lean boy having angular cheilosis, clubbing, generalised dry scaly skin and bilateral pedal edema. He was well below 3$^{rd}$ centiles both in his height

and weight (107 cms and 14 kg, respectively). He had dysmorphism in the form of broad forehead, small mouth and widely spaced eyes. He was having thin sparse easily pluckable hair (Figure 1). His systemic examination was normal except his abdominal examination, which showed enlarged liver 4 cm below right subcostal margin with total span of 13 cm.

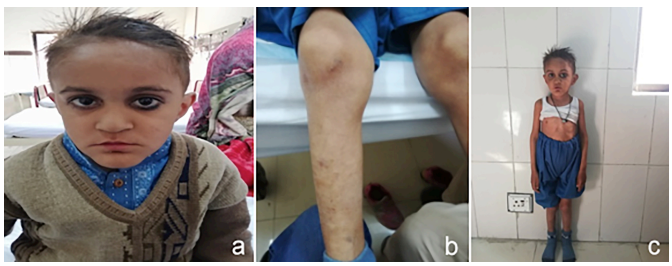


**Figure 1: (a), (b) and (c): An 11-year boy with failure to thrive, abdominal distention and bilateral pedal edema. Note facial dysmorphism (hypertelorism and broad nasal root).**

Laboratory workup showed microcytic hypochromic anemia and deranged liver function tests (LFTs), as shown in Table I. Alanine aminotransferase (ALT) was 121 IU/L, aspartate aminotransferase (AST), 55 IU/L, and alkaline phosphatase (ALP), 1231 IU/L. Prothrombin time (PT) was 19/14 seconds, which was corrected with vitamin K later on. Serum albumin was 2.1 g/dl. His immunoglobulin levels were normal except for immunoglobulin G (IgG), which was 205 mg /dl (normal >500 mg/dl), which could be attributed to low albumin levels. His sweat chloride test was within normal limits and delta F508 mutation was negative. Ultrasound (US) of abdomen revealed normal gut wall thickness and hepatomegaly with altered echo texture. Computed tomography (CT) chest and abdomen was unremarkable except for hepatomegaly. Esophago-gastro-duodenoscopy (EGD) and histopathology of small bowel were normal except for presence of lymphocytes in lamina propria, suggestive of non-specific duodenitis. His genetic testing solved the enigma of difficult-to-treat diarrhea, chest infection and abnormal hair. He was found to have homozygous mutation in TTC37 gene and both parents were heterozygous for same (Figure 2).

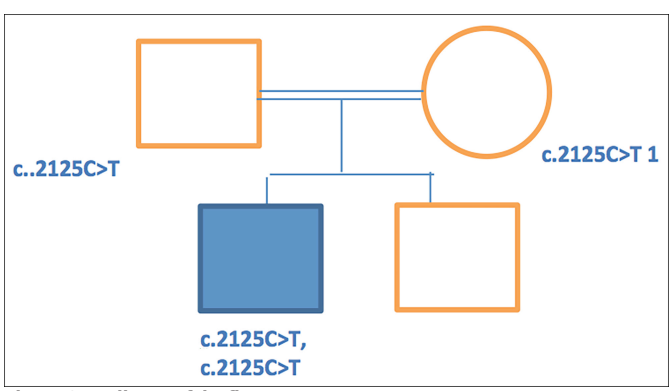


**Figure 2: Pedigree of the first case.**

We managed him with intravenous albumin, fat and water soluble vitamins and intravenous immunoglobulin (IVIG), leading to improvement in edema, dry skin, diarrhea and chest infections. He was discharged on 3-weekly IVIG; and is doing well with regular follow-ups.

## CASE 2

A 13-month Saudi-born Pakistani boy was well up to five months of life when he was admitted into hospital with bronchopneumonia for 15 days; and discharged on oral medications, but re-admitted after two weeks for the same complaints and needed ventilatory support. He was discharged home on oral medications and nebulisation. At 9 months of age, he developed loose motions 8-10/day, grade III-IV in consistency without mucus and blood. On examination, he showed evidence of failure to thrive with hepatosplenomegaly, mentioned in his medical history. He was investigated for liver disease and all workup turned out to be negative except deranged LFTs. During this 9 months period, he was admitted six times for his chest problems, diarrhea and worsening liver disease, but no diagnosis could be made.


**Figure 3 (a, b, c): A 13-month boy with prominent forehead and cheeks, hypertelorism and broad nasal root, developmental delay, failure to thrive and abdominal distention of the child.**

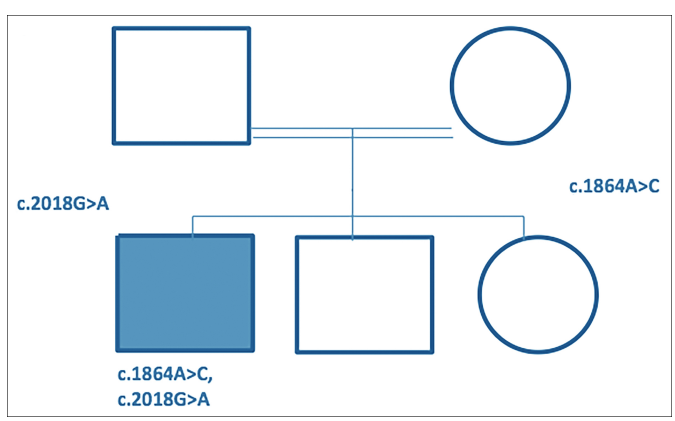


**Figure 4: Pedigree of the second case.**

He was born full-term to a consanguineous family with symmetrical intrauterine growth retardation (IUGR). He was exclusively breast fed till five months and topped up with formula milk because of frequent hospitalisation. The complementary food was started at 9 months of age but it could not be established adequately because of his difficult-to-treat diarrhea and lower respiratory tract infections. His development was delayed with normal hearing and vision.

**Table I: Demographic, clinical & laboratory parameters in both cases and comparison to published literature.**

| | Parameters | Case #1 | Case #2 | Hartley JL *et al* Gastroenterology, 2010[10] (n=11) | Fabre A *et al.* Front Immunol.2018[9] (n=9) | F.E Mahjoub Case Rep Pathol.2016[10] (n=3) |
|---|---|---|---|---|---|---|
| 1 | Age of presentation | 3 years | 5 months | 2weeks-7months | 31(0-335) days | 4 months |
| 2 | Duration of symptoms before diagnosis | 7 years | 8 months | 1-7 month | 3months-3years | 1-9years |
| 3 | 1st symptoms at onset of syndrome | Bronchopneumonia | Malabsorptive stools | Malabsorptive stools | Malabsorptive stools | Malabsorptive stools |
| | Anthropo metry | Height & weight both below 3rd centiles | Height & weight both below 3rd centiles | - | - | - |
| | Facies | yes | Yes | Yes11/11 | Yes9/9 | Yes3/3 |
| | Trichorhexis nodosa | yes | Yes | Yes 11/11 | Yes9/9 | Yes 3/3 |
| | Visceromegaly | Hepatomegaly | Hepatosplenomegaly | Hepatomegaly9/11 hepatosplenomegaly2/11 | Hepatosplenomegaly5/9 | - |
| 4 | Hemoglobin level at presentation | 7.2 g/dl | 6.4g/dl | - | - | - |
| | MCV | 71 fl | 62 fl | - | - | - |
| | MCH | 30 pg | 28 pg | - | - | - |
| 5 | TLC | 4900/uL | 7200/uL | - | - | - |
| 6 | Platelets count | 237,000/Ul | 56,000/uL | Normal5/11 Thrombocytosis6/11 | - | - |
| 7 | ALT | 121 IU/L | 235IU/L | - | - | elevated |
| 8 | AST | 55 IU/L | 125IU/L | - | - | elevated |
| 9 | ALP | 1231 IU/L | 1230IU/L | - | - | elevated |
| 10 | STB | o.5 mg /dl | 7.5 mg/dl | - | - | - |
| 11 | Blood urea | 26 mg/dl | 22 mg/dl | | - | - |
| 12 | Serum creatinine | 0.2 mg/dl | 0.3 mg/dl | - | - | - |
| 13 | Immuno globulins Level | IgG Low | Normal | Low11/11 | Low6/9 | - |
| 14 | Serum albumin level | | 2.3mg/dl | - | - | - |
| 15 | INR | 1.3(Corrected with IV vit K) | 1.7 (Not corrected with IV vit K) | - | - | - |
| 16 | Echo cardiography | Normal | Normal | Normal6/11 VSD1/11 TOF1/11 AI2/11 PS1/11 | Normal 9/9 | - |
| 17 | Skeletal anomalies | Normal | Normal | Normal10/11 Perthes disease1/11 | - | - |
| 18 | Renal anomalies | No | No | No10/11 small rt kidney1/11 | - | - |
| 19 | Developmental delay | No | Yes | Yes7/11 No2/11 unknown2/11 | - | Yes 3/3 |
| 17 | Small bowel biopsy | Non specific duedenitis | Could not done | Villous atrophy 11/11 | - | Mild to moderate villous atrophy 3/3 |
| 18 | Genetic mutation | c.2125C>T c.2125C>T | c.1864A>C c.2018G>A | | | |

*MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, TLC: Total leukocyte count, ALT: Alanine aminotransferase, AST: Aspartate amino transferase, STB: Serum total bilirubin, VSD: Ventricular septal defect, TOF: Tetralogy of fallot, PS: Pulmonary stenosis, AI: Aortic insufficiency.*

On examination, a cachectic child weighing 4.5 kg with length of 60 cm and fronto-occipital circumference (FOC), 45 cm, having broad forehead, small mouth, sparse fragile hairs and was slightly icteric (Figure 3). He had tachypnea and tachycardia with nasal flaring and bilateral coarse crepitations. Abdomen was distended with liver palpable 4 cm below right subcostal margin and spleen 3 cm below left subcostal margin: both were firm in consistency without any ascites. He was admitted in intensive care unit and mechanically ventilated for his bad chest.

His laboratory data, summarised in Table I, revealed normocytic normochromic anemia with thrombocytopenia, serum ALT, 235 IU/L, AST, 125 IU/L, ALP, 1230 IU/L, gamma glutamyl transferase (GGT), 55 IU/L serum total bilirubin (STB), 7.5 mg/dl (direct 5.5 mg/dl) serum albumin, 2.3 g/dl and international randomised ratio (INR) 1.7. Chest X-Ray (CXR) showed bilateral infiltrates, and ultrasonogram (USG) of abdomen revealed enlarged liver, 13 cm in size, with altered echotexture. His metabolic liver profile done previously showed normal urinary succinylacetone, normal galactose 1 phosphate uridyl transferase (GALT) assays and immunoglobulins levels, normal workup for lysosomal storage disorders (LSDs), and negative TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes simplex) profile. His genetic analysis showed homozygous mutation in TTC37 gene, confirming the diagnosis of THES (Figure 4).

He was started on elemental formula milk and infusion of IVIG. He had improvement in diarrhea, chest infection and was weaned off from ventilator successfully. He had global developmental delay and bad liver disease. His family was counselled for poor prognosis and outcome. He was discharged home and went back to Saudi Arabia and admitted once again with lower respiratory tract infection. His liver decompensated and unfortunately he expired at 18

months of age of liver failure.

## DISCUSSION

The term THES, introduced by Verloes *et al*. in 1997,[4] was previously known as syndromic diarrhea or phenotypic diarrhea since 1982.[5] Verloes *et al.* described a condition affecting a brother and sister, who were born IUGR and had intractable diarrhea with normal histologic and enzymatic studies. Both had facial anomalies; included low-set ears, hypertelorism, small mouths and upturned noses along with abnormal hair texture and pattern. The sister also had cholestatic jaundice. Both siblings expired at the age of six months. Our second case had same presentation and course of illness except for his chest infections.

Recurrent chest infections are not a part of this syndrome but both of our cases had bad recurrent lower respiratory tract infections without chronic lung disease, indicating low immunity for repeated viral infections. Although immunoglobulin levels were in normal range except for low IgG levels in our first case, probably due to low albumin. Fabre *et al*. have reported two unrelated male infants with all prominent features of THES and humoral immunodeficiency.[6]

It has been mentioned in the literature that few children get bowel control as they grow older, as reported by Barabino *et al*. about a girl diagnosed as THES at 15 days of life who attained her bowel autonomy at one year of age and became total parenteral nutrition (TPN)-free. Intestinal histology improved, which at diagnosis showed subtotal villous atrophy. At the age of 17 years, she had severe growth delay with an adequate pubertal development, mild mental impairment, intermittent diarrhea, and frequent upper respiratory infections. It showed that if one attains bowel autonomy, this would be a good prognostic factor.[6]

Severe liver disease in this syndrome is a bad prognostic sign with rapid progression of the disease to liver failure.[7] Our second case had severe phenotype of THES and as reported in literature, his liver involvement was a bad prognostic factor. But his severe lower respiratory tract infection needed assisted ventilation support four times, so we believe that this is also a bad prognostic factor. Moreover, in both of our cases, there was no chronic lung disease. Every time, it happened as a new acute episode, so there must be a cause other than depressed immunity behind these chest infections.

Hartley *et al.* reported 12 cases of THES with serially obtained histologic examination of jejunal biopsy specimens, showing that the villous atrophy can improve with age and the inflammatory infiltrates are not consistently present.[8] This was similar to our first case, but we were unable to get small bowel biopsy in our second case. He also reported cardiac anomalies in five of his cases including aortic insufficiency, peripheral pulmonary stenosis, ventricular septal defect and tetralogy of Fallot. Both of our cases did not have any cardiac anomaly as screened by multiple echocardiography examinations.

Platelet abnormalities including large platelets, thrombocytosis and on transmission electron microscopy, reduced platelet alpha-granules are present in these patients. Our second case had persistent thrombocytopenia but platelets were normal in first case. TTC37 mutation is diagnostic for this syndrome, which was detected in both of our cases.[9,10]

In conclusion, THES is a rare pediatric condition with facial dysmorphism, intractable diarrhea, and liver disease. Phenotype can be different in different patients with same genotype as is evident in our cases. Further insight and research is needed for managing this rare but highly morbid condition.

**PATIENTS' CONSENT:**
Informed consents were obtained from patients' parents to publish the data concerning this case.

**CONFLICT OF INTEREST:**
The authors declared no conflict of interest.

**AUTHORS' CONTRIBUTION:**
NW: Compiled all data, write it up and literature search.
AS: Helped in searching literature.
HAC: Helped in proofreading.

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