Introduction. Intractable diarrhea of infancy (IDI) includes several types of early onset diarrhea; one of the rare etiologies is trichohepatoenteric (THE) syndrome, also known as syndromic diarrhea (SD) which was primarily described by Stankler et al. in 1982, in two siblings, presenting with diarrhea, failure to thrive, abnormal facies, and unusual hair [2]. Following reports on other cases revealed similarities in signs and symptoms. The most common observed signs are intractable diarrhea, usually starting before six months of age, dysmorphic facies such as prominent forehead and cheeks, broad nasal root and hypertelorism, abnormal hair, disorders of immune system, intrauterine growth retardation, skin abnormalities, and liver function disorders [1, 3, 4]. Distinct hair abnormalities such as woolly, easily removable hair and poorly pigmented hairs are seen even in children with middle eastern origin [3]. Microscopic examination of hair shafts reveals nonspecific abnormalities such as twisted hair (pili torti), aniso- and poikilotrachosis, trichorrhexis nodosa, and longitudinal breaks [3]. Even with treatment, most patients have a small final stature [3–5]. Fine motor movement abnormalities and mental retardation are seen in most affected children [3]. Liver disease (liver enlargement and cirrhosis) is reported in more than half of the children [1]. Investigations show the association between mutations in TTC37 (encodes the putative
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Figure 1: (a) and (b) Note the prominent forehead and cheeks, hypertelorism and broad nasal root, short stature, and abdominal distention of the child.

Figure 2: A one-year-old girl with failure to thrive and motor delay. Note facial dysmorphism (hypertelorism and broad nasal root).

Figure 3: A nine-year-old boy with failure to thrive and abdominal distention. Note facial dysmorphism (hypertelorism and broad nasal root).

2. Report of the Cases

A three-year-old boy was born to healthy, related parents (cousins). The pregnancy was uneventful and he was born full term, weighing 3,100 kilograms, and 51 cm in height. He was breastfed and experienced normal growth for the first 4 months and reached 5 kilograms. He had poor weight gain afterwards (recent weight: 8.5 Kg) and began having intermittent steatotic diarrhea and abdominal distension and was hospitalized several times for workup of failure to thrive. As seen in the attached photo facial dysmorphism (prominent forehead, broad based nasal bridge, and hypertelorism) is evident (Figures 1(a) and 1(b)). Hair changes such as woolly and easily removable hair and light coloration were evident in our case. Two other children in the family (his cousin a one-year-old girl weighing 7 Kg with developmental delay and another cousin a 9-year-old boy weighing 16 Kg) also showed somewhat similar symptoms (Figures 2 and 3). Pictures were provided by the family and they were informed about writing of this paper and the paper was submitted after their consent for publishing the pictures with covered eyes.

Several stool exams were performed and were negative for ova, parasites, white blood cells, and red blood cells but were intermittently positive for fat. Stool trypsin activity test was normal. Complete blood cell count (CBC) constantly showed microcytic anemia. Two sweat tests were negative.
for cystic fibrosis. Multiple testing for Anti-TTG showed variable results (mostly revealed mild elevation). Gluten-free diet was instituted several times but was not effective. Human Leukocyte Antigen (HLA) typing for DQ2 and DQ8 was negative. Workup for Hirschsprung’s disease (due to abdominal distention) was performed at 21 months of age, but colon was ganglionic. Thyroid function tests were normal. Insulin Growth Factor 1 (IGF-1) was lower than normal in one occasion (7.34 ng/mL, normal: 27.4–113.5 ng/mL). Abdominal sonography at 1.5 years of age showed coarse and nonhomogeneous echo of liver. AST and ALT were mildly elevated. Upper gastrointestinal endoscopy showed evidence of esophagitis and mild atrophic duodenitis. Biopsy from esophagus and mucosa of second part of duodenum was performed. Microscopic examination of esophageal mucosa showed moderate esophagitis. In duodenal mucosa, the villi were mildly to moderately short in well oriented areas. Focal superficial epithelial changes were seen (reduced number of goblet cells, irregularity of lining cells) (Intraepithelial lymphocytes: under 10/100). Crypt hyperplasia cannot be assessed; however, crypts show marked difference in size, branching, and distortion. There was mild to moderate infiltration of lymphoplasma cells and some eosinophils (3–7/100) in lamina propria, distorting some of the crypts. No giardia lamblia parasites are seen (Figure 4).

Microscopic examination of hair shafts of the first case revealed aniso- and poikilotrichosis with kinking and breakage but no typical trichorrhaxis nodosa was seen (Figure 5).

Hair changes in cases 2 and 3 are mild and not as prominent as case 1, which denotes that spectrum of changes is seen in the family. Also the index patient suffers from severe dental problems (caries) leading to loss of most teeth. No skin or cardiac involvement is present in patients.
No further workup for liver disease and liver biopsy was performed for the patient.

The case was consulted with Professor Elizabeth Montgomery (Johns Hopkins School of Medicine, USA) and, in light of clinical symptoms (facial dysmorphism, hair anomaly, and hepatic involvement along with gastrointestinal symptoms) and affection of several family members, diagnosis of trichohepatoenteric syndrome was established. Genetic testing is not available yet in Iran. Diagnosis was accepted readily by pediatric gastroenterologists and the patient was relieved from further repetitive and time consuming workup tests.

3. Discussion

Despite high prevalence of diarrhea in children and availability of several tests for investigating different etiologies, still in many cases, even with extensive investigations, definite diagnosis cannot be reached. Moreover we are yet far from developing a way to control the etiology in many cases. Trichoenterohepatic syndrome was first described by Stankler et al. in 1982 [2]. Since then several cases have been reported and researchers have concluded that the diagnosis is mainly suspected by clinical signs and symptoms such as persistent diarrhea, facial dysmorphism, abnormal hair, and involvement of liver. To date the confirmatory diagnostic test is sequencing of TTC37 and SKIV2L genes [1, 4, 7] and microscopic examination of intestinal biopsies is more useful in ruling out other causes of chronic diarrhea such as tufting enteropathy and congenital microvillus atrophy. Treatment of these children is mainly symptom-relieving actions such as parenteral nutrition to help with growth, sometimes immunoglobulin supplementation, and, in those with severe liver disease, liver transplant [1]. Even with treatment, most patients have a small final stature [3–5]. About half of them show a slight mental retardation, but the main observed complications are liver disease and infections. Understanding the genetic defect of the disease gives hope to better perception of the pathology of the disease and perhaps a better management of patients.

Diagnosis was delayed for several years in our patient and he underwent unnecessary workups such as biopsy of colonic wall and testing for celiac disease several times. A careful clinical examination and thorough asking about family history (presence of affected members, consanguinity) would have helped to reach to a diagnosis sooner and save patient from time consuming and invasive workups.

Although genetic testing is the definite diagnostic test, unfortunately it is not yet available for this syndrome in our country; however, the symptoms and family history leave no doubt about the diagnosis.

Our cases showed no evidence of overt mental retardation which is seen in some cases although motor delay was seen in the one-year-old girl mentioned.

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Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.