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Clinical Report

Tricho-Hepato-Enteric Syndrome: A Case of Hemochromatosis With Intractable Diarrhea, Dysmorphic Features, and Hair Abnormality

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We report on a female infant with congenital iron storage disease, facial dysmorphism, intractable diarrhea, and hair abnormalities. The intractable diarrhea failed to resolve despite total parenteral nutrition and complete bowel rest for more than 3 weeks. The patient also had elevated liver enzymes and failure to thrive. Histopathologic examination of the liver revealed marked iron deposits in hepatocytes with portal edema, fibrosis, and septal formation. No metabolic abnormalities could be detected. She died at the age of 10 months. We suggest that this case could have a specific iron storage syndrome that is similar to the two sibs reported by Stankler et al. [1982; Arch Dis Child 57:212–216] and Verloes et al. [1997; Am J Med Genet 68:391–395]. The condition was called the tricho-hepato-enteric (THE) syndrome. © 2007 Wiley-Liss, Inc.

Key words: intractable diarrhea; iron storage disease; hair anomaly; hypertelorism; total parenteral nutrition; neonatal hemochromatosis; tricho-hepato-enteric syndrome

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INTRODUCTION

Neonatal hemochromatosis (NH) is a disorder of prenatal multivisceral iron deposition. It represents disordered iron handling prenatally leading primarily to severe liver dysfunction. Neonatal hemochromatosis has an unclear etiology and is likely not a single disorder. Despite the lack of a clear etiology and pathogenesis and the possibility that it is heterogeneous, the phenotype of NH now is widely recognized and universally found to have an aggressive course and to carry a poor prognosis [Bernard and Manci, 1991; Murray and Kowdley, 2001]. Intractable diarrhea is defined as protracted, severe chronic diarrhea associated with severe malnutrition not easily resolved by conventional management.

We report on a girl who presented in early infancy with hepatic iron storage associated with intractable diarrhea and other anomalies suggesting a syndromic iron storage disease. Her findings were similar to sibs reported by Stankler et al. [1982] and Verloes et al. [1997].

CLINICAL REPORT

This girl was born at term by normal vaginal delivery following an uneventful pregnancy. Her birth weight was 3,250 g (38th centile/−0.30 SD). The length and head circumference at birth were not available. Her newborn examination was normal and she was discharged home on breast-feeding. Her parents (father age 36 and mother age 29 years) were first cousins. The patient had three male and one female siblings in good health. The mother had one abortion.

Artificial infant formula was added to breast-feeding due to inadequate weight gain at the age of 1 month. She was not found to have any other abnormalities at that time. Her first episode of watery

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diarrhea occurred at the age of 50 days and she required hospitalization due to hypernatremic dehydration. The diarrhea persisted despite trying various dietary formulas including soy-based, protein hydrolysate, carbohydrate-free, and amino acid-based formulas. At the age of 65 days she received total parenteral nutrition and bowel rest for up to 3 weeks in the hospital without any noticeable improvement in her diarrhea.

At 3 months of age, she was re-hospitalized due to intractable diarrhea. Her growth parameters were as follows: weight 3,070 g (−4.18 SD), length 54 cm (−2.64 SD), and occipitofrontal circumference 36 cm (−3.86 SD). Physical examination showed sparse thin curly hair especially on the frontal and temporal regions, hypertelorism, broad nose, and prominent eyes as shown in Figures 1 and 2. She also had umbilical and bilateral inguinal hernias. Neurologically, the infant was normal, and she had no icterus or hepatosplenomegaly.

Investigations included the following: serum methionine was normal on two occasions (at 90 and 120 days). There was a moderate elevation of liver enzymes: alanine aminotransferase (ALT) 610 U/L (normal 13–45 U/L), aspartate aminotransferase (AST) 167 U/L (normal 15–60 U/L), and alkaline phosphatase 1,239 U/L (normal 150–420 U/L). Other normal studies included serum calcium, phosphorous, copper, urine organic acids, quantitative serum immunoglobulins, B- and T-cell subsets, thyroid function tests, and karyotyping (46, XX). Additionally, serum amino acid chromatography was normal on two occasions.

FIG. 1. A photograph of the Patient at 2 months of age showing sparse thin curly hair, hypertelorism, broad nose, and prominent eyes. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

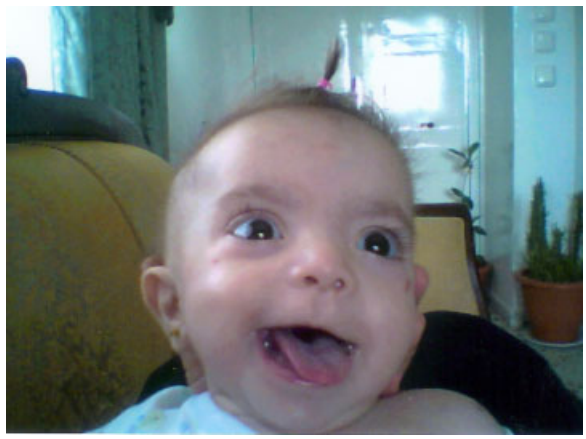

FIG. 2. The same clinical features a few months later. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

We excluded homocystinuria, tyrosinemia, other aminoacidurias, alpha-1-antitrypsin deficiency, cystic fibrosis, and infections caused by EBV, CMV, or hepatitis A, B, C, and HIV. Antinuclear antibody (ANA) was negative.

Iron studies revealed serum iron of 138 mcg/dl (normal: 40–100 mcg/dl) and total iron binding capacity of 88 mcg/dl (normal: 240–450 mcg/dl). She had an elevated serum ferritin (over 1,000 ng/ml) on 3 occasions (normal: 50–200 ng/ml). She had marked stool fat content, but a quantitative test was not done. Skeletal radiographs were normal with no rachitic changes. Ophthalmic exam was also normal.

Liver biopsy showed portal edema and fibrosis with septal formation. In the portal tract, there was minimal chronic inflammation and cholangiolar proliferation. The sinusoidal pattern was preserved with minimal sinusoidal and pericentral fibrosis. Iron stain revealed marked deposition (+3) of iron pigment mainly in hepatocytes. An upper endoscopic biopsy from the duodenum for histology and electron microscopy showed flattening of villi but did not detect a specific pathology.

The infant was discharged after 3 weeks of hospitalization on Neocate and pancreatic enzyme replacement for the remote possibility of Schwachmann–Diamond syndrome. Her bowel movements were loose at a daily frequency of 4–6 times. Her course, thereafter, was marked by recurrent episodes of intractable diarrhea necessitating multiple hospitalizations during which the diarrhea decreased in severity, but she never had normal bowel movements. She did not develop progressive hepatic dysfunction during her illness and continued to have normal psychomotor development.

The patient died at 10 months of age, at home, after an episode of severe intractable diarrhea. Her weight was 5,000 g.

DISCUSSION

Our patient has many clinical features that are similar to the two sibs reported by Stankler et al. [1982]. These include facial dysmorphism, intractable diarrhea, hair abnormality, failure to thrive, and hepatic hemosiderosis. The onset of diarrhea in the two sibs at the third week of life is somewhat similar to our case where diarrhea started at age of 50 days. Histological and electron microscopic exam of intestinal biopsy failed to find an explanation for the diarrhea in our patient as was the case for the sibs reported by Stankler et al. The differences include absence of hypermethioninemia, the inability to look for hemosiderosis of other organs and lack of hair analysis in our patient.

Verloes et al. [1997] also reported two sibs with clinical presentation similar to our case including hair abnormality, facial dysmorphism, intractable diarrhea, and hepatic hemosiderosis. Although hypermethioninemia was absent from our patient at 3 and 4 months of age, we did not have a methionine level performed after that because of lack of hepatic failure or progressive deterioration in hepatic function. Additionally, our patient had a later onset of diarrhea compared to the two sibs reported by Verloes et al. who developed intractable diarrhea after the introduction of enteral nutrition.

Landers and Schroeder [2003] described a patient similar to ours with brittle hair and trichorrhexis nodosa who had severe intractable diarrhea in infancy accompanied by hepatic cirrhosis and facial dysmorphism. Our patient, however, did not have developmental delay. Girault et al. [1994] described a syndrome of intractable diarrhea, dysmorphism, and immunodeficiency (i.e., abnormal humoral and cellular responses despite normal T and B cell numbers and normal serum immunoglobulin levels). Compared to their patients, our patient was not of low birth weight, had a normal neurologic and psychomotor exam, flattening of intestinal villi in the duodenum, normal B and T cell numbers, and normal immunoglobulin levels (including IgA). We did not test our patient's antibody responses or antigen-specific skin tests.

An unclassified congenital disorder of glycosylation (CDG-x) was reported by Mention et al. [2001] as a cause of severe intractable diarrhea in neonates. We did not test our patient (who presented at a later age) for this disorder; however, she lacked the dysmorphic features and progressive neurologic impairment that was described in their patient.

In summary, the girl reported here has a clinically similar infancy-onset hemochromatosis phenotype as the sibs reported by Stankler et al. [1982] and the sibs of Verloes et al. [1997], but with a characteristic absence of hypermethioninemia in our patient. Clinical and pathological aspects should be further studied in other cases of atypical hemochromatosis.

The tricho-hepato-enteric syndrome seems to represent a recognizable syndrome in infants presenting with neonatal hemochromatosis. The consanguinity in the parents of our patient suggests that THE is an autosomal recessive disorder.

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