Menkes disease with gastroesophageal reflux disease and successful surgical treatment: a case report and literature review

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The complication of Menkes disease (MD) and gastroesophageal reflux disease (GERD) is extremely rare. This report describes the very rare case of a one-year-old boy with MD complicated with GERD, and the successful surgical treatment of GERD. We review the literature on this relationship between MD and GERD, and discuss the clinical features of this association. Furthermore, the possible cause of the onset of GERD complicated with MD is explored in this report.

Key words: gastroesophageal reflux disease, Menkes disease, Nissen fundoplication.

Menkes disease (MD) is a rare progressive neurodegenerative and X-linked recessive disorder involving the abnormal expression or deletion of an ATP7A gene localized to chromosome Xq13.31.2. This results in the failure of copper metabolism, with impaired absorption at the intestinal level, and the failure of copper utilization and transport to various cells in the body2. The typical phenotype includes sparse and twisted hair, which is often lightly pigmented, mental retardation, marked hypotonia, seizures, and neonatal hypothermia. Less common associations are bladder diverticula, gastric polyposis and umbilical/inguinal hernias2.

Pathologic gastroesophageal reflux disease (GERD) is most commonly seen in children with neurologic impairment. On the other hand, the complication of MD with GERD is extremely rare3. Herein, we present the case of a one-year-old boy with MD complicated with GERD, and the successful surgery-based treatment of GERD. We review the literature on this relationship between MD and GERD and discuss the clinical features of this complication. Furthermore, possible causes of the onset of GERD associated with MD are explored in this report.

Case Report

A boy was born vaginally at 35 weeks’ gestation, weighing 2,466 g. His scalp hair was sparse, blondish in color and coarse at two months of age and showed 33 spiral appearance on microscopy, namely kinky hair (Fig. 1). He presented with convulsions at three months of age. Laboratory findings including complete blood cell counts, serum electrolytes, and liver and renal functions were normal at four months of age. However, serum copper and ceruloplasmin were decreased to 10 μg/dl (normal: 40-265 μg/dl) and 4.6 mg/dl (normal: 21-37 mg/dl), respectively. Brain magnetic resonance angiography (MRA) showed marked looping, elongation, and tortuosity of the internal jugular arteries and its branches (Fig. 2). Cystography showed multiple diverticula of the bladder. He was diagnosed with classical MD based on the lack of an increase in levels of serum copper and ceruloplasmin after oral copper administration, the clinical course, and findings on the brain MRA. Thereafter, treatment with subcutaneous copper-histidine administration was initiated at four months of age, and the levels of serum copper and ceruloplasmin increased to normal ranges.
At nine months of age, he often vomited, and experienced recurrent episodes of aspiration pneumonia and dyspnea. A Gastrografin™ upper gastrointestinal series revealed a small stomach without malrotation, and with no esophageal stenosis or hiatal hernia (Fig. 3). Thereafter, nasogastric tube feeding was started, and aspiration pneumonia recurred at 11 months of age. Based on upper gastrointestinal studies and 24-hour esophageal pH monitoring, GER was detected with 15.2% of the fraction at the time the pH was below 4.0.

He required surgical treatment due to aspiration pneumonia after tube feeding, and underwent Nissen fundoplication and gastrostomy at 12 months of age. No problems occurred under the general anesthesia, such as esophagitis or esophageal strictures, with upper gastrointestinal endoscopy. In open Nissen fundoplication, loose connective tissues were noted around the gastroesophageal junction, especially the crura of the diaphragm. The esophageal hiatus was narrowed posterior to the esophagus with the placement of two sutures. A 2-cm long and 360° fundic wrapping was thus constructed without difficulty despite the small stomach. During the Nissen fundoplication procedure, the anterior and posterior vagus nerves were carefully protected and preserved. Stamm gastrostomy for feeding was performed at the anterior wall of the middle gastric body through a short transverse upper abdominal incision.

The postoperative course was uneventful without vomiting or aspiration pneumonia, but he died from respiratory disorder of respiratory syncytial viral infection at 1 year and 7 months of age.

Discussion
Patients with MD show a primary defect in P-type cation-transporting adenosine triphosphatase (ATPase), leading to systemic copper deficiency, and most of the clinical manifestations can be explained by a deficiency of copper-containing enzymes, such as cytochrome c-oxidase, dopamine β-hydroxylase, tyrosinase, superoxide dismutase, and lysyl oxidase3. Of the copper-containing enzymes, lysyl oxidase appears to be among the most sensitive to defects in Menkes copper ATPase4, although the precise mechanisms remain to be fully clarified. Since copper enzymes are widely distributed throughout the body, MD represents a multisystemic disorder. Lysyl oxidase is a copper-dependent enzyme involved in the cross-linking of collagen and elastin and formation of the vascular architecture. Well-known symptoms of connective tissue

Fig. 1A. The scalp hair was sparse, blondish in color and coarse at two months of age. B. Characteristic spiral appearance on microscopy is termed kinky hair.

Fig. 2. Brain magnetic resonance angiography showed marked looping, elongation, and tortuosity of the internal jugular arteries and its branches.
abnormalities include tortuous vessels, skeletal changes, bladder diverticula, loose skin, and loose joints. We report herein an MD patient in association with GERD as another connective tissue symptom. Connective tissue abnormalities are characteristic complications of MD, and may reflect a failure in elastin and collagen cross-linking caused by a decrease in the functional activity of copper-dependent lysyl oxidase. Defective elastic fibers within the internal elastic lamina, tunica media, and intimal layers of arteries and arterioles result in vascular tortuosity and ectasia. GER is probably one of the connective tissue manifestations. Based on these pathophysiological characteristics of MD and the operative findings in the present patient, who was noted to have loose connective tissues around the gastroesophageal junction and especially the crura of the diaphragm, we speculate that there is some association between MD and GER. However, further studies regarding the association between the two diseases that involve a larger cohort of patients are warranted. GER should be carefully evaluated in patients with MD demonstrating recurrent gastrointestinal and/or respiratory symptoms, although larger studies involving histopathological findings will be required to determine the accuracy of the findings regarding connective tissue abnormalities. In the present case, we did not examine the connective tissue of the esophageal hiatus and esophago-diaphragmatic membrane histopathologically.

Menkes disease shows a neonatal onset, but patients are typically asymptomatic during the first two or three months of life, after which neurological deterioration occurs, with the loss of milestones, convulsions and hypotonia followed by spasticity and eventually lethargy. The classic form is usually lethal by the age of three years with onset in infancy. Other manifestations may include umbilical and inguinal hernias, urinary bladder diverticula, as well as gastric polyps, which may result in fatal gastrointestinal hemorrhage. As demonstrated in the present case, surgical treatment of GERD with Nissen fundoplication may be successful in GERD complicated with MD. A further accumulation of cases of MD with GERD is recommended to evaluate the relationship between the two entities. In summary, GERD should be carefully evaluated as a gastrointestinal complication of MD in patients with MD showing gastrointestinal and/or respiratory symptoms.

REFERENCES