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Patient Report

Esophago-gastric motility and nutritional management in a child with ATR-X syndrome

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Abstract X-linked alpha thalassemia mental retardation (ATR-X) syndrome is an X-linked recessive disorder that often involves gastrointestinal symptoms. Aspiration pneumonia related to gastroesophageal reflux has been reported as the major cause of death, but gastrointestinal function has not been well investigated. The present report describes a child with ATR-X syndrome who suffered from periodical episodes of refractory vomiting. We investigated the function of upper alimentary tract and found that esophago-gastric dysmotility and severe gastric volvulus were the major causes of gastrointestinal symptoms. This child was surgically treated with anterior gastropexy and jejunal alimentation through gastrostomy, and the symptoms were relieved with good weight gain. This report may provide insight into the gastrointestinal function and nutritional management in children with ATR-X syndrome.

Key words ATR-X syndrome, gastroesophageal reflux, motility, nutritional access, PEG-J.

X-linked alpha thalassemia mental retardation (ATR-X) syndrome, which was first described in 1990 by Wilkie *et al*., is associated with alpha thalassemia, profound developmental delay, genital abnormality, and facial dysmorphism.[1] Mutations in the *ATRX* gene locus Xq13.3 were first described in 1995,[2] and, to date, a number of mutations have been identified in patients with ATR-X syndrome.[3] Gastrointestinal symptoms such as feeding difficulties, regurgitation, abdominal distention and chronic constipation have been recognized as common complications.[4,5] Given that aspiration pneumonia related to gastroesophageal reflux (GER) has been identified as the major cause of death in these patients,[4–6] investigation of gastrointestinal abnormalities is considered to reduce mortality and morbidity. There have been few studies on gastrointestinal issues in patients with ATR-X syndrome. We report a child with ATR-X syndrome treated successfully with laparoscopic anterior gastropexy and gastrojejunal feeding tube placement based on esophago-gastric motility findings.

Case report

The male patient was born by normal spontaneous vaginal delivery at 36 weeks of gestation with a birthweight of 2581 g. He remained in the neonatal care unit for 1 month due to poor sucking, unstable respiratory condition, and failure to thrive. Developmental milestones were markedly delayed. Clinical examination indicated hypotonia and facial dysmorphism, which consisted of telecanthus, depressed nasal bridge, and triangular mouth. His characteristic facial features and profound intellectual disability led us to consider ATR-X syndrome. Peripheral red blood cells (RBC) were screened for hemoglobin H (HbH) inclusion bodies. HbH inclusions were detected in 5% of brilliant crystal blue-stained RBC, and this was consistent with the clinical diagnosis of ATR-X syndrome. Genomic DNA showed a single nucleotide substitution in exon 8 of the *ATRX* gene, and characterization of *ATRX* mRNA showed an abnormal splicing, which was thought to be translated into an ATRX protein with a deletion of 21 amino acids (c.536A>G; r.[532_594del]; p.V178_K198del).

The patient had gastrointestinal-associated symptoms including drooling, severe regurgitation and vomiting, dysphagia, irritability, tympanism, and chronic constipation. Periodic episodes of refractory vomiting resulting in dehydration forced repetitive hospitalizations. Height (94 cm, −2.0 SD) and weight (12.2 kg, −3.0 SD) indicated severe growth delay and malnutrition. He was referred to a pediatric surgeon at 5 years of age in order to evaluate possible surgical interventions that may provide symptomatic improvement. Video manometry was conducted using a 16-channel side-hole catheter with 1 cm distance between holes, and this showed a lack of swallow-related primary peristalsis, and lower esophageal sphincter (LES) tones ranging from 20 to 30 mmHg.[7] The extremely weak simultaneous contraction of the

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esophageal body was followed by adequate LES relaxation, finally clearing the esophageal contrast medium into the stomach. Fluoroscopy showed a slightly dilated esophagus with a to-and-fro movement pattern of contrast medium and slow esophageal clearance (Fig. 1). In addition, GER and gastric volvulus of organo-axial rotation were evident with poor passage of contrast medium to the duodenum (Fig. 2a). Intestinal function was preserved without arrest or delayed passage of the contrast medium. Delayed gastric emptying was obvious with an evacuation rate of 11% at 1 h on ^{99m}Tc scintigraphy. GER episodes were assessed on 24 h pH multichannel intraluminal impedance (Sandhill Scientific, Highlands Ranch, CO, USA). The percent time of acidic and non-acidic reflux episodes was 5.0% and 8.4%, respectively. The mean acid clearance time was 189 s. These data suggested more prevalent non-acidic GER and esophageal dysmotility. There was no endoscopic mucosal lesion, but mild histological esophagitis was observed.

According to the esophago-gastric motility study, slow esophageal clearance and delayed gastric emptying were the two major findings. In these conditions, fundoplication might have adverse effect on esophageal clearance and worsen vomiting. Thus, we decided to perform correction of gastric position and jejunal alimentation without fundoplication. The button percutaneous endoscopic gastrostomy with jejunal extension (PEG-J) is a device for gastric decompression that prevents GER and facilitates jejunal nutritional access (GB jejunal button®; Fuji Systems, Tokyo, Japan; Fig. 3). Laparoscopic anterior gastropexy and gastrostomy were conducted, and button PEG-J was inserted to the upper jejunum under radiographic guidance. Postoperatively, the contrast study showed corrected gastric position (Fig. 2b). Gastric decompression through the gastric hub of the button was sufficiently effective to control GER symptoms, and the jejunal tube enabled adequate enteral feeding without any complication. The patient did not have episodes of regurgitation and did not

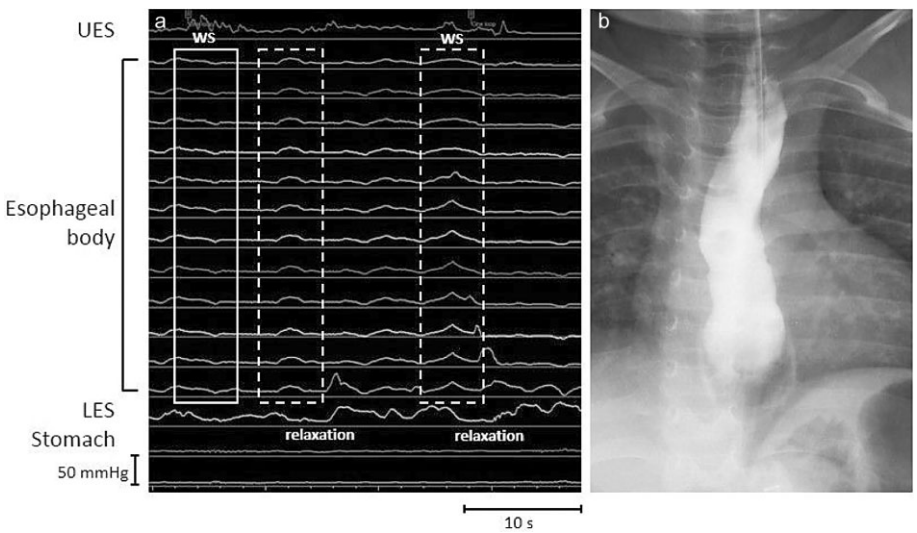

Fig. 1 (a) Manometric trace showing lack of swallowing-related primary peristalsis (rectangle). Note the weak simultaneous contraction of the esophageal body (dotted rectangle) and subsequent relaxation of the lower esophageal sphincter (LES). (b) Fluoroscopy showing impaired luminal clearance down to the stomach with spastic esophageal wall movement. UES, upper esophageal sphincter; WS, wet swallowing.

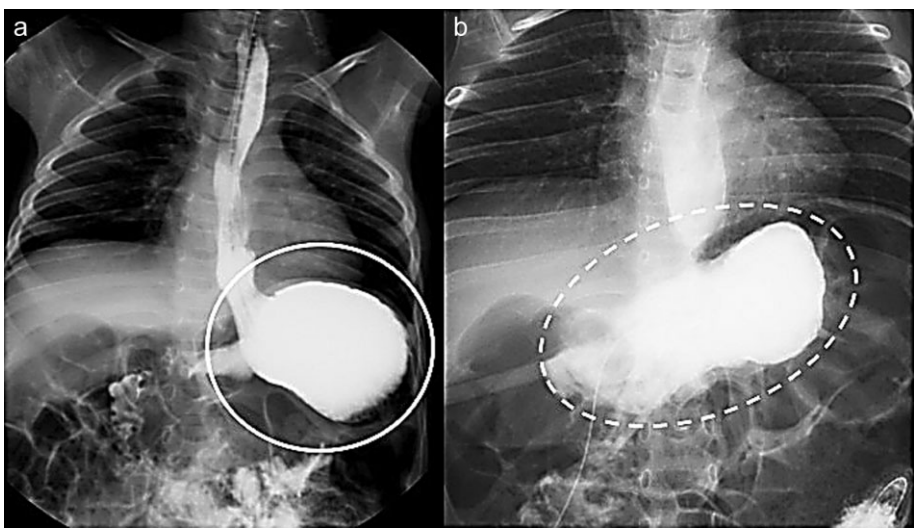

Fig. 2 (a) Fluoroscopy showing gastric volvulus with the stomach lying horizontally under the subphrenic space (circle). Note the striking gastroesophageal reflux into the upper esophagus. (b) The position of the stomach is corrected at the center of the abdomen by anterior gastropexy (dotted oval). The tip of the button PEG-J is located in the jejunum.

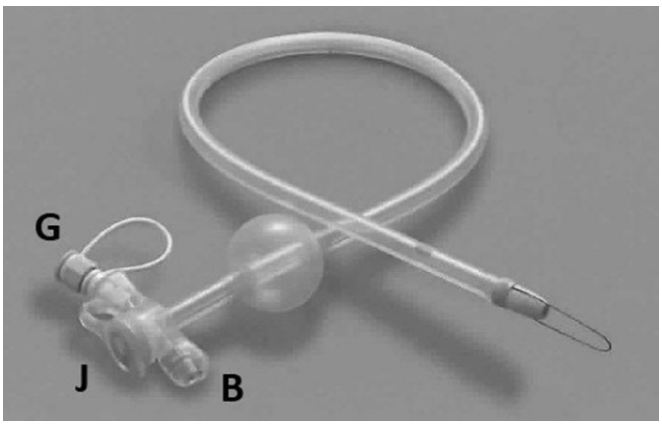

Fig. 3 The button-shaped percutaneous endoscopic gastrostomy with jejunal extension (PEG-J). Jejunal alimentation is conducted through hub J. This catheter enables gastric decompression with hub G. B, hub for balloon dilatation.

require further hospitalization. He began to take the full calorie requirement orally and water supplementation was given through the button PEG-J. He gained appreciable weight, and was at 16.1 kg (−1.8 SD) 26 months after surgery (Fig. 4).

Discussion

The ATR-X syndrome is an X-linked recessive disorder that results from mutations in the *ATRX* gene.[6] Although gastrointestinal problems including drooling, GER, constipation, gastrointestinal bleeding, gastric volvulus, intestinal malrotation, ileus or pseudo-obstruction, and refusal to eat, are common complications of ATR-X syndrome,[5] proper nutritional management has not been well discussed. To our knowledge, this is the first report of a child with ATR-X syndrome to describe esophago-gastric dysmotility and subsequent management with laparoscopic anterior gastropexy and jejunal alimentation through the PEG-J.

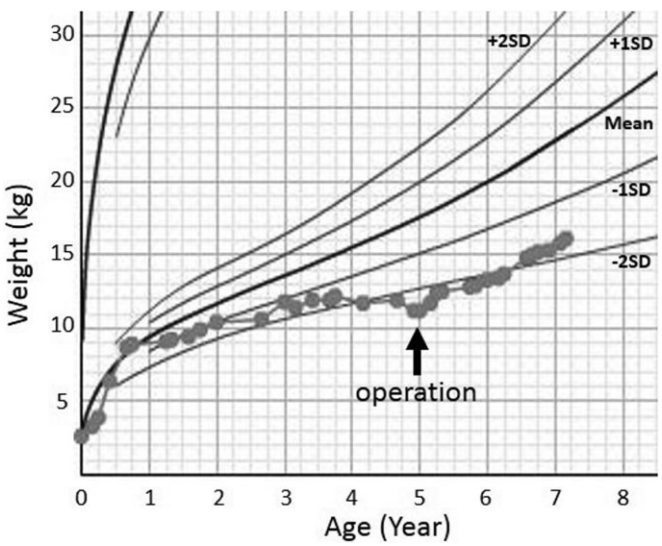

Fig. 4 Growth chart for weight. Note the drastic weight gain after surgery.

Given that patients with ATR-X syndrome have favorable life prognosis, appropriate nutritional management is of great importance.[6] The gastrointestinal phenotype of these patients includes diverse symptoms. According to analysis of 128 children with ATR-X syndrome, drooling (36%), GER (72%) and constipation (30%) have been described as the three major symptoms, as was the case with the present patient.[5] Moreover, some children suffered from upper gastrointestinal bleeding, aspiration of vomitus, intestinal malrotation, ileus, or pseudo-obstruction, and some of them died with these conditions.[5] Because of this situation, investigation of esophago-gastric motility is vital to provide understanding of physiological characteristics in each patient, and customize surgery, including nutritional access in patients with ATR-X syndrome. Laparoscopic fundoplication and tailored indication of gastrostomy have become the standard procedure in neurologically impaired children.[8] Although certain patients with ATR-X syndrome underwent fundoplication (10%) and gastrostomy (9%),[5] rash judgment to carry out fundoplication in those patients with GER who have poor esophageal clearance may worsen vomiting or disturb oral intake. Given that the present patient had slow esophageal clearance, we chose laparoscopic correction of gastric volvulus combined with button PEG-J placement.

PEG-J is often indicated in patients with gastroparesis for prevention of aspiration pneumonia and promotion of enteral feeding. The button PEG-J is a novel nutritional device, equipped with dual functions of post-pyloric feeding and gastric decompression via a cosmetic low-profile button. It is still inconclusive as to whether post-pyloric feeding results in decreased GER or aspiration.[9,10] Indeed, the present strategy was suitable for the condition of the patient, resulting in adequate calorie intake with weight gain, and advancement of oral feeding as well as ceasing of further admissions. In addition, because the outer part of the conventional PEG-J is large and often bothersome with risk of accidental tube removal in young children, this compact button-type device brings great peace of mind to the families or caregivers.

Recently, the ATRX protein has emerged as a critical mediator of cell survival during early neuronal differentiation in neuroblastoma[11] or glioma[12] in humans or in ATRX knockout mice.[13] Interestingly, Martucciello *et al*. reported non-identical twins diagnosed as having ATR-X syndrome in association with Hirschsprung disease and hypoganglionosis.[5] Thus, ATRX mutations may influences the development of the brain–gut axis or gut itself. Further research is expected in this field.

Conclusion

We investigated the gastroesophageal function of a child with ATR-X syndrome. In the present case, the lack of swallow-related primary peristalsis, and low-amplitude simultaneous contraction of the esophagus, gastroesophageal regurgitation secondary to gastric volvulus and delayed gastric emptying were the major causes of gastrointestinal symptoms. Laparoscopic anterior gastropexy and button PEG-J resulted in reasonable nutritional management with excellent quality of life. The present report may provide insight into the gastrointestinal function and

nutritional management of children with ATR-X syndrome. Further investigation is necessary to better manage this condition.

Acknowledgment

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