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**Han Chinese patient with pseudoileus caused by primary visceral myopathy with a rare *MYH11* mutation: A case report**

Li N *et al.* Case report of a CIPO patient

## Abstract

### BACKGROUND

Chronic intestinal pseudo-obstruction (CIPO) is a syndrome of intestinal motor dysfunction caused by intestinal nerves, muscles, and/or Cajal stromal cell lesions. CIPO is a serious category of gastrointestinal dynamic dysfunction, which can eventually lead to the death of patients with intestinal failure. Due to considerable phenotypic heterogeneity, the estimated incidence of CIPO is 1/476190 and 1/416666 in men and women respectively. According to the etiology, CIPO can be divided into idiopathic and secondary, of which secondary CIPO is the most common, often secondary to tumor, virus infection, connective tissue disease, neurological diseases, and endocrine diseases. Idiopathic CIPO in the intestinal tract is divided into visceral myopathy, neuropathy, and stromal cell lesions according to the location. Surgery is usually not recommended for CIPO, because surgery is difficult to benefit patients with CIPO, and postoperative intestinal obstruction is likely to occur, which may even worsen the condition.

### CASE SUMMARY

Here, we describe the case of a 43-year-old male Han Chinese patient with a 15 years history of recurrent abdominal distention with no clear cause. The results of physical, biochemical, and other relevant examinations showed no clear abnormalities. Contrast-enhanced computed tomography (CT) indicated a large duodenum, clear expansion of the intestinal lumen, and CIPO. Whole exome sequencing (WES) of the patient and his mother confirmed the diagnosis of primary familial visceral myopathy type 2 chronic pseudoileus with a rare heterozygous gene mutation in *MYH11*. This is the second reported case of CIPO with a *MYH11* [NM\_001040113.1: c.5819delC (p.Pro1940Hisfs\*91)] heterozygous mutation.

### CONCLUSION

This case report indicates that physicians can perform routine clinical examination, CT, and WES to achieve diagnosis and treatment of CIPO in early disease stages.

**Key Words:** Pseudoileus; Heterozygous *MHY11* gene mutation; Whole exome sequencing; Contrast-enhanced computed tomography; Case report

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**Core Tip:** Chronic intestinal pseudo-obstruction is a rare abdominal disease with high morbidity and mortality. The patient developed abdominal symptoms with no mechanical intestinal obstruction, characterized by symptoms of chronic intestinal obstruction; whole exome sequencing (WES) was used to analyze the patient and found a rare autosomal dominant mutation associated with primary familial visceral myopathy type 2, MYH11, NM\_001040113.1:c.5819delC (p.Pro1940Hisfs\*91) was detected, which is a rare heterozygous mutant. In this case, mechanical ileus and secondary causes of pseudoileus were excluded, and the location, nature and extent of the lesions were determined by small bowel computed tomography examination, and the etiology was determined by WES.

## **INTRODUCTION**

Chronic intestinal pseudo-obstruction (CIPO) is an intestinal motor dysfunction syndrome caused by intestinal nerves, muscles, and/or Cajal stromal cell lesions<sup>[1,2]</sup>. CIPO causes severe gastrointestinal dynamic dysfunction, which can eventually lead to death due to intestinal failure<sup>[3]</sup>. CIPO exhibits considerable phenotypic heterogeneity and has an estimated incidence of 1/476190 and 1/416666 in men and women, respectively<sup>[4]</sup>. According to its etiology, CIPO can be divided into idiopathic and secondary types. Secondary CIPO, the most common form, often occurs secondarily to

tumors, viral infections, connective tissue diseases, neurological diseases, and endocrine diseases<sup>[5]</sup>. Idiopathic CIPO in the intestinal tract is divided into visceral myopathy, neuropathy, and stromal cell lesions according to its location<sup>[4]</sup>. Surgery is usually not recommended for CIPO, because it often does not benefit patients, and postoperative intestinal obstruction is likely to occur and potentially worsen the condition.

Autosomal dominant mutations in the smooth muscle actin gene *ACTG2* occur in 44%-50% of patients with CIPO<sup>[6]</sup>. Moreover, studies have identified homozygous mutations in *MYLK6*, *MYH117-9*, *LMOD110*, *MYL911*, and *RAD2112*, as well as X-linked mutations in *FLNA13* in CIPO cases in recent years<sup>[7-11]</sup>. Among these genes, mutations in the *MYH11* gene have been associated with effects on smooth muscle cell contractile function, signaling, and cell motility; visceral myopathy type 2; familial thoracic aortic and aortic dissection type 4; giant bladder-small colon-bowel motility syndrome type 2; lung cancer, large bowel cancer, breast cancer, bladder cancer, and myeloid leukemia; and other diseases<sup>[12,13]</sup>. The *MYH11* gene maps to the middle of the short arm of chromosome 16<sup>[14]</sup>. Julie *et al* have performed exome sequencing in a newborn with megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) and identified a homozygous variant (c.3598A>T:p.Lys1200Ter) in *MYH11*, thus suggesting that loss-of-function variants in *MYH11* cause MMIHS<sup>[8]</sup>. Compound heterozygous mutations in *MYH11* have been found in several familial CIPO cases. Auriane *et al* have reported a case of mucopolysaccharidosis type I in a patient with early-onset CIPO, who had a 1.7-Mb heterozygous deletion of the chromosomal region 16p13.11p12.3, comprising *MYH11*<sup>[15]</sup>. Furthermore, a rare dominant mutation in *MYH11* has been found in one extended family with 13 affected members<sup>[16]</sup>.

CIPO often lacks specific laboratory findings, biomarkers, and symptoms, and its symptoms are similar to those of other peristaltic disorders<sup>[17]</sup>. Consequently, long times usually elapse before an accurate CIPO diagnosis is obtained, thus sometimes resulting in unnecessary surgery<sup>[18]</sup>. Because visceral myopathy is relatively common in CIPO, the clinical diagnosis of CIPO depends primarily on endoscopic or imaging examination. Next-generation sequencing has greatly increased the chances of

identifying known and new causal genes for CIPO. As whole exome sequencing (WES) becomes more widely used in clinical settings, the number of patients benefiting from applications of these methods is growing rapidly.

## **CASE PRESENTATION**

### ***Chief complaints***

A 43-year-old man was admitted to the Gastroenterology Department of Ruijin Hospital affiliated with Shanghai Jiao Tong University in October 2021 because of CIPO. His main clinical manifestation was the absence of a clear cause of lower abdominal distension, which had started 15 years prior.

### ***History of present illness***

The local hospital suggested a diagnosis of intestinal obstruction and superior mesenteric artery compression syndrome, and recommended adhesion reduction and superior jejunal partial resection.

### ***History of past illness***

In the prior 10 years, the patient experienced continued abdominal distension; frequent anal defecation; an absence of nausea; vomiting; and abdominal pain. In July 2021, he was diagnosed with small bowel obstruction, duodenal stasis, mild malnutrition, and urinary retention; symptomatic treatment and hospitalization were proposed. Since the onset of the disease, the patient had a clear mind and acceptable mental stomach; defecated three or four times per day with unformed stools; and had no abnormal urination or significant weight loss.

### ***Personal and family history***

The patient is married and has two children, both of whom are healthy. His mother privately reported a notable and concerning history of duodenal enlargement.

### ***Physical examination***

The patient is clearly thinking and energetic. He is thin, his abdominal distension, and the length of his abdomen is 110 cm. The longitudinal old surgical scar on the upper abdomen is about 10 cm long, without intestinal shape and peristaltic waves, tenderness, rebound pain and muscle tension. He had drumming in his abdomen, bowel hyperactivity (more than 10 beats/min), and dullness of negative activity. Physical examination showed that the body temperature of the patient was 36.7 °C, pulse 80 beats/min, breathing 18 times/min, blood pressure 87/52 mmHg, height 160 cm, weight 44 kg, body mass index (BMI) 17.19 kg/m<sup>2</sup> (Table 1).

### ***Laboratory examinations***

The patient had a clear mind and was energetic. He was thin and had abdominal distension, and the length of his abdomen was 110 cm. An old longitudinal surgical scar on the upper abdomen was approximately 10 cm in length; in addition, an absence of intestinal shape and peristaltic waves, tenderness, rebound pain, and muscle tension were noted. He experienced a drumming sensation in his abdomen, bowel hyperactivity (more than 10 beats/min), and dullness of negative activity. The physical examination indicated a body temperature of 36.7 °C, pulse of 80 beats/min, breathing at 18 times/min, blood pressure of 87/52 mmHg, height of 160 cm, weight of 44 kg, and BMI of 17.19 kg/m<sup>2</sup> (Table 1). Examination of biochemical parameters in routine blood tests indicated a red blood cell count of  $3.62 \times 10^{12}/L$ , and a hemoglobin level of 116 g/L. Blood gas analysis showed a pH of 7.29, partial pressure of oxygen of 16.63 kpa, partial pressure of CO<sub>2</sub> of 4.00 kpa, oxygen saturation of 98.4%, hydrogen ion concentration of 51.3 nmol/L, standard bicarbonate of 15.9 mmol/L, actual bicarbonate of 14.1 mmol/L, and standard residual base of 10.8 mmol/L. The 24-h urinary protein was 1168 mg/24 h; the 24-h urine potassium was 19.49 mmol/24 h; the 24-h urinary calcium was 7.74 mmol/24 h; and the 24-h urine phosphorus was 12.18 mmol/24 h (Table 2). Examinations of the endocrine system, immune system, connective tissue, and tumor index showed no clear abnormalities.

### *Imaging examinations*

Contrast-enhanced computed tomography (CT) (Figure 1) showed that the duodenum was large, and the intestinal tube was significantly dilated with a diameter of approximately 12.68 cm. The mucosal folds were normal, no clear obstruction point was identified, the intestinal wall did not show thickening. Moreover, no edema or inflammation was observed around the intestine, and the lymph nodes were not enlarged. The observed changes suggested chronic pseudo-intestinal obstruction, and the renal medulla showed delayed enhancement.

### **FINAL DIAGNOSIS**

The patient was CIPO.

### **TREATMENT**

We performed WES to detect the presence of any mutations in relevant disease-causing genes. A 2 mL blood sample in an ethylenediamine tetra-acetic acid-coated tube was sent to the Shenzhen BGI Medical Test Laboratory. Sequencing was performed through capture high-throughput technology, which detected nearly 20000 genes in the human genome. Sanger sequencing was used to verify the mutations. A suspected disease-causing mutation in *MYH11*, located on chromosome chr16:15802687; NM\_001040113.1:c.5819delC (p.Pro1940Hisfs\*91), was identified, which is a heterozygous gene mutation associated with primary familial visceral myopathy type 2 chronic pseudoileus<sup>[4]</sup>. The heterozygous mutation, a frameshift mutation caused by the deletion of one C nucleotide at position 5819 of the gene coding sequence, changes the proline codon at position 1940 being to histidine, and then produces a stop codon at position 91, thus elongating the C terminal sequence of the MYH11 protein and causing local changes in the three-dimensional structure of the protein (Figure 2). We subsequently collected blood samples from the patient's mother and verified the



mutation by Sanger sequencing, which confirmed that both the patient and his mother carried this heterozygous mutation (Figure 3).

### **Clinical management**

After being diagnosed, the patient received nutritional support, and his digestive tract motor function was restored. However, his abdominal distension symptoms did not substantially improve. No effective non-surgical treatment for this disease is currently available. In the acute period, fasting, gastrointestinal decompression, and correction of electrolyte disorders should be the main treatments. In the remission period, nutritional support, recovery of digestive tract movement function, and prevention and treatment of infection should be emphasized to improve patient quality of life.

### **OUTCOME AND FOLLOW-UP**

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### **DISCUSSION**

CIPO is a rare abdominal disease associated with high morbidity and mortality. Our patient developed abdominal symptoms with no mechanical intestinal obstruction, which were<sup>2</sup> characterized by chronic intestinal obstruction, such as abdominal pain, distension, and vomiting<sup>[4]</sup>. CIPO often lacks specific laboratory findings, biomarkers, and symptoms, and its symptoms are similar to those of other peristaltic disorders. Owing to this lack of specific findings, long time periods usually elapse before patients obtain an accurate CIPO diagnosis, and unnecessary surgery is sometimes performed<sup>[5]</sup>. In our case, according to the CT findings of a large duodenum and chronic pseudo-obstruction, we determined that the lesions were located mainly in the duodenum.

WES, a precision medical technology developed in recent years, captures DNA sequences of nearly 20000 coding genes in the genome with high throughput, and uses comparative bioinformatics analysis to determine the microbial species and abundance information contained in the samples. WES can detect most disease variants and is

gradually being adopted in clinical genetic testing and diagnosis, particularly in the diagnosis of rare genetic diseases<sup>[19,20]</sup>. The development of sequencing and gene editing technologies is expected to lead to therapeutic breakthroughs in gene therapy in the future.

In addition to the pseudo-intestinal obstruction, our patient had symptoms of urinary retention, which might have been associated with the abnormal smooth muscle cell function caused by the *MYH11* gene mutation. In clinical settings, visceral myopathic pseudointestinal obstruction caused by *MYH11* gene mutation is rarely encountered. In a previous study, two frameshift mutations in *MHY11* have been reported. The first was a 2-bp deletion in exon 22 (c.2809\_2810del, p.Arg937Glyfs\*7, paternal), whereas the second mutation in exon 26 was a 49-bp deletion (c.3422\_3470del, p.Lys1141Thrfs\*20, maternal)<sup>[8]</sup>. Kloth *et al*<sup>[21]</sup> have reported a patient with MMIHS with a novel heterozygous missense variant (c.379C>T) in *MYH11*. In another case, a *MHY11* frameshift mutation has been detected in exon 42 (NM\_001040113.1:c.5819delC, p.Pro1940HisfsTer91)<sup>[16]</sup>. In our case, WES revealed a rare autosomal dominant mutation in *MYH11*, NM\_001040113.1:c.5819delC (p.Pro1940Hisfs\*91), which was consistent with the results of a previously reported case<sup>[16]</sup>. Our study strengthens the understanding of CIPO etiology and provides genetic evidence supporting the diagnosis of CIPO.

Surgical treatment is usually not recommended for CIPO, because surgery often does not benefit patients, and postoperative intestinal obstruction is likely to occur and may aggravate the condition. If surgical treatment is necessary, careful and rigorous evaluation is required. Clinically, gastrostomy, jejunal catheterization or jejunostomy can effectively decrease abdominal distension and vomiting, thus providing an important means of providing enteral nutrition, and substantially increasing the transport capacity of the digestive tract, thus decreasing hospitalization and operation rates<sup>[22]</sup>. The disease is complex, and its treatment is difficult, thus requiring multidisciplinary teams from gastroenterology, gastrointestinal surgery, nutrition,

imaging, transplant surgery, psychology and other departments to formulate treatment plans.

### **CONCLUSION**

In our patient, mechanical ileus and secondary causes of pseudoileus were excluded, and the location, nature, and extent of the lesions were examined through small bowel CT. WES was used to identify a rare mutation in *MYH11* [NM\_001040113.1:c.5819delC (p.Pro1940Hisfs\*91)]. This case report may help clinicians understand the genetic basis of the etiology of CIPO.

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