Case report

TOTAL COLONIC AGANGLIONOSIS IN SIBLINGS

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Abstract Hirschsprung’s disease (HD) is attributed to failure of craniocaudal neural crest cell migration in the hindgut. Histopathology is absent of ganglion cells in the myenteric and submucosal plexuses. Most patients present with intestinal obstruction, in which delayed meconium passage is the most important history when suspecting HD. In eighty percent of cases, the pathology is limited limited to rectosigmoid region. Herein, we report two siblings from a Thai family, who presented total colonic aganglionosis and near total intestinal aganglionosis. With the advent of molecular technology, at least six mutation genes have been identified. It has been observed that longer the involved intestinal segment, the higher the penetrance rate and the lower the gender bias. Therefore, careful genetic counseling is important, particularly in a family that has a baby with long-segment HD. Chiang Mai Med Bull 2003;42(4):169-175.

Keywords: Hirschsprung’s disease, intestinal obstruction, pathogenesis, genetics

Case report

Hirschsprung’s disease (HD) was first described by Harald Hirschsprung in 1888.1 The incidence is 1:1,500 live births. However, this ratio varies among ethnic groups, in which Asians are more frequently affected than Caucasians.2,3 Males are much more commonly affect than females (4:1). Usually, HD is a single anomaly and it inherits as a multifactorial model. Herein, we report 2 siblings from a Thai family, who presented with total colonic aganglionosis and near total intestinal aganglionosis.

A 4-day-old female baby born to an uneventful term pregnancy was referred to us due to vomiting and obstipation. Her birth weight was 3,400 grams. Two days prior to admission, she developed billous vomiting and abdominal distention. There was a history of her once passing meconium on the first day of life, but thereafter, there was no record of passing a stool. On the third day of life, she appeared inactive and was treated for clinical sepsis with intrave...
nous cefotaxime and ampicillin. On physical examination, the abdomen was mildly distended and soft. Neither mass nor organomegaly was noted. Digital examination felt a rather tight sphincter tone without explosion of stools after withdrawal. An abdominal radiograph revealed small bowel dilatation and a small amount of air in the large bowel (Figure 1). Distal small bowel and proximal colon obstruction were initially suspected. A barium enema was performed, which demonstrated small caliber of the entire colon (Figure 2). Exploratory laparotomy was carried out, which found proximal small bowel dilatation with a transitional zone at the proximal ileum. No mechanical obstruction of the small intestine was found (Figure 3, 4). Ileal and colonic biopsies showed an absence of ganglion cells in the myenteric and submucosal plexuses. Ileostomy was constructed. The final diagnosis was total colonic aganglionosis. After the operation, the patient still had clinical bowel obstruction. A second exploratory laparotomy revealed an incomplete diversion and the real transitional zone that moved up to the proximal jejunum, and a jejunostomy was therefore created. This patient was later diagnosed as near total intestinal aganglionosis. After discussion with the family and physicians involved, the patient had to be totally parenteral nutrition dependent and might have needed small bowel transplantation. Due to limited resources, no aggressive treatment was provided for her. The patient finally died at home.

Figure 1. An abdominal radiography showing dilated small bowel and a small amount of air in the large bowel.
Her older brother was also treated in our hospital two years ago. He was born prematurely, with a birth weight of 2,100 grams. Shortly after birth, he developed familial total colonic aganglionosis.
abdominal distention and vomiting. Delayed passage of meconium was noted. An abdominal radiography revealed small bowel dilatation. Exploratory laparotomy was performed with the initial diagnosis being complete small bowel obstruction. The operative findings revealed small bowel dilatation and microcolon. A transitional zone was identified at the midileal region. Total colonic aganglionosis was diagnosed and subsequently confirmed by the absence of ganglion cells in the ileal biopsy. Ileostomy was created just proximal to the transitional zone. The patient had been dependent on total parenteral nutrition for the first 12 months of life because of short bowel syndrome. Ileal adaptation slowly occurred. The patient is now completely enteral fed with intermittent episodes of small bowel bacterial overgrowth syndrome. He is waiting for definite surgery. During hospitalization, he had an episode of urinary tract infection. Investigations revealed mild bilateral hydronephrosis.

Discussion

Most cases of HD are diagnosed during the newborn and infancy period, in which a main clinical presentation is intestinal obstruction, including delayed passage of meconium, abdominal distention, vomiting, and enterocolitis. In a minority of cases, HD is suspected and investigated because of chronic constipation and failure to thrive. The two patients reported in this study developed clinical presentation of gut obstruction during the neonatal period.
The pathogenesis of HD is principally failure of craniocaudal neural crest cell migration, termed neurocrinopathy, which leads to absent formation of ganglion cells in the myenteric and submucosal plexuses.\(^{(4,5)}\) This organogenesis occurs during the 4\(^{th}\) to 12\(^{th}\) week of gestation.\(^{(3)}\) As a result, the nonfunctioning segment of the aganglionic colon contributes to functional intestinal obstruction. It is generally classified into short- and long-segment HD, based on the level of obstruction, which is distal and proximal to the upper sigmoid colon, respectively.\(^{(2)}\) Seventy percent of the patients presented an isolated anomaly, however, as many as thirty percent of were associated with certain syndromes and other congenital anomalies.\(^{(6,7)}\) Trisomy 21 has been the most frequent association reported.\(^{(7)}\) In this study, the older brother also had associated hydronephrosis.

Regarding genetic studies, eighty percent of cases were S-HD, which was considered to be a multifactorial inheritance with male predominance (male: female ratio of 4:1).\(^{(2)}\) The recurrence risk was estimated to be 4% in subsequent siblings. On the contrary, there have been reports on L-HD of a higher penetrance rate and lower gender bias.\(^{(8,9)}\) Recent studies have identified at least six important mutation genes reputed to be the pathogenesis.\(^{(3)}\) The most frequent genetic mutation responsible for HD is located on chromosome 10, named protooncogene \(RET\).\(^{(2,3)}\) Additionally, the mutation of genes encoding ligands of \(RET\) (glial cell line-derived neurotrophic factor (\(GDNF\)) and neurturin (\(NTN\)) hardly attribute to HD.\(^{(10)}\) Although L-HD has been studied extensively, only 75% of it is associated with \(RET\) mutations.\(^{(11)}\)

Endothelin-3 (\(EDN3\)) and its receptor (\(EDNRB\)), encoded on chromosome 20 and 13, respectively, also play a major role in neural crest migration. Therefore, mutations IN the endothelin signaling pathway are another important genetic background on HD, and have been identified in 5% of HD cases.\(^{(12-14)}\) In addition, mutations of endothelin converting enzyme-1 (\(ECE-1\)), a gene encoding an enzyme essential for EDN3 biosynthesis, has been recently discovered to associate with HD.\(^{(15)}\) Finally, mutations of \(SOX10\), encoding transcriptional factors, could result in HD and Waardenburg syndrome 4, which consists of deafness and pigmentation abnormalities.\(^{(16,17)}\)

As shown in our case report, strong genetic predisposing in the siblings from a Thai family with L-HD was identified. Unfortunately, the mutation analysis is not available in our institute. Nonetheless, awareness of the high penetrance rate, particularly in a family with offspring having L-HD, should be emphasized on by general pediatricians. Therefore, careful genetic counseling is pivotal. Because accurate prenatal diagnosis of HD has not been feasible and the penetrance rate varies among diverse mutations, it is very difficult to perform impeccable genetic counseling.

The diagnosis of HD comprises barium enema, rectal suction/full thickness biopsy, and anorectal manometry.\(^{(2)}\) Once the diagnosis is established, the treatment of
choice for HD is surgical, such as Swen-
son, Soave, and Duhamel procedures. The most frequent complication encoun-
tered is recurrent enterocolitis. In severe cases, such as total colonic aganglionosis and near total intestinal aganglionosis, the prognosis is poor. The patients might be dependent on total parenteral nutrition on account of short bowel syndrome.

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ภาวะ TOTAL COLONIC AGANGLIONOSIS ในพี่น้อง

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บทคัดย่อ Hirschsprung’s disease (HD) เป็นจากความผิดปกติในการเคลื่อนตัวของเซลล์ neural crest ในลำไส้ที่มีการสร้างเซลล์ ganglion ใน Myenteric และ Submucosal plexuses ผู้ป่วยที่มี HD จะมีอาการลำไส้อุดตัน โดยประวัติสำคัญที่ทำให้นึกถึงภาวะนี้คือ การที่มีการถ่ายขี้เทาของลำไส้ใหญ่ โดยประมาณร้อยละ 80 ของผู้ป่วยจะมีพยาธิสภาพอยู่บริเวณใบเล็บและลำไส้ Sigmoid. การศึกษาข้อมูลจากนั้นปรากฏว่า 2 รายที่เป็นพี่น้องที่ได้รับการวินิจฉัยเป็น total colonic aganglionosis และ near total intestinal aganglionosis ในปัจจุบันมีการกำหนดให้ความผิดปกติ ปกติของเอ็นอย่างน้อย 6 ตัวผ่านที่มีผลต่อการเกิด HD โดยเฉพาะที่มีพยาธิสภาพที่เกิดขึ้นบริเวณอุจจาระจะทำให้ความเสี่ยงในการเป็น HD ขึ้นสูงขึ้น และพบในเพศชายและเพศหญิงไม่แตกต่างกัน โดยการให้ปรึกษาด้านพันธุกรรมจะมีความสำคัญในการครบถ้วนที่มุ่งเป็น long segment HD เชิงให้ข้อมูลการ 2546; 42(4): 169-175.

คำสำคัญ: Hirschsprung’s disease ลำไส้อุดตัน พาชีเทาของลำไส้ใหญ่ ห้องลำไส้