J Ped Surg Case Reports 3 (2015) 143–145

Contents lists available at ScienceDirect

Journal of Pediatric Surgery CASE REPORTS

journal homepage: www.jpscasereports.com

Skip segment Hirschsprung disease and Waardenburg syndrome

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ARTICLE INFO

Article history:
Received 10 November 2014
Received in revised form
13 February 2015
Accepted 16 February 2015

Key words:
Skip segment aganglionosis
Hirschsprung disease
Waardenburg syndrome
Neonatal obstruction

ABSTRACT

Skip segment Hirschsprung disease describes a segment of ganglionated bowel between two segments of aganglionated bowel. It is a rare phenomenon that is difficult to diagnose. We describe a recent case of skip segment Hirschsprung disease in a neonate with a family history of Waardenburg syndrome and the genetic profile that was identified.

Hirschsprung disease (HD) is a form of functional bowel obstruction that presents most commonly in the neonatal period. In HD, neural crest cells fail to migrate caudally, leaving a distal portion of aganglionated rectum. In the majority of cases, there is a single segment of bowel where the nerves terminate, known as the "transition zone." In this case report, we describe an atypical presentation of neonatal bowel obstruction and a rare case of skip segment HD, or segmental aganglionosis. This patient was found to be homozygous for a pathogenic variant in the endothelin-receptor B (*EDNRB*) gene, previously described in association with HD-Waardenburg syndrome.

1. Case report

A 4250 g term male was born at home and admitted for evaluation of abdominal distention and failure to pass meconium after 48 h of life. He was born to a family with a paternal history of hearing loss, HD, and white forelock, which had been clinically diagnosed as Waardenburg syndrome without molecular confirmation. There was no known history of consanguinity and the parents are from different Mennonite populations. The father had total colonic HD and the patient's sister was treated for rectosigmoid disease (Fig. 1). On physical exam, the neonate had a soft abdomen with no peritonitis and no other congenital anomalies. An abdominal radiograph showed bowel distention (Fig. 2). A rectal contrast study was performed, during which the colon was perforated. The neonate was taken to the operating room and found to have fecal peritonitis from a >50% circumferential mid-transverse colon perforation. Frozen biopsies were performed at the level of the perforation and the rectosigmoid colon. The transverse colon had ganglion cells and sigmoid colon lacked ganglion cells, confirming the diagnosis of HD. A colostomy was created at the level of the perforation.

For 24 days, there was no stool from the colostomy. Contrast studies showed a transition point in the right lower quadrant. On post-operative day 25, he was explored for adhesive bowel obstruction. Adhesions were indeed identified in the right lower quadrant, corresponding to the transition zone in the contrast study.

Post-operatively, there was no colostomy output. Irrigations were performed as well as contrast studies with limited results. The child was taken back to the operating room one month after adhesiolysis. Once again, the terminal ileum appeared dilated despite having no significant adhesions. Biopsies were sent from the terminal ileum, which showed no ganglion cells. Biopsies were then sent every 10 cm proximal to the ileocecal (IC) valve. Frozen section analysis identified ganglion cells at 60 cm from the IC valve

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http://dx.doi.org/10.1016/j.epsc.2015.02.005

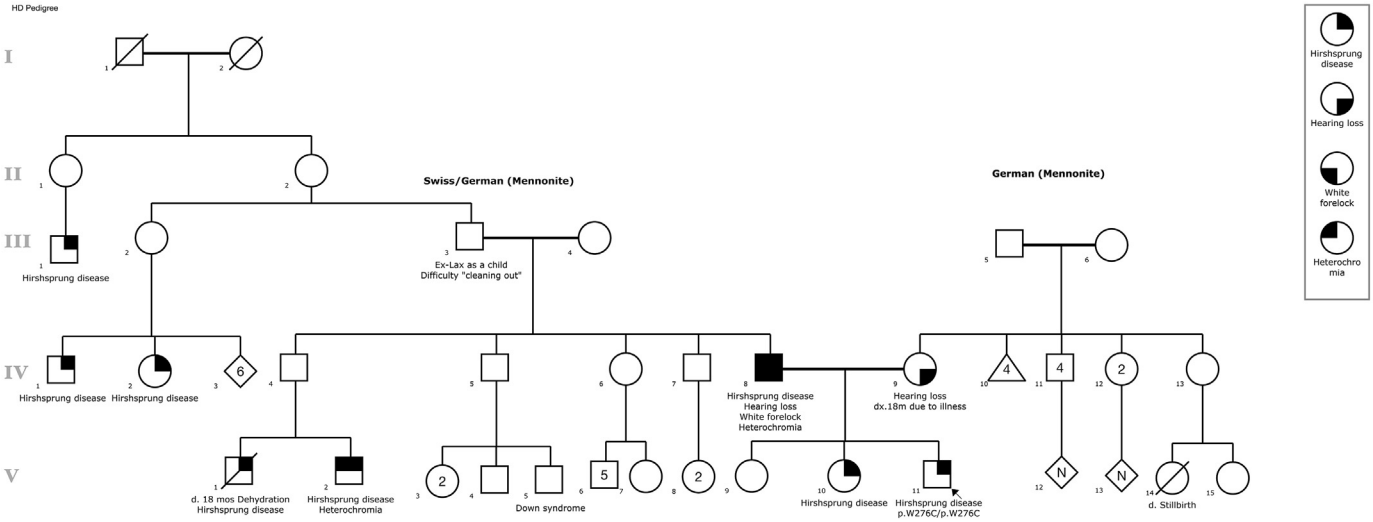

Fig. 1. Pedigree. Our patient is identified by number 11 in the fifth generation (↑). ○ = females, □ = males, Δ = miscarriage, ◇ = unknown sex, N = unknown number of offspring.

(Fig. 3). The aganglionated ileum was resected. An end ileostomy and a mucus fistula were created 5 cm from the IC valve, and a gastrostomy tube was placed.

The child began to have bowel function within two days of surgery and slowly progressed up to full enteral feeds. At the time of discharge, parenteral nutrition had been discontinued. Feeds were given continuously via the gastrostomy tube at night and ad lib orally during the day, to decrease high ostomy output. At one year of age, he is taking all nutrition by mouth, and his growth curves are in the 85th percentile. We are planning to perform a completion proctocolectomy and endorectal pullthrough.

1.1. Genetic profile

After diagnosis of skip segment HD in the setting of a strong family history of HD was made, the Genetics team was consulted. Given the family history of multiple paternal relatives with hearing loss, HD, and white forelock, the previous clinical diagnosis of Waardenburg syndrome (WS) was molecularly confirmed. WS with HD is specific to Waardenburg syndrome type IV (also called

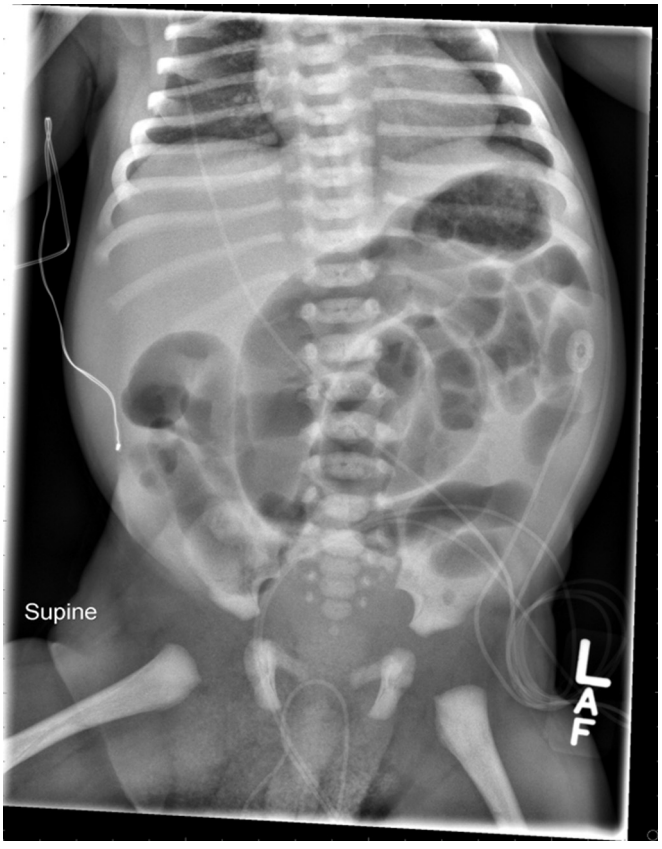

Fig. 2. Abdominal radiograph. Diffuse intestinal gaseous distention without rectal gas.

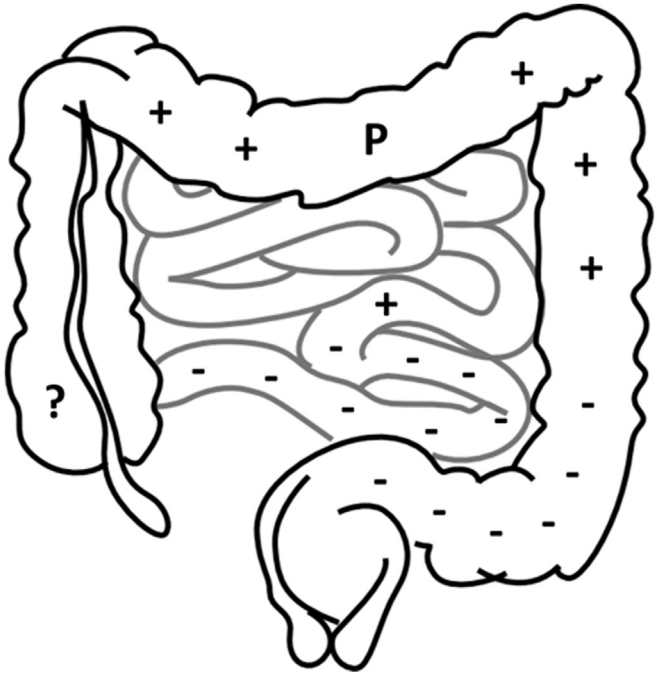

Fig. 3. Schematic of final intestinal pathology. Ganglion cells were present (+) in the transverse and descending colon but absent (−) in the terminal ileum and sigmoid colon. The site of perforation (P) was located in the mid-transverse colon.

Waardenburg-Shah syndrome) which has been molecularly associated with *EDNRB*, Endothelin 3 (*EDN3*) and *SOX10* [1]. Waardenburg syndrome type IV can be inherited in an autosomal dominant or an autosomal recessive pattern; however, the paternal family history was suggestive of autosomal dominant inheritance. To molecularly confirm the diagnosis, sequence analysis with multiplex ligation-dependent probe amplification (MLPA) for exon deletion and duplication testing was clinically performed on *EDN3* exons 1–5 (NM_207034.1), *EDNRB* exons 1–8 (NM_000115.1, NM_003991.1), and *SOX10* exons 2–4 (NM_006941.3). The results of this testing showed our patient was homozygous for *EDNRB* p.W276C without exon deletions. Unfortunately, familial testing for further segregation and clarification has been declined by the family. This variant has been previously described in Mennonite populations and this specific variant has resulted in disease in individuals who are both heterozygous as well as homozygous for this variant, with penetrance of HD being higher in homozygotes (74%) versus heterozygotes (21%) [2].

2. Discussion

The description of HD as a single aganglionic segment extending from the anal margin to a varying length of rectum or colon is widely accepted. Total colonic aganglionosis has also been well described. These aganglionic segments are believed to result from failed cranial-caudal migration of neural crest cells. It is also believed that the earlier the arrest of migration of these cells, the longer the segment of aganglionated bowel will be.

Skip segment HD, where there is a portion of ganglionated intestine between two segments of aganglionated bowel, has been reported in fewer than 40 patients and is easily overlooked or misdiagnosed. O'Donnell and Puri performed a systematic review of 24 patients with this entity of HD over a 50-year time span and noted that 75% of patients were male, 41% had a skip segment in the transverse colon, and 23% had multiple skip segments. The terminal ileum was aganglionic in 92% of patients reviewed [3]. Our patient's disease pattern is consistent with these observations.

The incidence of HD is 1:5000 live births, and it may present in more than one family member. In the majority of Hirschsprung cases, no clear pattern of inheritance exists. Patients with very long-segment aganglionosis seem to have a higher rate of familial incidence [4]. Gene pathogenic variants have been identified on chromosome 10 involving the *RET* proto-oncogene (non-syndromic) in 35% of sporadic and familial cases of HD [5]. HD has also been linked to pathogenic variants in the *EDNRB* and *EDN3* genes [2,4].

Waardenburg syndrome is a congenital disorder resulting from defective neural crest cell development, presenting as pigmentary disturbances and sensorineural deafness. WS occurs in 1 in 50,000 live births and is inherited in an autosomal dominant fashion; however, the degree of penetrance is variable [4].

Waardenburg-Shah syndrome (WS type IV) refers to the Waardenburg-HD association and is an autosomal recessive condition. The association of HD and WS has been ascribed to pathogenic variants of the *EDNRB* gene [6]. There are fewer than 80 case reports of HD occurring in combination with WS [7]. In these reports, there was no increasing penetrance of HD between generations, with the aganglionic length being very similar amongst family members [8]. No cases reported skip segment aganglionosis.

3. Conclusion

Skip segment aganglionosis is a rare phenotype of HD that is yet to be fully understood at a genetic or cellular level. This is the first documented case of skip segment HD with detailed family history and genetic profile.

Conflicts of interest

None of the authors have any conflicts of interest in writing this paper.

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