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Hirschsprung disease and anorectal malformations — An uncommon association

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ABSTRACT

Background: The simultaneous occurrence of Hirschsprung disease (HD) and anorectal malformation (ARM) is extremely rare, with only a very limited amount of cases published in the literature.
Constipation is a major problem in patients operated for ARM, and biopsies from the distal rectum in patients with ARM may not show ganglion cells owing to different reasons, leading to a false positive diagnosis of HD. A pull-through procedure for HD after previous anorectoplasty for ARM always leads to fecal incontinence.
The aim of the present study was to assess the incidence of simultaneous diagnoses of ARM and HD in a single large cohort of ARM patients and to demonstrate that biopsies from the anal canal, which are negative for ganglion cells, may mislead to a diagnosis of HD.
Materials and methods: A retrospective review of our database from 1980 to 2018 identified 164 patients with HD and 2397 patients with ARM. Four patients suffered from both HD and ARM.
Results: The incidence of HD in ARM patients was 4/2397 = 0.17%, and the incidence of ARM in HD patients was 4/164 = 2.4%.
Conclusion: Our results strongly suggest that the association of ARM and HD is less common than previously reported.
Type of study: Therapeutic
Level of evidence: IV

Current evidence about patients suffering from both HD and ARM is sparse, with only a limited amount of published reports. Up to 2020, less than 130 cases were described in the literature [1–24]. Since many surgeons perform biopsies from the distal rectum in ARM patients to assess for HD [19], the current evidence may be confounded by false positive HD diagnoses. We hence hypothesize that the true incidence of ARM and HD is lower than the published evidence [19]. We further suspect that several of those wrongly diagnosed patients were treated with an unnecessary pull-through procedure for HD [24].

This study provides the incidence of the combination ARM & HD in the largest database of ARM patients. It will further highlight and educate pediatric surgeons on how to avoid false positive diagnoses of HD in ARM patients. It will also provide treatment guidelines for the rare event of true combination of ARM and HD.

1. Materials and methods

A retrospective database review was performed from 1980 to 2018 resulting in a total of 164 patients with HD and 2397 patients with ARM. Only four patients had the confirmed diagnosis of both HD and ARM. This database containing all pull-through cases has been in existence since 1980 when the first pull-through procedure was performed and described by a coauthor of the present study (Dr A. Peña) [25]. IRB approval was obtained for the present study.

2. Results

In our cohort of patients the calculated incidence of HD in ARM patients was 4/2397 = 0.17%. The calculated incidence of ARM in HD patients was 4/164 = 2.4%. The clinical history of these four patients will be presented and they are summarized in Table 1.

3. Case 1

Female patient with unspecified chromosomal abnormality and developmental delay treated at an outside facility. She was suffering from severe constipation since birth. Since dietary modifications were not improving her symptoms, enemas were started. Finally, at the age of 11 months rectal suction biopsies were performed showing the diagnosis of Hirschsprung disease. Full-thickness rectal biopsies were done to confirm the diagnosis and subsequently a leveling sigmoid colostomy was created with reportingly normal ganglion cells. The patient was

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Table 1
Patient's data.

Patient	Gender (M/F)	ARM	Associated disorders	Diverting colostomy	Repair of ARM	Suspicion for HD	Diagnosis of HD	Treatment of HD
1	F	Rectoperineal fistula	Chromosomal abnormality, DD	Yes (11 months)	PSARP (17 months)	Constipation since birth	Full-thickness biopsies (AChE staining)	Pull-through (21 months)
2	F	Rectoperineal fistula	PHOX2B mutation, CCHS, neuroblastoma, VUR, PFO, PDA, TV regurgitation, PV regurgitation	Yes (1 month)	PSARP (2.3 years)	Constipation since birth	Full-thickness biopsies (AChE staining)	Pull-through (27 months)
3	M	No fistula	Trisomy 21	Yes (1 day)	PSARP (3 months)	After failed colostomy closure	Full-thickness biopsies (AChE staining)	Pull-through (19 months)
4	M	No fistula	Trisomy 21	Yes (2 days)	2× PSARP (4 and 8 months)	After failed colostomy closure	Full thickness biopsies (AChE staining)	Pull-through (30 months)

ARM = anorectal malformation, PSARP = posterior sagittal anorectoplasty, HD = Hirschsprung disease, AChE = acetylcholinesterase histochemistry, DD = developmental delay, PHOX2B mutation = PHOX2B gene mutation, CCHS = congenital central hypoventilation syndrome, VUR = left-sided grade III vesicourethral reflux, PFO = patent foramen ovale, PDA = patent ductus arteriosus, TV regurgitation = tricuspid valve regurgitation, PV regurgitation = pulmonary valve regurgitation, T21 = trisomy 21.

then referred to us for further management. Perineal inspection showed a rectoperineal fistula with the anal opening located just between the female genitalia and the center of the anal sphincter. On examination the orifice was very small, likely not providing sufficient exposure to perform a satisfactory biopsy well above the pectinate line. Giving the patient the benefit of the doubt, we did not proceed performing a pull-through for Hirschsprung disease. Instead, at the age of 17 months a posterior sagittal repair (PSARP) was performed, together with repeated full-thickness biopsies approximately 5 cm proximal to the fistula site (perineum) in order to be able to confirm or discard the diagnosis of HD. The patient tolerated the procedure well and the postoperative course was uncomplicated. The patient was sent home 48 h after surgery tolerating a regular diet. If the repeated rectal biopsy had shown normal ganglion cells excluding the diagnosis of HD, we would have proceeded with closing the ostomy. No ganglion cells were identified and calretinin immunostaining was negative confirming the diagnosis of HD. Four months later, an abdominoperineal resection of the aganglionic rectosigmoid colon and a Swenson-type pull through of normal ganglionic bowel (verified again by a full-thickness biopsy) 5 cm proximal to the colostomy were performed. The patient tolerated the procedure well and was kept fasting and on total parenteral nutrition for 7 days postoperatively according to our protocol. On postoperative day 7 she was advanced to a regular diet that was tolerated well. The patient's mother demonstrated a correct rectal irrigation technique prior to discharge. The patient was discharged on postoperative day 8. The patient suffers from fecal incontinence and remains clean for stool with daily enemas.

4. Case 2

The second patient was a 2-year old female with a rectoperineal fistula. In addition, she has a PHOX2B gene mutation, congenital central hypoventilation syndrome, thoracic neuroblastoma, left-sided grade III vesicourethral reflux, a patent foramen ovale, a patent ductus arteriosus, and tricuspid and pulmonary valve regurgitation. Owing to difficulties with stooling and a suspicious contrast enema, at one month of age the patient underwent an exploratory laparotomy and colonic biopsies showed aganglionosis in the descending and rectosigmoid colon. A left transverse colostomy and mucous fistula were created. At 11 months of age she had a tracheostomy placed, and one month later, a thoracic neuroblastoma was resected thoracoscopically. Further operations included the placement of a pacemaker, owing to long sinus pauses, and a feeding gastrostomy tube. The patient was then transferred to our clinic at 28 months of age and underwent a PSARP, repeated full-thickness colonic biopsies, takedown of the colostomy and the mucous fistula, resection of the aganglionic segment (left colon and rectosigmoid), and pull-through of the normoganglionic colostomy. An appendicostomy (Malone procedure) was also done for the management of the expected fecal incontinence. The patient did well postoperatively and remains clean in the underwear with daily antegrade enemas.

5. Case 3

Case 3 describes a one year old male with trisomy 21 and anorectal malformation without fistula. A sigmoid colostomy and mucous fistula were performed shortly after birth. Four months later a PSARP was performed, and again after 4 months the colostomy was closed. The patient was admitted 2 months later in septic shock owing to intestinal perforation and a diverting ileostomy had to be performed. Seven days later the patient had to be reoperated owing to evisceration. Full thickness rectal biopsies were performed showing no ganglion cells. The patient was then transferred to our hospital and seven months after the last surgery, the aganglionic rectosigmoid colon was resected, and the descending colon was pulled through. The ileostomy was closed two months later. The patient remains clean on daily enemas.

6. Case 4

The fourth patient is a two year old male patient born with trisomy 21 and anorectal malformation without fistula. He underwent colostomy and mucous fistula opening on day 2 of life. At four months of age he underwent a PSARP. Five months after, his colostomy was closed. On postoperative day 6 the patient developed an acute abdomen with free intraabdominal air, and another colostomy had to be created. Another colostomy closure was attempted after 7 months but owing to an anastomotic leak, an ileostomy had to be created on postoperative day 14. Rectal biopsies were performed, and aganglionosis was confirmed. The patient was transferred to our hospital and was found to have an anal stricture. A redo PSARP was performed with repeated full thickness rectal biopsies. Hereby, 20 cm of distal bowel was resected owing to aganglionosis, and normoganglionic bowel was pulled through. Five months later, the ileostomy was closed and a Malone procedure (appendicostomy for antegrade enemas) was performed. The patient is doing well and remains clean of stool in the underwear with daily enemas.

7. Discussion

Reported incidences of HD in ARM patients result from case reports, case series [6,19], and meta-analyses; summarizing all, the incidence ranges from 2% to 3.4% [1,22]. To our knowledge, our database is the largest database of ARM patients in the world, and the hereby identified incidence of HD in ARM patients is 0.17% (4 per 2397). Unfortunately, in

most of the published case series or case reports there is no mention on how the diagnosis of HD was made (i.e. with full thickness leveling biopsies versus rectal suction biopsies). In addition, most of the published reports do not indicate if diagnosis of HD was confirmed in the resected bowel specimen [9]. We suspect that a false positive diagnosis of HD was made in many published series since biopsies of the distal rectum during surgery for ARM frequently show absent ganglion cells. Part of our routine, during the repair of ARM, includes sending to pathology the most distal portion of the bowel (5–15 mm), which is resected to perform an anoplasty using healthy bowel tissue. Those specimens showed many histological abnormalities, including sometimes absent ganglion cells. None of those cases suffered from Hirschsprung disease. We are in the process of sending those results for publication. In addition, the occurrence of Hirschsprung associated enterocolitis is barely ever mentioned in these case reports and case series. Finally, constipation is the most common functional disorder in ARM patients, especially in lower malformations such as rectoperineal, rectourethral bulbar or rectovestibular fistulas, as well as in patients without fistulas. This might have led to a false high incidence of HD in ARM patients in the literature. Furthermore, different ARM classification systems were used by different authors, and the diagnosis of ARM remains questionable in some of the published case series since the authors are only mentioning a 'narrow anal canal' [10,26]. The opening in a rectoperineal fistula has three characteristics: it is narrow, not (completely) surrounded by sphincter muscle, and anteriorly displaced. Finally, some reported cases assigned to the diagnosis of Currarino triad (which would entail the triad of ARM, sacrococcygeal defect, and presacral mass [27]) together with HD were not reported having a true ARM [7]. Furthermore, many reports on patients with HD and ARM report on bowel control after surgery, which is hard to believe [2,8,19,20,28]. In patients with HD without ARM the aganglionotic bowel is resected, and normal ganglionic bowel is pulled down and anastomosed to the rectum 2 cm above the anal canal. Those patients are able to have bowel control because the anal canal (sensitive area) and voluntary sphincter are preserved. Most patients with ARM (except patients with rectal atresia) are born without an anal canal and different degrees of anal sphincter deficiency. In these patients, a true Swenson procedure cannot be done; in this manuscript, when we used the word "Swenson-type", we referred to a full thickness dissection/resection. Hence, the anastomosis of the bowel after a pull-through must be done all the way down to the skin, which leaves the patient fecally incontinent.

It is our opinion that patients with ARM suffering from constipation and without evidence of enterocolitis deserve the benefit of the doubt, with repeated full thickness biopsies with acetylcholinesterase staining, evaluated by an expert pathologist with experience in the diagnosis of Hirschsprung disease to avoid any unnecessary pull-through procedures in a patient with ARM and suspected HD.

8. Conclusion

Our results strongly suggest that the association of anorectal malformation and Hirschsprung disease is less common than previously reported. This is particularly relevant owing to the fact that the operation required for Hirschsprung disease performed in a patient with anorectal malformation results in permanent fecal incontinence.

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