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CLINICAL RISK FACTORS OF HIRSCHSPRUNG – ASSOCIATED ENTEROCOLITIS I: PREOPERATIVE ENTEROCOLITIS*

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Enterocolitis is still the main source of mortality and morbidity in Hirschsprung's disease (HD). Between 1976 and 1993, 79 (26%) of 302 Hirschsprung patients proved to have Hirschsprung-associated enterocolitis (HAEC). Mortality was 7.6 percent (6 patients). HAEC patients, those who died of HAEC and those without HAEC were analyzed for differences in 34 parameters. The length of the aganglionic segment was found not to be a risk factor for HAEC, but early diagnosis and prompt treatment were found to decrease the occurrence of preoperative HAEC. Although we defined HAEC as foul-smelling, explosive diarrhea, some other symptoms and signs, such as abdominal distention on physical examination, vomiting, dehydration, and a history of nonspecific diarrhea were encountered with significant frequency. None of the patients had Down's syndrome. Sepsis was detected in all of the patients who died of HAEC. The severity of HAEC did not increase with the number of attacks of HAEC, and mortality was greater in the first three attacks. Differences in results between some series seemed to be related to differing definitions of HAEC. *Key words: Hirschsprung's disease, preoperative enterocolitis.*

Enterocolitis related to Hirschsprung's disease (HD) was first recognized by Ehrenpreis in 1946, and other reports followed soon thereafter[1,2]. According to some authors, Hirschsprung-associated enterocolitis (HAEC) has a wide spectrum of symptoms ranging from mild diarrhea without any systemic symptom to abdominal distention, diarrhea and hypovolemic shock, ending in mortality[2,3]. Some others do not accept diarrhea alone to be HAEC[4]. Enterocolitis has been subdivided into inflammatory and ischemic (necrotizing) enterocolitis[5]. Pseudomembranous enterocolitis has also been reported in HAEC[6-8]. The incidence of HAEC was reported to be as high as 58 percent and its mortality rose to 30 percent in some series[9-10]. Suggested etiologies of the disease include: spasm of the aganglionic internal sphincter; infections, especially rota virus and Clostridium difficile; alterations in intestinal mucin and mucosal immune defense mechanisms; increased prostaglandin E_1 activity; and Schwatzman-type allergic reaction[17-26]. The clinical risk factors of the disease have also been studied[9,16,27].

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Trisomy 21 and a delay in diagnosis are the main risk factors reported in different series[9, 16]. Some authors have reported that long-segment aganglionosis is a predisposing factor, while others have found no association between the length of aganglionosis and HAEC[11, 12, 27, 16]. Thus a retrospective study was conducted in order to evaluate the clinical risk factors of preoperative HAEC.

Material and Methods

Over a period of 17 years between 1976 and 1993, 302 Hirschsprung patients were evaluated retrospectively for the presence of preoperative HAEC. The patients with preoperative HAEC were compared with Hirschsprung patients without preoperative HAEC, and patients who died due to HAEC were compared with the overall HAEC group in search of clinical factors influencing the occurrence and mortality. The diagnosis of HAEC was based on the existence of foul-smelling, explosive diarrhea.

The following information was obtained in all cases: A, history, physical examination and symptoms on admission: 1. sex, 2. age of diagnosis, 3. birthweight, 4. gestational age, 5. family history, 6. history of death of a sibling, 7. consanguinity, 8. associated anomaly, 9. delay in the passage of meconium, 10. abdominal distention in history, 11. abdominal distention on physical examination, 12. history of diarrhea, 13. fever, 14. vomiting, 15. dehydration, 16. bloody stool, 17. defecation frequency, 18. presence of stool on rectal examination, 19. intestinal obstruction, 20. intestinal perforation, and 21. length of aganglionic segment; B. clinical picture due to HAEC: 1. pericolic abscess, 2. sepsis, 3. total number of HAEC bouts, 4. number of HAEC bouts during hospitalization, 5. hospitalization period for HAEC, 6. type of microorganism in the stool, 7. duration of antibiotic usage, and 8. type of antibiotic used; C. relative to definitive operations: 1. choice of definitive operation, 2. duration between colostomy and definitive operation, and 3. death after definitive operation, D.relative to diarrhea after colostomy and enterocolitis after definitive operation: 1. diarrhea after colostomy, and 2. enterocolitis after definitive operation.

Short-segment aganglionosis (SS) is accepted to refer to aganglionosis extending from the rectum to the sigmoid colon, long-segment disease (LS) above the sigmoid to the ascending colon, and extensive aganglionosis (EA) as total colonic aganglionosis and beyond. For statistical comparisons, chi-square and Fisher's exact chi-square tests were used, and p values of less than 0.05 were considered to be significant.

Results

Between 1976 and 1993, 79 (26.2%) of 302 Hirschsprung patients were found to have preoperative HAEC, and six (7.6%) of these died due to HAEC. Among 79 patients with preoperative HAEC, 15 (19.0%) were female and 64 (81%) were

male. The female: male ratio was 1:43. Among patients without HAEC, 43 (19.3%) were female and 180 (80.7%) were male ($p > 0.05$). One female patient and five male patients died of HAEC. There was no difference between patients who died of HAEC and those who survived with HAEC in terms the of female: male ratio ($p > 0.05$).

Sixteen (24.1%) patients with preoperative HAEC were newborns, 30 (38.0%) were one to 12 months in age, 25 (31.7%) were 12 months to six years, and five (6.3%) were greater than six years old at the time of diagnosis. A significant difference was detected in terms of age of diagnosis ($p < 0.05$) in the one- to 12-month-old and the newborn groups. Among 114 newborns who were admitted with HD, 79 were diagnosed in one to five days, 13 in six to ten days, five in 11 to 15 days, and 17 in 16 to 30 days. All six patients who died of enterocolitis were less than 12 months of age. A significant difference was found between the patients who died of HAEC and those who survived with HAEC in terms of age of diagnosis ($p < 0.05$).

The birthweights in the HAEC group were 1500 to 2500 g in four (11.4%) paitents, 2500 to 3500 g in 23 (65.7%) patients, and greater than 3500 g in eight (22.9%) patients. In the group without HAEC, patients 2500 to 3500 g in weight constituted 62.8 percent of the total ($p > 0.05$). There were 47 (94.0%) term patients, one (2.0%) preterm patient and two (4.0%) postterm patients in the HAEC group. Of the patients without HAEC, 123 (94.6%) were found to be term infants ($p > 0.05$).

One sister and one brother of the patients in the HAEC group and one sister and three brothers of the Hirschsprung patients without HAEC had the diagnosis of Hirschsprung's disease. Eighteen patients (6.6%) in the HAEC group and 29 (10.6%) in the group without HAEC had a history of death of one of their siblings; six (two with HAEC) had died of verified HD, while 12 (five with HAEC) had a history suggesting HD but no verification. The families of 10 patients (12.7%) with HAEC and 26 patients (13.3%) without HAEC were found to have consanguinity ($p > 0.05$). In 13 patients (16.5%) with HAEC and 36 patients (16.1%) without HAEC, a congenital anomaly was detected ($p > 0.05$). None of the patients with HAEC had Down's syndrome.

Seven patients (12.5%) in the HAEC group passed meconium in the first 24 hours of life, 13 patients (23.2%) between 24 to 48 hours, and 36 patients (64.3%) after 48 hours. These figures were 14 (8.9%), 44 (27.9%) and 100 (63.3%), respectively, among patients without HAEC ($p > 0.05$). A history of distention was present in 77 patients (97.5%) in the HAEC group ($p > 0.05$).On the other hand, distention was found on physical examination statistically more frequently in the HAEC group ($p < 0.05$). The two groups were also searched for the presence of nonspecific diarrhea other than foul-smelling, explosive diarrhea. Seventy-one patients (89.3%) with HAEC had a history of nonspecific diarrhea, whereas only six patients (2.7%)

without HAEC had a history of this sort of diarrhea, with a statistically significant difference between the two groups ($p < 0.05$). Sixteen patients (20.3%) were found to have body temperatures greater than 38 °C ($p > 0.05$). Vomiting was detected in 61 patients (77.2%) in the HAEC group, and this result was statistically higher than in the group without HAEC ($p < 0.05$). Both mild and severe dehydration were significantly more common in the HAEC group (29 and 9 patients, respectively, $p < 0.05$). Bloody stools were detected in two patients (2.5%) in the HAEC group and three patients (1.4%) in the group without HAEC ($p > 0.05$). In the HAEC group 25 patients (35.2%) passed stool every one to three days, 14 (19.7%) every four to six days, seven (9.9%) every seven to 10 days, four (5.6%) at intervals greater than 11 days, 10 (15.5%) more than once a day and 11 (15.5%) only with an enema ($p > 0.05$). In 41 patients (52.6%) with HAEC and in 35 patients (16.3%) without HAEC there was passage of stool after rectal examination ($p > 0.05$). Thirty-four patients (43.1%) with HAEC and 104 patients (46.6%) without HAEC had an intestinal obstruction on x-ray ($p > 0.05$). Intestinal perforation was present in three (3.8%) patients with HAEC and eight (3.6%) without HAEC ($p > 0.05$).

Sixty-three patients with HAEC (82.9%) had SS, 11 (14.5%) had LS disease, and two (2.6%) had EA; among those without HAEC, 155 (78.3%) had SS, 34 (17.2%) had LS disease, and nine (4.6%) had EA ($p > 0.05$). Information on the length of the aganglionic segment was able to be obtained from 274 files. Four patients who died of HAEC (80.0%) and 59 who survived with HAEC (83.1%) had SS disease ($p > 0.05$).

None of the patients with preoperative HAEC had a pericolic abscess. Sepsis was present in all the patients who died of HAEC and nine (12.3%) of those who survived with it ($p < 0.05$). All six patients who died of HAEC died in one of the first three attacks of HAEC. Thirty-six of the patients who survived with HAEC (54.3%) had one to three attacks, and 32 (45.7%) had four or more ($p < 0.05$, Fisher's exact chi-square test). Five patients died of HAEC in the first hospitalization, and one in the second, In the group that survived with HAEC, 37 patients (50.7%) were hospitalized at least once, and 36 (49.3%) were never hospitalized ($p < 0.05$). Two (33.3%) of the six patients who died of HAEC were hospitalized less than three days, one (16.7%) four to seven days, and three (50.0%) for eight to 15 days.

The microorganisms detected in the two groups were as follows:

Died due to HAEC: E coli (1 patient), E.coli + Klebsiella (1 patient), Proteus + E.coli + Pseudomonas (1 patient).

Survived after HAEC: E.coli (5 patients), E.coli + Klebsiella (5 patients), Klebsiella (9 patients), Proteus + Klebsiella (3 patients), Proteus + Enterobacter aerogenes (2 patients), Proteus + Enterobacter aerogenes + E.coli (1 patient), Proteus + E.coli (1 patient), Pseudomonas (1 patient), E.coli + candida albicans (1 patient).

There was no significant difference in the period of antibiotic usage between patients who died due to HAEC and those who survived after HAEC. Antibiotics chosen were mainly penicillin + gentamicin (or tobramycine) + metronidazole in severe cases, and trimethoprim-sulfamethoxazole in mild cases without systemic symptoms.

In the HAEC group, 36 (65.5%) patients had undergone a Swenson operation, 17 (30.9%) a Duhamel operation, one (1.8%) a Boley operation, and one (1.8%) patient a myectomy procedure. One (1.8%) patient in the HAEC group and four patients (2.6%) without HAEC died after definitive operation ($p > 0.05$).

In the HAEC group, the period between the colostomy procedure and definitive operation was between one and three months in one patint (1.9%), three to six months in five patients (9.4%), six to nine months in 10 patients (18.9%) nine to 12 months in six patients (11.3%), 12 to 15 months in four patients (7.6%), 15 to 24 months in 10 patients (18.9%), 24 months to three years in seven patients (13.2%), and greater than three years in 10 patients (18.9%) ($p > 0.05$).

Diarrhea after colostomy was detected in seven patients (10.1%) with HAEC and 20 patients (10.8%) without HAEC ($p > 0.05$). Nine patients (20.5%) with and 25 patients (24.3%) without preoperative HAEC developed HAEC after definitive operation ($p > 0.05$).

Discussion

Although HAEC is still the major source of mortality and morbidity in Hirschsprung's disease, the number of research and retrospective studies on HAEC is limited[9, 16, 27].

In our series the incidence of preoperative HAEC was 26.2 percent and its mortality was 7.6 percent. Although in different series the incidence of HAEC has been as high as 58 percent and the mortality as high as 30 percent, lower mortality rates have been reported in recent publications[16-27].

Tietelbaum et al.[16] found a male predominance (75%) but Carnerio et al.[10] a female predominance. In the present study a male predominance (81.0%) was detected in patients with and without HAEC. The female: male ratios were 1:4.3 for the whole series and 1:4.2 in the HAEC group. The F:M ratio was 1:5 and 1:4.2 for patients who died of HAEC and who survived with HAEC, respectively.

The diagnosis was made most frequently in patients between the ages of one and 12 months. In our series HAEC was less common below one month of age. Early diagnosis of the disease and prompt treatment decrease the occurence of preoperative HAEC. Tietelbaum et al.[16] found that the mean age of diagnosis of HAEC was 16.6 ± 11.3 years and that it was significantly higher than in patients without HAEC. In our series 37.8 percent (114) of patients were diagnosed with HD in the neonatal period. Among the patients with HAEC who were diagnosed

in the neonatal period (19 patients), 47.4 percent were diagnosed in the first five days of life, suggesting that the symptoms can be more severe in the early neonatal period and force the family to bring the baby to the hospital earlier. In fact, all the patients who died of HAEC were less than 12 months of age, and 66.1 percent of them were neonates. Tietelbaum et al.[16] reported a mortality rate of five percent among infants.

Birthweight did not affect the occurrence of HAEC in our series. Tietelbaum et al.[16] reported a family history in their three (4.7%) patients. We detected six (2.0%) patients with a family history among the Hirschsprung patients and two patients (2.5%) in the preoperative HAEC group. Death due to HD was detected in five siblings with HAEC. Consanguinity, although high in both groups, was still below the overall percentages for Turkey[28].

Down's syndrome is being reported with increasing frequency with HD, and in recent years it has also been considered among the clinical risk factors for HAEC. In the series of Surana et al.[9] the incidence of Down's syndrome was reported to be 47 percent. In our series none of the patients with HAEC had Down's syndrome, and only five (1.7%) Down patients were detected in the whole series of 302 Hirschsprung patients. There was no difference in other anomalies between the two groups.

In our series there was no difference between the time of passage of meconium among patients with and without HAEC. Tietelbaum et al.[16] reported the contray, suggesting that patients with HAEC passed meconium later. A history of abdominal distention appeared in equal percentages in both groups. On the other hand, distention on admission proved to be a significant clinical factor in HAEC. We detected abdominal distention in 98.1 percent of our patients with HAEC. Elhalaby et al.[27] reported an 83 percent incidence of abdominal distention. Nonspecific diarrhea was detected in only 2.7 percent of patients without HAEC. Temperatures greater than 38 °C appeared in only 20.3 percent of HAEC patients while vomiting appeared in 77.2 percent of patients. Surana et al.[9] reported that 75.6 percent, and Elhalaby[27] 51 percent, of their patients had the complaint of vomiting. The latter group suggested that mild diarrhea without any other symptoms should be regarded as enterocolitis. In our series mild and severe dehydration was present in 46.8 percent of HAEC patients. These patients should be quickly managed owing to the fact that enterocolitis can result in hypovolemic shock and death. Tietelbaum[16], Surana[9] and Vinton[29] reported 25 five and 10-30 percent incidences of bloody stool in HAEC, respectively. In our series bloody stool was present in only 2.5 percent of HAEC patients. There was no difference in the defecation patterns of the two groups.

In HAEC patients, the rectal examination was found to be more specific, with the presence of stool on rectal examination in 52.6 percent of cases. Elhalaby et al.[27] stated that "gaseous intestinal distention with abrupt cutoff sign at the

level of the pelvic brim was both sensitive (74%) and specific (86%) for HAEC". In our series, intestinal obstruction and intestinal perforation were detected in both groups with no significant difference.

Kleinhaus et al.[11] and Ikeda et al.[12] reported an increased incidence of HAEC with long-segment HD. We found 82.9 percent SS, 14.5 percent LS, and 2.6 percent EA, which resembled the results of Tietelbaum et al.[16] Furthermore, we detected that four of our patients who died of enterocolitis had SS disease, and one had EA.

Sepsis was detected in 14 patients with HAEC and in all six patients who died of HAEC. No pericolic abscess was detected. In our series the first attacks were associated with higher mortality, and the severity did not increase with the number of attacks. This might again be related to the increasing age of the patient. Thirty-seven patients (50.7%) among those who survived with HAEC and all six who died of HAEC had been hospitalized at least once. The duration of hospitalization was less than seven days in 50 percent of the patients who died of HAEC, suggesting a fulminant course. Tietelbaum et al.[16] reported that be hospitalization periods of patients with HAEC were twice as long as those of other Hirschsprung patients. The most frequently isolated organisms were E.coli, Klebsiella and Proteus. We preferred a combination of penicillin + gentamicin (or tobramycin) + metronidazole in severe cases, and trimethoprim-sulfamethoxazole (TMS) + metronidazole (or ornidazole) or metronidazole alone in mild cases.

Patients with preoperative HAEC were treated in the same way as those without HAEC, after the colostomy procedure. The period between the colostomy procedure and definitive operation was not statistically different between the two groups. HAEC did not affect the death rate after definitive operations.

We detected diarrhea in 27 patients after colostomy opening. As the symptoms did not meet the criteria for HAEC diarrhea, this condition was regarded as diarrhea after colostomy. No correlation between preoperative HAEC and diarrhea after colostomy opening was present. The fact that the patient had preoperative attack(s) of HAEC did not imply that they would have HAEC attack(s) after definitive operation, and vice versa.

Since enterocolitis most frequently affects patients with HD between the ages of one and 12 months and it is potentially a lethal complication in this period of life, patients should be carefully evaluated and diagnosed before this period.

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