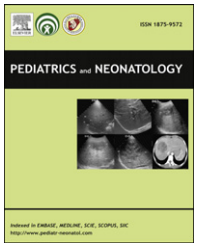
Pediatrics and Neonatology (2012) 53, 133–137

Available online at www.sciencedirect.com
SciVerse ScienceDirect
journal homepage: http://www.pediatr-neonatol.com



ORIGINAL ARTICLE

Clinical Impacts of Delayed Diagnosis of Hirschsprung's Disease in Newborn Infants

Chien-Chung Lee [a], Reyin Lien [a,*], Ming-Chou Chian [a], Peng-Hong Yang [a], Shih-Ming Chu [a], Jen-Hei Fu [a], Jin-Yao Lai [b]

[a] *Division of Neonatology, Department of Pediatrics, Chang Gung Memorial Hospital, Chang Gung University, School of Medicine, Taoyuan, Taiwan*
[b] *Division of Neonatology, Department of Pediatric Surgery, Chang Gung Memorial Hospital, Chang Gung University, School of Medicine, Taoyuan, Taiwan*

Received May 31, 2011; received in revised form Jun 16, 2011; accepted Jun 30, 2011

Key Words
delayed diagnosis;
enterocolitis;
Hirschsprung's disease;
neonate

Background: Asian infants are at a higher risk of having Hirschsprung's disease (HD). Although HD is surgically correctable, serious and even lethal complications such as Hirschsprung's-associated enterocolitis (HAEC) can still occur. The aim of this study was to investigate the risk factors of HAEC, and the clinical impacts of delayed diagnosis of HD in newborn infants.
Patients and methods: By review of medical charts in a medical center in Taiwan, 51 cases of neonates with HD between 2002 and 2009 were collected. Patients were divided into two groups based on the time of initial diagnosis: Group I, diagnosis made within 1 week after birth, and Group II after 1 week. Clinical features including demographic distribution, presenting features of HD, short-term and long-term complications related to HD were compared between the two groups of patients.
Results: There were 25 patients in Group I and 19 in Group II. Group II patients had more severe clinical signs and symptoms of HAEC than Group I patients. The incidence of preoperative HAEC was 12% in Group I and 63% in Group II (adjusted odds ratio = 12.81, confidence interval = 2.60–62.97). Patients with preoperative HAEC were more likely to develop adhesive bowel obstruction after operation (33% vs. 3%, $p = 0.013$) and failure to thrive (33% vs. 3%, $p = 0.013$). Also, patients with long-segment or total colonic aganglionosis were at risk of developing both postoperative HAEC (85% vs. 29%, $p = 0.001$) and failure to thrive (39% vs. 3%, $p = 0.002$).
Conclusion: In our study, we found that delayed diagnosis of HD beyond 1 week after birth significantly increases the risk of serious complications in neonatal patients. Patients with long-segment or total colonic aganglionosis have higher risk of postoperative HAEC and failure

* Corresponding author. Division of Neonatology, Department of Pediatrics, Chang Gung Children's Hospital, 5 Fu-Shing Street, Kweishan, Taoyuan 33305, Taiwan.
E-mail address: reyinl@adm.cgmh.org.tw (R. Lien).

doi:10.1016/j.pedneo.2012.01.011

to thrive. Patients with preoperative HAEC are more likely to have adhesive bowel obstruction and failure to thrive.

1. Introduction

Hirschsprung's disease (HD) is a congenital bowel motility disorder which occurs in approximately one of every 5000 live births. It appears to have a complex genetic predisposition, and the incidence of HD has been reported to be higher in Asian infants as compared to infants from other ethnic origin.[1,2] Hirschsprung disease's is caused by arrest of craniocaudal migration of neural crest cells (precursors of colonic ganglion cells) during the fifth to 12th weeks of gestation.[3] Unlike other congenital structural anomalies, HD does not cause any recognizable clinical features prenatally. With timely diagnosis, most affected children now can lead a normal and productive life with recent advances in understanding of its pathogenesis and improvement in surgical management. However, patients who have HD can still develop life-threatening bowel obstruction, colonic perforation, sepsis, or severe diarrhea and dehydration before surgery. These complications were first recognized by Swenson and Fisher in 1956, and later described in detail by Bill and Chapman in 1962.[4] Caneiro and coworkers further defined Hirschsprung's-associated enterocolitis (HAEC) as a distinct clinical syndrome of fever, diarrhea, abdominal distension, colicky pain, lethargy and passage of bloody stool.[5] Even today, HAEC remains the major cause of serious morbidity and mortality in HD.

Although HD typically presents in the newborn period, it can occasionally be diagnosed in older children or adults. Those presenting beyond neonatal period usually are of milder forms. Previous studies have suggested that HAEC occurs more often in patients whose diagnosis of HD is delayed[2] and that delayed diagnosis is also associated with poorer long-term outcomes.[6,7] However, these studies involved only older children. Correlation of timely diagnosis and disease outcome has not been studied in newborn infants with HD and bowel obstruction. The purpose of the present study aimed to investigate clinical impact of delayed diagnosis in newborn infants with HD and how it would affect their outcome.

2. Methods

2.1. Patients and clinical characteristics

This was a study of case series performed by retrospective chart review. We enrolled those patients who were admitted to the neonatal intensive care unit of Chang Gung Children's Hospital with the diagnosis of HD by 60 days after birth during the period from January 2002 to December 2009. Patients who declined treatment in this hospital or had additional gastrointestinal anomalies were excluded. The patients were divided into two groups based on the time of diagnosis. In this report, the term "time of diagnosis" refers to the time of the patient being recognized as having or at which was diagnosed presumptively and managed accordingly. Those who were diagnosed within 1 week of age were categorized as Group I, and those diagnosed beyond 1 week of age as Group II. Relevant clinical features including demographic data, age of diagnosis, level of aganglionosis segment, family history of HD, association with trisomy 21, history of delayed passage of meconium (beyond 48 hours of age) or constipation (subjective complaint from care taker), as well as symptoms related to HAEC, including foul-smelling diarrhea, bloody stool, abdominal distention, fever, vomiting, shock, dehydration (body weight loss more than 10% of birth weight), leukocytosis ($>$ 20,000 cells/mm^3), elevated C-reactive protein (CRP) level ($>$14 mg/dL) and colonic perforation[8] were reviewed.

2.2. Preoperative and postoperative complications

We investigated occurrence of preoperative and postoperative complications between the two groups. Patients with HD who developed any one of the symptoms of foul-smelling diarrhea, bloody stool or fever were thought to have enterocolitis (HAEC).[9–11] Preoperative complications included blood culture-proven sepsis, preoperative HAEC and perforation. Postoperative complications included postoperative HAEC, adhesive bowel obstruction, anastosmosis leakage, anal stenosis due to stricture formation, anal excoriation, enterocutaneous fistula, constipation that needed treatment with laxatives and failure to thrive (weight for age less than third percentile). We also looked into the existence of risk factors that have been linked to HAEC, such as trisomy 21[5,7,9,12–14] and HD with long segment (long-segment or total colonic) of aganglionosis.[6,8,15–17] Correlation between preoperative HAEC, level of aganglionosis, and development of postoperative complications were also examined.

2.3. Statistical analysis

The unpaired Student t test was performed to examine the differences between demographic and clinical characteristics in the groups. Significance of differences in categorical values was analyzed using the X^2 test. Fisher's exact probability test was applied when examining variables of low incidence. The logistic regression and odds ratio was used to estimate possible correlations between analyzed factors and the incidence of complications. All statistical analyses were completed using Predictive Analytics Software (PASW) Statistics 18 (IBM, Armonk, NY, United States), and $p < 0.05$ was considered statistically significant.

3. Results

3.1. Demographic data and clinical characteristics of patients

There were a total of 51 infants diagnosed with HD during the study period. However, the families of five patients declined treatment in this hospital and these patients were discharged without intervention. Two infants had other gastrointestinal anomalies (one had ileal atresia, and the other had intestinal malrotation and imperforate anus). Among the remaining 44 patients, 25 had HD diagnosed within 1 week of age in Group I, and 19 were diagnosed beyond 1 week of age in Group II. Demographic distributions of the two groups were similar (Table 1). In both groups of HD patients, there was a higher proportion (88% in Group I, 80% in Group II) of male than female. Mean gestational age at birth was 38.4 ± 1.4 weeks in Group I and 38.0 ± 2.7 weeks in Group II. Mean birth weight was 3194 ± 304 g in Group I and 3066 ± 613 g in Group II. Two patients had trisomy 21, one in each group. None of the patients had family history of previous HD. The distribution of levels of aganglionosis was similar: 76% rectosigmoid, 12% long segment and 12% total colonic aganglionosis in Group I, and 63% rectosigmoid, 11% long segment and 26% total colonic aganglionosis in Group II ($p = 0.475$). Only 28% of patients in Group I and 32% in Group II had the clinical symptom of delayed passage of meconium after birth. The incidence of constipation before diagnosis of the disease was similar in Groups I and II (52% vs. 53%).

Table 2 shows the clinical presentations of preoperative HAEC. The most common presentations of HAEC were elevated CRP level, foul-smelling diarrhea, bilious vomiting, fever, and dehydration. Comparing Group I with Group II patients, those in Group II (with delayed diagnosis of HD) were more likely to present with serious systemic symptoms when they developed HAEC: shock, 0% versus 25%; dehydration, 0% versus 58%; leukocytosis, 0% versus 25%; and elevated CRP levels, 67% versus 92%. No infants with early diagnosis in Group I were in shock, and none in either group had colonic perforation.

Table 1 Demographic data and clinical characteristics of the two groups.

	Group I ($n = 25$)	Group II ($n = 19$)	p
Male gender	22 (88%)	15 (80%)	0.443
Gestational age (mean ± SD, wk)	38.4 ± 1.4	38.0 ± 2.7	0.480
Birth body weight (g)	3194 ± 304	3066 ± 613	0.371
Trisomy 21	1 (4%)	1 (5%)	1.000
Level of aganglionosis			0.475
Rectosigmoid	19 (76%)	12 (63%)	
Long-segment	3 (12%)	2 (11%)	
Total colonic	3 (12%)	5 (26%)	
Delayed meconium	7 (28%)	6 (32%)	0.797
Constipation	13 (52%)	10 (53%)	0.967

Group I: Hirschsprung's disease diagnosed within 7 days.
Group II: Hirschsprung's disease diagnosed beyond 7 days.

Table 2 Clinical presentations of preoperative HAEC.

	HAEC ($n = 15$)	HAEC in Group I ($n = 3$)	HAEC in Group II ($n = 12$)
Foul-smelling diarrhea	10 (67%)	1 (33%)	9 (75%)
Bilious vomiting	10 (67%)	3 (100%)	7 (58%)
Fever	10 (67%)	2 (67%)	8 (67%)
Dehydration	7 (47%)	0 (0%)	7 (58%)
Bloody stool	5 (33%)	2 (67%)	3 (25%)
Leukocytosis	3 (20%)	0 (0%)	3 (25%)
Elevated CRP level	13 (87%)	2 (67%)	11 (92%)
Sepsis	4 (27%)	1 (33%)	3 (25%)
Shock	3 (20%)	0 (0%)	3 (25%)
Colonic perforation	0 (0%)	0 (0%)	0 (0%)

CRP = C-reactive protein; HAEC = Hirschsprung's-associated enterocolitis.

3.2. Diagnosis of HD

In this study, 36 patients received contrast enema (lower gastrointestinal, LGI) study. However, LGI studies failed to make the diagnosis of HD in nine of the 36 (25%) patients. In these nine patients, six were diagnosed as meconium plug syndrome and three were diagnosed as ileus. Forty patients received rectal suction biopsy before surgery. Five of the biopsies (13%) failed in making a diagnosis of HD because of inadequate sampling of the specimen and needed second biopsy to confirm HD.

3.3. Preoperative and postoperative complications

Comparison of the risks of developing preoperative and postoperative complications between the two groups is shown in Table 3. Risk of preoperative sepsis was 4% in Group I and 16% in Group II ($p = 0.3$), and risk of preoperative HAEC was 12% in Group I and 63% in Group II ($p = 0.000$). Although the chance of having various postoperative complications seemed higher in Group II, the difference did not reach statistical significance. When examining the risk factors associated with preoperative HAEC, impacts from other possible confounding elements, i.e., trisomy 21 and level of aganglionosis, were adjusted. The adjusted odds ratio of having preoperative HAEC in Group II infants (HD diagnosed beyond 1 week of age) was 12.81 (confidence interval: 2.60—62.97).

Table 4 depicts the association of preoperative HAEC with various postoperative complications. In the presence of preoperative HAEC, there were increased risks for postoperative adhesion bowel obstruction (33% vs. 3%, $p = 0.013$) and failure to thrive (33% vs. 3%, $p = 0.013$). In regard to the impact of length of the aganglionosis segment on the postoperative complications, longer length of the diseased segment (long-segment or total colonic HD) was associated with increased risk of postoperative HAEC (85% vs. 29%, $p = 0.001$) and failure to thrive (39% vs. 3%, $p = 0.002$), when compared to short-segment HD.

Table 3 Preoperative and postoperative complications between the two groups.

	Group I ($n = 25$)	Group II ($n = 19$)	p
Preoperative complications			
Sepsis	1 (4%)	3 (16%)	0.300
Preoperative HAEC	3 (12%)	12 (63%)	0.000*
Postoperative complications			
Postoperative HAEC	10 (40%)	10 (53%)	0.405
Adhesive bowel obstruction	2 (8%)	4 (21%)	0.378
Anastomosis leakage	1 (4%)	2 (11%)	0.570
Anal stenosis	3 (12%)	3 (16%)	1.000
Anal excoriation	15 (60%)	16 (63%)	1.000
Enterocutaneous fistula	2 (8%)	1 (5%)	1.000
Constipation	4 (16%)	3 (16%)	1.000
Failure to thrive	2 (8%)	4 (21%)	0.378

Group I: Hirschsprung's disease diagnosed within 7 days.
Group II: Hirschsprung's disease diagnosed beyond 7 days.
HAEC = Hirschsprung's-associated enterocolitis.
* Statistically significant.

4. Discussion

Clinical presentations of HAEC range widely, from mildly abdominal distension with no systemic manifestations; to life-threatening conditions such as severe dehydration, shock and sepsis. Our study showed that infants with HD have high risk of presenting with the most severe symptoms of HAEC during neonatal period, and HAEC is more likely to occur in infants whose diagnosis of HD is made beyond 1 week of age. In our study, compared to diagnosis made within 7 days after birth, delayed diagnosis put neonatal patients with HD at a 13-fold increased risk for HAEC before surgery. Our findings demonstrated an overall incidence of preoperative HAEC of 34%, while 47% of the neonates presented with severe dehydration, 27% with sepsis, and 20% with shock.

When Teitelbaum et al. defined the term Hirschsprung's-associated enterocolitis (HAEC), they also identified delayed diagnosis beyond 1 week, and the presence of trisomy 21 as significant risk factors for HAEC.[9] In our study, delayed diagnosis of HD was shown to be an independent risk factor for the development of HAEC in the preoperative period. Two of the 51 patients (4%) with HD had trisomy 21 in this case series. With the small case number in this study, we were unable to distinguish if trisomy 21 was a risk factor to HAEC, as some other earlier studies had also suggested.[7,13,18] However, it reiterates the fact that infants with intestinal stenosis have high likelihood of having trisomy 21.

As for the correlation to postoperative complications, although we did not find direct associations between delayed diagnosis of HD and the postoperative complications, our results revealed that postoperative complications, specifically adhesive bowel obstruction and failure to thrive, are associated with the presence of preoperative HAEC. Our study also showed that long-segment or total colonic aganglionosis are independent risk factors to postoperative HAEC and failure to thrive, as previous studies had demonstrated.[7,16,17]

So far, the pathogenesis of HAEC is still unclear, and its etiology could be multifactorial. Mechanical obstruction, abnormal mucin production, decreased secretion of immunoglobulin A (IgA), and dysfunction in white blood cells have all been proposed to explain the development of HAEC.[19] For example, the longer aganglionosis implies a greater proximal obstruction and a more extensive impairment of the bowel immune system, which in turn leads to higher susceptibility of intestinal stasis and bacterial production, whereas early recognition or diagnosis of this condition with prompt rectal or stomy decompression can relieve intestinal stasis and reduce bacterial overgrowth with time.[10,20]

The 34% incidence of preoperative HAEC in this study is higher than those of other previous reports.[10,19] This might be attributed to the fact that the majority of our neonatal intensive care unit patients were referred from local clinics or regional hospitals, and in the cases of HD, usually after they developed significant signs and symptoms of HAEC. In fact, all but two of our 15 patients with severe preoperative HAEC were referred to this medical center under the impression of sepsis, shock, or severe enterocolitis with dehydration. This unfortunate phenomenon attested to our concern about lack of awareness of HD among today's pediatricians. Advances in fetal ultrasonographic examination have aided in the precise *in utero* diagnosis of many

Table 4 Associations between preoperative HAEC and postoperative complications.

	No preoperative HAEC ($n = 29$)	Preoperative HAEC ($n = 15$)	p
Postoperative complications			
Postoperative HAEC	11 (40%)	9 (60%)	0.163
Adhesive bowel obstruction	1 (3%)	5 (33%)	0.013*
Anastomosis leakage	1 (3%)	2 (13%)	0.264
Anal stenosis	2 (7%)	4 (27%)	0.159
Anal excoriation	17 (59%)	10 (67%)	0.603
Enterocutaneous fistula	2 (7%)	1 (7%)	1.000
Constipation	4 (14%)	3 (20%)	0.675
Failure to thrive	1 (3%)	5 (33%)	0.013*

HAEC = Hirschsprung's-associated enterocolitis.
* Statistically significant.

major congenital surgical diseases. As a result, clinicians caring for newborn infants have gradually relied more on the obstetrician's prenatal findings and lost vigilance in the recognition of those congenital surgical conditions. However, distal bowel obstruction from ganglion cell disorder seldom causes any features that could be identified by fetal sonogram. In addition, patients with HD may only have subtle symptoms and develop enterocolitis as initial presentation.

"Delayed passage of meconium" has been emphasized as an early sign indicating presence of HD in newborn infants. However, although nearly all neonates pass meconium within 48 hours of life, only 60—90% of neonates with HD fail to pass meconium in that time period.[2,21] Furthermore, neonates with HD may also pass meconium within 48 hours after birth. We noted that only 30% of patients with HD had history of delayed meconium passage in our study. As for the presentation of constipation, another symptom that should arouse clinicians to the diagnosis of HD, is just as difficult to perceive or define during the neonatal period.

The current gold standard in the diagnostic confirmation of HD is histopathologic findings based on rectal suction biopsy,[22] although contrast enema study (LGI series) is usually performed to decide whether a suction biopsy is indicated. The sensitivity and specificity of rectal suction biopsy are reported to be 97—100% and 99—100%, and of contrast enema study 65—80% and 66—100%, respectively.[2] There are pitfalls in both studies leading to false-negative results. Inadequate biopsy sites or tissue amounts impair the reliability of rectal suction biopsy, whereas the contrast enema study might be misleading if patients with HD also had meconium plug in colon. Scott et al. reported 10—38% incidence in the association of meconium plug syndrome with HD. In this study, 12 out of 44 patients (29%) with HD were found to have meconium plug in their colon, and six of these 12 infants failed to be recognized as having HD radiographically. It needs to be reemphasized that one should be careful in interpretation of LGI study results, since the the presence of meconium plug may mask the radiologic features of HD, and HD may be the cause of meconium plug.[23]

In conclusion, our study showed delayed diagnosis of HD in newborn infants not only increases serious morbidities in the neonatal period, but also indirectly affects their long-term outcome. Clinicians need to be vigilant in the recognition of HD in newborn infants and provide appropriate care accordingly, to prevent the detrimental complications.

References

1. Puri P, Montedonico S. Hirschsprung's disease: clinical features. In: Holschneider AM, Puri P, editors. *Hirschsprung's disease and allied disorders*. 3rd ed. New York: Springer, 2008: 107—13.
2. Haricharan RN, Georgeson KE. Hirschsprung disease. *Semin Pediatr Surg* 2008;**17**:266—75.
3. Rudolph C, Benaroch L. Hirschsprung disease. *Pediatr Rev* 1995;**16**:5—11.
4. Bill AH, Chapman ND. The enterocolitis of Hirschsprung's disease: its natural history and treatment. *Am J Surg* 1962;**103**: 70—4.
5. Carneiro PMR, Brereton RJ, Drake DP, Kiely EM, Spitz L, Turnock R. Enterocolitis in Hirschsprung's disease. *Pediatr Surg Int* 1992;**7**:356—60.
6. Murthi GVS, Raine PAM. Preoperative enterocolitis is associated with poorer long-term bowel function after Soave-Boley endorectal pull-through for Hirschsprung's disease. *J Pediatr Surg* 2003;**38**:69—72.
7. Menezes M, Puri P. Long-term outcome of patients with enterocolitis complicating Hirschsprung's disease. *Pediatr Surg Int* 2006;**22**:316—8.
8. Elhalaby EA, Coran AG, Blane CE, Hirschl RB, Teitelbaum DH. Enterocolitis associated with Hirschsprung's disease: a clinical-radiological characterization based on 168 patients. *J Pediatr Surg* 1995;**30**:76—83.
9. Teitelbaum DH, Qualman SJ, Caniano DA. Hirschsprung's disease: identification of risk factors for enterocolitis. *Ann Surg* 1988;**207**:240—4.
10. Vieten D, Spicer R. Enterocolitis complicating Hirschsprung's disease. *Semin Pediatr Surg* 2004;**13**:263—72.
11. Haricharan RN, Seo J-M, Kelly DR, et al. Older age at diagnosis of Hirschsprung disease decreases risk of postoperative enterocolitis, but resection of additional ganglionated bowel does not. *J Pediatr Surg* 2008;**43**:1115—23.
12. Caniano DA, Teitelbaum DH, Qualman SJ. Management of Hirschsprung's disease in children with trisomy 21. *Am J Surg* 1990;**159**:402—4.
13. Quinn FMJ, Surana R, Puri P. The influence of trisomy 21 on outcome in children with Hirschsprung's disease. *J Pediatr Surg* 1994;**29**:781—3.
14. Surana R, Quinn FMJ, Puri P. evaluation of risk factors in the development of enterocolitis complicating Hirschsprung's disease. *Pediatr Surg Int* 1994;**9**:234—6.
15. Moore SW, Albertyn R, Cywes S. Clinical outcome and long-term quality of life after surgical correction of Hirschsprung's disease. *J Pediatr Surg* 1996;**31**:1496—502.
16. Pini Prato A, Gentilino V, Giunta C, et al. Hirschsprung disease: do risk factors of poor surgical outcome exist? *J Pediatr Surg* 2008;**43**:612—9.
17. Pini Prato A, Gentilino V, Giunta C, et al. Hirschsprung's disease: 13 years' experience in 112 patients from a single institution. *Pediatr Surg Int* 2008;**24**:175—82.
18. Moore SW, Sidler D, Zaahl MG. The ITGB2 immunomodulatory gene (CD18), enterocolitis, and Hirschsprung's disease. *J Pediatr Surg* 2008;**43**:1439—44.
19. Murphy F, Puri P. New insights into the pathogenesis of Hirschsprung's associated enterocolitis. *Pediatr Surg Int* 2005; **21**:773—9.
20. Nunez R, Torres A, Agulla E, Moreno C, Marin D, Santamaria JI. [Rectal irrigation and bowel decontamination for the prevention of postoperative enterocolitis in Hirschsprung's disease]. *Cir Pediatr* 2007;**20**:96—100 [in spanish].
21. Singh SJ, Croaker GD, Manglick P, et al. Hirschsprung's disease: the Australian Paediatric Surveillance Unit's experience. *Pediatr Surg Int* 2003;**19**:247—50.
22. Martucciello G, Pini Prato A, Puri P, et al. Controversies concerning diagnostic guidelines for anomalies of the enteric nervous system: a report from the fourth International Symposium on Hirschsprung's disease and related neurocristopathies. *J Pediatr Surg* 2005;**40**:1527—31.
23. Keckler SJ, St Peter SD, Spilde TL, et al. Current significance of meconium plug syndrome. *J Pediatr Surg* 2008;**43**:896—8.