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Histopathological changes and Hirschsprung's associated enterocolitis (HAEC) scores

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ABSTRACT

Histopathological changes that are usually permanent in the bowel of Hirschsprung's disease (HRSC) in children make susceptibility to the incidence of enterocolitis even after definitive therapy. The pathophysiology of HRSC is characterized by specific signs, and symptoms. Scoring system has been applied in diagnosis of Hirschsprung's associated enterocolitis (HAEC) due to its simplest and easiest. However, after a decade it has been several evaluated to obtain optimal benefits in the clinical setting. The aim of this study was to investigate the relationship between histopathological grade of enterocolitis and HAEC scores. Children with HRSC who underwent leveling colostomy or pull-through were sampled from the ganglionic segment. Those with a histopathological description of HAEC were included in the study. HAEC scores were evaluated retrospectively through medical records and interviews. Data were analyzed using the Spearman's Rank test. Twenty eight samples were involved in this study. The population was dominated by male (82.1%) and almost half the population (42.9%) were infants. The distribution of the histopathological grade was fairly even, except for grade V where it was only 7.2% of the total sample. Grade I & III samples were 21.4%, while grade II & IV were 25%, respectively. A significant relationship between histopathological grade and HAEC score was obtained ($r = 0.927$; $p<0.0001$). In conclusion, there is a relationship between the histopathological grade of enterocolitis and HAEC scores.

ABSTRAK

Perubahan histopatologi yang umumnya bersifat menentap pada anak dengan penyakit Hirschsprung (HRSC) membuat kereentanan akan terjadinya enterocolitis bahkan setelah terapi definitif. Patofisiologi HRSC ditandai dengan tanda dan gejala yang khas. Sistem skor telah digunakan dalam diagnosis enterocolitis akibat Hirschsprung (HAEC) karena paling sederhana dan aplikatif. Namun demikian, setelah satu dekade sistem skoring telah beberapa kali dievaluasi untuk memperoleh kemanfaatan klinik yang optimal. Tujuan penelitian ini adalah untuk mengkaji hubungan antara derajat histopatologi dan skor HAEC. Anak dengan HRSC yang menjalani kolostomi atau *pull-through* dilakukan pengambilan sampel dari segmen ganglion. Sampel yang menunjukkan deskripsi histopatologi HAEC diinklusikan ke dalam studi. Skor HAEC dievaluasi secara retropektif dari data rekam medis dan anamnesis. Data dianalisis dengan uji *Spearman's Rank*. Dua puluh delapan sampel di ikutkan dalam penelitian ini. Sebagian besar subjek adalah laki-laki (82.1%), Hampir setengahnya merupakan kelompok usia bayi (42.9%). Distribusi derajat histopatologi merata, kecuali derajat V hanya 7,2% dari total sampel. Jumlah sampel derajat I dan III sebanyak 21,4%, sedangkan derajat II dan IV masing-masing sebesar 25%. Terdapat hubungan yang signifikan antara derajat histopatologi dan skor HAEC ($r=0,917$; $p<0,0001$). Dapat disimpulkan bahwa, terdapat hubungan antara derajad enterokolitis dan skor HAEC.

Keywords:
Hirschsprung's associated enterocolitis (HAEC);
Histopathology;
HAEC Score;

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INTRODUCTION

The acronym Hirschsprung's disease (HRSC) has been used for aganglionic congenital megacolon since Dr. Harald Hirschsprung, a Danish pediatrician who presented two cases of infants with fatal constipation at the Berlin conference of the German Society of Pediatrics in 1886.[1] Even though more than a century has passed, the fatal complication of HRSC, Hirschsprung's-associated enterocolitis (HAEC), remains the most significant and potentially life-threatening problem.[2,3] It is a scourge for pediatric surgeons and pediatricians. As a major cause of morbidity and mortality, especially with the difficulty in diagnosing, a high level of suspicion must be instilled when dealing with HRSC. Mild clinical presentations such as slight abdominal distension, watery stool with perianal excoriation, and also fever, to more severe symptoms that include explosive and foul-smelling diarrhea or loose stools accompanied by blood, vomiting, lethargy, and shock due to the presence of life-threatening toxic megacolon, can occur in HAEC.[4]

Children with HRSC can get HAEC both before and after diversion or definitive resection of the aganglionic bowel. The incidence varies widely, from 6-26% preoperatively and 5-42% postoperatively. This may be due to differences in diagnostic standards for HAEC in the presence of overlapping symptoms with other pathological conditions.[5,6]

Although some pathophysiology hypotheses has been postulated, the biological mechanisms for HAEC is still unclear. As a result of abnormal intestinal motility that allows bacterial stasis and microflora dis-equilibrium, coupled with an innate immune response and several other mechanisms from the level of gene expression to the biochemical imbalance of the digestive tract, will cause intestinal barrier complex disorders that will appear as histopathological changes in bowel wall structure.[4,5,7-11] Other theories that have been proven are the retention of mucin in the colonic mucosa, as well as the shift from acidity of the mucin to neutral.[12] It was proposed that HAEC patients will sustain significant changes in theirbowel tissue characterized by mucin retention and dilatation of crypts which becomes the basis of HAEC histopathological classification.[4,5,13]

HAEC is diagnosed clinically. To promote early diagnosis and treatment, Pastor *et al.*[14] has formulated a standardized scoring system to help measure outcomes in research and clinical diagnostics in children with HRSC who were suspected of having enterocolitis. Due to many underdiagnoses of clinical use, a patient-based validation and evaluation of the HAEC scoring system has been performed, which reveals a cut-off score that is very different from previous studies. It was suggested that HAEC scores with cut-off 4 would increase sensitivity and specificity to detect HAEC episodes.[6,15]

Although several indicators have been investigated,[8-10] only the HAEC score is the easiest and most applicable in daily use for enterocolitis in HRSC. The absence of gold standard diagnostic tool for HAEC causes many delays in diagnosis that are parallel with the over and under treatment of this condition. We hypothesized that there was a relationship between the severity of histopathological grade and HAEC scores. To evaluate these issues, we conducted a study to identify the correlation between histopathological grade of enterocolitis with HAEC scoring system.

MATERIALS AND METHODS

Subjects

It was a cross sectional study with consecutive sampling involving pediatric HRSC patients in Universitas

Hasanuddin Academic Hospital and Dr. Wahidn Sudirohusodo General Hospital, Makasar who have a pathognomonic histopathology of HAEC and met the inclusion and exclusion criteria. The inclusion criteria consisted of all pediatric HRSC patients at an age of 18 years or younger who had not completed definitive pull-through surgery. The exclusion criteria are incomplete or missing of medical records. The diagnosis of HRSC was confirmed by rectal biopsy results, prior to leveling colostomy or pull-through. Colon samples were collected intraoperatively and were assessed histopathologicaly based on the HAEC classification of Teitelbeum (Hematoxylin Eosin staining under light microscope).

Procedure

At the time of operative procedure, parents were approached to obtain for their children involved in this study. Detailed clinical information including 16 items of HAEC scores were collected from retrospective review of medical record. The HAEC score component would be declared present if the description of symptoms, signs, laboratory and radiological examinations were registered during the children's hospitalization and follow-up period. Whereas the absence of HAEC was defined as a negative finding of these components in the medical record after being confirmed to the children's parents or guardians using standardized questionnaires. In cases with recurrent enterocolitis, we recorded the HAEC scores from the last episode of recurrence. For the purpose of this study, HAEC was established based on a histopathological diagnosis and then matched with past clinical history. The study was approved by the Health ResearchEthics Committee of Universitas Hasanuddin Academic Hospital/Dr. Wahidin Sudirohusodo General Hospital, Faculty of Medicine, Universitas Hasanuddin, Makasar (No 224/UN4.6.4.5.31/PP36/2020)

Statistical analysis

The data collected from the study were compare using Spearman rank test. Statistical analysis was performed using SPSS version 23.0 for Windowsandvalue of $p<0.05$ was considered statistically significant.

RESULTS

Thirty patients who underwent leveling colostomy or pull-through in the hospital were taken as samples from their distal ganglionic zone for histopathological examination. Hirschsprung-associated enterocolitis was histologically described in 28 operative specimens reviewed, the remaining two samples with non-HAEC histopathology were excluded from the study. The majority of patients in this study were male and the median age at the time of diversion or definitive procedure was 2 years old with a fairly wide age range, from 5 month infant to 14 years old adolescent. From the entire study population, 7 samples had a history of recurrent chronic constipation and ineffective washout, so diversion was performed, the remaining samples were obtained during definitive surgery. The HAEC score median was 7 (2-17) points. The period between the last episode of enterocolitis and the time of sampling, ranged from 1 to 13 months with a median of 5 months. TABLE 1 shows the demographic and characteristic details of the study population.

TABLE 1. Demographic & characteristic of study population

Variables	Number of chidren	Percentage (%)
Gender		
• Male	23	82.1
• Female	5	17.9
Age group (years old)		
• ≤ 1	12	42.9
• 2-3	9	32.1
• 3-5	3	10.7
• > 5	4	14.3
HAEC histopatologic grade		
• I	6	21.4
• II	7	25.0
• III	6	21.4
• IV	7	25.0
• V	2	7.2
HAEC score		
• < 4	3	10.7
• 4-9	14	50.0
• ≥ 10	11	39.3
Type of surgery		
• Leveling colostomy	7	25.0
• Pull-through	21	75.0
Last episode of enterocolitis		
• ≤ 6 months	18	64.3
• > 6 months	10	35.7

Six samples (21.4%) had grade I, 7 (25%) had grade II, 6 (21.4%) had grade III, 7 (25%) had grade IV and 2 children (7.2%) had grade V enterocolitis based on the classification of Teitelbaum. Histologically, the intestinal wall exhibits inflammation and neutrophil infiltration into the crypts (cryptitis), with associated crypt dilatation and retained mucus within the crypts. In milder stages, this description is similar to abnormalities in cystic fibrosis. In more advanced disease, there is progress ion microscopically to the presence of crypt abscesses, intraluminal fibrinopurulent debris, ulceration of mucosal epithelium, transmural necrosis, or intestinal and may appear similar to ulcerative colitis. Some histopathological images in this series are shown in FIGURE 1.

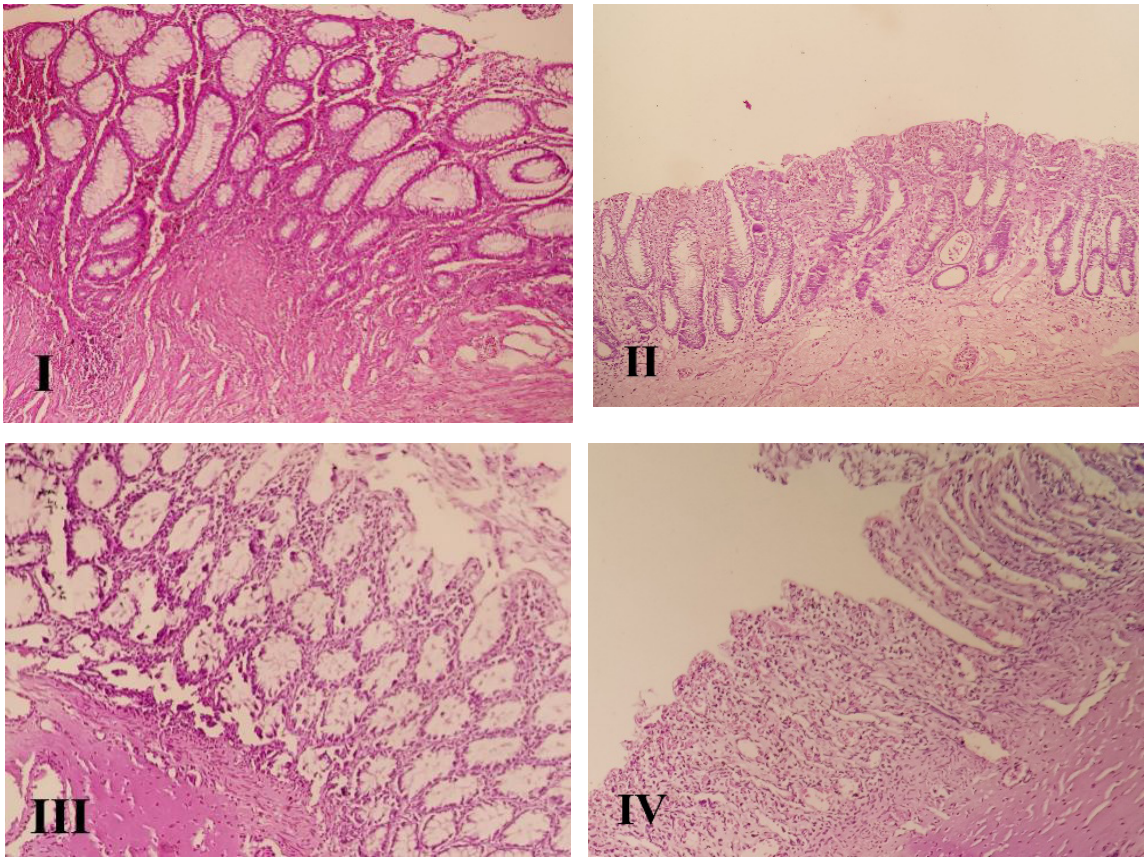

FIGURE 1. Histopathologic grades of HAEC based on Teitelbaum classification, grade I shows crypt dilation & mucin retention, grade II is characterized by cryptitis or two crypt abscesses, grade III describes the presence of multiple crypt abscesses, grade IV shows fibrinopurulent debris & mucosal ulceration, grade V (not shown) describes the transluminal necrosis or perforation

TABLE 2.Distribution of HAEC scores based on histopathological grade

HAEC score	Number of children (n) & percentage (%) based on grade											
	Grade I		Grade II		Grade III		Grade IV		Grade V		Total	
n		%	N	%	n	%	n	%	n	%	n	%
Diarrhea with explosive stool	2	33.3	6	85.7	6	100	7	100	2	100	23	82.1
Diarrhea with foul-smelling stool	0	0	0	0	3	50	6	85.7	2	100	11	39.3
Diarrhea with bloody stool	0	0	0	0	0	0	2	28.6	1	50	3	10.7
History of enterocolitis	0	0	0	0	1	16.7	4	57	2	100	7	25
Explosive discharge of gas and stool on DRE	2	33.3	0	0	4	66.7	6	85.7	2	100	14	50
Distended abdomen	5	83.3	7	100	6	100	7	100	2	100	27	96.4
Decreased peripheral perfusion	0	0	0	0	0	0	1	14.3	1	50	2	7.1
Lethargy	0	0	0	0	0	0	1	14.3	1	50	2	7.1
Fever	1	16.7	3	42.9	4	66.7	7	100	2	100	17	60.7
Multiple air fluid levels	0	0	0	0	4	66.7	7	100	2	100	13	46.4

Dilated loop of bowel	6	100	4	57.1	6	100	7	100	2	100	25	89.3
Sawtooth appearance with irregular mucosa lining	0	0	0	0	1	16.7	3	42.9	1	50	5	17.9
Cut-off sign in rectosigmoid with absence of distal air	0	0	0	0	0	0	4	57.1	2	100	6	21.4
Pneumatosis	0	0	0	0	0	0	0	0	1	50	1	3.6
Leukocytosis	1	16.7	4	57.1	5	83.3	6	85.7	2	100	18	64.3
Shift to the left	0	0	3	42.9	3	50	6	85.7	2	100	14	50

The correlation coefficient for establishing the strength of the relationship between histopathological grade and HAEC scores was calculated by the Spearman's Rank test. Analysis of the data in this study was statistically significant ($p<0.0001$) and had a very strong positive correlation ($r = 0.927$) (TABLE 3).

TABLE 3.Relationship of histopathological grade with HAEC score

Spearman's Rank test	n	r	p
Grade Histopatology & HAEC Score	28	0.927	<.0001

DISCUSSION

In accordance with previous studies on HRSC,[2,16,17] the gender comparison in our study was dominated by male with 82.1%. Most patients received definitive surgical management in the infant period (42.9%), the youngest child who underwent surgery was five months old infant. These findings are consistent with the conclusions of a study from Sosnowska *et al.*[18] which states that in children with HRSC, definitive surgery should be considered to be carried out after 4 months of age because it might have an influence on better long-term outcomes, although there was a contradiction from other study.[3] There also were many incomplete data on the age of the patients were first diagnosed with HRSC. This research implies that patients who come to the hospital might has been previously diagnosed in their respective regions because the hospitalwas a tertiary referral hospital in eastern Indonesia. But the presence of some children who underwent definitive surgery at an older age and even teenagers (12 y.o female and 14 y.o male), showed a delay in diagnosis or poor health education with ignorance, poverty and refusal to surgery. Limited access to competent pediatric surgeons and facilities for standard therapy are also unresolved issues in developing country.

According to Gosain *et al.*[19] the classic manifestations of HAEC include abdominal distention, fever, and diarrhea. These were also seen in our study where the most common findings from the components of the HAEC score were abdominal distention (96.4%) and bowel dilatation (89.3%), followed by explosive diarrhea (82.1%), leukocytosis (64.3%), and also fever (60.7%). As another comparison, the general percentage of the HAEC score components of our sample has shown similarities with previous study conducted by Yulianda *et al.*[16] Although there were large gaps in lethargy (7.1 vs 72.7%) and cutoff sign in rectosigmoid (21.4 vs 72.7%) between these two studies. This situation may be caused by differences in sampling methods

and diagnostic criteria. We traced HAEC children through histopathological results and many of our samples had HAEC scores less than 10, while they used a cut-off point of 10 as a determinant for HAEC. Based on a critical evaluation study of the score, submitted by Frykman *et al.*[15] and has also been clinically re-evaluated by subsequent study,[6] a cut-off score of 10 seems to be too restrictive and would exclude more than half of patients suspected of being HAEC. In other words, mild HAEC episodes will be missed.

Since the HAEC histopathological classification system was introduced, many studies have shown its correlation in predicting future incidents of HAEC recurrence. As previously stated by Elhalaby *et al.*[13] that the risk of future clinical HAEC was statistically greater in those patients who had a previous histopatological grade ≥ III. It was an interesting finding where all children with a history of recurrent enterocolitis (7 children, 25%) had histopathological grade ≥ III. This was an endorsement of a predictive conclusion from this study by providing evidence from our retrospective study. These demographic data also similar to study conducted by Haricharan *et al.*[20] but they found that recurrent HAEC was present in populations with enterocolitis grade of II or higher, although statistically it was not significant.

Decreased peripheral perfusion and lethargy were found only in children with grade IV and V, while pneumatosis was seen only at grade V (TABLE 2). These data may show a relationship of high histopathological degrees of HAEC with a decrease in peripheral perfusion, lethargy, and pneumatosis on X-rays abdomen as part of severe HAEC criteria according to clinical guidelines that have been used before.[19]

The entire samples were taken from the ganglionic segment and varied in the time span of their last episode of enterocolitis (1-13 months). This evidence corroborates previous studies which found that histopathological changes in HAEC occurred not only in the aganglionic and transitional segments, but can also affect the ganglion segments of bowel in HRSC. This abnormality can last for a long time or it may also be permanent[4,12,13,17] and make susceptibility to the incidence of postoperative enterocolitis. So ongoing management for prevention and long-term observation must still be carried out against the risk of enterocolitis.

This study highlights the very strong positive correlation between severity of histopathological grade and HAEC score that statisticallysignificant ($p<.0001$), the higher the histopathological grade severity, the higher the HAEC score.

To the best of our knowledge, this is the first study that correlates the histopathology of HAEC and its scoring system. The limitation of this study lies in its retrospective design with its dependence on history and physical examination in hospital medical records, although crosschecks have been carried out from the parents or guardians of these children. The histopathological grading system used in this study was designed to include all HAEC children including those with mild symptoms. Finally, it suggests that sampling from the ganglionic segment every time a definitive operation is performed is logical and valuable for further research it might have a predictive function in postoperative enterocolitis that is strengthened by calculating the preoperative HAEC score if a previous episode of enterocolitis is detected.

CONCLUSION

In conclusion, a correlation between histopathological grade and HAEC score is reported. If histopatological grade increases, so does HAEC score.

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