นิพนธ์ต้นฉบับ

Ganglion cell in vermiform appendix

ธวัชชัย พูนแก้ว[1]
ปิยวรรณ เชียงไกรเวช[2]
สมรมาศ กันเงิน[3]
วรพงศ์ เชาวน์ชูเวชช[4]
ศักดา ภัทรภิญโญกุล[5]
สุรศักดิ์ สังขทัต ณ อยุธยา[6]

Ganglion cell in vermiform appendix

Phoonkaew T, Chiengkriwate P, Kun-Ngern S, Chowchuvech V, Patrapinyokul S, Sangkhathat S.
Department of Surgery, Department of Pathology,
Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, 90110, Thailand
E-mail: chiengkriwate_piyawan@hotmail.com
Songkla Med J 2007;25(5):425-429

[1]MD. (General Surgery) [2]MD. (Pediatric Surgery) [4]MD. (General Surgery, Plastic and Reconstructive Surgery)
[5]MD. (General Surgery, Pediatric Surgery), Assist. Prof., [6]MD., Ph.D. (Pediatric Surgery), Assist. Prof., Department of Surgery,
[3]MD. (Pathology) Department of Pathology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, 90110, Thailand
รับต้นฉบับวันที่ 4 กรกฎาคม 2550 รับลงตีพิมพ์วันที่ 11 กันยายน 2550

Abstract:

Background/purpose: *Presence of ganglion cells in the appendix excludes total colonic aganglionosis. However, it remains unclear whether or not absence of ganglion cells in this organ should be a criterion to rule in the disease. The aim of this study was to examine for presence and number of myenteric ganglion cells in vermiform appendix taken from various surgical conditions and controls.*

Methods: *One hundred and thirty two appendectomy specimens were available for the study; group I, total colonic aganglionosis (TCA); group II, other type of Hirschsprung's disease (HSD); group III (control), incidental appendectomy in cases without aganglionosis; group IV, acute appendicitis. Amount of ganglion cells was evaluated semiquantitatively in blinded fashion.*

Result: *The number of ganglion cells in any given high power field (HPF) was very variable in all groups; group I no ganglion cells found, group II 1.03 (0-2.9), group III 0.67 (0-2.4), group IV 0.46 (0-1.8) cells/HPF. There was significant difference between the HSD group and groups with TCA or appendicitis. Absence of ganglion cells in the appendix could be detected in 100%, 16.7%, 13.1% and 27.3% in groups I, II, III and IV, respectively.*

Conclusions: *Aganglionosis of the vermiform appendix could not provide a diagnostic clue to total colonic aganglionosis because the condition could be found in other conditions.*

Key words: *Hirschsprung's disease, total colonic aganglionosis, appendicitis, appendix vermiformis*

บทคัดย่อ:

บทนำ: *การมีเซลล์ประสาทในไส้ติ่งสามารถวินิจฉัยแยกโรค total colonic aganglionosis (TCA) ออกไปได้ แต่อย่างไรก็ตาม การไม่มีเซลล์ประสาทในไส้ติ่งยังคลุมเครือในการวินิจฉัยโรคนี้ การศึกษานี้มีวัตถุประสงค์เพื่อเปรียบเทียบจำนวนเซลล์ประสาทในไส้ติ่งที่ได้รับการผ่าตัดในโรคต่าง ๆ และไส้ติ่งปกติ*

วิธีการ: *ศึกษาโดยการสุ่มนับจำนวนเซลล์ประสาทในไส้ติ่งจากแผ่นชิ้นเนื้อ แล้วมาแบ่งกลุ่มตามการวินิจฉัยเดิม มี 132 ตัวอย่าง แบ่งเป็น 4 กลุ่มคือ กลุ่มที่ 1-TCA 5 ตัวอย่าง, กลุ่มที่ 2-Hirschsprung disease 12 ตัวอย่าง, กลุ่มที่ 3-ไส้ติ่งปกติหรือกลุ่มควบคุม 38 ตัวอย่าง, และกลุ่มที่ 4-ไส้ติ่งอักเสบเฉียบพลัน 77 ตัวอย่าง*

ผลการศึกษา: *จำนวนเซลล์ประสาทในไส้ติ่งโดยเฉลี่ยจาก 10 high power field (HPF) มีดังต่อไปนี้ 0, 1.03 (0-2.9), 0.67 (0-2.4), และ 0.46 (0-1.8)/HPF ตามลำดับ กลุ่มที่ 1-4 พบว่าไม่มีความแตกต่างทางสถิติในจำนวนเซลล์ประสาทในไส้ติ่งจากกลุ่มที่ 2-Hirschsprung disease เทียบกับกลุ่มที่ 1-TCA หรือกลุ่มที่ 4-ไส้ติ่งอักเสบเฉียบพลัน ภาวะไม่มีเซลล์ประสาทในไส้ติ่งคิดเป็นร้อยละ 100, 16.7, 13.1, และ 27.3 ในกลุ่มที่ 1-4 ตามลำดับ*

สรุป: *โดยสรุป การไม่มีเซลล์ประสาทในไส้ติ่งเพียงอย่างเดียวไม่สามารถนำมาใช้ในการวินิจฉัยโรค total colonic aganglionosis แต่หากพบว่ามีเซลล์ประสาทในไส้ติ่งบอกได้ว่าไม่ได้เป็นโรค total colonic aganglionosis*

คำสำคัญ: *เซลล์ปมประสาท, โรคลำไส้ใหญ่โป่งพองแต่กำเนิด, ไส้ติ่งอักเสบ, ไส้ติ่ง*

Introduction

When total colonic aganglionosis (TCA) is suspected in a patient with intestinal obstruction, the vermiform appendix is frequently removed as a sampling organ for an examination of myenteric ganglion cells. It has become widely accepted that the presence of ganglion cells in the vermiform appendix excludes TCA.[1-2] On the other hand, whether an absence of ganglion cell in the appendix is a diagnostic clue for such extensive aganglionosis of the gastrointestinal tract remains unclear. It is a common agreement among pathologists that

vermiform appendix is not a reliable representative tissue source to indicate the ganglionic status of the same level of colon. Aganglionosis of vermiform appendix in patients whose cecum is normally innervated has been reported.[2-3] However, whether the cases were exceptional or not was not clear. Moreover, when a ganglion cell was not present in the vermiform appendix, how much chance that the case will be TCA has not been defined.

In addition, variation of the number of ganglion cells in the vermiform appendix with the disease process of the colon or the appendix itself remains unelucidated. The objective of this study was to examine and draw the predictive value of ganglion cell status in the diagnosis of TCA and to compare the number of ganglion cells found in the wall of appendix in different disease status; i.e. TCA, rectosigmoid-type Hirschsprung's disease, acute appendicitis and histologically normal appendix.

Materials and methods

Specimens from 132 appendectomies were retrieved for retrospective histological review. The specimens were categorized into 4 groups: Group I consisted of 5 appendices from patients with TCA; Group II had 12 appendices from patients with Hirschsprung's disease whose extent of aganglionosis involved colonic segment distal to the ascending colon; Group III comprised 38 specimen of histologically normal vermiform appendix from incidental appendectomy; and Group IV which had 77 appendices from patients diagnosed with acute appendicitis.

Each specimen was fixed in formalin and embedded in paraffin. Histological slide was prepared for routine light-microscopy examination by haematoxylin and eosin staining. During the examination for ganglion cell number, the pathologist was blind to clinical diagnosis. Each slide was examined randomly for ganglion cells in the neural plexus between the circular and longitudinal muscle, so called Myenteric plexus (Figure 1). A total of 10 high power field (HPF) were randomly selected for a manual count for ganglion cells. Care was taken not to reexamine the same field twice. Number of ganglion cells in each specimen was recorded in terms of cell (s) per HPF and total of cells counted in 10 HPF. Average number of ganglion cells per one HPF and total count was calculated for each group.

Data were analyzed using STATA for Windows (version 8.1). Parametric data are presented as median and range, unless otherwise stated. Comparison of variables used anova-Bonferroni tests; statistical significance was achieved with a p-value less than 0.05.

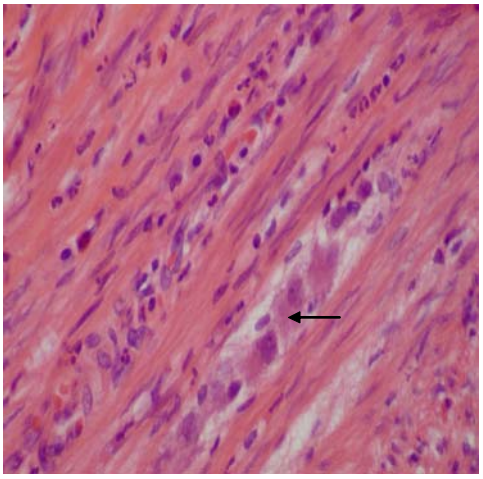

Figure 1 Ganglion cell in a normal appendix (arrow) from high power field (x40)

Results

Except for the Group I (TCA), highly variable numbers of ganglion cell were found in the vermiform appendix from various indications of appendectomy. No ganglion cells were identified in the vermiform appendix from patients with TCA. Group II (rectosigmoid Hirschsprung's disease) had an average of 1.03 cells/HPF (0-2.9 cells/HPF), with a total number in total 12 patients of 124 cells. Group III (incidental appendectomy) ranged from 0 to 2.4 cells/HPF for an average of 0.67 cells/HPF and a average total count of 255 cells (38 patients). In group IV (acute appendicitis), a total number of 358 cells was counted in specimens from 77 patients, giving an average 0.46 cells/HPF (0-1.8 cells/HPF) (Table 1).

Table 1 Number of ganglion cells in high power fields

Group	No.	Average No. per high power field	Std. Dev.	Range
I TCA	5	0	0	0
II HSD	12	1.03	0.88	0-2.9
III Control	38	0.67	0.58	0-2.4
IV Appendicitis	77	0.46	0.46	0-1.8

No significant difference was found when the average numbers of ganglion cells in each disease group was compared to that number in the vermiform appendix from an incidental appendectomy, which could serve as a normal control. Interestingly, the number of ganglion cells in Group II (rectosigmoid Hirschsprung′s disease) was higher than the group of acute appendicitis ($p<0.01$).

′Absence of ganglion cells in the vermiform appendix′ could be detected in 100%, 16.7%, 13.1% and 27.3% in groups I, II, III and IV, respectively. Using the ′absence of ganglion cells′ as a criterion, positive predictive value to diagnose TCA (chance to be TCA when no ganglion cells is detected in the vermiform appendix) was 15% and negative predictive value (chance not to be TCA when at least one ganglion cells was detected) was 100%.

Discussion

To make a diagnosis of total colonic aganglionosis is one of challenging problems for surgeons. There are no pathognomonic radiological findings for the diagnosis of TCA[4-6] and, as a result, the ′Gold standard′ diagnostic method is to demonstrate aganglionic status of the entire length of colon, which usually means serial seromuscular biopsy along the length of intestine.

The vermiform appendix is an outpouching part of the cecum. Based on the theory of cranial to caudal migration of neural crest cells and the fact that the appendix is situated at the most proximal part of the colon, absence of ganglion cells in the appendix is believed to represent aganglionosis of the entire colon and distal ileum.[3] Unexplained perforation of the small bowel is one of common circumstances in which functional colonic obstruction from extensive aganglionosis needs to be excluded.[7-9] Because the vermiform appendix can be removed with ease and safety, the organ is frequently removed for histological diagnosis during laparotomy of patients in whom TCA is suspected.[1-3, 7-9] Presence of ganglion cells on the vermiform appendix is generally accepted as a reliable evidence to exclude TCA. On the other hand, whether the absence of enteric ganglions could be use as a clinical clue to diagnose extensive aganglionosis of the colon or not remains unclear.

Fekete et al. reported that appendices invariably showed aganglionosis in all 17 cases of TCA and were ganglionic in other types of Hirschsprung′s disease.[10] Anderson and Chandra described a case of long segment Hirschsprung′s disease with ganglion cell present in the hepatic flexor but absent in the vermiform appendix.[3] In the same study, the author studied ganglion cells number in the vermiform appendices and found ranges of ganglion cell number at 0.5-5.1 cells/HPF in rectosigmoid Hirschsprung′s disease, 0-4.1 cells/HPF in the long segment form and 1.4-5.9 cells/HPF. The authors speculated that the index case, showing aganglionosis vermiform appendix in short Hirschsprung′s disease might be an exceptional case.

Our study found that approximately 15% of appendix from incidental appendectomy exhibited aganglionosis of the appendix. The figure was even higher in cases with appendicitis which might be explained by the morphology of the ganglion cells being distorted by the inflammatory process. Taken together with previous studies, the evidence suggests that while the presence of ganglion cells in the vermiform appendix excludes TCA, aganglionosis could not be used as a diagnostic criterion. Shih et al. reported a case of 6-day-old male neonate with distal ileum perforation, aganglionosis of appendix but ganglion cells presented in a small segment of ileum, ascending colon, transverse and sigmoid colon.[2] The so-called ″skip area of ganglionosis″ was theoretically explained by an interruption of neuroblast migration. The phenomenon could also have resulted from a separate origin of neuroblasts from the caudal portion of neural crest. More-

over, dysganglionosis; i.e. immature ganglia or hypoganglionosis may cause small size and sparse neurons which were not included in serial sections of the vermiform appendix.[2, 11]

It was interesting that the average number of ganglion cells in the group of Hirschsprung's disease was higher than that in the a cute appendicitis group. The evidence suggests that the inflammatory process may exert negative effects on the mature enteric ganglion cells. To explain this observation, further study is necessary.

Conclusion

In summary, the number of myenteric ganglion cells in vermiform appendices is studied semiquantitatively. The study found no difference among various diseases. Aganglionosis of appendix could be found in normal appendix in a comparable number with Hirschsprung's disease. Aganglionic vermiform appendix should not be used as a diagnostic clue of TCA or rectosigmoid Hirschsprung's disease.

Reference:

1. Holschneider A, Ure MB. Hirschsprung disease. In: Ashcraft WK, editor. Pediatric surgery. 4rd ed. WB. Saunders; 2005;477-95.
2. Shih TY, Chuang JH, Huang CC. Aganglionosis of the appendix: is it reliable for diagnosis of total colonic aganglionosis? J Pediatr Gastroenterol Nutr 1998;27:353-4.
3. Anderson KD, Chandra R. Segmental aganglionosis of the appendix. J Pediatr Surg 1986;21:852-4.
4. De Campo JF, Mayne V, Boldt DW, De Campo M. Radiological finding in total aganglionosis coli. Pediatr Radiol 1984;14:205-9.
5. Gupta AK, Guglani B. Imaging of congenital anormalies of the gastrointestinal tract. Indian J Pediatr 2005;72: 403-14.
6. Okamoto E, Ueda T. Embryogenesis of intramural ganglia of the gut its relation to Hirschsprung's disease. J Pediatr Surg 1967;2:437.
7. Newman B, Nussbaum A, Kirkpatrick JA Jr, Colodny A. Appendiceal perforation, pneumoperitoneum, and Hirschsprung's disease. J Pediatr Surg 1988;23:854-6.
8. Arliss J, Holgersen LO. Neonatal appendiceal perforation and Hirschsprung's disease. J Pediatr Surg 1990; 25:694-5.
9. Lally KP, Chwals WJ, Weitzman JJ, Black T, Singh S. Hirschsprung's disease: a possible cause of anastomotic failure following repair of intestinal atresia. J Pediatr Surg 1992;27:469-70.
10. Fekete CN, Martelli H, Jacob SL, Pellerin D. Total colonic aganglionosis (with or without ileal involvement): a review of 27 cases. J Pediatr Surg 1986;21:251-4.
11. de Chadarevian JP, Slim M, Akel S. Double zonal aganglionosis in long segment Hirschsprung's disease with a "skip area" in transverse colon. J Pediatr Surg 1982;17: 195-7.