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Evaluation of PRMT1 gene expression in Hirschsprung's disease and its association with Hirschsprung- associated enterocolitis

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Abstract

Purpose: PRMT1 is a protein-coding gene involved in neuronal development, differentiation, and inflammatory regulation. This study evaluated PRMT1 expression in Hirschsprung's disease (HD) and whether it is associated with Hirschsprung-associated enterocolitis (HAEC).

Methods: Thirty-four patients with HD were included (14 with a history of HAEC). PRMT1 expression was assessed by immunohistochemistry in archived tissue specimens. Colostomy specimens from 14 patients with anorectal malformations served as controls.

Results: PRMT1 expression was significantly reduced in aganglionic versus ganglionic bowel at the submucosal endothelium (47.1% vs. 73.5%, $p<0.05$), submucosal plexus (14.7% vs. 91.2%, $p<0.001$), and intermuscular plexus (14.7% vs. 97.1%, $p<0.001$). Ganglionic colon PRMT1 expression was similar in patients with and without HAEC. Submucosal endothelial PRMT1 expression yielded a p value of 0.055 when patients with recurrent enterocolitis were compared with those who had fewer episodes. Patients with HAEC had longer aganglionic segments (13.25 vs. 7 cm, $p=0.018$) and higher aganglionic segment-to-resected bowel length ratios (0.82 vs. 0.57, $p=0.009$).

Conclusion: PRMT1 expression differs between ganglionic and aganglionic bowel in HD at the submucosal and intermuscular plexus levels. The differences in PRMT1 expression characterize aganglionic tissue rather than predict enterocolitis. The extent of aganglionosis correlated more closely with HAEC.

Introduction

Hirschsprung disease (HD) is a congenital disorder of enteric nervous system characterized by the absence of ganglion cells in the submucosal plexuses, impaired peristalsis and functional intestinal obstruction[1, 2]. Despite advances in diagnosis and surgical management, Hirschsprung-associated enterocolitis (HAEC) remains the most serious complication of HD and may occur both before and after definitive surgery. Reported incidence rates vary widely, reflecting differences in definitions, patient populations, and follow-up periods[3–6].

The pathogenesis of HAEC is considered multifactorial and is not yet fully understood. Proposed mechanisms include fecal stasis, altered intestinal barrier function, microbial dysbiosis, and dysregulated mucosal immune responses[5, 7, 8]. However, the molecular factors that may contribute to susceptibility to HAEC remain poorly defined.

Protein arginine methyltransferase 1 (PRMT1) is the predominant arginine methyltransferase in mammalian cells and plays a central role in post-translational protein modification, transcriptional regulation, neuronal differentiation, and inflammatory signaling[9–12]. Because PRMT1 is involved in both neural development and immune regulation, it may be relevant to the pathobiology of HD and its inflammatory complications. Experimental and tissue-based studies suggest that PRMT1 expression is associated with enteric neuronal structures, but evidence in human HD tissue remains limited [9, 10, 13].

Given the biological relevance of PRMT1 to both neuronal integrity and inflammation, we hypothesized that PRMT1 expression may differ between ganglionic and aganglionic bowel in HD and may also be associated with HAEC. Therefore, this study aimed to evaluate PRMT1 immunohistochemical expression in bowel specimens from patients with HD and to investigate its relationship with HAEC.

Methods

Study Design and Ethical Approval

This was a single-center cohort study combining retrospective clinical data review with additional immunohistochemical analysis of archived tissue specimens. Medical records of patients treated at the Department of Pediatric Surgery, Istanbul Medeniyet University Faculty of Medicine, between January 1, 2010 and December 31, 2022 were reviewed. The study was approved by the Marmara University Faculty of Medicine Ethics Committee (Protocol No. 09.2024.460; April 22, 2024) and was supported by the Scientific Research Projects Coordination Unit of Istanbul Medeniyet University (Project No. T-TP-2024-0003).

Patient Selection and Study Groups

Patients with HD confirmed by rectal biopsy who underwent definitive surgery during the study period and had at least 1 year of follow-up were eligible for inclusion. The occurrence of HAEC before and/or after surgery was determined from the medical records.

Colonic tissue samples from non-syndromic patients with anorectal malformations (ARM) who underwent colostomy formation followed by its closure during the same period were included as the control group. Patient records were collected through the hospital records.

The study population was divided into three groups:
Group 1 (HAEC−): Patients with HD without enterocolitis during at least one year of follow-up before or after surgery (n=20).

Group 2 (HAEC+): Patients with HD who developed enterocolitis before and/or after definitive surgery during follow-up (n=14).
Group 3 (Control, ARM): Patients with ARM without HD who underwent colostomy and subsequent stoma closure (n=14).

Definition of HAEC

HAEC was defined on the basis of documented clinical and radiologic findings in the medical records, in accordance with the institutional clinical diagnostic approach. Recorded findings included abdominal distension, explosive and/or foul-smelling stools, diarrhea, fever, vomiting, and supportive abdominal radiographic findings such as bowel dilatation and/or air–fluid levels. The patients with enterocolitis episodes occurring before and/or after definitive surgery were included in HAEC+ group. The patients included in the HAEC- group did not have any enterocolitis episodes at any stage of the follow up period.

Clinical Data Collection

All relevant hospital database including medical records, operative reports, radiologic findings, and histopathologic findings were reviewed. The following variables were recorded: sex, age at presentation, presenting symptoms, associated anomalies and comorbidities, stoma status and type, definitive surgical procedure, follow-up duration, history and number of enterocolitis episodes. The resected bowel length and the aganglionic segment length were routinely included in all histopathology reports. The ratio of the aganglionic segment length to the total resected bowel length was subsequently calculated.

Tissue Selection and Histopathologic Assessment

Formalin-fixed, paraffin-embedded tissue blocks archived in the hospital's pathology department were used for immunohistochemical analysis. In the HD group, both ganglionic and aganglionic bowel segments obtained during definitive surgery were examined. In the control group, colonic tissue obtained during stoma closure was analyzed.

Immunohistochemistry

Immunohistochemical staining for PRMT1 was performed using a monoclonal antibody against PRMT1 (sc-166963, clone B-2; Santa Cruz Biotechnology, Dallas, TX, USA). at a dilution of 1:50 with an incubation time of 60 minutes. Antigen retrieval was carried out using Cell Conditioning 1 (CC1, EDTA; Roche) for 60 minutes according to the standard protocol. Detection was performed using the UltraView Universal DAB Detection Kit (Roche) on an automated staining platform (Ventana BenchMark ULTRA; Roche/Ventana, Tucson, AZ, USA). Histological images were captured using an Olympus DP72 digital microscope camera.

Immunohistochemical Evaluation

PRMT1 staining was first assessed as either present or absent in the mucosal epithelium, submucosal endothelium, submucosal plexus, intermuscular plexus, muscle layer, and ganglion cells/nerve fibers. In tissue compartments demonstrating positive immunoreactivity, staining intensity was subsequently graded as weak, moderate, or strong.

All histopathologic and immunohistochemical evaluations were performed by a single pathologist who was blinded to the clinical group assignments.

Statistical Analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± standard deviation or median, as appropriate, and categorical variables as number and percentage. A two-sided p-value <0.05 was considered statistically significant. Group comparisons were performed using the Mann–Whitney U and Kruskal–Wallis tests for continuous variables and the chi-square test or Fisher exact test for categorical variables, as appropriate. Paired comparisons between ganglionic and aganglionic segments were assessed using the McNemar test. Correlations were analyzed using Spearman correlation analysis. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminatory ability of selected variables for HAEC.

Results

Clinical Characteristics of Hirschsprung Disease Patients

A total of 48 patients were included in the study, comprising 34 patients with HD and 14 patients with ARM who served as controls (Table 1). Overall, 35 patients (72.9%) were male with no significant gender difference among HAEC+, HAEC-, and ARM groups (p=0.404).

Delayed passage of meconium beyond the first 24 hours was observed in 50% of patients in both HD subgroups. Constipation as the presenting symptom was more frequent in the HAEC− group (45.0% vs 7.1%, p=0.017).

In the HAEC+ group, 57.1% (n=8) of patients experienced their first enterocolitis episode before definitive surgery. Abdominal distension was present in all HAEC cases, vomiting in 92.9% (n=13), foul-smelling or explosive stools in 64.3% (n=9), diarrhea in 35.7% (n=5), and fever in 21.4% (n=3). Radiographs showed air–fluid levels in 92.9% (n=13) and bowel dilatation in 85.7% (n=12) of patients. The mean number of episodes was 5.21±2.72, and the mean duration of hospitalization during the first episode was 9.46 ± 6.2 days.

The median age at definitive surgery was 10.03 (IQR, 4.56–15.90) months in the HAEC+ group, 5.78 (IQR, 4.76–15.01) months in the HAEC− group, and 13.63 (IQR, 10.77–22.33) months in the ARM group, with no significant difference (p=0.155). Stoma formation was performed in 78.6% of HAEC+ patients and 50.0% of HAEC− patients (p=0.091). Among patients undergoing a stoma formation, ileostomy was more common in HAEC+ group compared to HAEC− group (p=0.091).

Among 34 patients with HD, long-segment aganglionosis (splenic flexure or beyond) was particularly common (52.9%, n=18), followed by rectosigmoid involvement (35.3%, n=12) and total colonic aganglionosis (11.8%, n=4). No significant difference was observed in the type of definitive pull-through procedure (p=0.447). In the HAEC+ group, 64.3% underwent the Duhamel procedure and 35.7% underwent transanal endorectal pull-through (TERPT), and in the HAEC− group, 45.0% underwent the Duhamel procedure and 55.0% underwent TERPT. The mean follow-up duration after definitive surgery was 4.03±2.07 years in the HAEC+ group and 5.33±2.91 years in the HAEC− group (p=0.142).

Extent of Aganglionosis and Association with HAEC

Total resected bowel length did not differ significantly between the HAEC+ and HAEC− groups (median 19 cm vs 16 cm, p=0.183) (Table 1). The aganglionic segment was significantly longer in patients with history of HAEC compared to those without (median 13.25 cm vs 7 cm, p=0.018). The ratio of aganglionic segment length to total resected bowel length was also significantly higher in the HAEC+ group (0.82 vs 0.57, p=0.009). ROC analysis showed that both aganglionic segment length (AUC=0.744, p=0.018) and the aganglionic segment/resected bowel length ratio (AUC=0.771, p=0.009) were associated with HAEC. In addition, age at presentation was negatively correlated with the number of enterocolitis episodes (ρ=−0.683, p=0.007) (Figure 1).

PRMT1 Expression in HD and ARM Tissues

In ganglionic HD segments, presence of PRMT1 expression was comparable to that observed in ARM control tissues in the mucosa, submucosal endothelium, submucosal plexus, intermuscular plexus, and nerve fibers (Table 2). The only significant difference was observed in the muscle layer, where PRMT1 positivity was more frequent in ganglionic HD segments than in ARM controls (76.5% vs 42.9%, p=0.042).

Aganglionic HD segments showed markedly reduced PRMT1 expression compared with ARM control tissues at both the submucosal and intermuscular plexus levels (both p<0.001). PRMT1 positivity was detected in only 14.7% of aganglionic segments, compared with 100% of ARM controls at both sites. No significant differences were found in the mucosa, submucosal endothelium, nerve fibers or muscle layer.

Comparison of Ganglionic and Aganglionic Bowel in HD

Compared with ganglionic segments, aganglionic segments showed lower PRMT1 positivity in the submucosal endothelium (47.1% vs 73.5%, p=0.047), submucosal plexus (14.7% vs 91.2%, p<0.001), intermuscular plexus (14.7% vs 97.1%, p<0.001), and muscle layer (45.5% vs 76.5%, p=0.025). No significant difference was detected in the mucosal epithelium or nerve fibers. Representative histopathologic and immunohistochemical findings are shown in Figure 2.

Association Between PRMT1 Expression and HAEC

When ganglionic bowel segments were compared according to HAEC status, PRMT1 expression did not differ significantly between the HAEC+ and HAEC− groups in the mucosa, submucosal endothelium, submucosal plexus, intermuscular plexus, nerve fibers or muscle layer (Table 3). Similarly, PRMT1 staining intensity did not differ significantly between the HAEC+ and HAEC− groups in ganglionic bowel segments.

Among patients with a history of HAEC, PRMT1 expression in the ganglionic submucosal endothelium was present in all patients with recurrent enterocolitis defined as ≥5 episodes (8/8, 100%), whereas it was observed in 50.0% of those with fewer than 5 episodes (3/6), (p=0.055). No significant differences were detected in the mucosa, submucosal plexus, intermuscular plexus, nerve fibers, or muscle layer (Table 4).

Discussion

In this cohort, PRMT1 immunohistochemical expression differed between ganglionic and aganglionic bowel in HD, with the most prominent differences observed at the submucosal and intermuscular plexus levels. In contrast, PRMT1 expression did not distinguish patients with and without HAEC. Instead, HAEC was more closely associated with the extent of aganglionosis, as reflected by longer aganglionic segments and a higher aganglionic segment/resected bowel length ratio. Together, these findings suggest that PRMT1 primarily reflects ganglionated enteric plexus architecture rather than HAEC susceptibility in this cohort.

HD is a congenital disorder of the enteric nervous system characterized by the absence of ganglion cells in the distal bowel, resulting in impaired peristalsis and functional intestinal obstruction[13, 14]. HAEC remains its most serious complication with a reported prevalence of 6–60% preoperatively and 25–37% postoperatively[3, 4, 7, 15]. HAEC is thought to arise through a multifactorial process involving stasis, barrier dysfunction, microbial alterations, and dysregulated mucosal immunity[3, 4, 16]. Although molecular mechanisms underlying HD and HAEC are being increasingly explored, clinically useful tissue-based markers remain limited.

PRMT1 is the predominant arginine methyltransferase in mammalian cells and has recognized roles in neuronal differentiation, transcriptional regulation, and inflammatory signaling[17–21]. Because of its biologic relevance to both neural integrity and immune regulation, it represents a plausible candidate for investigation in HD and HAEC. In a previous study of colon tissues from eight neonates, PRMT1 expression was reduced in aganglionic segments and preserved in ganglionic and ARM segments[9]. Our findings are consistent with this general pattern and further localize the most prominent differences to the submucosal and intermuscular plexuses.

The comparison between ganglionic and aganglionic bowel within the HD cohort showed that PRMT1 positivity was significantly reduced in aganglionic segments at the submucosal endothelium, submucosal plexus, intermuscular plexus, and muscle layer. In addition, compared with ARM control tissues, aganglionic HD segments demonstrated markedly reduced PRMT1 expression at the submucosal and intermuscular plexus levels, whereas ganglionic HD segments were largely similar to ARM controls except for the muscle layer. PRMT1 expression in the muscle layer of ganglionic segments was higher than that in ARM tissues. Although the biological significance of this finding is uncertain, it may represent an adaptive change in the ganglionated bowel adjacent to aganglionosis. All these findings indicate an association between PRMT1 expression and preserved enteric plexus structures. However, although PRMT1 appears to reflect ganglionated bowel architecture, further investigation is needed as a potential adjunctive histopathologic marker that warrants further validation.

A major objective of this study was to determine whether PRMT1 expression was associated with HAEC. Our results did not support such an association. PRMT1 expression in ganglionic bowel did not differ between HAEC+ and HAEC− patients in any evaluated tissue compartment. Neither presence-based nor semiquantitative intensity-based PRMT1 assessment discriminated between patients with and without HAEC. In the ganglionic submucosal endothelium, PRMT1 positivity was observed in all patients with recurrent HAEC (≥5 episodes) but in only half of those with fewer episodes ($p=0.055$). However, given the very small subgroup size and the lack of significance in other compartments as well, this finding should be interpreted cautiously and regarded as hypothesis-generating rather than confirmatory. Overall, the present results suggest that PRMT1 is more closely linked to enteric neuronal structure than to enterocolitis status.

In contrast to PRMT1, the extent of aganglionosis showed a clearer relationship with HAEC. Patients with HAEC had significantly longer aganglionic segments and a higher aganglionic segment/resected bowel length ratio, and both variables showed discriminatory value on ROC analysis. These findings are in line with previous studies indicating that longer aganglionic involvement is associated with a higher risk of enterocolitis[22, 23]. A greater extent of aganglionosis may impose increased functional stress on the remaining ganglionated bowel, thereby promoting stasis, impaired motility, bacterial overgrowth, and mucosal dysfunction[15].

Another clinically relevant observation was ileostomy was performed more frequently than colostomy in the HAEC+ group. The clinical data was retrospective in nature and this finding should not directly be interpreted causally. There is, however, a possibility that it reflects a greater clinical disease severity or more complex bowel dysfunction in patients who later develop enterocolitis. This possibility may be further supported by the finding that there is a negative correlation between the age at presentation and number of enterocolitis episodes in our cohort. Earlier presentation may reflect a more severe disease, which could partly explain the observed association with recurrent HAEC.

Although it is generally assumed that the length of aganglionosis is positively correlated with HAEC development, there is heterogeneity across published studies in this regard[24, 25]. In our study, longer aganglionic segments and a higher aganglionic segment/resected bowel length ratios were observed in patients who developed enterocolitis. On the other hand, the type of definitive pull-through procedure did not differ between HAEC+ and HAEC- groups. This suggests that HAEC was more closely related to the anatomical extent of the disease than to the operative technique in our cohort.

This study has several limitations. First, it was a retrospective single-center study with a relatively small sample size, particularly for subgroup analyses. Second, PRMT1 assessment was based solely on immunohistochemistry, without molecular validation at the RNA or quantitative protein level. Third, ARM tissue was used as a non-aganglionic control because normal pediatric colonic tissue is rarely available, but ARM specimens cannot be considered entirely normal bowel. Fourth, because of the retrospective nature of the study, HAEC was identified according to the clinical diagnosis documented in the medical records at the time of patient care, rather than by retrospectively applying a consensus scoring system. Finally, although all histopathologic evaluations were performed by a single blinded pathologist, interpretation of immunostaining remains observer-dependent to some extent. These limitations should be considered when interpreting the findings.

Despite these limitations, the study has notable strengths. To our knowledge, this is the first study to examine PRMT1 expression in relation to HAEC while also comparing ganglionic and aganglionic HD segments with ARM control tissues. In addition, the study integrates tissue-based immunohistochemical findings with clinically relevant anatomic predictors of HAEC, particularly aganglionic segment length and its ratio to total resected bowel length.

Conclusion

PRMT1 expression differs between ganglionic and aganglionic bowel in HD, particularly at the submucosal and intermuscular plexus levels, supporting its close association with enteric plexus structures. However, PRMT1 expression was not directly associated with HAEC in this cohort. Instead, the extent of aganglionosis appeared to be more closely related to enterocolitis risk. Larger multicenter studies with molecular validation are needed to clarify biological and potential clinical relevance of PRMT1 in HD.

Declarations

Acknowledgements:

The study was financially supported by the Scientific Research Projects Coordination Unit of Istanbul Medeniyet University (Project No. T-TP-2024-0003).

Conflict of Interest:

The authors declare that they have no competing interests.

Ethics Approval:

The study was approved by the Marmara University Faculty of Medicine Ethics Committee (Protocol No. 09.2024.460; April 22, 2024) and was supported by the Scientific Research Projects Coordination Unit of Istanbul Medeniyet University (Project No. T-TP-2024-0003). The study was conducted in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Tables

Tables 1 to 4 are available in the Supplementary Files section.

Figures

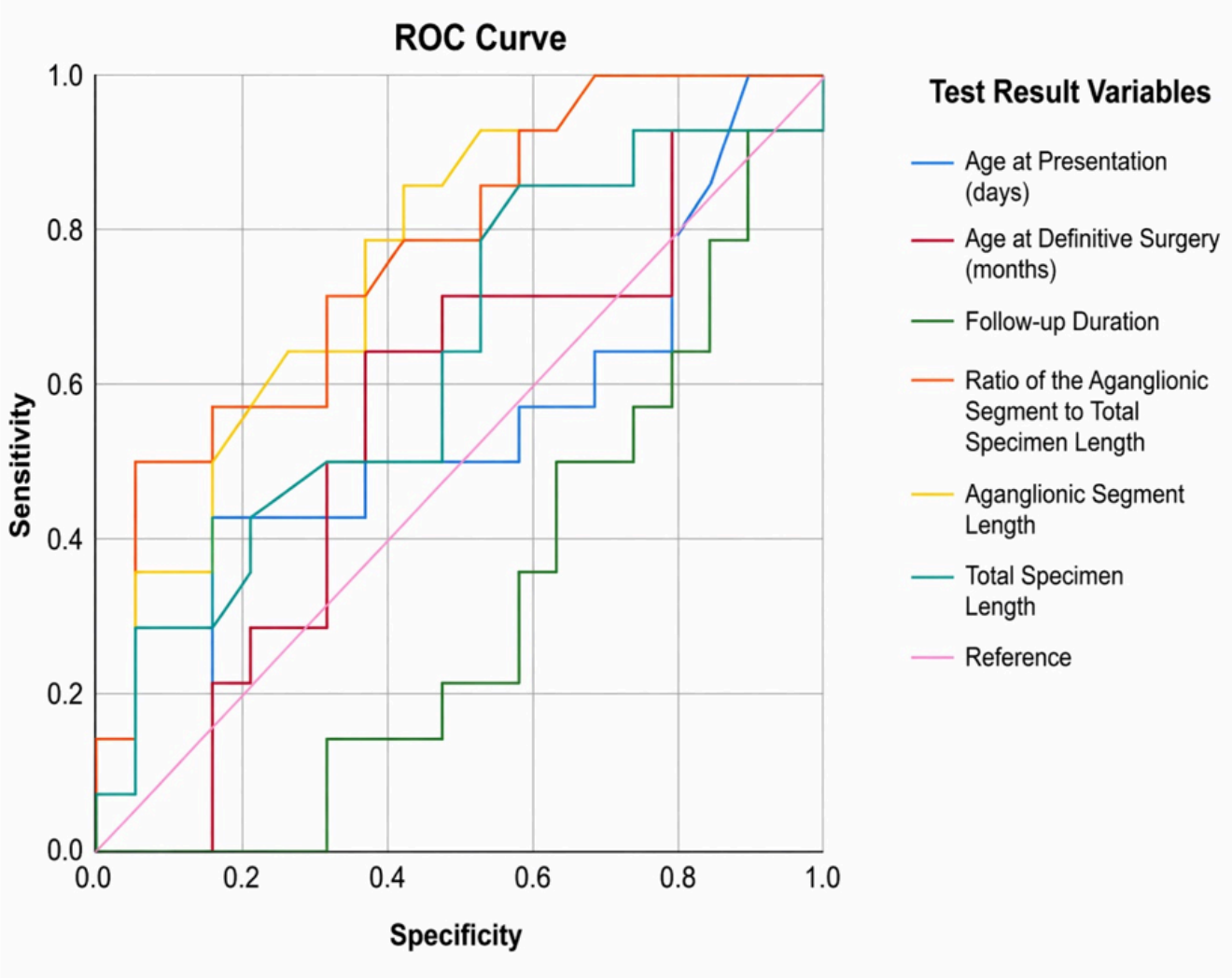


Figure 1

Receiver operating characteristic curves for variables associated with HAEC

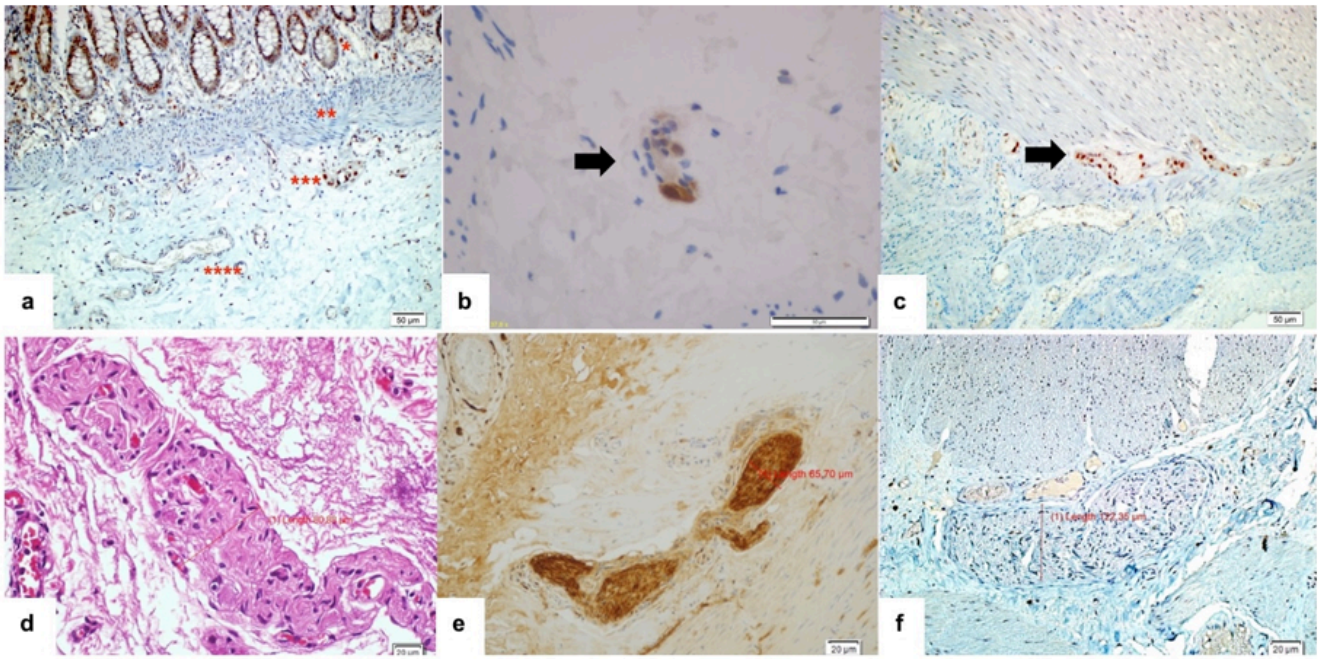


Figure 2

Representative histopathologic and immunohistochemical findings in ganglionic and aganglionic bowel from patients with HD **(a)** Ganglionic bowel segment from a patient with Hirschsprung disease showing PRMT1-positive immunoreactivity in the colonic epithelium, submucosal endothelium, muscle layer, and ganglion cells (*mucosa, **submucosal endothelium, ***ganglion cells, ****endothelium (PRMT1 ×20) **(b)** Calretinin-positive ganglion cells in the submucosal plexus (Calretininx20). **(c)** PRMT1-positive ganglion cells in the intermuscular plexus (PRMT1 ×20). **(d)** Aganglionic bowel segment showing hypertrophic nerve fibers on hematoxylin and eosin staining (H&E x40). **(e)** S-100-positive hypertrophic nerve fiber in the aganglionic segment (S-100x20). **(f)** Absence or marked reduction of PRMT1 staining in the hypertrophic nerve fiber of the aganglionic segment (PRMT1 ×20).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1ClinicalandsurgicalcharacteristicsofpatientswithHirschsprungsDiseaseaccordingtoHirschsprungassociatedenterocolitisstatus.docx
- Table2ComparisonofPRMT1expressioninganglionicandaganglionicbowelfromHirschsprungdiseaseandanorectalmalformationcontrols.docx
- Table3ComparisonofPRMT1expressioninganglionicbowelaccordingtoHirschsprungassociatedenterocolitisstatus.docx
- Table4PRMT1expressioninganglionicbowelaccordingtothenumberofHirschsprungassociatedenterocolitisepisodes.docx