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ORIGINAL ARTICLE

Histopathological findings in enteric nervous plexuses in children with intestinal motility disorders – a single center experience

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Summary

Introduction/Aim: The aim of the study was to determine the frequency of various histopathological findings in biopsies of children with intestinal hypomotility and the incidence and characteristics of Hirschsprung disease (HD).

Methods: Biopsies of colon and rectum taken due to intestinal hypomotility and chronic constipation at the Department of Pediatric Surgery of the University Children´s Hospital in Belgrade over the 10-year period (from 2009 to 2018) were reviewed using pathology reports from the archive of the Institute of pathology, Faculty of Medicine, University of Belgrade.

Results: A total of 287 patients with intestinal motility disorder were identified, with 554 biopsy samples. Of the total number of patients, 56% (161/287) were without any morphological changes in enteric nervous system (ENS). The most common histopathological findings were HD (69/287; 24%) and immaturity of ganglion cells (29/287; 10%). Isolated hypoganglionosis of ENS was found in 5 (2%) cases. Heterotopia of ganglion cells was the only finding in 8 (3%) cases. Rare causes of intestinal dysmotility were: eosinophilic proctitis/colitis (EPC) (4/287), neuronal intestinal dysplasia B (2/287), unclassified disganglionoses (3/287). Rectosigmoid variant of HD was the most frequent HD variant (80.3%). Acetylcholinesterase method and immunohistochemical staining were used in 19.5% cases.

Conclusions: HD and immaturity of ganglion cells were the most common pathological findings in ENS of constipated children. It is important to differentiate EPC from other lesions of enteric plexuses due to different natural history and therapy.

Key words: Hirschsprung disease, suctional biopsy, full thickness biopsy, intestinal motility disorders

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INTRODUCTION

Intestinal motility disorders present a relatively common problem in children, particularly in the first year of life (1). The typical clinical presentation of intestinal dysmotility, including dyspepsia, vomiting, abdominal pain and distension, bloating, and constipation is nonspecific (2). The most prevalent pathological finding causing motor intestinal disorders in infancy and childhood is Hirschsprung disease (HD) (3). HD is a congenital aganglionosis affecting the rectum and a variable length of the bowel segment proximal to the rectum. The delayed passage of meconium in the first days of life is a crucial clinical sign that raises suspicion of HD. The absence of ganglion cells in the segment of the enteric nervous system (ENS) leads to pseudoobstruction. An early diagnosis of HD is crucial for preventing severe enterocolitis, a complication with a potentially fatal outcome (4).

On the other hand, there are other rare disorders of the ENS that can clinically manifest as chronic constipation or symptoms resembling HD. The aim of this study was to analyze the frequency of various histopathological findings in biopsies of neonates, infants, and children with intestinal hypomotility and chronic constipation, as well as to determine the incidence and characteristics of Hirschsprung disease (HD) in a Serbian regional center.

METHODS

We conducted an analysis at the Institute of Pathology in Belgrade, examining histopathological slides and pathology reports of colon and rectum biopsies taken due to intestinal hypomotility and chronic constipation at the Department of Pediatric Surgery, University Children's Hospital, Belgrade. This study covers a 10-year period, from 2009 to 2018. In cases where there was suspicion of Hirschsprung disease (HD), fresh suction biopsies were stained using the acetylcholinesterase (AchE) histochemical method. The majority of biopsies were routinely fixed in formalin, embedded in paraffin, cut into 5 μm thick sections, and stained with hematoxylin & eosin (H&E). Additionally, in some cases, immunohistochemical staining was performed using various antibodies. The antibodies and their dilutions commonly used are listed in **Table 1**.

Table 1. Details of antibodies used in the analysis of suction intestinal biopsies

Antibody	Clone	Source	Dilution
Calretinin	DAK-calret 1	DAKO	1:50
MAP-2	HM-2	Abcam	1:1000
Glut-1	SPM948	Lab Vision	1:200
S-100	Z0311	DAKO	1:400
GFAP	GF2	DAKO	1:50
Synaptophysin	SY38	DAKO	RTU
SOX-10	BC34	Abcam	1:100
Bcl-2	Bcl-2/100/D5	Novocastra	1:100
CD117	104 D2	DAKO	1:300

RESULTS

Over the 10-year period, we identified 287 patients with intestinal motility disorders, comprising a total of 554 biopsy samples. The majority of the patients were males (178/287, 62%). The median age at the time of the first biopsy was 5 months, ranging from the first day of life to 209 months. More than half of all patients underwent only one biopsy (165/287; 57.5%) **(see Figure 1)**. In 6 cases (2%), the samples were deemed inadequate for analysis.

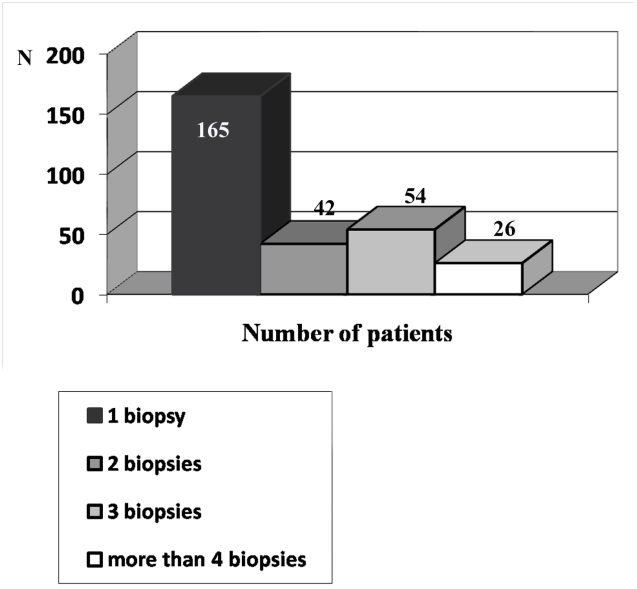

Figure 1. The distribution of the total number of biopsies in children with intestinal dysmotility problems

About half of the patients exhibited symptoms suggestive of Hirschsprung disease (HD) (151/287, 53%). One-fifth of the patients (56/287; 19.5%) had intestinal dysmotility caused by anal atresia. The remaining patients presented with intestinal hypomotility and various clinical manifestations, such as chronic constipation, subocclusion, and intestinal perforation.

All biopsies underwent routine H&E staining. The acetylcholinesterase method was applied in 22 patients (7.6%): in 16 patients as the sole additional staining and in 6 patients in conjunction with immunohistochemical staining. Immunohistochemical staining was applied in 53 biopsies, with 30 patients receiving it as the only additional staining. The most commonly used antibodies were calretinin, MAP-2, and Glut-1 **(Table 2)**. Notably, there were no false positive or false negative results.

The majority of patients (161/287, 56%) with intestinal motility disorders did not exhibit any morphological changes in the ENS. HD was the most frequent pathological finding (69/287; 24%). In 46% (69/151) of clinically suspicious HD cases, the diagnosis was confirmed by histopathology. The rectosigmoid variant of HD (RS-HD) was the most prevalent HD subtype (49/61; 80.3%). Less common variants included long segment HD (8/61;

Table 2. The frequency of usage of primary antibodies for immunohistochemical staining in the biopsies of children with intestinal dysmotility problems

Antibody	Number of biopsies (N)	Percentage of all immunostained biopsies (%)
Calretinin	42	79%
MAP-2	40	75%
Glut-1	33	62%
S-100	8	15%
GFAP	2	4%
Synaptophysin	6	11%
SOX-10	2	4%
Bcl-2	7	13%
CD117	10	19%

13.1%), total colonic aganglionosis (3/61; 4.9%), and ultra-short HD (US-HD), diagnosed in only one case.

The median age of patients at the time of histopathological diagnosis of HD was 19.5 days (ranging from the first day of life to 140 months). The median age at the time of surgical resection of the agangliotic colon was 4.5 months (ranging from 24 days to 11 years and 9 months). In 6 cases, reoperation was necessary, with a median of 36.1 months (ranging from 8 months to 50.6 months). Primary surgical resection in two patients was performed at another institution. In all cases requiring a redo operation, aganglionosis of the colon affected a long segment – TCA was present in one case, while hypoganglionosis was associated with HD in another case.

Long-segment HD was diagnosed in 13.1% of patients. US-HD was diagnosed in one patient, while TCA was diagnosed in 3 (4.9%) patients. The transanal endorectal pull-through resection was the most common surgical technique applied in all cases with classical RS-HD and US-HD. In other cases, various procedures such as the Soave, Duhamel, or Swenson technique were applied. Immaturity of ganglion cells was the second most common finding (29/287; 10%) in the ENS in children with intestinal motility disorders in our center, particularly within the first year of life **(see Figure 2)**.

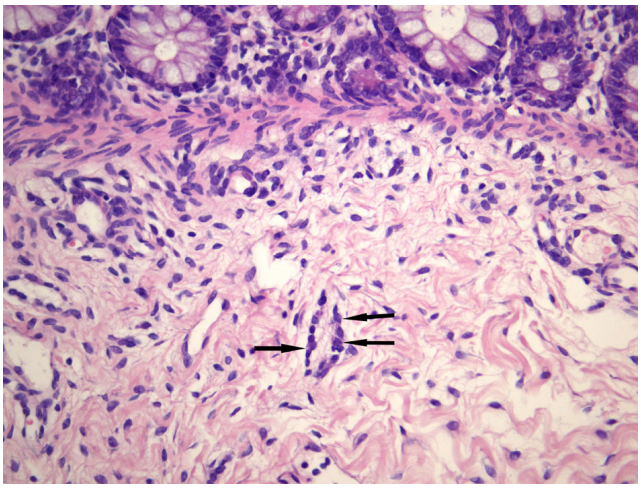

Figure 2. Immaturity of ganglion cells in the submucosal nervous plexus (H&E, x400). The ganglion cells (arrows) exhibit small basophilic nuclei and a limited amount of cytoplasm – it is difficult to distinguish them from glial cells on H&E slides.

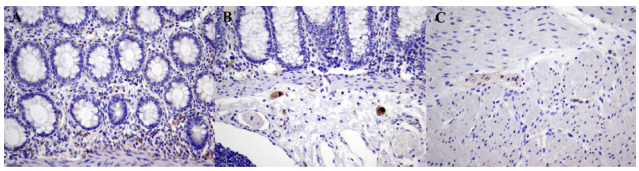

Figure 3. The biopsy from a patient with hypoganglionosis associated with Hirschsprung disease (HD) revealed the following features: in the lamina propria of hypoganglionic segment, intrinsic nerve fibers were present (A), small ganglia were found in the submucosa (B), and rare small ganglia were noted without calretinin expression in ganglion cells in the myenteric nervous plexus (C) (A, B, C: Calretinin, x400).

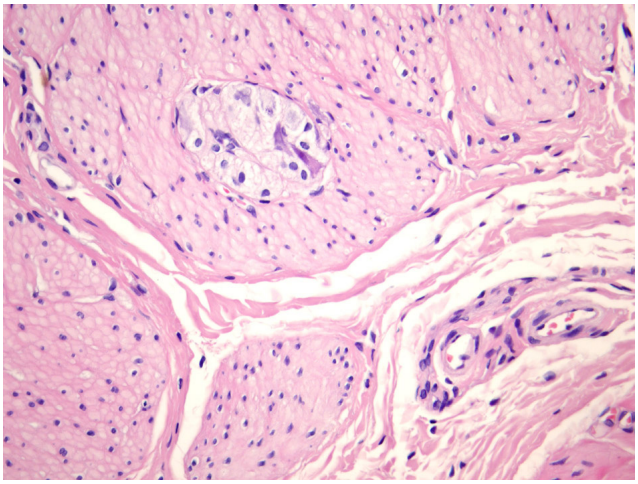

Figure 4. Heterotopic ganglia in the circular muscular layer: it is surrounded by muscular fibers (H&E, x400).

Hypoganglionosis of the enteric nervous system was identified as the sole pathological finding in 5 (2%) cases, while in one patient, it was associated with HD **(Figure 3)**.

Heterotopic ganglia were the exclusive finding in 8 (3%) cases. Ectopic ganglia were identified in the muscular coat, surrounded by muscular fibers **(Figure 4)**.

Rare causes of intestinal dysmotility included eosinophilic proctitis or colitis (4/287), intestinal neuronal dysplasia B (IND B) (2/287) and non-classified disgan-

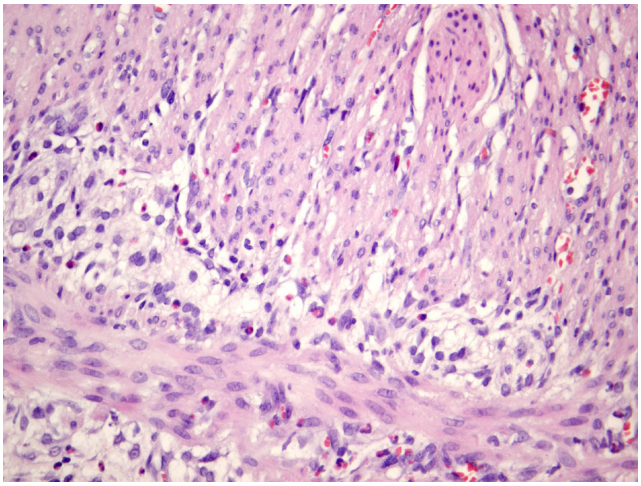

Figure 5. Rare findings in enteric nervous plexuses as a cause of intestinal dysmotility include eosinophilic ganglionitis within eosinophilic colitis. Eosinophils surround myenteric ganglia and are also present within ganglia, as well as between muscular fibers (HE, x400).

glionoses (3/287) **(Figure 5)**. In both cases of IND B, it was an isolated finding. The histological findings in enteric nervous plexuses in dolichocolon were variable, and we categorized them as non-classified disganglionosis. This included the presence of thick nerve bundles with ganglion cells in the submucosa of the proximal rectum and sigmoid colon, several megaganglia in the submucosa (less than 20%), relative hyperplasia of glial cells within myenteric ganglia, and the presence of heterotopic ganglia within muscular layers.

DISCUSSION

Constipation in children, especially in the first year of life, is a common problem. The majority of constipated children experience functional issues, but it is crucial to rule out organic causes of chronic constipation (5,6). The primary cause of intestinal dysmotility in the first year of life is HD, consistent with larger global studies (7). The absence of meconium stool within first 48 hours of life may indicate possible rectal aganglionosis and serve as an indication for rectal biopsy. In our study, the median age at the time of histopathological confirmation of HD was 19.5 days. In rare cases, the diagnosis was established later, with the oldest HD patient being 11.5 years old. Late HD diagnosis is often associated with complications and a long recovery (8,9).

The "gold standard" for HD diagnosis is histopathological analysis of suction rectal biopsy (10). In previous years, frozen sections stained with H&E and AchE method were considered the "gold standard" (3). However, due to limitations of AchE usage, calretinin immunohistochemical staining has become a new standard in many laboratories (4). Calretinin immunohistochemistry has several advantages, being applicable on formalin-fixed tissue and superficial biopsies (11,12). However, it is not an ideal marker, especially as HD diagnosis is based on the absence of its expression. Additionally, in euganglionic intestines in patients with Down syndrome, calretinin expression may be absent (13). Different recommendations exist for utilizing immunostaining in HD diagnostics, suggesting the application of several antibodies (10,14,15). In our center, over a 10-year period, both AchE and immunohistochemical staining were used with similar success in HD diagnosis. With the advancements in artificial intelligence, deep learning approaches have shown potential to standardize and facilitate the diagnostic process (16).

The majority of children with HD in our study were treated using the transanal endorectal pull-through technique, which has demonstrated superior effectiveness compared to alternative methods. Earlier onset, lower incidence, and mild complications make this procedure more favorable, reducing the need for additional surgeries (17). Previous surgical methods had more long-term complications, with fecal and urinary incontinence being significantly more common compared to the general population in long-term follow-up studies. Earlier surgical methods were also associated with reduced fertility in female patients (18).

Most children with intestinal hypomotility in our group were male, consistent with larger global series (18). The distribution of HD variants was similar to other large studies (15), and it did not differ from a previous study in the same institution during a different period (19).

Immaturity of ganglion cells can be a cause of intestinal dysmotility, often presenting in the first year of life, usually in premature babies, and typically does not require intervention (15). It is an obligatory pathological finding after the fourth year of life (20).

Isolated hypoganglionosis is a rare pathological finding, often with a clinical presentation similar to HD. It can also be associated with HD (2). Typical histopathological findings include rare small myenteric ganglia and damaged AChE activity (20). The estimation of the number of ganglion cells is delicate, without an exact cut-off. Recommendations suggest that each laboratory establishes its own cut-off values related to age (21).

Ectopic ganglia within the muscular layers are considered a pathological finding in the majority of the gastrointestinal tract (21), while their presence in the mucosal lamina propria in children is considered normal (2,21).

Clinical manifestations of eosinophilic enterocolitis could include chronic constipation or pseudoobstruction, similar to HD (22,23). However, the significance of eosinophils in the aganglionic segment and in the transition zone is not clear (24).

IND B is a controversial diagnosis, often associated with HD (24,25). Its clinical presentation can be very similar to HD, but histopathological features are distinctive. While HD is more of a qualitative diagnosis, IND is more of a quantitative diagnosis, based on the estimation of the percentage of megaganglia in the submucosa (25). Non-classified dysganglionoses are complex, with different features of ganglionic abnormalities. Although "unclassified," there is a complex classification of non-classified disganglionoses (26) to provide better treatment. In rare cases with chronic constipation, disorders of Cajal cells should be considered as a possible cause of intestinal pseudoobstruction (27). Also, transitory dysfunction of Cajal cells can be the cause of postoperative dysmotility in patients with surgically treated Hirschsprung's disease (28). In some cases, routine histopathological methods may not be helpful, and the underlying pathological mechanisms are sometimes unclear. A very few associated genetic mutations have been identified (29). In some rare cases, extraintestinal causes such as syringomyelia could be identified as the cause of chronic constipation (30).

CONCLUSION

More than half of patients with intestinal motility disorders did not show any morphological changes in the ENS. The most prevalent causes of chronic constipation in the pediatric age group in our center are HD and immaturity of ganglion cells. Furthermore, rare causes of intestinal hypomotility, such as hypoganglionosis, heterotopic ganglia, IND B, or eosinophilic colitis, should be considered as potential contributors to intestinal hypomotility.

Conflicts of interest

None

Author contributions

Conception and design: RJ, SSA, ML, MĐ, DV, JJ; data collection: JJ, MĐ, DV, MB, DP, ĐT; writing the article: RJ, SSA, MĐ, DV, NR; critical revision of the article: RJ, SSA, DV, MĐ, NZ, NR, ML; final approval of the article: RJ, SSA, MĐ, DV, NR, JJ, ĐT, MB, NZ, DP, ML

Ethical approval

This study positively stated by the local Ethics committee (University of Belgrade, Medical School-29/VII-2, 1st July 2015 and University Children's Hospital Tiršova, Belgrade (26/185, 4th June 2015).

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HISTOPATOLOŠKI NALAZ U ENTERIČKIM NERVNIM PLEKSUSIMA KOD DECE SA POREMEĆAJIMA INTESTINALNOG MOTILITETA - ISKUSTVO JEDNOG CENTRA

Radmila Janković[1,3], Sanja Sinđić-Antunović[2,3], Miloš Đuknić[1,3], Dragana Vujović[2,3], Nina Ristić[3,4], Jovan Jevtić[1,3], Đorđe Topličić[2], Milena Backović[3,5], Nenad Zdujić[2], Dunja Putniković[3], Marija Lukač[2,3]

Sažetak

Uvod/cilj: Cilj istraživanja je utvrđivanje frekvencije različitih histopatoloških nalaza u biopsijama dece sa intestinalnim hipomotilitetom i određivanjem učestalosti i karakteristika Hirschsprungove bolesti (HD).

Metode: Retrospektivna analiza histopatoloških izveštaja arhive Instituta za patologiju Medicinskog fakulteta u Beogradu biopsija dece sa hipomotilitetom creva i hroničnom opstipacijom u desetogodišnjem periodu (od 2009. do 2018. godine), lečene u Univerzitetskoj dečjoj klinici "Tiršova" u Beogradu.

Rezultati: Analizom je obuvaćeno 287 pacijenata sa poremećajem crevne pokretljivosti sa ukupno 554 biopsijska uzorka. Više od polovine pacijenata (56%; 161/287) je bilo bez morfoloških promena u enteričkom nervnom sistemu (ENS). Najčešći histopatološki nalazi bili su HD (69/287; 24%) i nezrelost ganglijskih ćelija (29/287; 10%). Izolovana hipoganglionioza ENS identifikovana je u 5 (2%) slučajeva. Heterotopija ganglijskih ćelija bila je jedini nalaz u 8 (3%) slučajeva. Retki uzroci crevnog hipomotiliteta bili su: eozinofilni proktitis/kolitis (EPC) (4/287), intestinalna neuronalna displazija tip B (2/287) i neklasifikovane disganglionoze (3/287). Rektosigmoidna HD-a bila je najčešća HD varijanta (80.3%). Metoda acetilcholinesteraze i imunohistohemijsko bojenje korišćeni su u dijagnostici kod 19,5% slučajeva.

Zaključak: HD i nezrelost ganglijskih ćelija bili su najčešći patološki nalazi kod dece sa hroničnom opstipacijom. Važno je razlikovati EPC od ostalih lezija enteričnog pleksusa zbog različite prirode bolesti i preporučene terapije.

Zaključak: U ovoj studiji, poremećaj penjanja je dokazan samo kod *dFMR1*^{B55} mužjaka, dok su *dFMR1*^{B55} ženke imale slične sposobnosti penjanja sa kontrolnim *w*^{1118}.

Ključne reči: Hirschsprungova bolest, sukciona biopsija, biopsija pune debljine zida creva, poremećaji crevnog motiliteta

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