

## Nervous structure of Meckel's diverticulum in children

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### Abstract

Meckel's diverticulum, being considered as the most frequent malformation of the digestive tract, has been largely presented in scientific papers, but a complete physiopathological mechanism for its natural history has not been yet described. We have studied the nervous system and the differences observed in eight Meckel's diverticula with enteric or ectopic gastric mucosa, using specific immunohistochemical markers. It has been noted a significantly higher density of myenteric nerve fibers in areas with enteric mucosa compared with the areas with gastric heterotopias, while the transition zone had intermediate nerve fibers density. The ileal wall near the diverticulum had a myenteric plexus density similar to gastric mucosa intradiverticular area. The density of Meckel's diverticulum myenteric plexuses determines the local peristalsis. The enteric type mucosa diverticula has more intense peristaltic activity which leads more frequent to intussusception or, in case of intraluminal obstruction, might be also involved in germ spreading and progression of infectious process. The lower density of Auerbach's plexus nerve fibers in cases with gastric heterotopia Meckel's diverticulum determines less effective drainage of diverticular content, favoring the contact of intradiverticular mucosa with acid secretion of gastric mucosa area. The gastric mucosa's defense mechanisms and the intense peristaltic activity in the zone with enteric mucosa offer a certain protection against the apparition of intradiverticular ulcerative lesions, which usually are observed on the ileum, near the diverticulum. The age related decreasing number of myenteric nerve fibers density explains the higher frequency of Meckel's diverticulum complications in children.

**Keywords:** Meckel's diverticulum, immunohistochemical, myenteric, density, complications.

### Introduction

The persistence of Meckel's diverticulum, as a malformative state, due to a closure defect in the separation between the yolk sac and embryonic intestine, has been widely presented in scientific papers through various clinical presentations and subsequent complications. One of the major factors that influence the natural history of a Meckel diverticulum should be its intrinsic innervation. The only study found in the medical literature about Meckel's diverticulum innervation was published more than 50 years ago, describing its nervous structure [1], although long before present study techniques offered by the immunohistochemical markers.

The aim of this study is to investigate the enteric nervous system in both types of Meckel's diverticulum (with enteric mucosa) and ectopic gastric mucosa Meckel's diverticulum, with or without other ectopic wall inclusions (pancreatic tissue).

Considering the differences found, we discuss the possibility of correlations between the intrinsic diverticulum nervous system and the evolutive complications.

### Materials and Methods

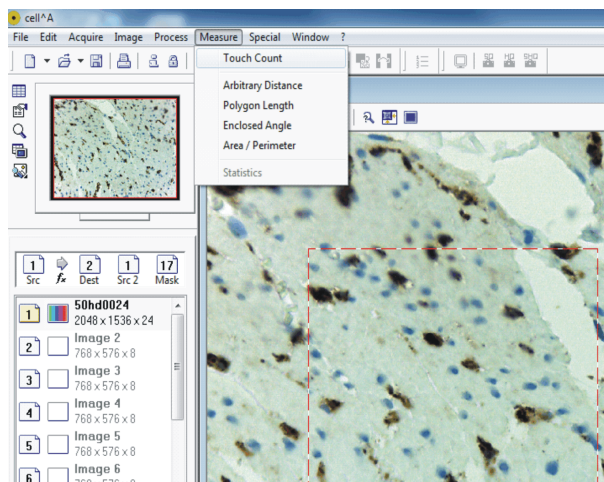
We have investigated the nerve structure of Meckel's

diverticula found and resected in children during abdominal surgery, after histological processing of the surgical specimens, for a period of two years, between 2010 and 2011, at the Clinic of Pediatric Surgery from Cluj-Napoca.

There were processed histological sections from eight cases, aged between 2 months and 18 years. The histological sections were stained using the routine Hematoxylin–Eosin method and immunohistochemical staining using monoclonal antibodies against S100 protein and neuron specific enolase (NSE). S100 protein is positive in neurons and glial cells, NSE being positive only in neuronal cells.

The samples were photographed, using a 4 Mp Olympus Camedia C4040 photo camera and Olympus BX40 microscope at 200× magnifying power. The morphometric analysis of the images has been made using Cell®A Olympus software, for establishing the nerve fiber density in enteric mucosa and gastric mucosa Meckel's diverticula. The density was calculated as the ratio between the number of fibers per unit area, repeated for each case three times (three distinctive microscopic fields), resulting in a mean density for each case and a mean density per studied groups – enteric

mucosa and gastric mucosa Meckel's diverticulum (Figure 1).

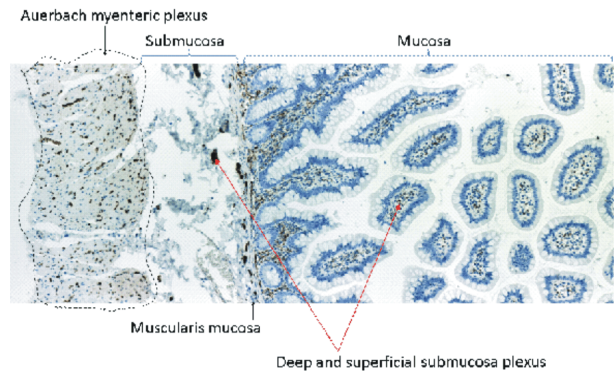
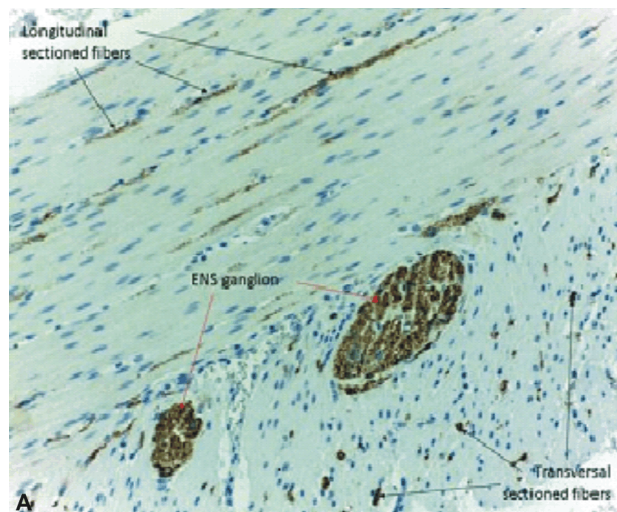


**Figure 1** – Screen capture during the counting process (function “Touch Count” of Cell®A software) of enteric nervous system fibers in a Meckel's diverticulum.

## Results

The analysis of histological samples shows enteric mucosa in six cases, gastric mucosa with pancreatic inclusions in one case and one case with combined enteric and gastric mucosa.

Immunohistochemical stains showed enteric nerve fibers in the diverticulum's wall (Figure 2).

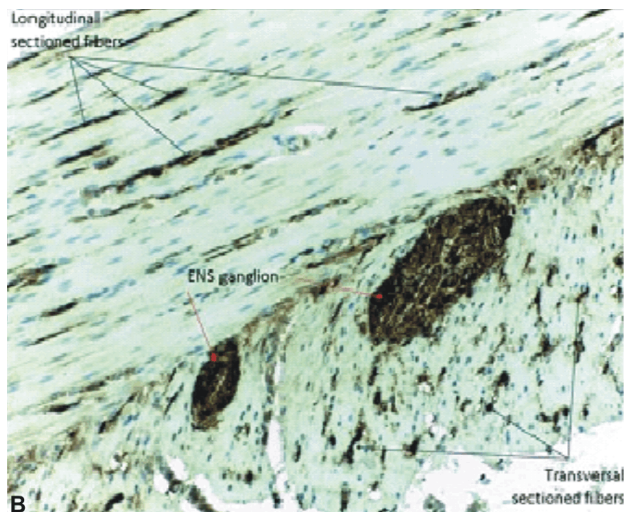


**Figure 2** – Identification of NSE in Meckel's diverticulum with NSE stain.

The higher reactivity of S100 protein staining used for glial and neuronal cells generates more intensely colored images of nerve fibers, compared to NSE staining.

The examination of enteric nerve fibers of the diverticular wall showed the network type arrangement of myenteric (Auerbach's) plexus fibers.

In the longitudinal muscle layer, the nerve fibers have a longitudinal disposition, in the same direction with the muscular fibers, while in the internal muscular layer the nerve fibers have transversal disposition, along with the muscular fibers. This created a 90° angle arrangement of myenteric fibers. Between the longitudinal and circular muscle layers there were nerve bundles forming myenteric plexus ganglia. These are the only visible structures in Hematoxylin–Eosin staining (Figure 3).



**Figure 3** – Difference in intensity of immunohistochemical reaction against NSE and S100 protein: (A) Anti-NSE staining; (B) Anti-S100 staining.

The comparative analysis of Meissner's plexus nerve fibers density of diverticulums with enteric mucosa and with gastric mucosa revealed a lower density of nerve fibers in the region containing gastric mucosa. This observation is clearly visible in the diverticulum having both enteric and gastric mucosa, the gastric mucosa area having lower density of nerve fibers, compared with enteric mucosa region. The transition zone had intermediate nerve fibers density.

The morphometric analysis (Table 1) of NSE and

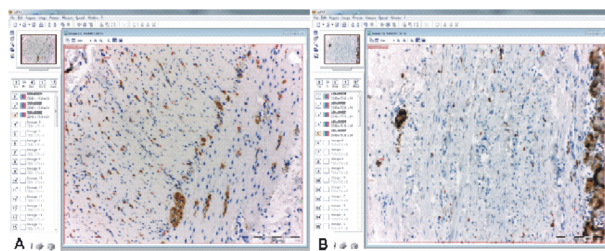
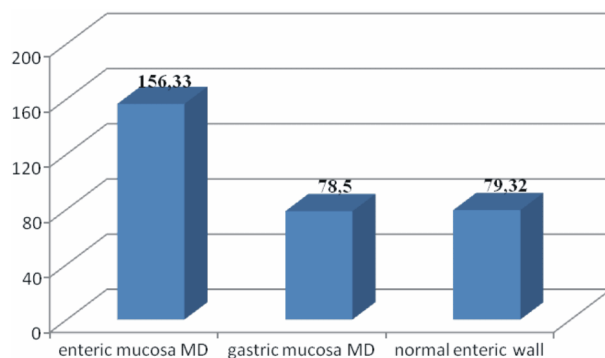
S100 nerve fibers of enteric and gastric mucosa areas in Meckel's diverticulum revealed a significantly higher density of NSE fibers in areas with enteric mucosa (Figure 4A) than in areas with gastric mucosa (Figure 4B).

Compared to the normal density in the ileal wall (unpublished personal study) Meckel's diverticulum with gastric type mucosa has a similar density with the normal surrounding intestinal wall. This suggests that the density in the wall of Meckel's diverticulum with enteric mucosa is pathologic (Figure 5).



**Table 1 – The morphometric results of Auerbach's plexus nerve fibers mean density**

Study group	Case No.	Auerbach's plexus nerve fibers mean density [No./mm <sup>2</sup> ]	Mean/group
Enteric mucosa Meckel's diverticulum	1.	158	156.33
	2.	160	
	3.	154	
	4.	157	
	5.	155	
Gastric mucosa Meckel's diverticulum	1.	58.75	79.02
	2.	99.29	
Normal enteric wall	1.	98.51	79.32
	2.	60.13	

**Figure 4 – Screen captures of Cell®A software during counting density of NSE fibers in the wall of Meckel's diverticulum with enteric mucosa (A) and gastric mucosa (B).****Figure 5 – The mean density of Auerbach's plexus nerve fibers in the ileal region [No./mm<sup>2</sup>]. MD: Meckel's diverticulum.**

## Discussion

The Meckel's diverticulum motility is responsible for the physiologic evacuation of mucus production and enteric content, depending of the conjoined activity of intrinsic and extrinsic nerve supply, Cajal interstitial cells and enteric muscular and neuroendocrine systems. The different types of mucosa and subsequent nerve fibers density are responsible for Meckel's diverticulum activity and local complications. The appendix has different, colonic type, nerve fibers arrangement and the evolution of an appendix should be expected only if a colonic type arrangement of nerve fibers and smooth muscle displacement would have been present.

Irwin DA [2] and Furness JB [3] have made observations regarding the myenteric plexus density of different regions of the digestive tract. Furness JB described the higher density of nerve fibers in the pyloric region.

Current literature considers Meckel's diverticulum with areas of gastric heterotopia as a benign, non-neoplastic condition, in most instances without clinical involvement [4]. It has been recognized that the existence of acid secretion of gastric heterotopic Meckel's diverticulum mucosa might lead to peptic ulceration adjacent to gastric mucosa zone or the possibility of *Helicobacter pylori* infection, which may influence the clinical outcome of Meckel's diverticulum [5]. The lower density of Auerbach's plexus nerve fibers in cases with gastric heterotopias Meckel's diverticulum, as shown above, determines less effective drainage of diverticulum content, favoring enteric mucosa contact with diverticulum's acid secretion and developing ulcerations, followed by local bleeding. The intense peristaltic activity in the zone with enteric mucosa offers a certain protection against the apparition of intradiverticular ulcerative lesions, which usually are observed on the ileum, near the diverticulum. If there is a small zone with gastric mucosa, in the distal part of the diverticulum, the enteric secretion partially neutralizes the acid secretion, due to superior enteric mucosa zone peristaltic activity. In presence of a large surface of diverticulum's gastric mucosa or if the zone with gastric mucosa is situated proximally, close to the ileal opening, the defense mechanisms of the enteric mucosa are less effective, due to lower peristaltic activity and longer contact with the acid secretion.

The enteric diverticulum mucosa determine the Cajal cells to generate more frequent electric waves and consequently higher density of Auerbach's nerve fibers results in more intense diverticulum peristaltic activity which may lead to conditions favoring intussusception. The invaginated or inverted Meckel's diverticulum leads to intussusception, which is usually very difficult to treat by water-soluble or an air-contrast enema and even if conservative treatment is successful the intussusception will recur [6].

The higher frequency of Meckel's diverticulum peristaltic waves in cases with enteric diverticular mucosa should favor intraluminal evacuation, but in case of intraluminal obstruction it might be also involved in the progression of local infectious process, favoring rapid evolution and worsening the infectious state and possibility of earlier perforation. It was not yet clearly established whether infectious complications or ulcerative lesions secondary to gastric diverticular mucosa determines a higher perforation rate, but both nervous system particular conditions may determine, through different mechanisms, the progression to perforation. In case of intraluminal infection, the progression appears earlier, comparing to the ulcerative lesions.

Progressive loss of myenteric neurons with age in humans was noted by previous studies [7, 8], who demonstrated the interplay of diet and loss of myenteric neurons and subsequent motility disorders. The myenteric neurons decreasing evolution during childhood in humans, but Gabella observed the loss of 40–60% of Auerbach's nerve fibers from young adult period to aged guinea pigs, with shape transformation of myenteric fibers [9]. The influence of the nervous system on the motility and evolution of Meckel's

diverticulum will be influenced by age, circulatory system modification, catabolism and apoptosis, and the diverticular complications should not be closely related to nervous system activity. The complications due to Meckel's diverticulum decrease with age. Soltero MJ and Bill AH [10] and Dumper J *et al.* [11] found the risk of complications for Meckel's diverticulum in elders to be close to 0%. This consideration involves the major role of enteric nervous system and the interplay of intense neuronal activity in childhood and higher frequency of complications in younger patients.

## ☐ Conclusions

The Meckel's diverticulum nervous system and histologic local variations play a major role in its evolution and may offer local conditions, which influence the clinical outcome. The higher density of nerve fibers in presence of enteric diverticular mucosa determines intense peristaltic activity and the diverticulum's content drainage, while lower density offers conditions of apparition of diverticulitis and, if a large area of gastric mucosa is present, close to the intraluminal opening, the possibility of apparition of ulcerative ileal lesion is to be expected.

The age-related decreasing number of myenteric nerve fibers explains the most frequent Meckel's diverticulum complications in children and the age-decreasing rate of complications in adults.

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