Case Report

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Features in the Diagnosis and Course of Hirsch Sprung's Disease

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Abstract

Hirsch sprung's disease is a congenital disease of the colon that lacks ganglion cells in the myenteric plexus, responsible for the movement of food in the intestine, which causes chronic constipation or bowel obstruction. HD occurs in approximately 1 in 5,000 live births with a total male: female ratio of 3:1 to 4:1.The diagnosis of Hirsch sprung's disease is not always easy and poses serious medical problem in cases in which part of the diagnostic criteria is missing or unconvincing. The enteric nervous system is a complex of neural network and glia that controls intestinal function. In cases in which this system is absent, the part of the intestine that is affected remains inactive. The patient with a typical history of chronic constipation, physical signs of a bloated abdomen, a large colon with a narrow distal segment in contrast to X-ray examination, with an empty rectal ampoule, does not represent diagnostic problem. Loss of ganglion cells is established after performing a rectal biopsy, offered as an aid in the diagnosis of these cases.

Keywords: Constipation; Ganglionic cells; Children

Case Study

3 patients have been included in the research (2 years and 5 years old boys and 11 years old girl) operated in Clinic of Pediatric Surgery, University Hospital in Stara Zagora, Bulgaria. The diagnostic methodology is contrasted X-ray, CT, rectal biopsy with histology. The biopsy specimens are investigated in the Department of General and Pediatric Suregery, Medical Faculty, Stara Zagora. Diagnostic techniques include anorectal manometry, barium slurry and rectal biopsy. Radiologic methods assist the accurate diagnosis. The following antibodies are used for immunohistochemistry: Calretinin monoclonal mouse antihuman (M7245 DAKO Denmark) ready to use, and c-kit (CD117) polyclonal rabbit antihuman (A4502 DAKO Denmark) as well as detection system EnVision™ FLEX, High pH (Link) (K8000), DAKO Denmark.

Case 1

Two years old boy /D.D./ admitted to Clinic of Pediatric Surgery, University Hospital in Stara Zagora, Bulgaria with diagnosis of constipation and abdominal pain. The anamnesis is for a child suffering from persistent constipation for 1 year, with lack of defecation up to 7-10 days. It is constantly smeared with faeces. Treatment with high dose laxatives has no effect. An irrigography was performed and conservative treatment with cleansing enemas was performed. A biopsy was performed 2 cm proximal to the linear dents on the posterior rectal wall. After a result for the presence of ganglion cells and a rejection of the diagnosis Hirschsprung I disease, an extended left hemicolectomy was performed, the proximal expanded half of the rectum, colon descensus, sigma were removed and 1/3 from transverse colon.

The physical examination shows a markedly distended abdomen. Laboratory investigation on admission reveals a blood cell count WBC 10.0, RBC 4.46, hemoglobin level 116.0, hematocrit value 0.338, kalium value 4.5 mmol/l, chloride value 136 mmol/l. Therefore, an abdominal X-ray has been obtained. It has revealed a large amount of retained barium contrast within moderately dilated descending and severely dilated proximal sigmoid colon with and rectum **(Figures 1 and Figure 2)** /по 13/. A surgical consultation is performed, and the results from biopsy reveal absence of ganglion cells and confirm the diagnosis of HD. In immunohistochemistry with calretinin no ganglia are detected in any area of the HD tissue. Absence of expression of c-kit is also detected. Positive calretinin reaction in mast cells served as an additional, internal positive control.

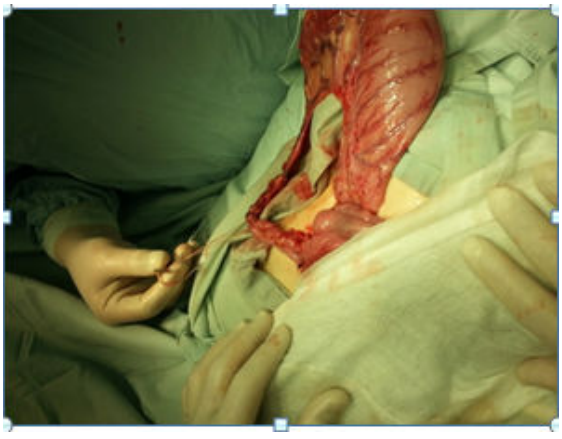

Figure 1: Case I-Intraoperative time.

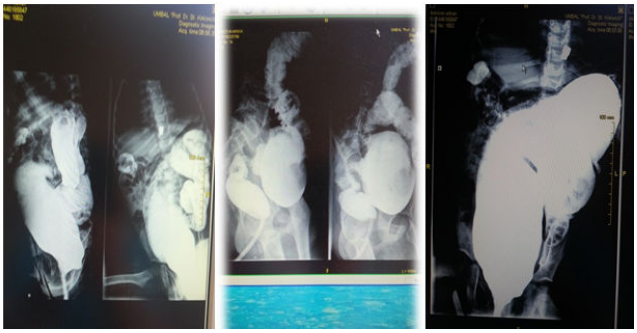

Figure 2: Case I Abdominal X-ray barium slurry.

Case 2

Our second patient is an 11 year old girl /N.P./, admitted to the Clinic of Pediatric Surgery with diagnosis of severe constipation. This study presents the case of a patient with megacolon **(Figure 3)**. The child has long periods of prolonged constipation and abdominal pain. She has neurological symptoms and childhood cerebral palsy. Laboratory investigation on admission reveals a blood cell count WBC is normal' RBC, Hemoglobin level and hematocrit show anemia; kalium value 3.5 mmol/l, chloride value 130 mmol/l. Patchy enlargement of ganglionic cells is present throughout the colon, in the submucosa and in the mesenteric plexus. Immunostaining of ganglion cells is presented as chromogenic deposition in the cytoplasm. In IND the immunohistochemical reaction presented with an increase of positive calretinin and c-kit ganglionic cells in mesenteric and submucosal plexuses **(Figure 4)**.

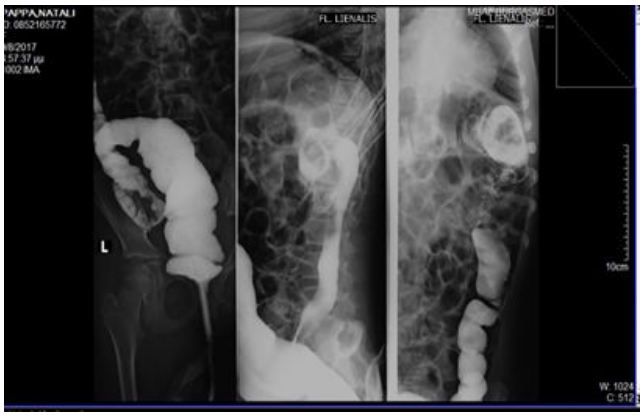

Figure 3: Case II, Abdominal X-ray barium slurry.

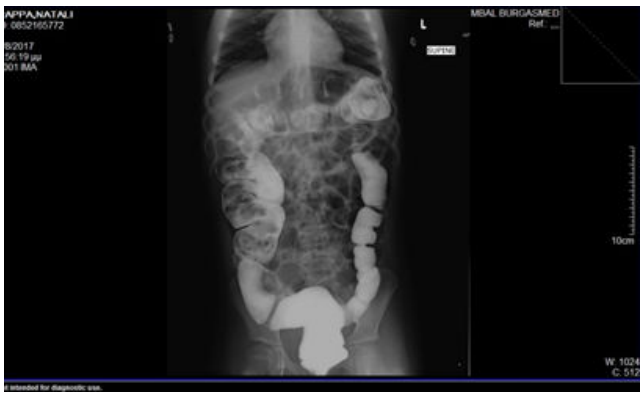

Figure 4: Case II abdominal X-ray

Case 3

5 years old boy, K.K, who has abdominal pain and periods of constipation. The physical examination shows a markedly distended abdomen. Laboratory investigation on admission reveals a blood cell count WBC, RBC, Hemoglobin level, hematocrit value are normal. Irrigation revealed the characteristic signs of congenital megacolon, but parents continued treatment with enemas and diet and reported good response. **(Figure 5)** shows the MRI and confirmatory information from the X-ray examination.

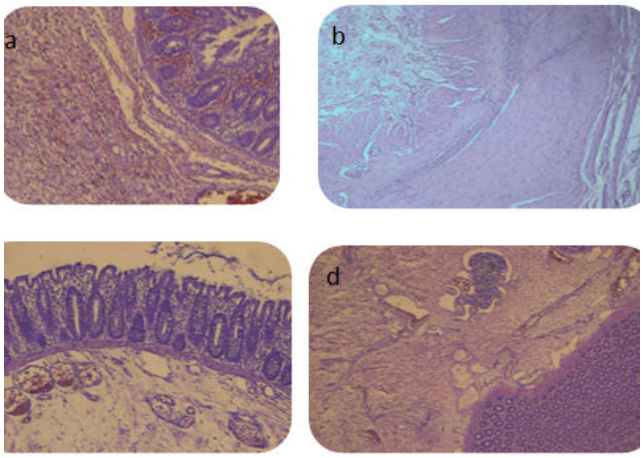

Figure 5: Positive nerve fiber keratin immunostain in lamina propri (a), sub mucosa (b) and muscle mucosa (c). Nuclear and cytoplasmic calretinin ganglion cell immunostains (d).

Discussion

Hirch sprung disease (HD) is a congenital disorder characterized by the absence of enteric ganglia along a variable length of intestine that can lead to tonic contraction of the affected segment and massive distension of the bowel above. The disease is named after Harald Hirsch sprung, a Danish physician who described it in two newborns in 1888. In some cases, Hirsch sprung's disease is associated with other congenital diseases or syndromes-Down, Mowat-Wilson and others. Normally 90% of infants secrete meconium within the first 24 hours, and 99% of them within 48 hours after birth. If the baby has not given meconium, it is suggested that Hirch sprung's disease may be present. Other symptoms include vomiting of green or brown matter, increased gas content, bloody diarrhea [1,2].

In the same year, Swenson performed and described the first etiopathogenetically validated operation with resection of the dilated and a ganglionic segments.

Ethiopathogenesis

According to Okamoto and Ueda's theory, various pathogenic factors impair the migration of neuroblasts from the primary neural tube to the large intestine (so-called cranio-caudal migration) so that it does not reach its extremities. This causes a permanent spasm of the distal colon, functional obstruction and subsequent dilation of the proper region, which is clinically demonstrated with the picture of colon ileus.

The disease is genetically predetermined. It occurs at 1:5000-6000 live births, more often in boys-an average of 3.5:1. Longer forms predominate in girls. Often associated with other abnormalities-Down syndrome, atresia of the small intestine. Occurring as an isolated condition in 70% of cases, it can be associated with other associated congenital anomalies, as well as with a number of syndrome phenotypes. In these syndrome phenotypes, a number of different genetic sites have been identified that show potential underlying genetic associations of the disease and indicate the likely interaction between a gene and a gene in its pathogenesis [3-5]. Abdominal retention is observed in almost 100% of cases and can be marked. The child does not develop normally and is often thin and malnourished. Congenital anomalies of GIT (8.05%), as well as of the genitourinary system (6.05%) and the central nervous system (6.79%) have been reported. In addition, anomalies in the musculoskeletal system (5.12%) and those affecting the cardiovascular system (4.99%), craniofacial area (3%) and skin (ectodermal dysplasia) [6,7]. More than 90% of cases can be diagnosed in the neonatal period but are often overlooked in poor resource health situations, which is why late presentation is common [6,8].

Diagnostic techniques include anorectal manometry, barium slurry and rectal biopsy. Radiologic methods can assist in accurate diagnosis. Diagnostic evaluation should begin with an X-ray of the abdomen (diagnostic accuracy 52%), but it is normal practice to proceed with contrast enema to further evaluate the diagnosis. The X-ray examination should show a change in the size of the lumen (the so-called transition zone), in addition, may have an irregular "saw" shape.

Histological examination biopsies are obtained from sites 2 and 4 cm from the dental line (3 and 5 cm in older children) to avoid the normal a ganglionic area in the first centimeter near the dental line. The fresh biopsy specimens are then frozen and cut (± 15 μm sliced), stained and histopathologically examined. Despite the innovations in biopsy forceps over the years and the development of a superior disposable capsule tool, these problems remain. As a result, a full thickness biopsy procedure [8-10] is often required.

These markers are calretinin-a vitamin D-dependent 29-kDa [10-12] protein that binds to calcium and has important roles as a senior and modulator of calcium ions. The absence of calretinin leads to the accumulation of calcium ions in the cytoplasm of nerve cells, promoting hyperexcitability and neurodegeneration. The enteric nervous system (ENS) is comprised of complex network of neurons and glial cells that resides in the wall of the gastrointestinal system. These cells have been shown to arise from progenitors that migrate from the vagal level of the neural crest and populate the entire length of the intestine with a smaller contribution of the sacral crest-derived cells to the distal intestine. The ENS plays a crucial role in normal gastrointestinal motility [12,13].

Multistage surgical treatment is applied. Any infant who has no meconium output within the first 48 hours of birth should be screened for Morbus Hirschsprung. A two-stem, unnatural sigma anus is performed, which is brought out into the area with normal ganglion cells and the problem with the colon is resolved. Within 6 months, a radical operation is performed: resection of the spastically contracted aganglionic segment and part of the dilated area, including the unnatural anus, and then histologically the normal distal colon is drawn through the pull-trought.

Restoration of the patency of the colon is done through different methodologies. The method of choice is transrectal Soose rectosigmoidectomy, which is performed by Booley modification: the area to be resected is mobilized, then repairs a serous-muscular cuff of the distal rectum and through it the intestine moves out where transanal anastomosis is performed. Prophylactic dilations of endorectal anastomosis are performed postoperatively. Usually the treatment is surgical removal of the aganglionic part. On the other hand, the intestinal neural dysplasia (IND) denotes an increased proportion of hyperplastic submucosal ganglia. IND is characterized by structural changes containing hyperplasia of the myenteric plexus, an increase in acetyl cholinesterase activity and the formation of giant ganglia. Diagnosing IND or HD is fundamentally dependent on histopathological analysis. Several immunohistochemical markers have been used for diagnosis [13]. Hirsprung sufferers may be significantly more likely to contract enterocolitis (inflammatory disease).

This analysis of amino acids and related metabolites was performed using High Pressure Liquid Chromatography. The test provides fundamental information on the adequacy of dietary protein, digestive disorders, mood and sleep disorders, and vitamin and mineral deficiencies. When the level of a specific amino acid or metabolite deviates significantly from the norm, an interpretive paragraph is presented which briefly discusses the possible causes, clinical implications and remedies for metabolic aberrations. If no significant abnormalities are detected, interpretative paragraphs and amino acid supplementation schedules are not provided. Because some staining techniques (eg AChE) are performed mainly in specialist centers and require frozen sections, many histopathology services encounter logistical problems and rely on the use of alternative special histochemical spots for evaluation. When diagnostic difficulties with hematoxylin and eosin staining occur, additional histochemical and immunocytochemical staining may be required [8,14]. However, a clear understanding of the potentialities of these staining methods and limitations is necessary to interpret the results. Immunohistochemical stains such as dehydrogenase stains, neurospecific enolase (NSE), S100 and PGP9.5, carretinin and synaptophysin [1,2,11,14] are currently used.

The choice of operative approach depends on the identification of the outermost segment of the intestine with ganglion cells. Often this can be suggested by contrast enema, but is usually determined by a biopsy with a frozen section examination performed in the operating room. Transition zone diagnosis should be provided by histological examination prior to colostomy or final withdrawal.

Conclusion

These guidelines serve as a first step towards standardizing the diagnosis and treatment of congenital megacolon. Against the background of routinely performed diagnostic procedures and genetic testing, histologic examination relevant to the type and volume of colon resection is of great importance for the type of surgery.

Our study confirms as other investigators do, the growing evidence that calretinin immunohistochemistry is a valuable marker in diagnosis of problematic cases and in differential diagnosis of HD or IND. The staining pattern is simple and distinct, and equivocal or misleading results are rare, as the stain is either positive or negative.

In conclusion, our investigation further emphasizes the value of calretinin immunohistochemistry as a diagnostic aid in histopathology evaluation of rectal biopsies for HD or IND. The final fix usually uses one of the 3 basic download operations. The techniques of these procedures are well documented. Each can be used as a technique for primary or staged repair with a laparoscopic approach. A definitive biopsy of the frozen section of the withdrawal segment prior to anastomosis is recommended.

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