Paediatr Croat. 2014;58:227-30
PRIKAZ BOLESNIKA / *CASE REPORT*
www.paedcro.com
http://dx.doi.org/10.13112/PC.2014.40

Immature colonic ganglion cells as a cause of megacolon in infancy: case report

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Immaturity of ganglion cells is a rare form of dysganglionosis that belongs to the group of dysmorphic types, characterized by a normal or mildly decreased number of ganglion cells, with the cells and their nuclei being considerably smaller in size. The disorder usually manifests clinically early after birth with abdominal distension, vomiting, feeding intolerance, and delayed passing of meconium. Diagnostic evaluation may include radiological studies; however, biopsy of colonic mucosa with histochemical analysis is considered the most reliable method. Manometry is a reliable noninvasive diagnostic study to confirm motility disorder. Treatment may be medical in mild cases and more commonly surgical due to complications of the disorder. We present a case of immature colonic ganglion cells as a cause of megacolon in infancy. In our case, medicamentous treatment was effective and led to normalization of bowel emptying and stool consistency. Considering that follow up rectosigmoidoscopy was refused by the patient's parents, we were not able to compare the histopathologic findings before and after the medicamentous treatment; however, the favorable clinical course made us assume that the ganglion cells had probably fully matured.

Keywords: colon; ganglia; dygestive system abnormalities; megacolon; infant

INTRODUCTION

The enteric nervous system is the basis of the gastrointestinal function, „the brain of the gut" and, along with the parasympathetic and sympathetic nervous system, it is considered the third part of the autonomic nervous system. The function of the enteric nervous system is very complex. Its main components are ganglion cells, which are mainly parasympathetic, and its primary target cells are secretory mucosal cells, gastrointestinal neuroendocrine cells and gastrointestinal musculature (1).

Since normal motility of the colon depends on the intactness of the anatomic characteristics, muscles and innervation of the intestinal wall, any impairment in these structures will lead to impaired intestinal motility. One of the causes of gastrointestinal motility disorder is dysganglionosis.

The first systematic classification of dysganglionoses was proposed by *Schärli* in 1995 (2), and ganglion cell immaturity and ganglion cell degeneration were later included as a new type, dysmorphic type (3-5). Ganglion cell immaturity is a rare form of dysganglionosis. In this type, the number of ganglion cells is normal or mildly decreased, but the cells and their nuclei are significantly smaller in size. This disorder was first described by *Spencer* in 1966 (6), and *Munakata et al*. (7) were the first to measure diameter of the ganglion cell nuclei in this disorder.

The disorder usually manifests clinically in the first days after birth with abdominal distension, vomiting, feeding intolerance, and delayed passing of meconium. Difficulty in the diagnosis of the disorder may be the small size of ganglion cells, and because of their dark nuclei and small nucleoli surrounded by thin basophilic cytoplasm, they may be easily mistaken for lymphocytes.

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Primljeno/Received: 5. 11. 2013., Prihvaćeno/Accepted: 27. 2. 2014.

CASE REPORT

Our patient was a female infant four months of age, born from a regularly controlled pregnancy, delivered by caesarean section in gestational week 34 5/7, with the following body parameters: weight 2320 g, length 44 cm, and Apgar score 6/7. The patient's mother had been diagnosed with diabetes mellitus type 1 at the age of 12, and had been suffering from celiac disease for the past four years.

The patient was admitted to the infant pathology department of our institute for pronounced distension of the abdomen and for emptying hard, dry stools, without slime or blood. The complaints had been present from birth, and the patient was admitted to hospital because of an extremely distended abdomen and enlarged inguinal hernias. On admission, the infant was febrile (38°C), of poor general condition, with reduced subcutaneous fat tissue in all predilection areas, and with a pronouncedly distended abdomen with an increased vascular pattern. There were prominent inguinal hernias on both sides. Axial muscle tone was reduced and segmental muscle tone was variable. Other clinical findings were normal.

Plain x-ray of the abdomen performed immediately after admission showed pronounced gaseous distended intestines with no signs of pneumoperitoneum (Figure 1). The diagnostic work-up was therefore directed to gastrointestinal and neurological evaluation.

Thorough laboratory evaluation was performed: complete blood count, erythrocyte sedimentation rate, liver and kidney function tests, blood glucose, serum electrolytes, acid-base balance, peripheral blood smear, parameters of coagulation, creatine phosphokinase, total protein, serum albumin, alkaline phosphatase, lactate dehydrogenase, ammonia, and lipase levels were all within the normal ranges; normal female 46,XX karyotype. Repeated sweat tests excluded cystic fibrosis. Because of maternal celiac disease and unreliable data on gluten intake, we performed a test for tissue transglutaminase antibody, which was negative. The latter, along with normal repeated findings of the stool with regard to the appearance and digestibility made us conclude that malabsorption was not likely. Small bowel biopsy was not available at the moment. Colonography showed a complete colon, with wider lumens of the ascending colon, cecum and sigmoid colon.

Gastroduodenal x-ray and small bowel follow-through were normal. Rectosigmoidoscopy of the mucosa up to 12 cm was normal. Specimens of the colon were obtained by suction biopsy, which was the reason why only the mucosa and submucosa were examined, and not the muscular layer of the mucosa. Considering the patient's age, biopsy sections were small and, therefore, frozen section analysis was not performed, but fixed paraffin sections were analyzed. H&E stained biopsy specimen of colonic mucosa showed preserved but very immature ganglion cells in the submucosa (Figure 2), which was the reason to abandon further analysis, i.e. acetyl cholinesterase activity and other histochemical analyses.

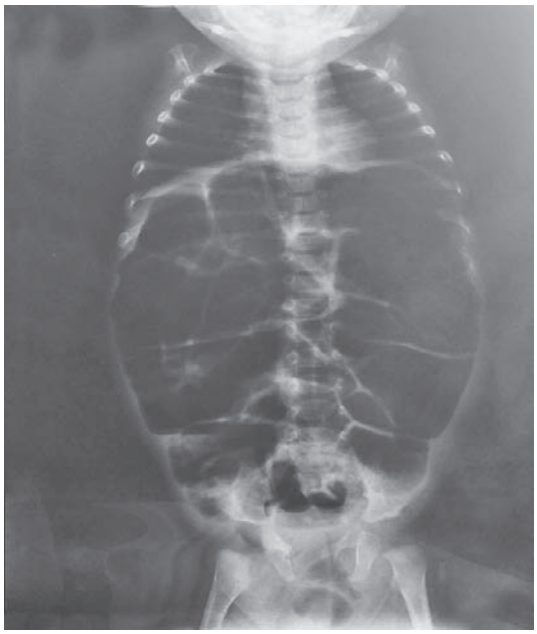

FIGURE 1. Plain abdominal x-ray showing pronounced gaseous distended intestines with no signs of pneumoperitoneum

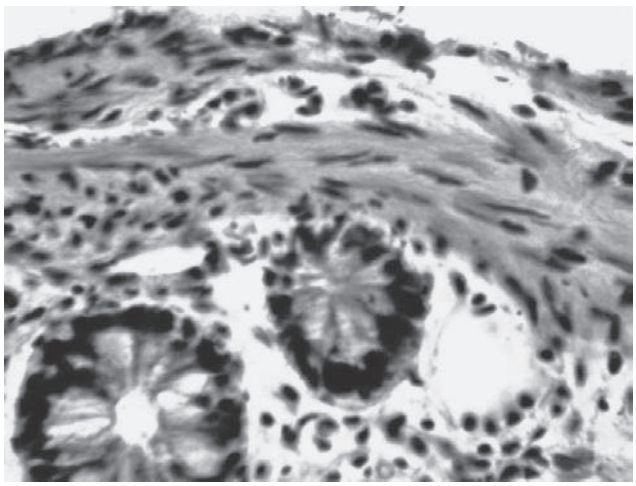

FIGURE 2. Microphotograph of colonic mucosa showing small, immature ganglion cells (HE, X200)

Considering the pronounced dystonic condition observed during examination, electromyography of lower extremities and brain magnetic resonance imaging were performed, and were normal. Psychological testing showed a global developmental quotient of 48 and delayed psychomotor development of both global and individual functions. An endocrinologist was consulted for diabetic foetopathy of

the patient's mother, and there were several consultations with a neurologist.

In consultation with a surgeon, medical therapy was introduced with antibiotics, intestinal prokinetics, stool softeners, and enemas. There was no satisfactory response to this treatment, so parenteral parasympathomimetic therapy (neostigmine) was introduced; every 6 hours in individual doses of 0.05 mg *per* kilogram of body weight. This therapy was effective and led to normalization of bowel emptying, stool consistency, reduced meteorism, and significant body development. The treatment was continued after discharge from the hospital, with gradual tapering the dose until the age of 10 months, when complete recovery was achieved. The recommended follow up rectosigmoidoscopy was refused by the patient's parents, so it was not possible to compare the biopsy sections before and after the conservative treatment.

DISCUSSION

Gastrointestinal motility disorders and chronic constipation are common problems in daily practice of paediatricians and paediatric surgeons. In large series of patients with neuronal intestinal malformations, it was found that only one-fourth suffer from aganglionosis (Hirschsprung's disease), but others have some type of dysganglionosis. Proposed by *Schärli,* immaturity of ganglion cell is a dysmorphic type of dysganglionosis (6). This category is characterized by the pathologic finding where the number of ganglion cells is either normal or slightly increased, whereas the nuclear size is small. Chronologically, this pathologic abnormality improves and becomes normal before the patient reaches one year of age. Clinically, most cases show evidence of small intestinal obstruction in the neonatal period and thus undergo ileostomy during the first days of life, but others do not need surgical treatment (4). To our knowledge, immaturity of ganglion cells is a known but rare problem in the clinical practice with a frequency of 3.6% -12.9% (8), which demands critical attitude and good judgment by the medical team as regards the treatment approach, taking into account that conservative treatment may be ineffective, while an early decision on surgical treatment may be risky and hasty. In general, the diagnosis of immaturity of ganglion cells can be made from rectal suction biopsy. Nicotinamide adenine dinucleotide phosphate diaphorase (NADPHd) and neural cell adhesion molecule (NCAM) staining, as well as enzyme histochemistry for succinate and lactate dehydrogenase have been suggested as neuronal markers to show the small ganglion cells more clearly. In our case, these special techniques were not available. Available literature data do not offer clear treatment algorithms in case of immature ganglion cells; however, the most commonly reported conservative treatment includes laxatives and enemas. In severe clinical cases, surgical treatment is recommended. In our patient, the clinical picture of ganglion cell immaturity was milder and did not require surgical treatment. Since in our case the application of laxatives and enemas was not satisfactory, we introduced intestinal prokinetics and neostigmine, given that colonic dysganglionosis may be a cause of motility disorder (9-12). The use of the intestinal prokinetic erythromycin had poor effect, whereas the application of the cholinesterase inhibitor neostigmine was very effective and led to normalization of bowel emptying and stool consistency, reduced meteorism, and body development until ganglion cells have completely matured. Literature data show that at birth, there is a combination of completely mature and small, immature ganglion cells (13). Maturation of ganglion cells and normalization of colonic motility usually occur by the age of 12 months, as in our patient, although there are cases reported of ganglion cells still maturing after 16 months of age. In all situations when dysganglionosis is suspected, if manometric studies are not available, repeated morphological and histochemical analyses of rectal biopsy specimens are recommended. In our case, manometric studies were not available, either initially or after treatment, and follow up rectosigmoidoscopy to evaluate final ganglion cell maturity was refused by the patient's parents. The histochemical findings of immature ganglion cells may indicate transient functional immaturity of the intestine that responded well to treatment with cholinesterase inhibitor (neostigmine). The favourable clinical course indicated that functional maturity and probably anatomic maturity of ganglion cells had been reached. The relationship between maternal diseases (diabetes and celiac disease) and the presence of immature ganglion cells in her child, however, may be a subject of further study.

NOVČANA POTPORA/*FUNDING*

Nema/*None*

ETIČKO ODOBRENJE/*ETHICAL APPROVAL*

Nije potrebno/*None*

DOPRINOSI AUTORA/*DECLARATION OF AUTHORSHIP*

Svi autori jednako su doprinijeli izradi rada/*All authors have equally contributed to a manuscript writing.*

SUKOB INTERESA/*CONFLICT OF INTEREST*

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REFERENCES

1. Paran Th, Rolle U, Puri P. Enteric nervous system and developmental abnormalities in childhood. Pediatr Surg Int. 2006;22:945-9. http://dx.doi.org/10.1007/s00383-006-1782-9
2. Schärli AF. Standardization of terminology of intestinal innervation disorders. Pediatr Surg Int. 1995;10:440. http://dx.doi.org/10.1007/BF00176383
3. Puri P, Rolle U. Variant Hirschsprung's disease. Semin Pediatr Surg. 2004;13:293-9. http://dx.doi.org/10.1053/j.sempedsurg.2004.10.017
4. Taguchi T, Masumoto K, Leiri S, Nakatsuji T, Akiyoshi J. New classification of hypoganglionosis: congenital and acquired hypoganglionosis. J Pediatr Surg. 2006;41:2046-51. http://dx.doi.org/10.1016/j.jpedsurg.2006.08.004
5. Markiewicz Kijewska M, Kowalski A, Bacewicz L, et al. Immaturity of ganglion cells – A study of our own material. Polski Przeglad Chirurgiczny. 2009;81:95-102. http://dx.doi.org/10.2478/v10035-009-0013-1
6. Spencer B. Problems in rectal biopsy due to immaturity of ganglion cells. Arch Dis Child. 1966;41:149.
7. Munakata K, Okabe I, Morita K. Hypoganglionosis. Pediatr Surg Int. 1992;7:8-11. http://dx.doi.org/10.1007/BF00180994
8. Schärli AF. Neuronal intestinal dysplasia. Pediatr Surg Int. 1992;7:2-7. http://dx.doi.org/10.1007/BF00180993
9. Hasler WL. Pharmacotherapy for intestinal motor and sensory disorders. Gastroenterol Clin North Am. 2003;32:707-32.
10. Schuurkes JA. Pharmacotherapy of gastrointestinal motor disorders. Rev Gastroenterol Mex. 1994;59:165-70.
11. Amaro R, Rogers AI. Neostigmine infusion: new standard of care for acute colonic pseudo-obstruction? Am J Gastroenterol. 2000;95:304-5.
12. Broad J, Kung VW, Boundouki G, Aziz Q, De Maeyer JH, Knowles CH, Sanger GJ. Cholinergic interactions between donepezil and prucalopride in human colon: potential to treat severe intestinal dysmotility. Br J Pharmacol. 2013;170:1253-61. http://dx.doi.org/10.1111/bph.12397
13. Burki T, Kiho L, Scheimberg I, Phelps S, Misra D, Ward H, Colmenero I. Neonatal functional intestinal obstruction and the presence of severely immature ganglion cells on rectal biopsy: 6 year experience. Pediatr Surg Int. 2011;27:487-90. http://dx.doi.org/10.1007/s00383-010-2850-8

SAŽETAK

Nezrele ganglijske stanice kolona kao uzrok megakolona u dojenačkoj dobi: prikaz bolesnika

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Nezrelost ganglijskih stanica je rijedak oblik disganglionoze koji spada u skupinu dismorfičnih tipova, a obilježen je normalnim ili blago povišenim brojem ganglijskih stanica, pri čemu su stanice i njihove jezgre znatno manje veličine. Klinički se bolest obično očituje rano poslije rođenja uz nadutost trbuha, povraćanje, nepodnošenje hranjenja i odgođen prolazak mekonija. Dijagnostička procjena može obuhvatiti radiološka ispitivanja, međutim, biopsija sluznice kolona uz histokemijsku analizu smatra se najpouzdanijom metodom. Manometrija je pouzdana neinvazivna dijagnostička pretraga za potvrdu poremećaja pokretljivosti. Liječenje može biti medikamentno u blažim slučajevima, ali je češće kirurško zbog komplikacija bolesti. Prikazuje se slučaj gdje su nezrele ganglijske stanice kolona uzrokovale megakolon kod dojenčeta. U našem slučaju se medikamentno liječenje pokazalo učinkovitim i dovelo je do normalizacije pražnjenja crijeva i konzistencije stolice. Kako su bolesnikovi roditelji odbili kontrolnu rektosigmoidoskopiju, nismo mogli usporediti histopatološke nalaze prije i poslije medikamentnog liječenja, ali povoljan klinički tijek ukazuje na to da su ganglijske stanice vjerojatno sazrele.

Ključne riječi: kolon; ganglija; abnormalnosti probavnog sustava; megakolon; novorođenče