Microvillous inclusion disease

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Summary. *Congenital defects in the intestinal mucosa can provoke diarrhea in the neonatal period. This kind of diarrhea is difficult to treat and the outcome is bad if intestinal transplantation is not done. We describe the case of newborn female with severe protracted secretory diarrhea, which started after first oral intake of breast milk. The newborn presented with severe dehydration and persistent metabolic acidosis though potential treatment was not stopped. Endoscopy with the biopsies from the distal part of duodenum mucosa was done on the third week of life. Histological examination revealed the pathological mucosa with the total microvillous atrophy, surface epithelium thinning and histochemical PAS (Periodic acid-Schiff reaction) positivity of enterocytes apical region. These changes are typical for rare microvillous inclusion disease. When the diagnosis of microvillous inclusion disease is made, the only treatment is total parenteral nutrition and intestinal transplantation.*

Introduction

The very first case of intractable diarrhea of infancy was described in 1968 (1). Three main parameters were assigned for this diagnosis: 3 consecutive negative stool culture results, more than 2 weeks lasting diarrhea and patient's age up to 3 months. Microvillous inclusion disease (MID), small intestine epithelial dysplasia, diarrhea syndrome, immune enteropathy and autoimmune enteropathy are the discernible forms of protracted diarrhea of infancy (1-3). Biopsy from small bowel mucosa during endoscopy has a great value as a modern diagnostic tool. Routine histological biopsy specimen examination in addition with other special histochemical staining methods enables to diagnose small intestine diseases.

When newborn diarrhea starts after breast-feeding, microvillous inclusion disease - congenital small intestinal mucosal defect can be suspected. Bowel movement typically is frequent, profuse and watery up to 100-500 ml/kg/day (1, 4). G. P. Davidson with colleagues reported on 5 infants with diarrhea since first days of life and offered MID term in 1978 (1, 5). Disease is very rare. Male to female ratio is 2:1 (4). There are only approximately 30 cases registered in the international centers' databases till 1987 and also few cases beyond (4, 5). The incidence is higher in North Arizona reservation of Navajo, USA and is 1:12000 of survived infants (4).

Clinical case report

Female infant R. S. was born in 37-gestation week, weighted 2530 g, 9-10 scores according to Apgar scale. For mother it was the first pregnancy as well as childbirth. Mother suffered from non-complicated respiratory viral infection during the pregnancy. Baby suckled breast milk unwillingly and started to diarrhea at the natal day. Weight dropped down, and dehydration progressed. Patient was transported to regional center hospital with worsening condition and symptoms of hypovolemic shock at the 4th day of life. Repeated blood tests showed increasing acidosis. Defecation was frequent, profuse with watery stool. Feeding stylet was entered in to stomach because of refuse to suckle. Set milk was pumped out of the stomach before each feeding. Weight dropped from 1834 g to 496 g within 7 days. Suspected bacterial infection was treated with antibiotics, however with no effect. Patient was took to the Department of Neonatal Intensive Care of Kaunas University of Medicine Hospital at 8th living day. Diarrhea pursued without

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reference to any nutriment. Stool amount increased over 200 ml/kg per day and health condition worsened even after water intake. Multiple consultations with pediatric surgeon, neurologist, endocrinologist, oculist were taken, but diagnosis was not clarified. Ultrasound showed no specific changes. Blood tests showed high acidosis level and intravenous solutions were injected to control this. Pathogenic microorganisms were not cultured from any blood, stool and urine specimens. Pediatric gastroenterologist suspected congenital enteropathy and recommended to perform duodenal biopsy also immunological tests to differentiate with autoimmune enteropathy. Antinuclear (ANA), anti-smooth muscle (ASMA) and anti-DNA antibodies immunological tests were negative. Diarrhea stopped after the complete parenteric nutrition was applied. Newborn gained weight and blood acid-alkaline balance normalized. Four biopsy pieces were taken from duodenal distal part mucosa during endoscopic procedure. Histological examination revealed abnormal duodenal mucosa structure: mucosa surface almost flat, slightly humpy. Epithelium attenuated, flat to cuboidal, with low mucous secretion and decreased number of intestinal type goblet cells. Periodic Acid-Schiff (PAS) positive granules in the apical epitheliocytes side were found. They formed bright purple margin. Total villous atrophy, attenuated epithelium and PAS positive marginal zone in epithelium apical side were main pathological changes (Fig.), typical for MIL. Diagnosis was determined combining clinical course and investigations including histological biopsy evaluation also effect of parenteral feeding.

The latter in continuation was complicated with septic infection several times. For further treatment patient was transferred to Klaipėda pediatric hospital. Patient died on 47 day of life due to life functions exhaustion caused by congenital metabolism disorder. Autopsy findings showed lung and brain edema, intrahepatic cholestasis and dystrophy of hepatocytes, myocardium fibers and renal cells. Duodenal mucosa villi were found short, broad or totally atrophic. Epithelium was dystrophic, attenuated without mucous secretion. Epithelium and lamina propria was slightly infiltrated by mixed inflammatory cells. Macroscopically duodenal mucosa was pale, unlined, lumen spacious, filled with green mucous. In autopsy report concluded death causes were imbalanced homeostasis and immune insufficiently resulted by malfunctioning small intestine mucosa with digestive tract disturbance.

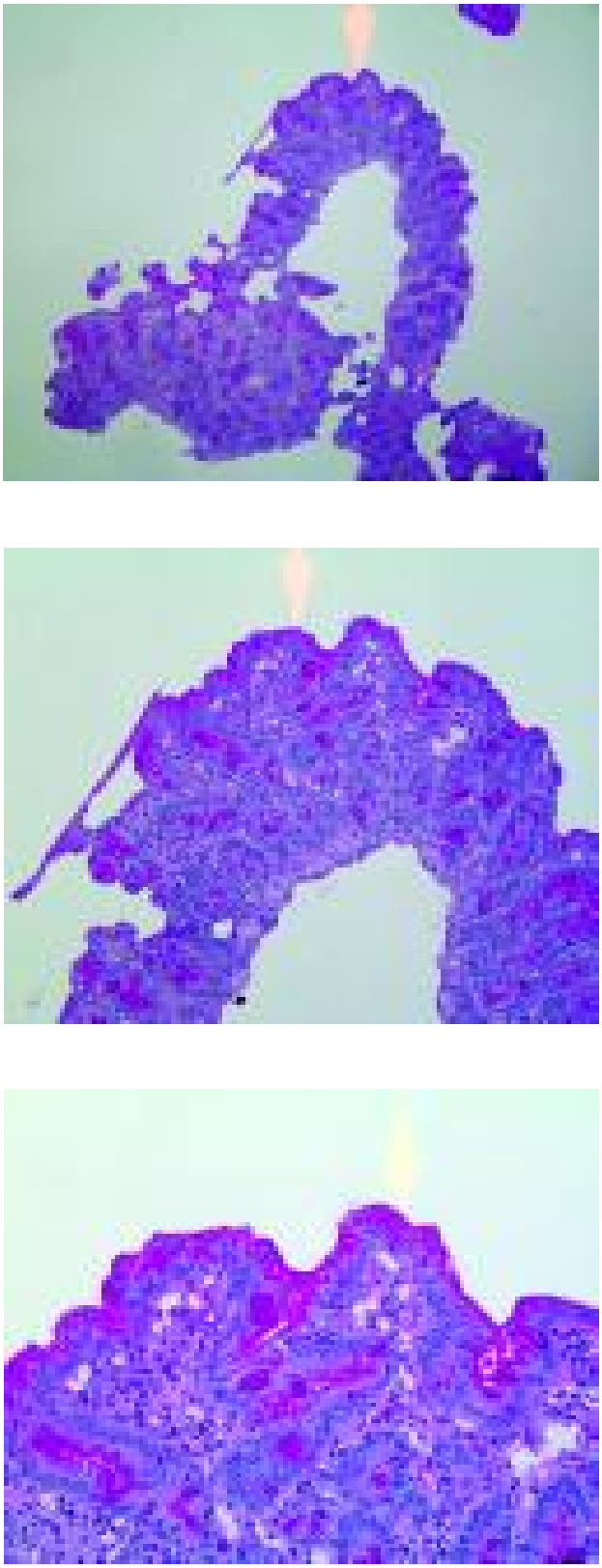

Fig. **Shortened and blunted duodenal mucosa villi (arrows)**
Attenuated, with PAS positive apical pole epithelium (purple color); decreased goblet cells (white stars). PAS + hematoxylin staining method.

Discussion

Congenital small intestine mucosa pathology should be suspected when diarrhea starts within the first 72 hours of life. It is necessary to take in mind other possible metabolic disorders and bacterial infections. Secretory diarrhea is characteristic of MID with no reference to nutriment or fluid sort (4, 5). Defecation continues during total parenteral nutrition, but stool becomes less voluminous and without mucous. MID causes rapid and heavy dehydration also pronounced electrolyte and alkaline-acidic imbalance in the blood if fed enterally. Disease is inherited by autosomal-recessive gene, however exact pathogenesis is still not known (2, 6). Five cases of MID with ferment dihydropyrimidinase deficiency are known and it is possible disease inheritance by the same gene (4). One case of MID together with rare hypochondrodysplasia syndrome for girl was reported (7). There are three MID forms: typical (80), with late onset and atypical (put together 20). Mortality is hundred-percent if intestine transplantation is not performed. International medical investigations statistics show mortality of 74 within first 9 months of life (6). Prognosis is more favorable if symptoms appear later, i.e. within 6-9 weeks of life. Such case was reported in the literature: MID was diagnosed at 2 weeks of age and parenteral feeding was continued till 3 years passed. Normal child growth was observed and partial peroral feeding was recommended. Repeated biopsy showed lower degree of mucosa damage when compared with initial biopsy results at first month of life. Peroral feeding continuation thereby was recommended due to clinical improvement and positive histological changes (6). Atypical MID is when disease course and symptoms are similar except that microvillous inclusions are not found. This form was suggested entitle microvillous dystrophy (4, 8).

Congenital and acquired causes should be differentiated if diarrhea starts in neonatal period. Acquired causes include various viral and bacterial infections with enterocolitis symptoms. Congenital causes include composite immunodeficiency states, protein and lactose intolerance, secretory diarrhea with chloride and sodium loss, biliary acid malabsorption, glucose-galactose malabsorption, and immune enteropathy. Searching for diarrhea cause there is important routine blood, urine, alkaline-acid balance testing, stool culture as well as specific immunological investigations. Diagnosis can be ascertained with histological investigation of biopsy material, taken from duodenal mucosa during fibrogastroduodenoscopy. Light microscopy enables to see various changes: partial or total villous atrophy, epithelium attenuation, PAS (+) secretory granules (polysaccharides, glycoproteins, glycolipids, neutral mucopolysaccharides) aggregation in the apical pole of epitheliocytes. These features are typical for MID and valuable in combination with other clinical data and investigations results, however not specific. Electronic microscopy is even more valuable investigating biopsy specimens (1, 4, 6). Normal epithelium with number of microvilli is deeply in the crypts. Damaged enterocytes are luminal, especially located on shortened villi apices. Microvilli here are sparse, short, wrongly situated. Intracytoplasmic degenerative vacuoles containing microvilli are found in part of enterocytes. Abundant vesicles related to cytoplasmic membrane and containing electronically dense material is another important feature of MID (9-11).

There are published data concerning rapid diagnostics: it is reasonable to perform rectoscopy and biopsy for rectal mucosa histopathology. Expected changes, such as microvillous degeneration and secretory granules abundance, can be found (4, 6).

Complete parenteral feeding and small intestine transplantation is the only effective treatment after MID was established (12). Complete parenteral feeding in most instances complicates with fatal septic infections and liver insufficiency (1, 4, 13). There are obscure data in the literature concerning MID medicamental treatment, however investigated corticosteroids, epithelial growth factor, loperamide showed no effect on disease course (1). Results of one study suggested beneficial octreotide (somatostatin analogue) effect, but later investigations denied these data (14). 5 children suffering from MID underwent small intestine transplantation (12, 15). Two children died and three were improved significantly (10). One patient underwent small intestine and liver transplantation, after what good condition improvement was achieved. Another 3 patients underwent small and partly large intestine transplantation due to changes in large intestine epithelium causing secretory diarrhea (12). Two last cases with small intestine transplantation were more successful in post operative period, because of large intestine was spared and even short segment of small intestine was not resected (12, 15). Survival rate is 50 after small intestine transplantation for children (4).

Mikrogaurelinių intarpų liga

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Raktažodžiai: kūdikių viduriavimas, įgimta mikrogaurelių atrofija, mikrogaurelinių intarpų liga.

Santrauka. Naujagimio viduriavimą gali sukelti įgimti plonosios žarnos gleivinės defektai. Tokį viduriavimą sudėtinga gydyti. Be to, jei nepadaroma plonosios žarnos transplantacija, ligos prognozė bloga. Aprašomas sunkaus sekrecinio viduriavimo atvejis, prasidėjęs naujagimiui, pirmą kartą pamaitinus jį motinos pienu. Naujagimiui nustatyta didelio laipsnio dehidracija ir metabolinė acidozė, nors buvo skirtas intensyvus gydymas. Trečiąją gyvenimo savaitę atliktas endoskopinis tyrimas, paimta biopsija iš dvylikapirštės žarnos distalinės dalies gleivinės. Histologinis gleivinės vaizdas įvertintas kaip patologinis dėl visiškos gaurelių atrofijos, epitelio išplonėjimo ir histochemiškai nustatytos jodo perrūgšties su Šifo reagentu teigiamos zonos apikaliniame epiteliocitų poliuje. Šie pakitimai būdingi retai plonosios žarnos gleivinės mikrogaurelinių intarpų ligai. Nustačius mikrogaurelinių intarpų ligą, vienintelis gydymas – parenterinis maitinimas ir plonųjų žarnų transplantacija.

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