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ORIGINAL PAPERS

# Megacystis Microcolon Intestinal Hypoperistalsis Syndrome Berdon's syndrome - First Report in Romania

Mihaela BIZUBAC[1,2,6], Luminita NINE[1], Andrada GEORGESCU[1], Loredana POPA[3,6], Andrei CAPITANESCU[4], Sebastian IONESCU[5,6], Carmen HERISEANU[1,2,6], Catalin CIRSTOVEANU[1,2,6]

## Abstract

Megacystis Microcolon Intestinal Hypoperistalsis Syndrome (MMIHS) is a rare motility disorder with high mortality rate described by Berdon in 1976. We present the first case of Berdon's syndrome (heterozygous pathogenic variant in the ACTG2 gene) reported in Romania, a female newborn admitted in NICU "Marie S. Curie" Emergency Children's Hospital Bucharest for intestinal obstruction after birth. Total parenteral nutrition, ileostomy, gastrostomy, clean intermittent bladder catheterisation, evaluation for multivisceral transplantation were performed. She was discharged from our NICU ward at the age of 4 years and 2 months with home total parenteral nutrition administered by her mother in sterile condition, clean intermittent catheterisation for bladder evacuation performed by her mother, monitored monthly for about three years, with normal cardio-respiratory function, no signs of thrombosis, she maintained relatively low platelet count without positive blood culture, good liver and renal function test. Normal neurological and psychomotor development according to age. Her course was complicated by multiorgan failure with death ensuing at the age of 7 years and 10 months.

**Keywords:** MMIHS, ACTG2 gene, total parenteral nutrition, ileostomy, gastrostomy, clean intermittent catheterization, multiorgan failure.

[1]Neonatal Intensive Care Unit, "Marie S. Curie" Emergency Children's Hospital, Bucharest, Romania
[2]Department of Neonatal Intensive Care, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[3]Pediatric Nephrology, "Marie S. Curie" Emergency Children's Hospital, Bucharest, Romania
[4]Hemodialysis Centre, "Marie S. Curie" Emergency Children's Hospital, Bucharest, Romania
[5]Department of General Pediatric and Orthopedic Surgery, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[6]Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

**Corresponding author:**
**Andrada GEORGESCU,** Neonatal Intensive Care Unit, "Marie Curie" Emergency Children's Hospital, Bucharest, Romania
**E-mail:** nicolaeandradateodora@gmail.com

## BACKGROUND

Berdon's syndrome or MMIHS (megacystis-microcolon-intestinal hypoperistalsis syndrome)[1] was first reported in 1976 by Berdon et al[2] who described 5 cases of females newborn, two of whom were sisters, with marked abdominal distension and bilious vomiting[3], malrotation[4], hypoperistalsis or aperistalsis of gastrointestinal system[5], dilate proximal ileum and colon, either normal or increased mature ganglion cells in intestine wall[4], nonobstructive bladder distension and vesicoureteral reflux present. It is a rare and fatal inherited syndrome[6]. According to current literature (1976-2019), 450 cases were reported[1].

It is transmitted autosomal dominant or recessive[7,8], the last one has been defined in most reports with family history and siblings' cases. MMIHS has a female predominance of 3 or 4 to 1[1]. As in most paediatric cases, it belongs to the primary causes of chronic intestinal pseudo-obstruction syndrome[9]. Secondary chronic intestinal pseudo-obstruction usually occurs in adults and can have numerous causes (muscular dystrophy, connective tissue disease, chronic infections- Chagas disease)[10].

The genes involved in 50% of MMIHS cases are ACTG2 (44.1% of genetic cases, the most severe form)[11,12], MYH11 (myosin heavy chain 11)[13], MTLK (myosin light chain kinase), LMOD1 (leiomodin 1)[14], MYL9 (myosin light chain 9)[15].

Autosomal dominant forms of MMIHS are caused by de novo variants of ACTG2[16], while homozygous variants in MYH11, MYL9, MYLK or LMOD1 cause recessive forms[17] with parental consanguinity[18].

The antenatal diagnosis is very difficult. Prenatal ultrasound has been the most frequent utilized method before the second trimester[19,20]. The presence of polyhydramnios, severe dilatation of the urinary bladder (88% of cases), bilateral hydronephrosis (66% of cases)[4] it is insufficient in establishing the viability of the gastrointestinal tract[21] and microcolon. IRM performed between 23 and 28 weeks of gestation appears useful for diagnosis[22] although it is rarely used in the prenatal assessment[23].

The histopathological study is essential to diagnose MMIHS. A lack of nicotinic receptor subunits, a fibre synthesis defect, an inflammatory process of the gastrointestinal and urinary tract[24], primary disfunction of the architecture of the smooth muscle cell membrane (thin longitudinal smooth muscle fibres of the gut wall or bladder, degenerative vacuoles and increased collagen deposits[6]) or intestinal generalized axonal dystrophy in central and peripheral nervous system determine various clinical features of the Berdon's syndrome[25,19]: microcolon, dilated and hypoperistaltic or aperistalsis small bowel loops with thin wall as in prune belly syndrome[2,10,26], malrotation, constipation, nonobstructive giant bladder (megacystis) with urinary retention and hydronephrosis[6]. Normal or excessive immature ganglion cells have been reported, but also one case without ganglion cells[27].

Treatment of Berdon syndrome is supportive and assumes limited surgical options for frequently bowel decompression (including gastrostomy, ileostomy, jejunostomy and colostomy), total parenteral nutrition[24,28,29,30]. The attempts to improve peristalsis using prokinetic agents or gastrointestinal hormones such as gastrin, cholecystokinin and secretin have failed[31,32,33]. Intermittent bladder catheterization and prophylactic antibiotic treatment is the therapeutic option for urological management[34].

Multivisceral transplantation is a valuable alternative[34], but the survival rate is minimal, sepsis being the main complication[24,28,29]. The first report was in 1990, when three patients with MMHIS underwent multivisceral transplantation, patients survived 44 days, 17 and 24 months after surgery[35]. In 2005, Loinaz et al. noticed 12 patients with CIPOS, 6 of them with Berdon's syndrome; fifty percent survived from 2 to 7 years after transplantation and have not required TPN[36]. In 2021, Krishnapriya et al. identified 25 patients with MMIHS (68% girls, 13 transplanted), with 100, 100 and 86 % for 5- 10- and 20-year survival rate, the transplanted patients were followed for a median period of 6.1 years, with the longest post-transplant follow-up of 16.6 years[37].

Long-term survival rates have increased from 10-20% to 55.6% (cases diagnosed in 2004-2011)[1] with recent advances in management of TPN complications and multivisceral transplantation.

MMIHS patients die from malnutrition, sepsis, kidney failure, thrombosis, liver failure depending on TPN and complications of TPN[1,23].

## CASE PRESENTATION

We present the case of B.E., a female infant born at 37 weeks gestational age by caesarean section, weighed 3650 g, Apgar scores were 8 at one minute and 8 at five minutes.

Second trimester prenatal ultrasound findings showed polyhydramnios, megacystis with 1.8 mm wall and right transient hydronephrosis (Fig. 1).

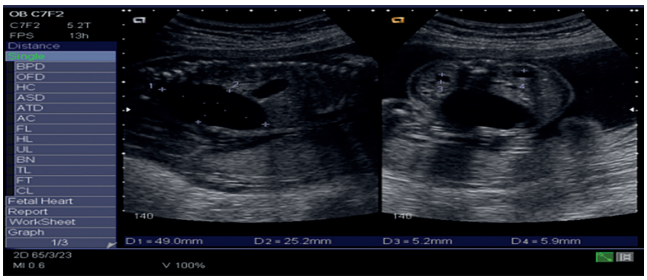


**Figure 1.** Prenatal ultrasound: polyhydramnios, megacystis, right hydronephrosis

She was admitted in our unit at one day of life for abdominal distension, bile staining vomiting, without meconium passage, stool or spontaneous micturition.

Abdominal X-Ray revealed dilated stomach, minimal gas in the distal intestinal segments. Abdominal ultrasound showed enlarged stomach and urinary bladder, malrotation. Upper gastrointestinal series identified enlarged stomach, malrotation, absence of peristaltism, microcolon (Fig. 2).

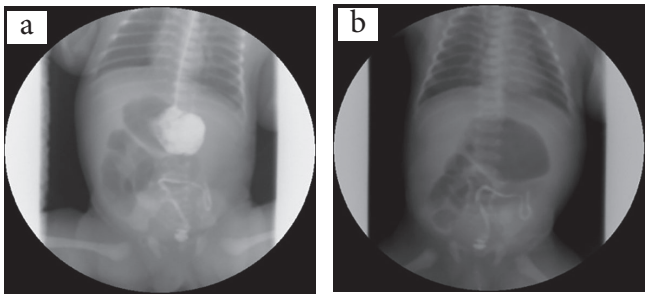


**Figure 2.a.** Upper gastrointestinal serie: enlarged stomach, malrotation, aperistaltic small bowel loops; **b.** Irigography: malrotatied microcolon

Ileostomy, gastrostomy and histopathologic exam were performed. The terminal ileon and colon histology confirmed hypertrophy and hypoplasia of nerve fibers, ganglia cell, thin muscle layer, edema (Fig. 3).

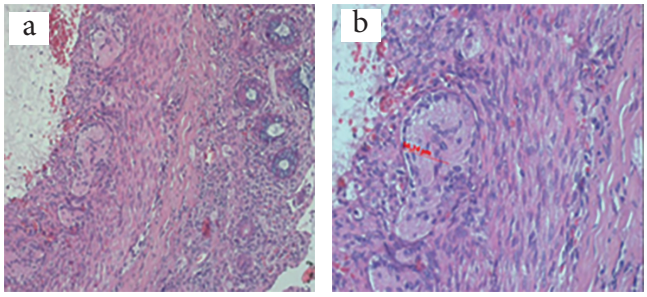


**Figure 3.** Histology of the terminal ileon and colon: **a.** hypertrophy and hypoplasia of nerve fibres, ganglia cell, thin muscle layer, edema; **b.** extensive vacuolar degeneration (56.24μm)

Through clinical examination, intraoperative findings, paraclinical tests including ultrasonography, upper gastrointestinal series, histopathological results and whole exome sequencies (heterozygous pathogenic variant in the ACTG2 gene), the diagnosis was established-megacystis-microcolon-intestinal-hypoperistalsis syndrome (MMIHS).

Gastrointestinal output was maintained in large amounts with minimal ileostomy output after performing dilatations at this level and with medication. Total parenteral nutrition on central venous line was provided. The attempts of enteral nutrition have failed due to enema episodes and abdominal distension.

Upper gastrointestinal series carried out periodically identified absence of peristaltism movements, microcolon, reduced intestinal pneumatization, not unidentifiable esophageal peristalsis, mild esophageal stasis with slow evacuation, verticalized stomach without radiological kinetics. Barium solution was administered through gastrostoma tube with the view of a few intestinal loops, without peristalsis; after one hour: unchanged aspect of bowel opacification, barium present at gastrostoma level; homogenous hepatomegaly, portal hypertension, progressive splenomegaly, no signs of deep vein thrombosis upon imaging of the femoral veins, internal right jugular vein, right subclavian vein.

Clean intermittent catheterisation for bladder evacuation was performed.

During hospitalization our patient had 11 documented episodes of sepsis, with favourable response to antibiotic and antifungal therapy.

She underwent a detailed transplant assessment in the first year of life and at 4 years of age at a specialized centre: liver biopsy showed severe liver fibrosis; CPE and ESBL colonization. Transplant option to be kept open for the future.

B.E. was discharged from our NICU ward at the age of 4 years with home total parenteral nutrition (through Broviac central venous catheter) administered by her mother in sterile conditions. Clean intermittent catheterisation for bladder evacuation performed by her mother 4-6 times per day. She was monitored monthly with normal cardio-respiratory function, no signs of thrombosis, maintained relatively low platelet count without positive blood culture, good liver and renal function test. Normal neurological and psychomotor development according to age.

Upper gastrointestinal series carried out periodically showed absence of peristaltism movements, microcolon.

Barium transit series identified barium base contrast material solution administered through gastrostoma tube confirmed slow evacuation through central pylorus. During the examination, we noted the slow progression of the contrast substance in orthostatism, probably under the action of the gravitational force.

Abdominal and Pelvic Ultrasound and IRM showed moderate enlarged liver, partially contracted gallbladder with sludge, lymph node image, splenomegaly, accessory infrahilar spleen, both kidneys with increased size, mild pyeloureteral hypotony, distended bladder with thin walls, homogenous liquid content, ovaries not visible, intestinal malrotation (without duodenal horseshoe shape, small intestinal lops located in the right abdominal flank and in the mesogastric, colon located in the left abdominal flank), dilated distal esophagus, stomach and small intestinal loops with thin walls, hydroaeric levels, without visible obstruction, colon with reduced caliber, air content, without haustration, wall of normal thickness (microcolon), middle celio-mesenteric and lumbo-aortic adenopathies, with reactive appearance.

At 7 years and 5 months of life B.E. was readmitted in our hospital with respiratory failure, anasarca, no ileostomy passage, oligury. Laboratory studies identified severe inflammatory response syndrome; abdominal ultrasound pleurisy, ascites, heparosplenomegaly; IRM, fibroscan showed severe liver fibrosis; progressive cronic kidney disease. She had intermittent hemodialysis, abdominal drainge. Her course was complicated by multiorgan failure, with death ensuing at the age of 7 years and 10 months.

## CONCLUSION

Megacystic microcolon intestinal hypoperistalsis syndrome is a rare and severe smooth muscle myopathy that affects the intestines and urinary bladder[18] transmitted autosomal recessive or dominant. Genetic counselling to families with a history of MMIHS is recommended. The antenatal diagnosis is very difficult, most cases die within the early months of their lives, undiagnosed or misdiagnosed[23]. The high female to male sex ratio (3 or 4 to 1)[1] it is possible due to underdiagnosis in males, misdiagnosed as isolated cases of prune belly syndrome[9].

B.E. is the first case of MMIHS reported in Romania, a female infant who was the 3-rd life birth of non-consanguineous caucasian parents, her sisters in good health. Prenatal ultrasound performed at 22 weeks gestational aged and antenatal investigation indicated polyhydramnios, megacystis and right transient hydronephrosis.

The severity and broad spectrum of clinical manifestation causes a complicated management of Berdon's syndrome. Some of them involved deafness, blindness, congenital heart disease, prune belly syndrome[38]. Our patient was diagnosed with MMIHS by clinical findings (abdominal distension, bile staining vomiting, without meconium passage, stool or spontaneous micturition), abnormal imagining studies (X-ray and abdominal ultrasound showed enlarged stomach and urinary bladder, malrotation, right hydronephrosis; upper gastrointestinal series revealed enlarged stomach, malrotation, aperistaltism, microcolon), surgical data, laboratory/histopathological findings (hypertrophy and hypoplasia of nerve fibers, ganglia cell, thin muscle layer, edema) and genetic testing (whole exome sequencies- heterozygous pathogenic variant in the ACTG2 gene, the most severe form).

Treatment is supportive, surgical choices are limited and involves gastrostomy, ileostomy, jejunostomy and colostomy. For gastric decompression, we performed ileostomy at 12 cm from ileocecal valve, gastrostomy. Total parenteral nutrition was provided (14 central lines during hospitalization). The attempts of enteral nutrition have failed because of significant oral aversion.

During hospitalization, B.E. had 11 documented episodes of sepsis, 8 of them in the first 2 years of life with positive culture with favourable response to antibiotic and antifungal therapy. The prognosis of these

patients is poor, death occurs because of sepsis, total parenteral nutrition complications, malnutrition, catheter- related sepsis, multiorgan failure. There are an increasing number of patients with prolonged survival, probably with advances in intestinal rehabilitation and transplantation.

Due to the absence of neonatal/paediatric intestinal transplantation specialized centre in our country, after birth and at 1 year and 4 years of age our patient was referred for multiorgan transplantation and this option was kept open. To date, transplantation is the only viable option for patients with gastrointestinal dysmotility who cannot be adequately managed with total parenteral nutrition[39]. The improvement in outcomes and survival rates for transplant patients over the past decade is based in improvements in surgical technique and postoperative management[10].

B.E. was discharged from our NICU centre at 4 years of age with home total parenteral nutrition (through Broviac catheter) administered by her mother in sterile conditions, clean intermittent catheterisation for bladder evacuation performed by her mother 4-6 times per day in sterile conditions. For about three years she was monitored monthly, with normal cardio-respiratory function, no signs of thrombosis, she maintained relatively low platelet counts without positive blood culture, good liver and renal function test. Normal neurological and psychomotor development according to age, at 5 years of age diagnosed with reduced hearing, for which she received hearing aids.

Our patient was readmitted in the hospital at 7 years and 5 months due to respiratory failure, anasarca, no ileostomy passage, oligury, severe liver fibrosis, progressive kidney failure. Parenteral nutrition-associated liver disease occurs in 43-74% of infants with intestinal failure. The risk factors for the development are preterm birth, low birth weight, macronutrients excess, trace element imbalances, multiple surgical procedures, absence of enteral feeding, prolonged use of parenteral nutrition, recurrent sepsis from central venous catheter- associated infections[40]. Urological management was intermittent bladder catetherization and prophylactic antibiotic therapy. Both kidneys with moderate increased size, kidney stones, mild pyeloureteral hypotony, distended bladder with thin walls, homogenous liquid content, multiple urinary tract infections contributed over time to progressive kidney failure. She had intermittent hemodialysis.

Her course was complicated by multiorgan failure, with death ensuing at the age of 7 years and 10 months.

We conclude that the best option for infants or children with intestinal hypoperistalsis syndrome is intestinal transplantation in an US or European specialized centre.

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