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Megacystis microcolon intestinal hypoperistalsis syndrome

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KEYWORDS
Megacystis microcolon intestinal hypoperistalsis syndrome;
Functional intestinal obstruction;
Non-obstructed urinary bladder distention;
Newborn

Megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) is a rare and the most severe form of functional intestinal obstruction in the newborn. The major features of this congenital and usually lethal anomaly are abdominal distension, bile-stained vomiting, and absent or decreased bowel peristalsis. Abdominal distension is a consequence of the distended, unobstructed urinary bladder with or without upper urinary tract dilation. Most patients with MMIHS are not able to void spontaneously. This article reviews the pathogenesis of MMIHS as well as the clinical, radiological, surgical and histological findings in all reported cases of this syndrome.

Megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) is a rare congenital and generally fatal cause of functional intestinal obstruction in the newborn. This syndrome is characterized by abdominal distension caused by a distended non-obstructed urinary bladder, microcolon and decreased or absent intestinal peristalsis.[1] Usually incomplete intestinal rotation and shortened small bowel are associated.

Pathogenesis

The MMIHS was first described in 1976 by Berdon and coworkers and to date, 182 cases have been reported in the literature.[1-87] The etiology of this syndrome remains unclear. Several hypotheses have been proposed to explain the pathogenesis of MMIHS: genetic,[20,28,36,37,42,44,52,61,63,75] neurogenic,[5,8,12,15,20,21,35,39,40,53,63] myogenic,[2,57,80,81] and hormonal origin.[11]

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Histologic studies of the myenteric and submucosal plexuses of the bowel of MMIHS patients have found normal ganglion cells in the majority of the patients, decreased in some, hyperganglionosis and giant ganglia in others.[63] An imbalance between several kinds of intestinal peptides was suggested as one of the possible causes of hypoperistalsis in MMIHS patients.[39,60] Recently, Piotrowska and coworkers[81,87] reported absence of interstitial cell of Cajal (ICCs) in the bowel and urinary bladder of patients with MMIHS. ICCs are pacemaker cells which facilitate active propagation of electrical events and neurotransmission and their absence may result in hypoperistalsis and voiding dysfunction in MMIHS. Puri and coworkers[2] showed, in 1983, vacuolar degenerative changes in the smooth muscle cells (SMCs) with abundant connective tissue between muscle cells in the bowel and bladder of patients with MMIHS and suggested that a degenerative disease of smooth muscle cells could be the cause of this syndrome. Several subsequent reports have confirmed evidence of intestinal myopathy in MMIHS.[57,80,81] Ciftci and coworkers[57] reported a case without vacuolar degeneration but with excessive smooth muscle glycogen storage. They postulated that the pathogenesis involves a defect of glycogen-energy utilization. Other investigators have reported absence or marked

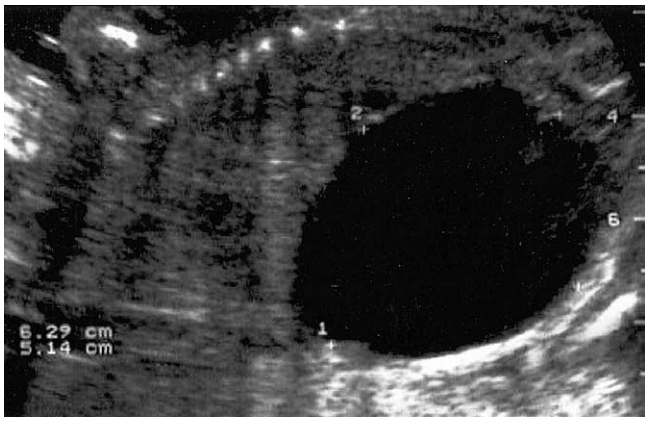

Figure 1 Large fetal bladder seen on a longitudinal view of abdominal ultrasound at 22 weeks gestation. The fetus is in prone position.

reduction in α-smooth muscle actin and other contractile and cytoskeletal proteins in the smooth muscle layers of MMIHS bowel.[80,81] Contractile and cytoskeletal proteins are important structural and functional components of SMCs and play a vital role in the interaction of the filaments in smooth muscle contraction.

Recent work with transgenic mice lacking certain nicotinic acetylcholine receptor (ηAChR) subunits, which show some of the phenotypic features of MMIHS suggests a basis for this condition. Xu and coworkers[88,89] produced MMIHS phenotype in $\beta 4/\alpha 3$ (two of the seven neuronal nicotinic acetylcholine receptor subunits) knockout mice. The $\alpha 3$ and $\beta 4$ subunits have been localized to human chromosome 15. Recently, Richardson and coworkers[74] performed in situ hybridization and immunocytochemistry studies to examine if $\alpha 3$ mRNA or $\alpha 3$ subunit protein were expressed in the resected specimens of small bowel from patients with MMIHS. They found lack of $\alpha 3$ ηAChR staining in most MMIHS tissues, thus suggesting that the absence of functional $\alpha 3$ subunit containing ηAChR may provide a possible explanation for the underlying pathogenesis of MMIHS.

Prenatal diagnosis

Fifty-four previous reports have described fetal ultrasound findings associated with MMIHS. The most frequent finding was enlarged bladder (88%) (Figure 1), with hydronephrosis seen in 31 patients (57%).[63,72,84] Normal amniotic fluid volume was revealed in 32 cases (59%), increased volume in 18 (33%) and decreased volume in 4 (7%). In 3 cases (5%)[19,36,52] abdominal distention caused by dilated stomach was detected. Three cases of oligohydramnios during the second and early third trimesters were reported,[13,23,46] probably related to the functional bladder obstruction. In 1 case,[46] oligohydramnios changed into polyhydramnios at the end of the third trimester.

Serial obstetrical ultrasonography showed that the earliest finding in MMIHS is enlarged bladder, detectable from 16 weeks of gestational age. A later finding is hydronephrosis, caused by the functional obstruction of the bladder. Usually polyhydramnios develops late, appearing during the third trimester.

Clinical presentation

Of the 182 cases reported in the literature, sex of the patient was mentioned in 149 patients. Ninety-eight were females and 43 were males. In 4 cases, pregnancy was terminated after ultrasonography detected MMIHS, which was confirmed at autopsy in all cases. The duration of pregnancy was reported in 98 cases. Fifty-eight patients (59%) were born at term, 25 (25.5%) at 36 to 39 weeks of gestation, 12 (12%) at 32 to 35 weeks and 3 (3%) at 31 weeks and less. Dystocia delivery caused by abdominal distention was reported in 8 cases. In four cases Caesarean section was required[14,33,36,45] and in four cases the bladder was so distended that the baby could only be delivered vaginally after removal of 250, 500, 650, 500 mL of urine, respectively, from fetal bladder by paracentesis.[2,39,43,56] The mean birth weight was normal (3 kg) for gestational age.

The clinical symptoms of MMIHS are similar to other neonatal intestinal obstructions. Characterized by abdominal distention, bile-stained vomiting and absent or decreased bowel sounds, abdominal distention was a constant and early finding. A consequence of the distended, nonob-

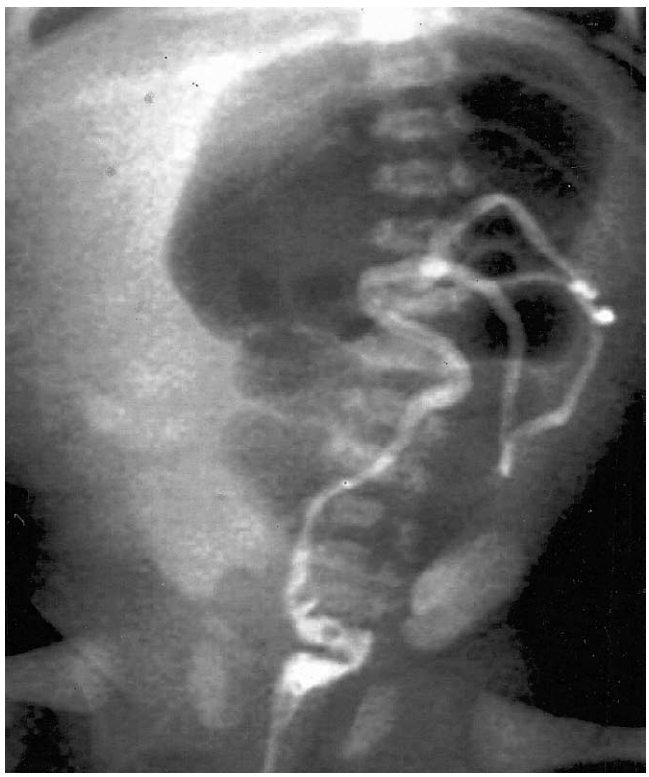

Figure 2 Voiding cystourethrogram showing a massively enlarged bladder in an MMIHS patient.

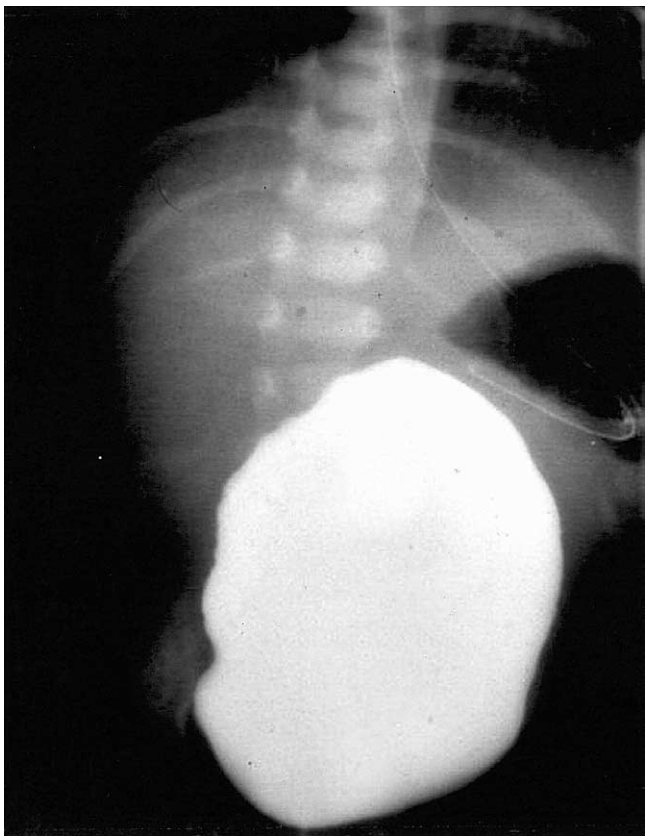

Figure 3 A contrast enema showing microcolon in an MMIHS patient.

structed urinary bladder was relieved by catheterization. Of 182 cases 61 had bilious vomiting and failure to pass meconium was clearly reported in only 23 cases. The majority of patients were not able to void spontaneously.

Nineteen sets of siblings affected with MMIHS were reported. Eighteen families had two affected siblings and one had three. Four sets of affected siblings occurred to consanguineous parents.[20,29,36,37] In another case[52] an affected child was born to a member of the family reported by Penman and consanguinity was also present in these parents. In three further cases an elder sibling of the affected child died just after birth because of intestinal obstruction[5] or multiple abnormalities[34,54]; in another case a sibling of the patient was affected by prune-belly syndrome.[16] The occurrence of MMIHS in 19 sets of affected siblings together with consanguinity in 4 sets of parents suggests an autosomal recessive pattern of inheritance.[29,36,52]

Radiologic findings

Radiologic evaluation usually suggested the diagnosis of MMIHS. Plain abdominal films showed either dilated small bowel loops or a gasless abdomen with evident gastric bubble. An enlarged urinary bladder was present in all patients who had cystography or ultrasonography (Figure 2). Cystography showed vesicoureteral reflux in 8 patients[6,10,19,62,63] and an urachal remnant in 1 case.[16] Intravenous urography or ultrasonography detected unilateral or bilateral hydronephrosis in 84 patients.[62,63] In 1 case ultrasonography detected a dysplastic right kidney.[44] One case had bilateral duplex kidneys.[82] Forty-four patients had an upper gastrointestinal series both before and after laparotomy: hypo- or aperistalsis in stomach, duodenum and small bowel was a constantly detected symptom. In 3 cases reverse peristalsis from small bowel into the stomach was also observed.[1-11] In 2 cases hypoperistalsis was associated with gastroesophageal reflux[7,28] and in 1 case the esophagus was aperistaltic.[46] Barium enema showed microcolon in all 71 patients in whom this study was performed (Figure 3); in 39 cases malrotation was associated.

Surgical or autopsy findings

Megacystis and microcolon were the two most frequent findings at surgery or autopsy and were present in all patients (Figure 4). Short-bowel syndrome was found in 37 cases, dilated proximal small bowel in 19 segmental stenosis of the small bowel in 3, duodenal web in 1, Meckel's diverticulum in 1. Malrotation was found in a total of 81 cases. Although surgical management was not mentioned in several reports, 93 patients (70%) underwent 1 or more surgical procedures. Different kinds of interventions were performed: gastrostomy, jejunostomy, ileostomy, cecostomy, segmental resection of jejunum and ileum, lysis of adhesions and internal sphincter myectomy. Surgical manipulation of the gastrointestinal tract generally has been unsuccessful and in most patients total parenteral nutrition was required. In 37 patients vesicostomy was performed to decompress the urinary tract and to preserve renal function.

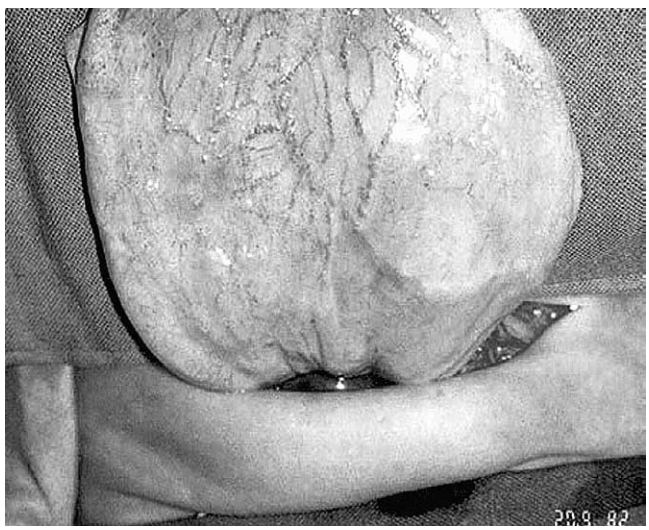

Figure 4 Operative photograph of a massively dilated urinary bladder in MMIHS.

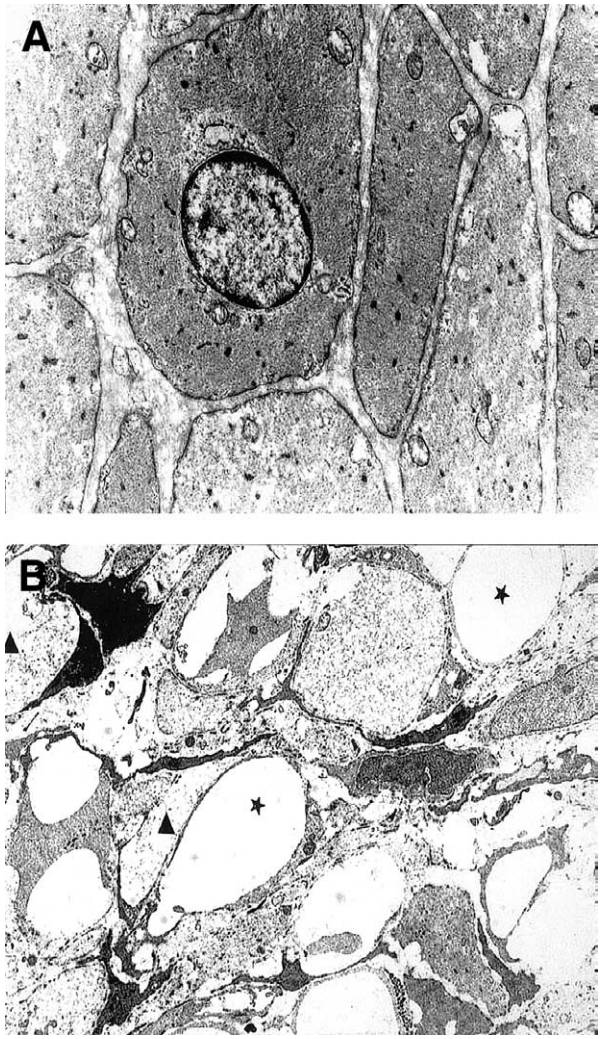

Figure 5 Electron microscopy (A) smooth muscle cells from normal ileum and (B) ileum from a patient with MMIHS showing vacuolar changes in the center of smooth muscle cells.

Histological findings

Histologic studies of the myenteric and submucous plexuses were reported in 93 of 182 cases. In 72 the ganglion cells were normal in appearance and number. Young[12] found 1 case of diffuse hypoganglionosis and Vezina[5] found aganglionic zones together with hyperganglionic zones in another case. Immature ganglion cells were found by Manco[21] in 1 case. Kirtane[20] found 2 cases with immature ganglion cells and hypoganglionosis. Krook[7] found both aganglionic zones and immature zones throughout the bowel. In 4 cases hyperganglionosis[11,15,53] was evident. Bindl[35] reported neuronal intestinal dysplasia type B in 1 case. In 26 cases observations on the nerve fibers in the intestinal plexuses were reported: In 15 cases the appearance was normal, in 9 the nerve fibers were observed to be increased and in 2 they were decreased. Taguci[39] noted an abnormal peptidergic innervation caused by a decrease in vasoactive intestinal polypeptide and peptide histidine methionine fibers and an increase in substance P and leucine-enkephalin fibers. At autopsy, neonatal axonal dystrophy was found in a patient with previous findings of hypertrophic nerve bundles and dystrophic neuritis in the rectal biopsy.[48] Kobayashi and coworkers[53] observed hyperganglionosis of the submucous and myenteric plexuses, giant ganglia and ectopic ganglia throughout the entire gastrointestinal tract in 2 patients. Acetylcholinesterase staining and neural cell adhesion molecule (NCAM) staining of the uterus in 1 patient demonstrated a large number of ganglioneuromas.[53] Recently Piotrowska and coworkers[81,87] reported absence of ICCs in the bowel and bladder of patients with MMIHS.

The majority of reports do not mention the histologic findings in the muscle layers of bowel and bladder wall. Nevertheless some authors found significant abnormalities in SMCs. In 9 cases[2,19,33,34,42,53] thinning of the longitudinal muscle was found on light microscopy. Electron microscopy showed vacuolar degeneration in the center of the smooth muscle of the bowel in 11 cases[2,33,34,44,80,81] and of the bladder in 8 cases.[2,33,34,53] Connective tissue proliferation was found in the bowel in 9 cases[15,53,80] and in the bladder in 8 cases.[34,42,50,80] In 3 more cases the bladder showed elastosis.[12,19] In 2 patients electron microscopy revealed vacuolar degeneration of smooth cells in the muscle layers of the bowel and the bladder in addition to neuronal abnormalities (Figure 5).[53] Ciftci and coworkers[57] reported a case without vacuolar degeneration but with excessive smooth muscle glycogen storage. They postulated that the pathogenesis involves a defect of glycogen-energy utilization. Other investigators have reported absence or marked reduction in α-smooth muscle actin and other contractile and cytoskeletal proteins in the smooth muscle layers of MMIHS bowel.[80,81]

Outcome

The management of patients with MMIHS is frustrating. A number of prokinetic drugs and gastrointestinal hormones have been tried without success. Surgical manipulation of the gastrointestinal tract has generally been unsuccessful. The outcome of this condition is generally fatal: only 23 of the 182 reported patients were alive, the oldest being 18 years old. Twenty-one of the 23 patients were being maintained by total or partial parenteral nutrition. The need for surgical intervention should be made carefully and individualized, in that most explorations have not been helpful and probably are not necessary.

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