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Megacystis microcolon intestinal hypoperistalsis syndrome in two sisters with a rare disease gene

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ABSTRACT

Introduction: Megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) is an inherited autosomal recessive condition (AR). MMIHS is a rare disease that is characterized by functional urinary bladder obstruction and functional intestinal obstruction. MMIHS is a fatal congenital disease with a poor prognosis. *Case presentation*: We report the cases of two MMIHS patients who were referred to us due to esophageal perforation in the first patient and prenatal distended urinary bladder and stomach and abdominal wall weakness in the second patient. *Conclusion:* MMIHS is a rare inheritance syndrome that is associated with morbidity and mortality, and patients usually die within the first year of life.

Keywords: MMIHS, Berdon Syndrome, Distended Urinary Bladder

1. INTRODUCTION

Megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) (also known as Berdon syndrome) is a rare congenital syndrome that is characterized by decreased tone in the urinary tract and intestinal muscles. MMIHS is more common in females (Hiradfar et al., 2013; Clark & O'Connor, 2015). Neonatally, patients with MMIHS tend to have a flaccid abdomen and lack the ability to spontaneously void. Generally, there are similarities in the clinical manifestation of MMIHS and prune belly syndrome (PBS). MMIHS is a rare syndrome that has a poor prognosis, and it is associated with high morbidity and mortality (Hiradfar et al., 2013; Wymer et al., 2016; Elrouby et al., 2019).

2. CASE REPORTS

Case 1

A 34-year-old Saudi female (gravida, 6; para, 5 [G6P5]) delivered a baby girl by emergency cesarean section. The neonate was preterm at 34+ weeks, birth weight was 2870 g, and her Apgar score was 3 in the first minute after birth.

The patient failed to take a spontaneous breath, and intubation was performed at 2 minutes after birth after a trial with positive-pressure ventilation. After intubation, her partial pressure of oxygen (SpO_2) was 99% and heart rate was 167 beats/min. The patient's vital signs then stabilized. Examination revealed dysmorphic features, brachycephaly, packed nose, short neck, low-set ears, decreased bilateral air entry, small chest, and abdominal distention. An antenatal scan demonstrated bilateral hydronephrosis. The urinary bladder and stomach were distended. The neonate also failed to pass meconium. She had a family history of a sister who died of prune belly-like syndrome. The patient's parents were consanguineous.

Further investigations included a chromosomal analysis, skeletal survey, echocardiogram, chest and abdominal X-ray with barium swallow, and brain and abdominal ultrasound (US). The skeletal survey showed no gross skeletal anomalies. The genetic study demonstrated homozygosity for the *MYH11* gene, pos 16:15880479, transcript NM_002474.2, nomenclature c.633+4_633+7del, which is a variant that is of uncertain significance. Del/Dup (CNV) analysis results were negative. Phenotype aortic aneurysm, familial thoracic; autosomal recessive mega-cystic microcolon intestinal hypoperistalsis syndrome (MMIHS) not yet listed in Online Mendelian Inheritance in Man [OMIM]).

A plain abdominal X-ray demonstrated no signs of extraluminal air. A large single air bubble was observed at the presumed site of the stomach, and the rest of abdomen was gasless. Abdominal US showed bilateral hydroureter and hydronephrosis with a very dilated bladder. A barium swallow and meal showed a markedly dilated stomach and upper part of the small intestine, and a lower contrast enema showed a small unused microcolon. An Abdominal computerized tomography (CT) with contrast showed a dilated stomach and megaureter (Figure 1). A voiding cystourethrogram show a massively enlarged urinary bladder with vesico ureteric reflux. Conservative management and total parental nutrition (TPN) were applied.

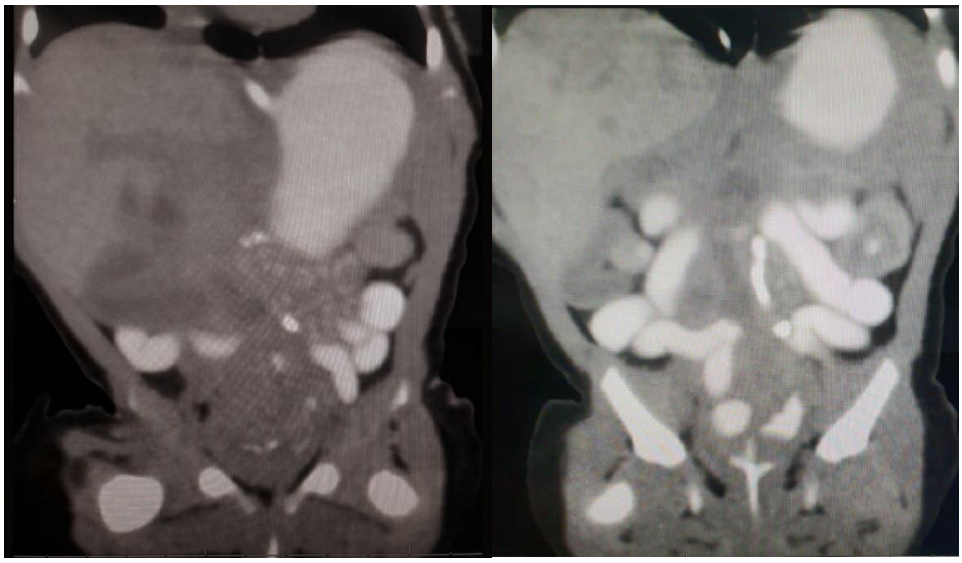

Figure 1 A coronal section of the abdominal CT scan with contrast showed a dilated stomach and megaureter.

Case 2

A female neonate was referred to the Pediatric Surgery department due to esophageal perforation after insertion of a nasogastric tube (NGT). Examination revealed a distended abdomen and dysmorphic features (brachycephaly, packed nose, short neck, low-set ears, abdominal wall weakness, and distended abdomen). There was a delay in passing meconium. Intraoperatively during the esophageal repair, a distended stomach, microcolon, megacystis, and intestinal hypoperistalsis were incidentally noted (Figure 2). The patient's parents were consanguineous. The patient was referred to Riyadh.

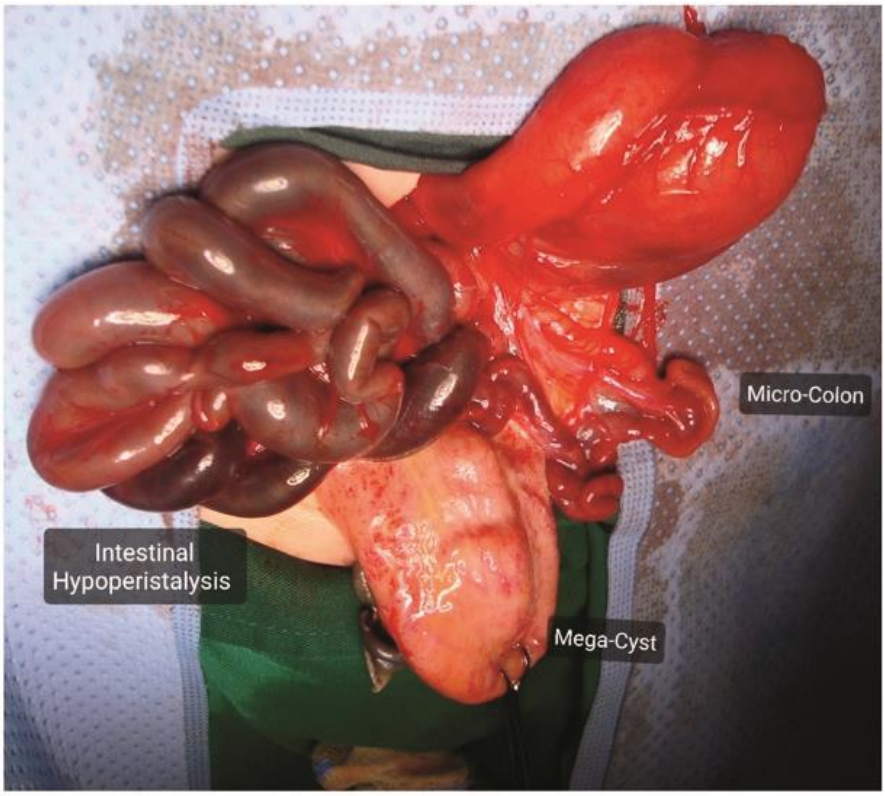

Figure 2 Intraoperative photo showing a dilated stomach, small intestines, small microcolon, and markedly dilated urinary bladder in patient B.

3. DISCUSSION

In 1976, MMIHS was first reported by Berdon and his colleague in five females, of whom two were sisters (Clark & O'Connor, 2015; Al-Salem, 2020). MMIHS is a rare congenital syndrome. Approximately 450 cases of MMIHS have been reported in the literature between 1976 and 2018 (Nakamura et al., 2018). MMIHS manifests as a non-obstructive dilatation of the urinary bladder, microcolon, and decreased or absent intestinal peristalsis that causes functional bowel obstruction in a newborn (Al-Salem, 2020). This syndrome might be suspected antenatally on US by the presence of a huge neonatal bladder. Additionally, amniotic fluid might be normal or polyhydramnios. Suspicion is increased if the neonate is female with a 3–4:1 female-to-male ratio (Buinoiu et al., 2018).

Antenatal diagnosis remains challenging for physicians because of the rarity of the disease and overlap between MMIHS and other diseases such as PBS, lower urinary tract obstruction, and posterior urethral valve (Joseph et al., 2020). The usual clinical manifestation of newborns with MMIHS is a distended abdomen. This is due to marked dilatation, and the non-obstructed urinary bladder fills the whole abdomen and may reach up to the xiphisternum (Al-Salem, 2020). Omphalocele, umbilical hernia, hydronephrosis, renal dysplasia, abdominal wall weakness, and truncus arteriosus and other cardiovascular complications are other clinical manifestations that might be present in MMIHS (Gauthier et al., 2014). The exact etiology behind this syndrome remains unknown. There are several theories to explain its pathogenesis, but the most widely accepted theory is that MMIHS is a form of visceral myopathy. This theory is supported by histological studies that demonstrated that smooth muscle myopathy is the most common intestinal manifestation that is involved in both the circular and longitudinal layers of the small bowel muscularis propria (Al-Salem, 2020).

Cases of MMIHS are sporadic, but it has been reported in offspring of a consanguineous marriage or in various siblings with a normal healthy mother and father. However, there may be an autosomal recessive mode of inheritance in some patients, and the risk increases in those with a consanguineous marriage (Gauthier et al., 2014). In our report study, there was a consanguineous marriage and two daughters were affected, while the sons developed normally. The manner of causation of MMIHS is heterozygous and most patients are autosomal dominant, which is sporadic due to *de novo* heterozygous variants in the actin gamma 2 (*ACTG2*) gene that encodes actin gamma as a cytoskeleton component and is a mediator of internal cell motility (Wang et al., 2019).

There have been recent reports of MMIHS in the offspring of consanguineous families suggesting autosomal recessive inheritance. Leiomodin 1 (*LMOD1*), which is a gene that is preferentially expressed in vascular and visceral smooth muscle cells, is involved in MMIHS due to a homozygous premature termination mutation in the myosin light chain kinase gene (*MYLK*), which encodes an important kinase that is required for myosin activation and subsequent interaction with actin filaments. It is related to the recessive form of MMIHS, which is a homozygous deletion in myosin light chain 9 (*MYL9*) that encodes a myosin light chain and is a candidate gene for the AR form of MMIHS (Wang et al., 2019).

One of our patients underwent a rare gene genetic study, which showed homozygosity for the *MYH11* gene, pos 16:15880479, transcript NM_002474.2, nomenclature c.633+4_633+7del, which is a variant that is of uncertain significance. Del/Dup (CNV) analysis results were negative. Phenotype aortic aneurysm, familial thoracic; autosomal recessive MMIHS was not listed in OMIM.
There is no curative treatment for MMIHS, only supportive management, and management of MMIHS remains a challenge for physicians and parents. It requires multi-disciplinary care including a pediatric surgeon, pediatric gastroenterologist, and pediatric urologist (Nakamura et al., 2018). Supportive treatment includes decompression of the small intestine by ileostomy, insertion of a central line for TPN, urinary catheter or a vesicostomy to drain the urinary bladder, and a vesicostomy to decompress the distended urinary bladder is proffered for long-term urinary bladder drainage (Al-Salem, 2020). Survival with MMIHS has been either based on TPN-dependence or various organ transplantations (Wang et al., 2019). However, MMIHS patients have a poor prognosis, with most dying within the first 12 months of life. The cause of death is mainly sepsis, malnutrition, or multiple organ failure (Elrouby et al., 2019).

4. CONCLUSION

MMIHS is a very rare syndrome with a poor prognosis. Females are more often affected than males. Homozygous autosomal recessive genes tend to be more frequent with consanguineous parents. MMIHS remains a challenge for physicians, and most patients with MMIHS die within the first 12 months of life due to sepsis or complications related to TPN or multiorgan failure.

Abbreviations

MMIHS	Megacystis microcolon intestinal hypoperistalsis syndrome
AR	Autosomal Recessive
SpO_2	Partial Pressure of Oxygen
OMIM	Online Mendelian Inheritance in Man
CT	Computerized Tomography
TPN	Total Parental Nutrition
ACTG2	actin gamma 2 gene

Authors' contributions

Mohammad S. Mohammad Alnoaiji: Primary author read and approved the final manuscript.
AsmaaGhmaird, Tahani Alrashidi, Khaled Alqoaer, Rafik Abdelmalek, Eid Alshahrani: This work carried out in collaboration among all authors. All authors read and approved the final manuscript.

Conflict of interests

The authors declare no conflict of interest.

Ethical Approval and Patient consent

Ethical approval was taken by ethics research committee at Armed Forces Hospital Northwestern region, Tabuk, Saudi Arabia [Ethics ID No.: KSAFH-REC-2020-366]. Written & Oral informed consent was obtained from all individual participants included in the study.

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Data and materials availability

All data associated with this study are present in the paper.

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