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Case Report

A Case Report of a 30-Year-Old Male With Megacystis-Microcolon-Intestinal Hypoperistalsis Syndrome With De Novo ACTG2 Gene Mutation

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SUMMARY

Introduction: Megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) is a very rare genetic disorder of visceral motility of the gastrointestinal and genitourinary system. According to our knowledge, so far there has been no description of a patient with megacystis-microcolon-intestinal hypoperistalsis syndrome and chronic secretory diarrhea.
Case report: We have presented a case report of a 30-year-old male with a genetically verified novel (de novo) mutation p.R257H in the smooth muscle actin (ACTG2) gene. At 8 months of age he was diagnosed with suspected Hirschsprung's disease, partial resection of the colon was performed. During the first year of his life, subtotal colectomy with cecorectal anastomosis was performed and, simultaneously, deteriorated emptying of the urinary bladder was confirmed. The patient was subjected to several unsuccessful abdominal and urological operations. At age of 18, the differential diagnosis was narrowed to microvillus inclusion disease and congenital chloride diarrhea. The patient was tolerant to oral feeding all the time, where intermittent parenteral nutrition started only in adolescence. At the age of 26, due to urethral stenosis, perineal urethrostomy was performed. Since the age of 29, due to complications of the underlying disease the patient was administered chronic dialysis treatment, and a year later, genetic testing provided the definitive diagnosis of MMIHS. Therefore, combined kidney and intestinal transplantation was proposed. The patient continued the treatment with daily fluid and electrolyte compensation along with adequate parenteral nutrition through a triple-lumen central catheter.
Conclusion: Timely genetic testing leads to avoiding repeated surgical interventions and numerous complications. Multivisceral transplantation represents a significant improvement in the treatment of patients with this syndrome.

Keywords: Megacystis-Microcolon-Intestinal Hypoperistalsis Syndrome, Chronic Secretory Diarrhea, Chronic Kidney Disease

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INTRODUCTION

Megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) is a very rare genetic disorder that was first described by Berdon in 1976 [1]. Based on several decades of research, MMIHS is considered to be most likely caused by mutations of several specific genes encoding proteins involved in contractile smooth muscle cells. There are two types of inheritance: autosomal recessive and autosomal dominant, both due to de novo mutation [2, 3]. Women are more likely to get affected by either type of inheritance [4]. This syndrome is manifested by diminished or absent peristalsis of the intestines and clinical symptoms of distension of the urinary bladder [1]. Most patients with MMIHS are diagnosed prenatally after a suspected ultrasound scan of the dilated urinary bladder with a normal or reduced amount of amniotic fluid [5]. Plain radiograph examination of the abdomen reveals extremely dilated loops of bowel and air-fluid levels without signs of obstruction, which probably contributes to repeated explorative laparotomies [2,3,6]. The treatment of this syndrome is mostly supportive considering the poor prognosis and high mortality in the neonatal period [4].

CASE REPORT

The patient was born at term by cesarean section, after a pregnancy that has passed without complications. Before his birth, the patient's parents had a pre-term child, born in the eighth month of pregnancy who had died of an unknown cause ten days after the delivery. The patient's symptoms occurred early, during the first months of his life in the form of expressed visceral motility dysfunction. Since the moment of birth constipation was dominant, therefore the mother manually evacuated stools until the eighth month of the patient's life, when, under the suspicion of Hirschsprung's disease, partial resection of the colon was performed. As the symptoms persevered and progressed, during the first year of his life, subtotal colectomy with cecorectal anastomosis was carried out and, simultaneously, deteriorated emptying of the urinary bladder was confirmed. Postoperatively, there were heavy diarrheal stools on a daily basis, on average about 10 times per day, followed by disorders of acid-base and electrolytic status. Therefore, when he was a child, the patient underwent several unsuccessful abdominal and urological operations with the aim of reducing the symptoms. For the purpose of examining the etiology of chronic secretory diarrhea, a long-term complex study was conducted, by which known potential infectious, non-infectious, gastroenterological, inflammatory, endocrine, immunological, hematological and other causes were excluded. By the age of 18, the differential diagnosis was narrowed to microvillus inclusion disease and congenital chloride diarrhea. Genetic testing was performed in the direction of chloride diarrhea, with mutation analysis of all 21 exon genes of congenital chloride diarrhea (SLC26A3) revealing only heterozygous change in nucleotides (c.1314C>t9 in exon 12), thus the report was interpreted with regard to the clinical condition. Considering the significant fecal loss of electrolyte and fluid which was consequently followed by hypochloremic alkalosis, the patient continued daily supportive treatment with fluid and electrolyte compensation. Regular check-up endoscopic examinations were performed and, besides surgically altered anatomy of the gastrointestinal tract, they revealed also the signs of gastroesophageal reflux disease and extremely dilated stomach (Figure 1). A pathohistological finding of the rectal biopsy confirmed a massive damage to the wall architecture, a complete damage to the collagen fiber strings, subsegmentation of the circular muscle layer, massive smooth muscle atrophy; reduced, slightly irregular, partially granulated expression of smooth muscle actin; inserted collagen aggregates into the circular muscle layer; globularized eosinophilic intraplasmic fibrillary aggregates in muscularis propria; hypoganglionosis; massive reduction of interstitial cells of Cajal. Evaluation of the liver function did not confirm liver damage (intestinal failure-associated liver disease - IFALD) due to long-term parenteral nutrition.

Over the years, total daily intake of fluid (peroral and parenteral) ranged from 6-10 L depending on the fluid loss through stool and urine. During childhood, the patient was first followed by a pediatric gastroenterologist, and then later an adult gastroenterologist both of whom carefully balanced peroral nutritional caloric intake (over 2200Kcal/day) along with intermittent parenteral feeding (on

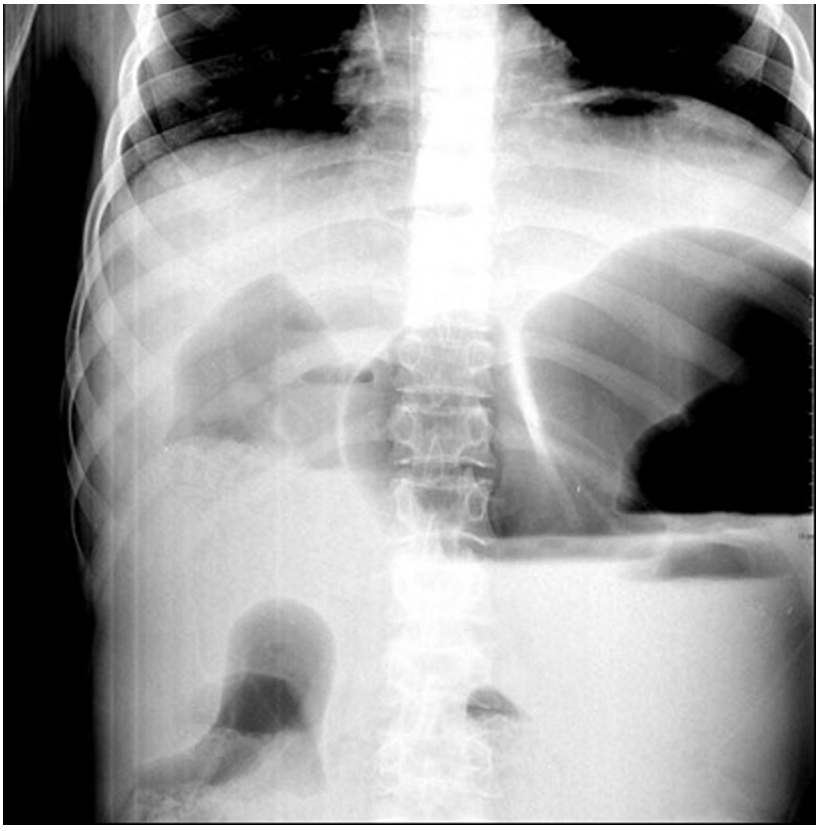

Figure 1. Abdominal native RTG: extremely dilated stomach and bowel loops

average 3 times a week) through a placed port-a-cath, which was repositioned several times due to the infection. Over the time, due to the malabsorptive syndrome, complications of the underlying disease, such as osteoporosis, anemia and nephrocalcinosis, also developed. These generally complicate the treatment and reduce the quality of life. At the age of 26, due to the diagnosed complication - urethral stenosis - as well as several attempts of dilation of the urinary bladder, perineal urethrostomy was performed, after which the patient was intermittently catheterized. The resulting obstructive nephropathy with recurrent urinary infections and urosepsis, as well as excessive daily intake of electrolytes - predominantly calcium-based medications - resulted in chronic renal insufficiency. Since the age of 29, the patient has been treated with chronic hemodialysis. Immediately before the hemodi-

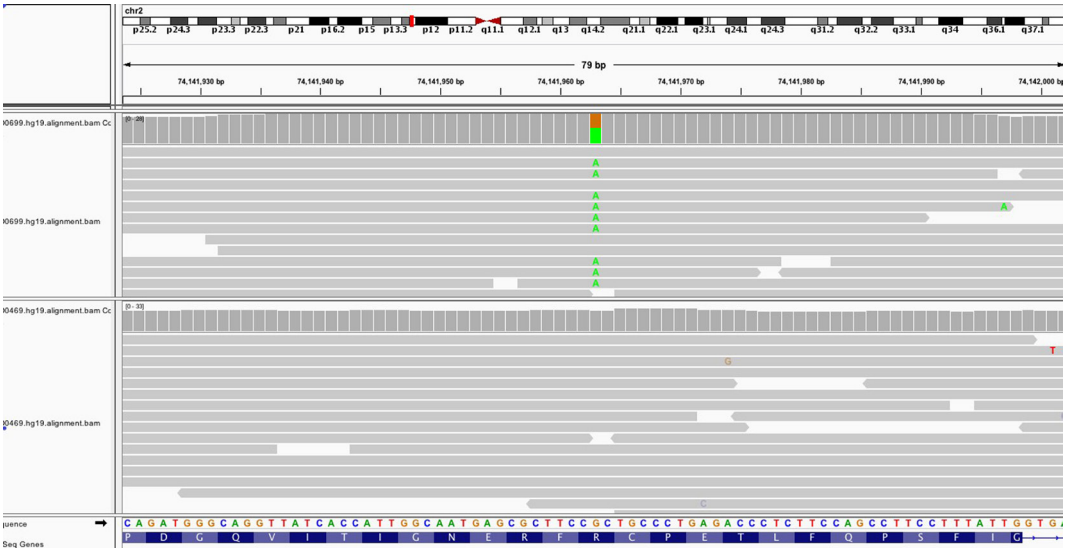

Figure 2. Genetical test MMIHS

Figure 3. Genetical test MMIHS

MEGACYSTIS-MICROCOLON-INTESTINAL HYPOPERISTALSIS SYNDROME; MMIH
INFANTILE VISCERAL MYOPATHY
MEGADUODENUM AND/OR MEGACYSTIS
BERDON SYNDROME
PSEUDOOBSTRUCTION, IDIOPATHIC INTESTINAL

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
2p13.1	Visceral myopathy	155310	AD	3	ACTG2	102545

alysis, the latest port-a-cath was displaced due to a verified thrombus in the right atrium. On several occasions, during the treatment with hemodialysis, double and triple-lumen dialysis catheters were repositioned due to thrombosis and catheter-related infections. Until the present day, the conditions for creating a permanent vascular approach have not been met.

It should be noted that the insight into the available medical documentation has not revealed hereditary diseases. However, the definitive diagnostic verification of MMIHS by genetic testing has only recently been obtained (Figure 2 and 3) after starting the dialysis treatment.

Multivisceral transplantation (combined kidney and intestinal transplantation) was proposed to the patient. However, this proposition was further abandoned due to the general condition of the patient and recurrent urinary infections with multi-resistant germs which had prevented implementation of planned urodynamic tests and other necessary diagnostic procedures for the purpose of preparation for the transplantation.

DISCUSSION

Megacystis-microcolon-intestinal hypoperistalsis syndrome is a very rare genetic disorder manifested by the dysfunction of visceral motility of the gastrointestinal and genitourinary system followed by deteriorated evacuation of stool and urine. So far, cases of association of secretory diarrhea and other rare congenital disorders, such as microvillus inclusion disease and congenital chloride diarrhea, have been described; MMIHS, however, has not [7,8]. We have presented a case of a 30-year-old male with a genetically verified novel (de novo) mutation p.R257H in the smooth muscle actin (ACTG2) gene. De novo mutation was five times more frequent than autosomal recessive cases in 227 reported patients between 1976 and 2013 [6]. Previous studies have shown that de novo MMIHS is most commonly associated with the mutation of the smooth muscle actin (ACTG2) gene, which encodes the protein of the visceral smooth muscle [9-11]. This claim is confirmed in our patient, since genetic testing has verified de novo mutation p.R257H in the smooth muscle actin (ACTG2) gene. Patients with MMIHS are most frequently in need of lifelong parenteral nutrition and urinary catheterization.

MMIHS is often initially presented with symptoms and signs of other known congenital diseases such as Hirschprung's disease, which was also the case in our patient. Therefore, in the first months of his life, partial colon resection was performed, followed by subtotal colectomy with cecorectal anastomosis. However, most children with de novo mutation ACTG2 are not tolerant to peroral feeding, have intestinal malrotation, and even after a successful surgical correction that most often involves Ladd procedure and resection of the dilated intestinal segment, non-mechanical intestinal obstruction persists. Therefore, these children require lifelong total parenteral nutrition [9]. However, our patient has chronic secretory diarrhea, tolerates peroral feeding, whereas intermittent parenteral nutrition has only begun in adolescence as an addition to the peroral feeding with the aim of reducing the effect of ever-increasing malabsorption.

The literature shows that the pathohistological findings in patients with this syndrome have been inconclusive. The results of the findings have included damage to gangli-

on cells, absent or decreased actin in smooth muscles, vacuolar degeneration in the smooth muscle layer with infiltration of connective tissue between muscle cells in the intestines and the urinary bladder [12], which has been verified by the pathohistological finding of the rectal biopsy in our patient. During their lifetime, patients with MMIHS have repeated abdominal surgeries, infections due to necessary urinary and vascular catheters, malnutrition, anemia, liver damage due to long-term parenteral nutrition (intestinal failure-associated liver disease - IFALD), cholestasis, thromboembolic and numerous other complications [13-17]. Most of these complications are also present in our patient. The prognosis is very poor, given that half of the patients with confirmed family MMIHS survived only two months after birth and so far there are only two cases with a lifetime close to three decades [6]. In most cases, death occurs due to severe malnutrition, sepsis, renal and hepatic insufficiency [13-17]. Total survival in all MMIHS cases reported until now is 2-20% [6]. Our patient is 30 years old, which is exceptionally rare regarding all the cases described in the literature so far. Patients with severe gastrointestinal motility are advised to undergo multivisceral transplantation, which mainly included combined kidney and intestinal transplantation, apart from one described case of isolated transplantation of the intestine [13,18-22]. In a series of 12 patients who underwent multivisceral transplantation, the majority was denied total parenteral nutrition in post-transplantation. However, urinary catheterization was still necessary [21]. Chronic urinary bladder dysfunction, with increased risk of ureteral dilation and ureteral nephrolithiasis, as well as recurrent urinary infections impair renal function. Our patient developed renal insufficiency in terminal stage, therefore, multivisceral transplantation that would include transplantation of the intestine and kidneys was proposed. Nevertheless, the idea of transplantation was abandoned due to the general condition of the patient and the infections with multi-resistant germs that had prevented the implementation of planned urodynamic tests and other diagnostic procedures. Considering the reduced diuresis and the need to achieve adequate ultrafiltration during dialysis, an even greater need arises, and at the same time, challenges of the team work of gastroenterologists and nephrologists towards best balanced conservative therapy. Continuation of treatment involves substitution of fluids, electrolytes and satisfactory parenteral nutrition.

CONCLUSION

Timely diagnostic confirmation by genetic testing is crucial in order to avoid repeated surgical interventions and numerous complications that may be fatal for patients with MMIHS. Multivisceral transplantation is a significant improvement in the treatment of patients with this rare genetic disorder and it requires a multidisciplinary approach.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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Prikaz slučaja 30-godišnjeg muškarca sa megacistis-mikrokolon-intestinalnim hipoperistaltičkim sindromom sa de novo mutacijom gena ACTG2

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KRATAK SADRŽAJ

Uvod: Megacistis-mikrokolon-intestinalni hipoperistaltički sindrom je veoma redak genetski poremećaj visceralnog motiliteta gastrointestinalnog i genitourinarnog sistema. Prema našim saznanjima, do sada nije bilo opisa bolesnika sa sindromom megacistis-mikrokolon-intestinalne hipoperistaltike i hroničnom sekretornom dijarejom.
Prikaz slučaja: Predstavili smo izveštaj o slučaju 30-godišnjeg muškarca sa genetski verifikovanom novom (de novo) mutacijom p.R257H u genu za aktin glatkih mišića (ACTG2). Sa 8 meseci mu je dijagnostikovana sumnja na Hirschsprungovu bolest, urađena je delimična resekcija debelog creva. U prvoj godini života urađena je subtotalna kolektomija sa cekorektalnom anastomozom i istovremeno je potvrđeno pogoršano pražnjenje mokraćne bešike. Pacijent je podvrgnut nekoliko neuspešnih abdominalnih i urooloških operacija. Sa 18 godina, diferencijalna dijagnoza je sužena na bolest inkluzije mikrovilusa i kongenitalnu hloridnu dijareju. Pacijent je sve vreme bio tolerantan na oralno hranjenje, pri čemu je intermitentna parenteralna ishrana počela tek u adolescenciji. U 26. godini, zbog stenoze uretre, urađena je perinealna uretrostomija. Od 29. godine, zbog komplikacija osnovne bolesti, pacijentu je primenjena hronična dijaliza, a godinu dana kasnije genetskim testiranjem je postavljena konačna dijagnoza MMIHS. Zbog toga je predložena kombinovana transplantacija bubrega i creva. Pacijent je nastavio lečenje svakodnevnom kompenzacijom tečnosti i elektrolita uz adekvatnu parenteralnu ishranu preko trolumenskog centralnog katetera.
Zaključak: Pravovremeno genetsko testiranje dovodi do izbegavanja ponovljenih hirurških intervencija i brojnih komplikacija. Multivisceralna transplantacija predstavlja značajno poboljšanje u lečenju pacijenata sa ovim sindromom.

Ključne reči: megacistis-mikrokolon-intestinalni hipoperistaltički sindrom, hronična sekretorna dijareja, hronična bolest bubrega

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