Microvillus Inclusion Disease: Prenatal Ultrasound Findings, Molecular Diagnosis and Genetic Counseling of Congenital Diarrhea

Chih-Ping Chen[1,2,3,4,5,6]*, Ming-Chou Chiang[7], Tzu-Hao Wang[8], Chuen Hsueh[9], Shueen-Dyh Chang[8], Fuu-Jen Tsai[4,10], Chao-Ning Wang[8], Schu-Rern Chern[2], Wayseen Wang[2,11]

Departments of [1]Obstetrics and Gynecology and [2]Medical Research, Mackay Memorial Hospital, [5]Institute of Clinical and Community Health Nursing, [6]Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, and [11]Department of Bioengineering, Tatung University, Taipei; [3]Department of Biotechnology, Asia University, [4]School of Chinese Medicine, College of Chinese Medicine, China Medical University, and [10]Departments of Medical Genetics and Medical Research, China Medical University Hospital, Taichung; Departments of [7]Pediatrics, [8]Obstetrics and Gynecology, and [9]Pathology, Lin-Kou Medical Center, Chang-Gung Memorial Hospital, Chang-Gung University, Tao-Yuan, Taiwan.

SUMMARY

Objective: To present prenatal ultrasound findings and molecular diagnosis of microvillus inclusion disease, and to review the literature of abnormal prenatal ultrasound findings associated with congenital diarrhea.

Materials, Methods and Results: A 21-year-old woman, gravida 1, para 0, had generalized bowel dilation of the fetus on prenatal ultrasound at 29 gestational weeks. She and her husband were non-consanguineous, and there was no family history of congenital diarrhea. Prenatal ultrasound at 29 gestational weeks revealed a honeycomb appearance of the bowel without ascites or intraperitoneal calcification. At 36 gestational weeks, polyhydramnios dilated bowel loops were observed, and a 3,355-g male baby was delivered with a distended abdomen. Postnatally, the neonate suffered from watery diarrhea and abdominal distension but there was no mechanical bowel obstruction. An endoscopic biopsy of the small bowel revealed intracytoplasmic inclusions lined by intact microvilli in the apical surface of the intestinal epithelial cells consistent with the diagnosis of microvillus inclusion disease. Mutation analysis of blood samples of the neonate and parents revealed a heterozygous nonsense mutation of c.445C>T, p.Q149X in exon 4 of the *MYO5B* gene in the father and proband, and a heterozygous nonsense mutation of c.1021C>T, p.Q341X in exon 9 of the *MYO5B* gene in the mother and proband.

Conclusion: Prenatal sonographic identification of dilated bowel loops in association with polyhydramnios suggests congenital diarrhea and a differential diagnosis of microvillus inclusion disease in addition to congenital chloride diarrhea and congenital sodium diarrhea. Molecular analysis of the *MYO5B* gene is helpful in genetic counseling and prenatal diagnosis of recurrent microvillus inclusion disease in subsequent pregnancies. [*Taiwan J Obstet Gynecol* 2010;49(4):487–494]

Key Words: congenital diarrhea, microvillus inclusion disease, *MYO5B*, prenatal diagnosis, ultrasound

Introduction

Congenital diarrheal disorders (CDD) are a group of rare chronic enteropathies caused by heterogeneous genetic defects and are characterized by severe diarrhea in infancy. Berni Canani et al [1] suggested that CDD be classified into four categories in relation to the defects: (1) defects of digestion, absorption and transport of nutrients and electrolytes: congenital lactase deficiency

*Correspondence to: Dr Chih-Ping Chen, Department of Obstetrics and Gynecology, Mackay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei, Taiwan.
E-mail: cpc_mmh@yahoo.com
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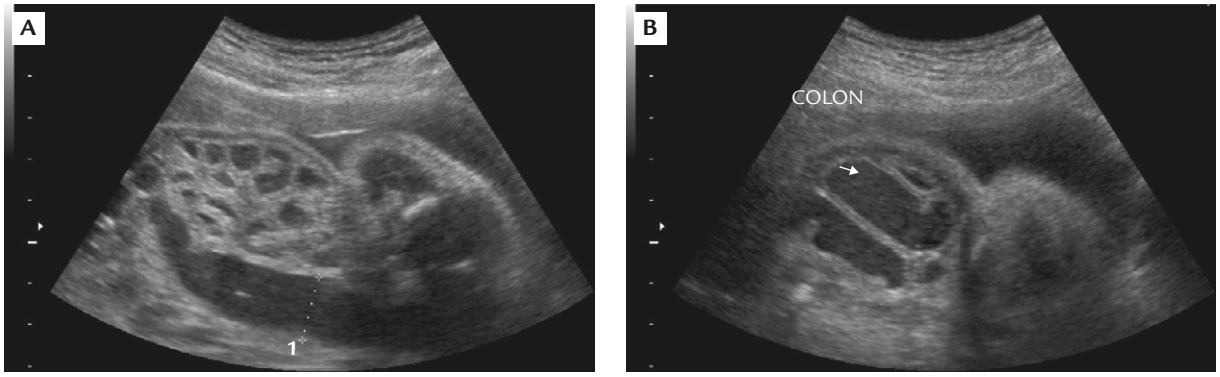

Figure 1. Prenatal ultrasound at 29 gestational weeks showing (A) a honeycomb appearance of multiple dilated loops of bowel and (B) fluid-filled large bowel.

(*LCT* gene), sucrase-isomaltase deficiency (*SI* gene), maltase-glucoamylase deficiency (*MGAM* gene), glucose-galactose malabsorption (*SLC5A1* gene), fructose malabsorption (*GLUT5* gene), Fanconi-Bickel syndrome (*GLUT2* gene), cystic fibrosis (*CFTR* gene), acrodermatitis enteropathica (*SLC39A4* gene), congenital chloride diarrhea (*SLC26A3* gene), congenital sodium diarrhea (*SPINT2* gene), lysinuric protein intolerance (*SLC7A7* gene), congenital bile acid diarrhea (*SLC10A2* gene), enterokinase deficiency (*PRSS7* gene), trypsinogen deficiency (*PRSS1* gene), pancreatic lipase deficiency (*PNLIP* gene), abetalipoproteinemia (*MTP* gene), hypobetalipoproteinemia (*APOB* gene) and chylomicron retention disease (*SAR1B* gene); (2) defects of enterocyte differentiation and polarization: microvillus inclusion disease (MVID) (*MYO5B* gene), congenital tufting enteropathy (*EpCAM* gene) and syndromic diarrhea; (3) defects of enteroendocrine cell differentiation: enteric anendocrinosis or congenital malabsorptive diarrhea (*NEUROG3* gene), enteric dysendocrinosis and proprotein convertase 1 deficiency (*PCSK1* gene); and (4) defects of modulation of the intestinal immune response: immunodysregulation polyendocrinopathy, enteropathy and X-linked syndrome (IPEX) (*FOXP3* gene), IPEX-like syndrome, immunodeficiency-associated autoimmune enteropathy, autoimmune polyendocrine syndrome-1 (*AIRE* gene) and autoimmune enteropathy with colitis-generalized autoimmune gut disorder. Most defects of CDD are inherited as an autosomal recessive trait, and IPEX is inherited as an X-linked recessive trait. We present here the prenatal ultrasound findings and molecular genetic diagnosis of MVID, a very rare autosomal recessive disorder, which belongs to CDD category II.

Materials, Methods and Results

A 21-year-old woman, gravida 1, para 0, had generalized bowel dilation of the fetus on prenatal ultrasound

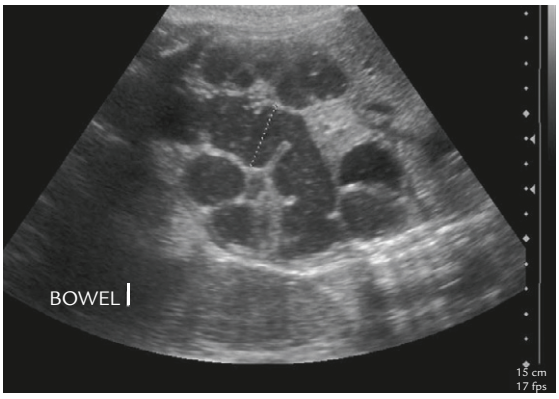

Figure 2. Prenatal ultrasound showing fluid-filled bowel loops at 36 gestational weeks.

at 29 gestational weeks. Her husband was 37 years old. She and her husband were non-consanguineous, and there was no family history of congenital malformations or CDD. During this pregnancy, a maternal serum screening test for Down syndrome was negative. Routine sonographic examinations were normal until 29 gestational weeks when prenatal ultrasound showed a honeycomb appearance of the bowel with generalized dilation of the bowel from the small intestines to colon with a thick intestinal wall but without ascites or intraperitoneal calcification (Figure 1). The amniotic fluid index was normal. Other organs were unremarkable. Maternal TORCH (toxoplasmosis, rubella, cytomegalovirus and herpes simplex) serologic test results were negative. A tentative diagnosis of congenital megacolon or imperforate anus was made. At 36 gestational weeks, polyhydramnios (amniotic fluid index = 27.3 cm) was evident in addition to the dilated bowel loops (Figure 2), and a 3,355-g male baby was delivered with a distended abdomen and respiratory distress. Postnatally, the neonate suffered from watery diarrhea and abdominal distension but there was no mechanical bowel obstruction. An endoscopic biopsy of the small bowel revealed intracytoplasmic inclusions lined by intact microvilli in

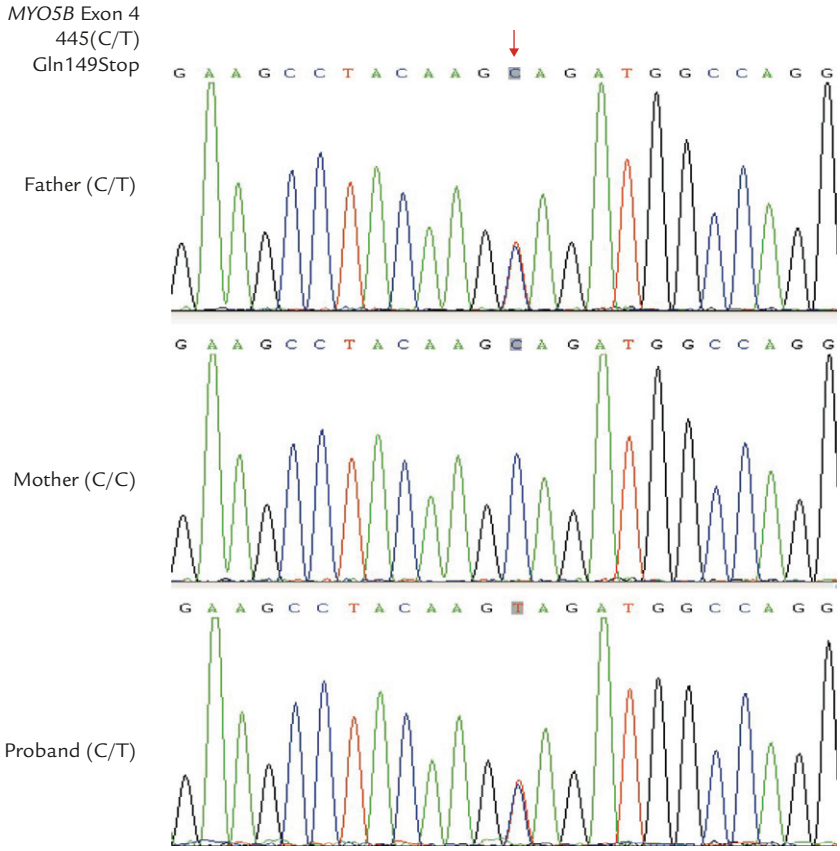

Figure 3. A heterozygous nonsense mutation (c.445C>T, p.Q149X) in exon 4 of the *MYO5B* gene in the father and proband.

the apical surface of the intestinal epithelial cells consistent with the diagnosis of MVID. The neonate was on long-term total parenteral nutrition but died of sepsis, malnutrition and multiple organ failure at the age of 6 months. Mutation analysis of peripheral blood samples of the neonate and the parents revealed a c.445C>T nonsense mutation in exon 4 of the *MYO5B* gene that predicts a p.Q149X in the neonate and the father (Figure 3), and a c.1021C>T nonsense mutation in exon 9 of the *MYO5B* gene that predicts a p.Q341X in the neonate and the mother (Figure 4).

Discussion

MVID or DIAR2, diarrhea 2 with microvillus atrophy (OMIM 251850), is an autosomal recessive disorder of intestinal epithelial cells. MVID is characterized by intractable life-threatening watery diarrhea during infancy and can be caused by mutations in the *MYO5B* gene (OMIM 606540) on chromosome 18q21. MVID was first described by Davidson et al [2] in 1978 as familial enteropathy presenting with protracted diarrhea from birth, failure to thrive and hypoplastic villus atrophy. Characteristic pathologic and electron-microscopic findings of MVID include atrophy of microvilli on mature enterocytes, apical accumulation of numerous periodic-acid-Schiff-positive secretory granules in immature enterocytes, and microvillus inclusion bodies containing rudimentary or fully differentiated microvilli in mature enterocytes [3–5].

Other DIAR categories in OMIM include DIAR1: congenital chloride diarrhea (OMIM 214700) caused by mutations in the *SLC26A3* gene (OMIM 126650) on chromosome 7q31; DIAR3: congenital sodium diarrhea (OMIM 270420) caused by mutations in the *SPINT2* gene (OMIM 605124) on chromosome 19q13.1; DIAR4: congenital malabsorptive diarrhea (OMIM 610370) caused by mutations in the *NEUROG3* gene (OMIM 604882) on chromosome 10q21.3; and DIAR5: congenital tufting enteropathy (OMIM 613217) caused by mutations in the *EpCAM* gene (OMIM 185535) on chromosome 2p21. All are rare autosomal recessive disorders.

The present case was associated with early-onset MVID and novel heterozygous nonsense mutations in the *MYO5B* gene (c.445C>T, p.Q149X and c.1021C>T, p.Q341X). Both nonsense mutations predict early truncation of MYO5B and cause loss of MYO5B function. Müller et al [6] first identified seven different nonsense, missense, splice-site or in-frame insertion mutations in the *MYO5B* gene in patients with MVID from seven

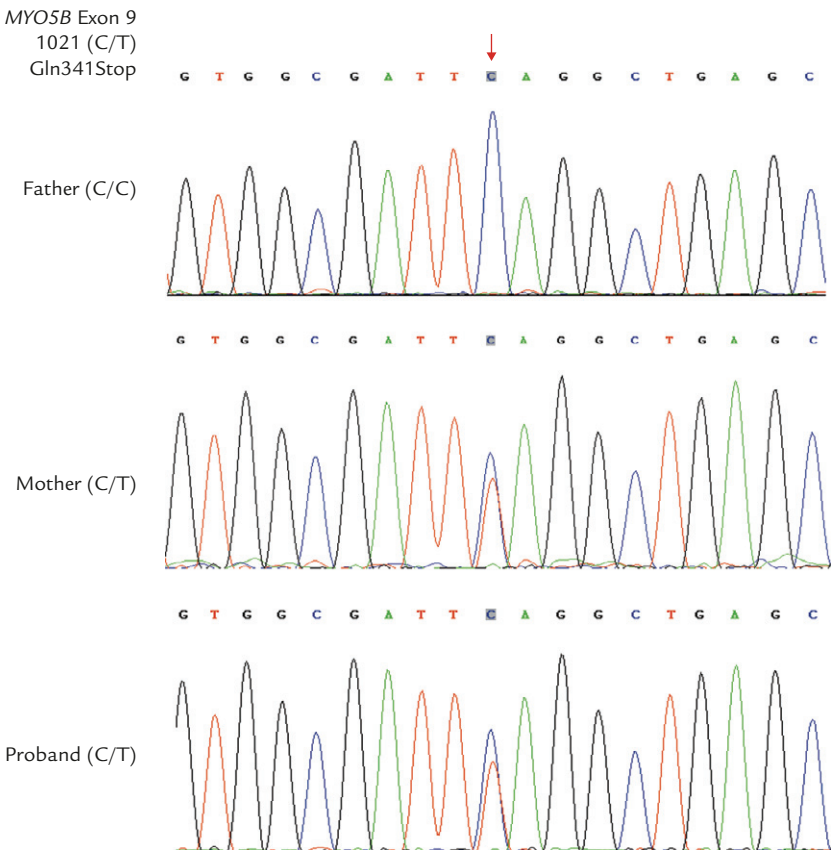

Figure 4. A heterozygous nonsense mutation (c.1021C>T, p.Q341X) in exon 9 of the *MYO5B* gene in the mother and proband.

families. *MYO5B* encodes the unconventional class V dimeric non-filamentous myosin, or myosin Vb, which regulates membrane trafficking along the recycling pathway in polarized epithelial cells [6,7]. Mutations of the *MYO5B* gene disrupt epithelial cell polarity, and loss-of-function mutations of *MYO5B* are a major cause of MVID [6,8,9]. There are two types of MVID: the early-onset type presenting watery diarrhea within the first day of life and the late-onset type presenting symptoms after 3 or 4 months of life [6]. In patients with MVID without transplantation, the prognosis is very poor because there is no successful medical treatment, and the patients remain dependant on total parenteral nutrition and are likely complicated with metabolic decomposition, sepsis and/or liver failure. Recently, small bowel transplantation with or without liver transplantation and colon grafting for the treatment of MVID have achieved variable success [10–14].

The present case manifested multiple dilated loops of small and large bowel at 29 gestational weeks and polyhydramnios at 36 gestational weeks. The present case provides evidence that fetuses with MVID may present multiple dilated loops of bowel and polyhydramnios mimicking intestinal obstruction in the early third trimester. To date, there has only been one report of MVID prenatally presenting as multiple dilated loops of bowel and polyhydramnios [15]. To our knowledge, the present case is the second case report of this condition. Phillips and Schmitz [3] surveyed 23 cases of MVID but did not describe abnormal prenatal findings of bowel dilation and polyhydramnios in their series. Ruemmele et al [4] suggested that in cases of MVID, the pregnancy and delivery are generally uneventful, and there is no polyhydramnios except in rare isolated cases. Our case is one of those rare isolated cases. We consider that the unusual severe prenatal phenotype in this case may be in part due to a genotype-phenotype correlation of concomitant nonsense mutations of the *MYO5B* gene in association with early truncation of MYO5B, and prenatal severe bowel dilation and polyhydramnios. We suggest that prenatal diagnosis of dilated bowels should include a differential diagnosis of MVID in addition to jejunoileal atresia, volvus, meconium ileus, meconium peritonitis, Hirschsprung's disease, cystic fibrosis, enteric duplications, anorectal atresia, congenital sodium diarrhea, and congenital chloride diarrhea.

Enterocyte differentiation and polarization defects and iron transport defects associated with CDD have been reported to present dilated bowel and polyhydramnios on prenatal ultrasound (Table). Kirkinen

Table. Reported cases of congenital diarrhea with abnormal prenatal ultrasound findings of the gastrointestinal tract

Author (year)	Disease	Maternal age (yr)	Gestational age at diagnosis (wk)	Prenatal ultrasound findings and management	Family history and outcome
Kirkinen and Jouppila [16] (1984)					
Case 1	CLD	26	33	Polyhydramnios, distended intestinal loops	Delivery at 36 wk, 3,000 g, female, severe diarrhea after birth with a high chloride concentration in the stool, normal development at 3 years old following substitute therapy
Case 2	CLD	31	26	Polyhydramnios, distended intestinal loops	Delivery at 30 wk, 1,840 g, female, postnatal diarrhea, hypochloremia, high chloride concentration in the stool, normal development at 4 years old following substitute therapy
Case 3	CLD	27	35	Polyhydramnios, distended intestinal loops	Delivery at 36 wk, 2,880 g, female, watery stool rich in chloride, condition improved after specific electrolyte therapy
Groli et al [19] (1986)	CLD	32	28 31 34	Distended intestinal loops, polyhydramnios	Delivery at 35 wk, 2,450 g, male, watery stool with a high chloride concentration after birth, normal at 3 years old following oral administration of chlorides
Patel et al [20] (1989)	CLD	25	30	Polyhydramnios, distended intestinal loops	Two previous pregnancies with polyhydramnios and fetal CLD; birth weight of 1,760 g, watery diarrhea with high chloride concentration, normal at 7 weeks old after chloride therapy
Langer et al [17] (1991)	CLD	25	30	Polyhydramnios, dilated bowel loops	Delivery at 35 wk, 3,000 g, female, postnatal watery stool with a high chloride concentration, normal at 6 months old after chloride therapy
Rose et al [21] (1992)	CLD	28	24	Polyhydramnios, massively dilated small and large bowel, negative TORCH test, therapeutic amniocentesis for amnioreduction, AF: 46,XX	Delivery at 32 wk, 2,773 g, female, dilated bowel, ileostomy for decompression, dehydration and electrolyte losses after surgery
Poggiani et al [22] (1993)	CLD	NA	33	Polyhydramnios, distension of the intestinal loops	Delivery at 36 wk, 3,300 g, female, abnormal yellowish liquid feces with no meconium, abdominal distension, exploratory laparotomy to exclude anatomical obstruction or meconium ileus, normal results of bowel biopsy, high chloride concentration in the stool, normal at 4 years old after treatment with NaCl and KCl

Table. *(Continued)*

Author (year)	Disease	Maternal age (yr)	Gestational age at diagnosis (wk)	Prenatal ultrasound findings and management	Family history and outcome
Lundkvist et al [23] (1996)					
8 case series	CLD	NA	NA	Eight cases showed pronounced polyhydramnios and fetal intestinal dilation of all intestine with normal intestinal peristalsis	Three of eight cases had family histories, two cases were falsely diagnosed as having aganglionosis, one underwent ileostomy, and the other underwent sigmoidostomy before the correct diagnosis
Rowlands et al [24] (1996)	CLD	34	28	Marked polyhydramnios, multiple dilated loops of fetal bowel with peristalsis, amniocentesis: 46,XX, no evidence of maternal infection	Delivery at 37 wk, 3,415 g, female, cystic fibrosis was excluded, watery stool, hypochloremia, normal at 19 days old after treatment with KCl and NaCl
Husu et al [25] (2001)	CLD	NA	32	Polyhydramnios, fluid within small bowel, distended bowel	Delivery at 36 wk, female, no passage of meconium, abdominal distension, hyperbilirubinemia, hyponatremia, hypokalemia, hypochloremia, metabolic alkalosis, high fecal chloride concentration
Kennea et al [15] (2001)	MVID	28	35	Polyhydramnios, multiple dilated loops of small and large bowel	Birth weight of 3,720 g, male, watery diarrhea after birth, stool electrolyte study excluded CLD, small bowel biopsy confirmed MVID, treatment with TPN and survival
Kim and Kim [26] (2001)					
1st pregnancy	CLD	25	33	Multiple dilated bowel loops with peristalsis	Delivery at 38 wk, male, watery diarrhea after birth without evidence of mechanical bowel obstruction, watery stool with ionic content, recovery after electrolyte correction
2nd pregnancy	CLD	30	26	Polyhydramnios, dilated bowel loops	Family history of a previous child with CLD, delivery at 38 wk, male, CLD, electrolyte replacement and recovery
Tsukimori et al [27] (2007)	CLD	36	32	Polyhydramnios, generalized dilation of the bowel with peristalsis, negative TROCH test, amnioreduction, AF: 46,XY, elevated AF chloride level	Delivery at 36 wk, 2,755 g, male, watery diarrhea, high stool chloride concentration, recovery after electrolyte correction
Colombani et al [18] (2010)					
Case 1	CLD	27	27	Polyhydramnios, fetal bowel dilation, multiple dilated bowel loops, AF chloride level at the upper threshold of normal values, normal karyotype at amniocentesis	Delivery at 34 wk, 2,300 g, male, watery diarrhea, high chloride in stool, recovery, a mutation of the *SLC26A3* gene

Case 2	CSD	NA	22	Polyhydramnios, multiple dilated bowel loops, elevated AF sodium level, normal karyotype at amniocentesis	Delivery at 33 wk, 3,200 g, female, abdominal distension, acid and watery stool emission, high sodium in the stool, ileostomy
Case 3	CSD	NA	30	Polyhydramnios, multiple dilated bowel loops, elevated AF sodium level, normal karyotype at amniocentesis	Consanguineous couple; delivery at 37 weeks, 3,300 g, male, abdominal distension, acid and watery stool emission, high sodium in stool, fluid replacement therapy
Case 4	CLD	NA	30	Polyhydramnios, multiple dilated bowel loops	Delivery at 32 wk, 2,500 g, female, watery diarrhea, high chloride in the stool, replacement therapy, normal karyotype
Present case	MVID	21	29 36	Multiple dilated bowel loops, polyhydramnios	No family history; delivered at 36 wk, 3,335 g, male, diffuse bowel dilation, watery diarrhea, TPN treatment, bowel biopsy confirmed MVID, death at 6 months old due to sepsis and multiple organ failure, heterozygous nonsense mutations in the *MYO5B* gene

CLD = congenital chloride diarrhea; TORCH = toxoplasmosis, rubella, cytomegalovirus, herpes simplex; AF = amniotic fluid; NA = not available; MVID = microvillus inclusion disease; TPN = total parenteral nutrition; CSD = congenital sodium diarrhea.

and Jouppila [16] first reported distended loops of fetal intestine and polyhydramnios at 26–35 gestational weeks in three fetuses affected with congenital chloride diarrhea. Langer et al [17] reported a false diagnosis of intestinal obstruction in a fetus with congenital chloride diarrhea. The fetus manifested multiple dilated fluid-filled loops of intestine and polyhydramnios on prenatal ultrasound similar to that seen with intestinal obstruction. Kennea et al [15] reported congenital MVID presenting as prenatal bowel obstruction in a 35-gestational-week fetus with polyhydramnios and multiple dilated loops of small and large bowel. They suggested that ultrasound may prenatally identify some cases with MVID, and careful postnatal assessment of congenital enteropathy is needed in such cases if there is no evidence of bowel obstruction. Colombani et al [18] reported prenatal diagnosis of multiple dilated bowel loops, polyhydramnios and elevated amniotic fluid electrolyte concentrations in two cases with congenital chloride diarrhea and in two cases with congenital sodium diarrhea at 22–30 gestational weeks.

Since MVID is an autosomal recessive disorder, the recurrence risk is 25% for the family that has had a previous affected child with MVID. Currently, prenatal diagnosis can be made by molecular genetic diagnosis in early pregnancy or by preimplantation genetic diagnosis in addition to prenatal ultrasound diagnosis of a dilated bowel and polyhydramnios in pregnancies with a positive family history. We suggest that MVID be considered a possible diagnosis in cases in which prenatal ultrasound findings manifest a distended bowel in combination with polyhydramnios.

Acknowledgments

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