

Background

Myelomeningocele (MMC) impacts 3 in every 10,000 live births in the United States. Concordance of MMCs in the setting of twin and triplet pregnancies is an incredibly rare phenomenon, with less than 30 cases of twins with concordant MMCs having been reported in the literature. To date, there are no clearly documented inherited forms of meningomyelocele, and the exact etiology of MMC remains poorly understood. The occurrence of myelomeningoceles within multifetal gestations and among families with intergenerational myelomeningoceles suggests that there could be genetic factors contributing to these conditions.

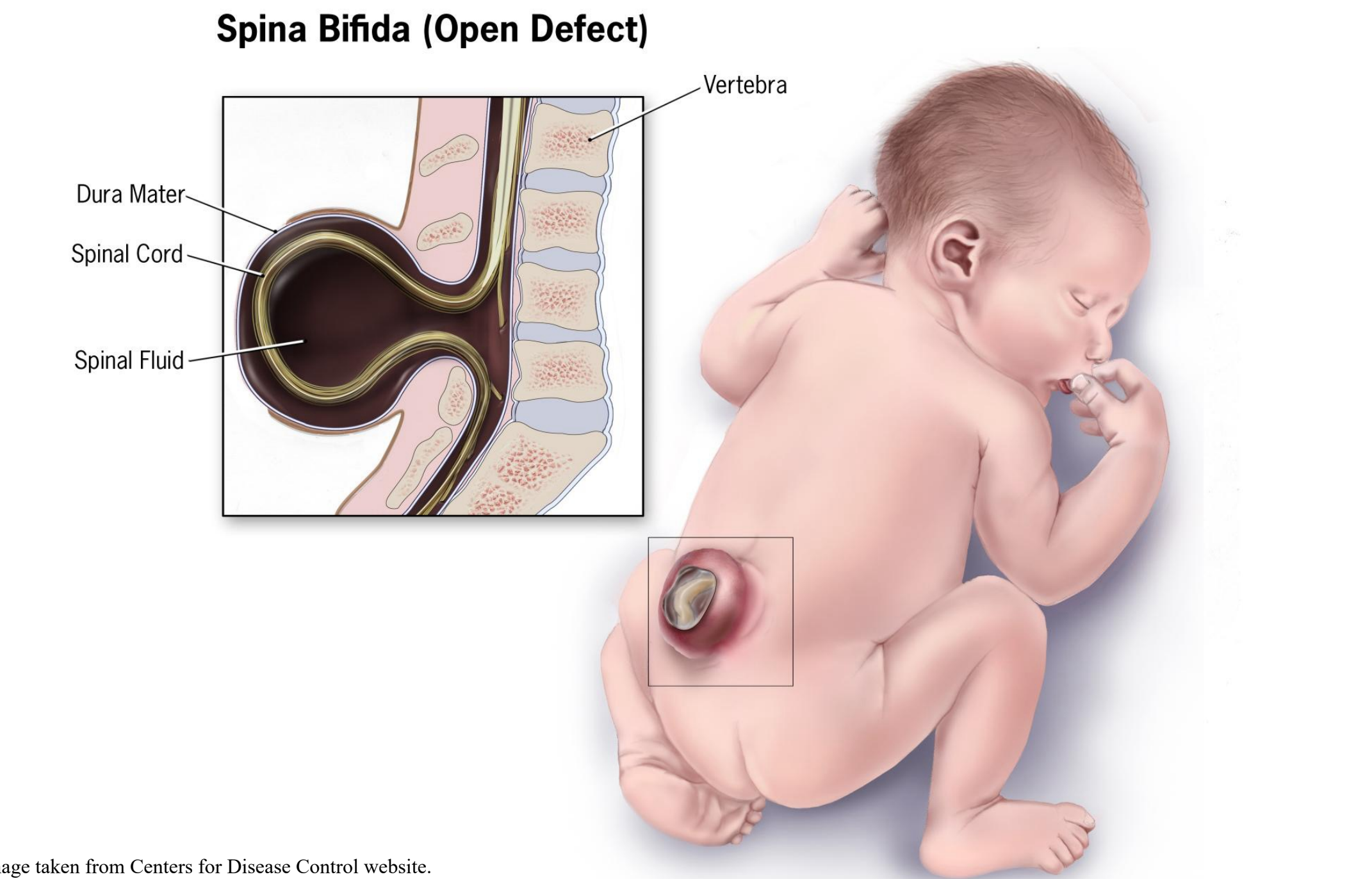


Image taken from Centers for Disease Control website.
https://archive.cdc.gov/www_ehc_gov/ncbddd/birthdefects/surveillancemanual/quick-reference-handbook/spinaBifida.html

Twin studies reveal intriguing patterns: while myelomeningoceles in monozygotic twins would support the hypothesis that there is a genetic predisposition to this malformation, dizygotic twins demonstrate a greater number of dual myelomeningoceles, which could instead support the role of environmental exposures in the development of neural tube defects. Only 5% of cases of myelomeningocele have a positive family history. Currently, genetic factors, dietary elements, and environmental exposures are the risk factors most strongly associated with this condition. In this case report, we discuss a rare case of dichorionic-triamniotic triplets in which the monochorionic-diamniotic pair were both diagnosed antenatally with myelomeningocele.

Case Summary

A 31 year-old G5P4003 patient presented for routine prenatal care at 11 weeks of gestation. Medical history was remarkable for ongoing tobacco use and prior history of neonatal demise secondary to a congenital heart defect. Pre-pregnancy BMI was 23. She denied any history of folate deficiency, environmental exposures, teratogens, or antiepileptic medication use. She took a prenatal vitamin with 0.24 mcg folic acid daily. A limited ultrasound at 18 week and 6 days gestation confirmed dichorionic-triamniotic triplets with Triplet A and Triplet B sharing a placenta while Triplet C had a distinct placenta. Detailed anatomic surveys were undertaken at 22 weeks and 5 days gestation, which demonstrated myelomeningocele of Triplet B at L4-S2 and suspected open neural tube defect in Triplet A based upon scalloped frontal bones, bowing of the cerebellum, and posterior fossa collapse. Triplets A and B were also found to have mild bilateral cerebral ventriculomegaly. Triplet B was diagnosed with fetal growth restriction at that time as well with an estimated fetal weight at the 9th percentile. Triplet C was appropriately grown and had no apparent abnormalities on ultrasound.

The patient was offered amniocentesis at the time of these findings but declined. Initial laboratory evaluation revealed iron-deficiency anemia. Otherwise, she had normal thyroid function studies, triglyceride studies, and a normal folate level.

Further ultrasound evaluation demonstrated Chiari II malformations of both Triplet A and Triplet B, as well as bilateral talipes equinovarus of Triplet B. On antenatal echocardiogram, both Triplets A and B had evidence of small muscular ventricular septal defects.

The patient was referred for genetics and pediatric neurosurgery consultations at a tertiary maternal-fetal care center, as well as delivery planning. The patient was ultimately admitted to the referral center at 31 weeks and 4 days gestation for fetal monitoring and antenatal corticosteroids following a new diagnosis of absent end-diastolic flow on umbilical artery Doppler studies of Triplet B.

Case Summary

She was subsequently delivered via uncomplicated classical Cesarean section at 31 weeks and 5 days gestation. The infants were delivered by classical Cesarean out of concern for the open neural tube defects of Triplets A and B. Triplet A had Apgars of 5 and 8, Triplet B had Apgars of 8 and 9, and Triplet C had Apgars of 5 and 5 at 1 and 5 minutes of life respectively.

The neonates were admitted to the neonatal intensive care unit. Triplet A was confirmed to have a lumbosacral MMC with Chiari II malformation and ventriculomegaly. She underwent MMC closure and repair on the third day of life. Serial head imaging ultimately revealed progressive macrocephaly and hydrocephalus. She was discharged home with outpatient neurosurgery follow-up and underwent endoscopic 3rd ventriculostomy and ventriculoperitoneal shunt placement between 4 and 5 months of life. Following this surgery she experienced seizures requiring an additional 7-day hospitalization. To date, Triplet A requires anti-epileptic drugs and follows with neurology. She was also found to have a neurogenic bladder but does not presently require intermittent catheterization. A small to moderate sized apical ventricular septal defect was also confirmed after delivery and has been monitored in the outpatient setting.

MMC and Chiari II malformation was also confirmed in Triplet B after delivery. She underwent repair of MMC on day of life 3. Serial head ultrasounds and MRIs showed stable mild to moderate ventriculomegaly. Triplet B also had bilateral calcaneovalgus foot deformities and two small apical ventricular septal defects with a moderate VSD shunt. Her cardiac concerns are being expectantly managed in the outpatient setting. Triplet C was found to have a trivial anterior muscular ventricular septal defect, right ear hemangioma, and later developed intraventricular hemorrhage and laryngomalacia attributed to prematurity. Chromosomal microarrays performed on Triplets A and B after delivery were negative for any variants. The triplets were all discharged from the NICU at 62 days of life.

Discussion

This is the only reported case of triplets in which the genetically identical pair were similarly impacted by MMC. Myelomeningocele appears to result from complex multifactorial interplay of genetic and environmental factors. Because most of the cases of MMC in monozygotic twins are non-concordant, the role of genetic etiology remains ambiguous. Our case differs from this trend in that the monochorionic-diamniotic pair were both impacted, suggesting a shared single cause. Though one instance of monozygotic twins (in this set of triplets) does not prove that a single mutation can cause MMC, it raises the compelling possibility of a single gene or locus responsible. Because only a limited number of potentially causative genes have been discovered to date, identifying specific genetic factors in isolated non-syndromic NTD is particularly challenging. While establishing definitive genetic causality is uncertain, employing whole exome sequencing on twin subjects with concurrent MMC could potentially unveil underlying genetic mechanisms contributing to their condition.

Since a landmark randomized clinical trial of prenatal versus postnatal repair of MMC in 2010, in-utero repair of MMC has become an increasingly accepted practice and may confer significant developmental advantages to the impacted infant. Multifetal gestations have not been included in the MMC repair trials due to potential harm to the unaffected fetus or fetuses. However, our case raises the interesting question of in-utero repair for pregnancies in which both or all fetuses are impacted by MMC. Future studies may investigate the feasibility of in-utero repair of MMC for multifetal gestations as well as the potential for single-gene mutations driving the development for MMC.

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