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CASE REPORT

Dizygotic opposite-sex twins with surgically repaired concordant myelomeningocele conceived by in vitro fertilization using intracytoplasmic sperm injection: a case report and review of the literature

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Abstract

Background Myelomeningocele (MMC) is a common subtype of congenital neural tube defects (NTD). Although congenital malformations including NTD are more common in twins, concordance, especially in dizygotic twins, is extremely rare and is found mostly in same-sex twins. The role of genetic and environmental factors in the etiology of MMC is unclear.

Case report Dizygotic twins of opposite sex were born at term to a 35-year-old woman conceived with in vitro fertilization (IVF) using intracytoplasmic sperm injection (ICSI). Prenatal ultrasonography (US) revealed concordant lumbosacral MMC at 18 weeks of gestation as well as ventriculomegaly and Arnold-Chiari malformation type II at 28 weeks. Both twins underwent surgical repair of the MMC within 48 h after birth and required a ventriculoperitoneal shunt in the second week of life.

Discussion The case presented raises questions concerning the etiology of MMC, since in twins, it is compelling to attribute the etiology to genetic factors. In the literature, 22 pairs of twins with concordant MMC have been reported, and of the 10 dizygotic twins described, four were of opposite sex. However, in monozygotic twins, most of the cases are non-concordant; therefore, the role of genetics remains unclear. In addition, environmental factors such as nutrition, metabolic folic acid deficiency, and assisted conception with IVF and ICSI might play a role as well.

Conclusion The appearance of concordant MMC in opposite-sex dizygotic twins, conceived by IVF using ICSI, intrigues questions concerning the etiology of MMC. In such cases, genetic counseling and evaluation should be considered.

Keywords Dizygotic twins · Congenital malformations · Neural tube defects · Myelomeningocele · Spina bifida · IVF

Abbreviations

ICSI	Intracytoplasmic sperm injection
IVF	In vitro fertilization
MMC	Myelomeningocele
MRI	Magnetic resonance imaging
NTD	Neural tube defects
US	Ultrasonography
MTHFR	Methylenetetrahydrofolate reductase
VP shunt	Ventriculoperitoneal shunt

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Introduction

Myelomeningocele (MMC), a subtype of congenital neural tube defects (NTDs), results from impaired closure of the neural tube during primary neurulation in the 4th week of embryogenesis and can cause neurological deficits below the affected level. NTDs are stated to be the second most common group of birth defects with a prevalence of 0.5–2/1000 pregnancies and an estimated 140,000 cases per year worldwide [1, 2]. Twins show higher rates of NTD with an incidence of concordance of 1/32,000 [3]. Concordance has been reported in both mono- and dizygotic twins and is more common among same-sex twins than in opposite-sex twins [3–5]. In

this report, an unusual case of twins of opposite sex with concordant MMC conceived by in vitro fertilization (IVF) using intracytoplasmic sperm injection (ICSI) is described and reviewed in the literature.

Case report

Dichorionic diamniotic twin pregnancy of a girl and a boy was conceived using ICSI in the sixth attempt of IVF to a 35-year-old woman (gravida 1, para 1). The mother had a history of endometriosis and hypothyroidism. Folic acid was supplemented periconceptionally and during pregnancy. A mild gestational diabetes was treated with diet only. Ultrasonography (US) revealed MMC at 18 weeks and ventriculomegaly at 28 weeks of gestation as well as club feet in the boy. Criteria for fetal MMC repair were not fulfilled [6].

The twins were born at 38 weeks of gestation by cesarean section. The girl weighed 2700 g and presented with lumbar MMC (L3-5) and hexadactyly of the left foot (Fig. 1a). She showed minimal movements of the lower limbs on the level of the hips. The boy weighed 2830 g and showed a lumbosacral MMC (L3-S1) and club feet (Fig. 1b). He did not have significant movements of the legs. Both did not have anal and grasp reflexes, nor a Babinski sign.

They underwent successful standard surgical repair of the MMC within 48 h after birth, including dissection of the neural placode and secondary neurulation with reconstruction of the neural tube, followed by multiple layer closure including dura mater, myofascial flap, and skin. A ventriculoperitoneal (VP) shunt was indicated on the 5th (girl) and 7th (boy) postoperative day followed by a magnetic resonance imaging (MRI), which showed sound closure of the MMC (Fig. 2). Due to pronounced ventriculomegaly, evaluation of further cerebral malformations was not possible. All wounds healed well without appearance of fluid collection in the postsurgical lumbar area. They were discharged to their home after 16 days with an unchanged neurological status.

Further infant care focused on orthopedic and urological management. The boy received treatment for club feet and hip dysplasia. Both babies suffered from neurogenic bladder, requiring transurethral catheterization and rectal dysfunction. The parents received genetic counseling including whole exome sequencing analysis of the mother and the twins. While the mother's gene sequencing did not show a clear mutation associated to neural tube defects, further genetic analysis of the twins is still ongoing.

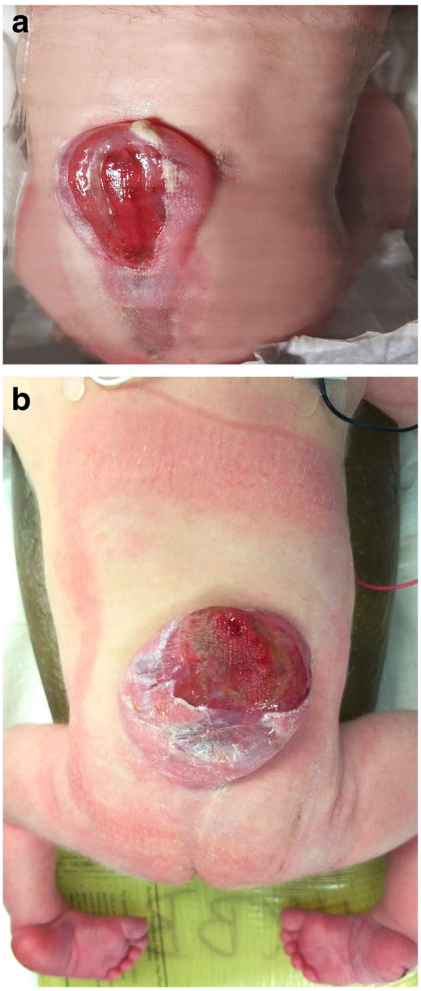

Fig. 1 Preoperative situs showing lumbar MMC L3-5 with a diameter of 8 cm in the girl (**a**) and lumbosacral MMC L3-S1 with a diameter of 4 cm in the boy (**b**)

Discussion

The etiology of MMC remains unclear. Possible associated factors include genetic (especially maternal genetic), epigenetic, and environmental factors, such as medications and folic acid deficiency [7]. The presented case describes dizygotic opposite-sex twins conceived with IVF using ICSI with concordant MMC. After successful surgical repair of the MMC, both needed a VP shunt. Since these are twins, it is compelling to attribute genetic factors to the etiology; however, association with environmental factors such as the IVF and ICSI should be considered as well. According to Copp et al., polygenetic etiology in non-syndromic NTDs is most likely [2]. For the purpose of research, genetic analysis of selected cases, such as the one reported, might contribute to a better understanding of the pathophysiology of MMC. Although folic acid was sufficiently supplemented, deficiency could also result from a maternal defect in mitochondrial folate one-carbon metabolism, namely, methylenetetrahydrofolate reductase (MTHFR) gene polymorphism [2]. According to the practice guideline of the American College of Medical Genetics and Genomics,

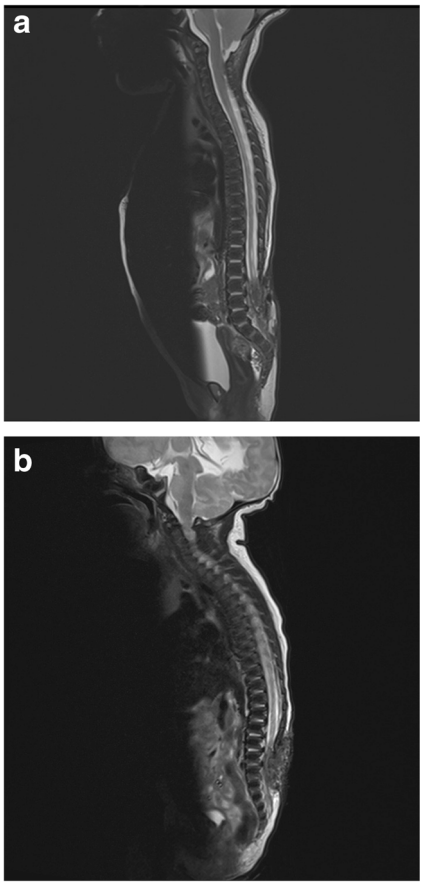

Fig. 2 Spinocranial MRI after MMC repair, on the day of VP shunt implantation in the girl (**a**) and 7 days after VP implantation in the boy (**b**) showing sound closure of the MMC. The Arnold-Chiari malformation type II persists in the girl and is no longer seen in the boy

the MTHFR status does not change the recommendations of standard dose of periconceptional folic acid supplementation [8].

Although NTDs are more common in twins, concordance, especially in dizygotic twins, is extremely rare [3–5]. Cases found in the literature were summarized in Table 1. Of the 22 pairs of twins (including this report), 10 were dizygotic, four of which are of opposite sex. Concordant MMC was found mostly in same-sex twins (14 of 16), similar to the report of Kallen et al. [24]. Unlike previous reports [7, 24], there was no female predominance. Since in monozygotic twins most of the cases are non-concordant, the role of genetic etiology remains unclear [3]. Defining a genetic component in isolated non-syndromic NTD is complex, especially since only few potentially causative genes have been identified [25]. Although claiming causality is uncertain, whole exome sequencing in the reported twins could possibly help identify underlying genetic pathology.

Opinions concerning the risk for congenital malformation after assisted conception remain controversial [26]. The increase of 42% in IVF conceptions could be explained by parental characteristics, the high rate of multiple births, and possibly, synergistic effects of twinning and IVF [27]. ICSI procedure, compared to standard IVF, was not found to represent an increased risk for NTD [28].

Table 1 Summary of twins with concordant MMC reported in the literature [3, 4, 9–23]

	Dizygotic	Monozygotic	Unknown zygosity
Sex			
- Same sex, female	1	2	1
- Same sex, male	3	3	0
- Same sex, gender unknown	0	1	4
- Opposite sex	5	x	x
- Unknown	2	0	0
Pregnancy outcome			
- Live birth	7	3	3
- Still birth	0	1	0
- Terminated	1	1	0
- Unknown	2	2	2

Prenatal screening with US and maternal serum alpha-fetoprotein levels are indispensable for the early detection and optimal management of NTD. Prenatal counseling of morbidity and mortality guides decisions regarding termination of pregnancy and fetal or postnatal surgery [27]. Fetal MRI could further help in the characterization of the lesion, thereby contributing to assessment of the prognosis and guidance of the management [29].

Genetic counseling should be considered in selected cases of prenatally diagnosed NTD in high-risk pregnancies (such as twin pregnancies, siblings with NTD, parental consanguinity, and associated congenital malformations seen on the fetal US) [2, 30].

Conclusion

The reported rare instance of concordant MMC in opposite-sex dizygotic twins, conceived by IVF using ICSI, intrigues questions concerning the etiology of MMC. Further research of the genetic components leading to MMC is important to better understand its pathophysiology. In addition to standard prenatal US screening, fetal MRI and genetic counseling should be considered in selected cases.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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