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Abstract

Spina bifida is one of the most common NTD's (neural tube defects) to occur during embryonic development, when the neural tube fails to close properly during neurulation.

Myelomeningocele is the most severe form of spina bifida. Characterized by an open posterior neuropore with meninges and parts of the spinal cord protruding from the fetus's body, it manifests in a variety of physical and neurological symptoms that vary both by the individual and by the state of the lesion. Until the late 1990's, the standard course of treatment was surgical closure of the lesion at birth, followed by standard protocols and treatments to treat the accompanying issues. However, once the first in-utero repair of myelomeningocele was performed in 1997, a new world of possibilities opened up. In-utero repair demonstrated distinct advantages over the standard method of postnatal repair; specifically, it reduced the likelihood of hydrocephalus and hindbrain herniation and showed significant improvement in motor and neurological function. This paper will discuss, analyze, and compare the outcomes of both the prenatal and postnatal methods of repair and discuss emerging research in the field as well as some of the inherent risks of the procedure.

Introduction

Fetal development, with all its extraordinary inner workings, is considered by many to be one of the most remarkable miracles of life—yet the more intricate processes involved, the greater the potential for damage. Neural tube defects, or NTD's, are among the possible disorders in fetal development, the most common of which are anencephaly and spina bifida. Spina bifida, in turn, is one of the most widespread birth defects, as well as the most common congenital defect of the central nervous system that is actually compatible with life (Adzick et al., 2013). As such, it is the focus of much study and intervention.

Spina bifida is characterized by an open vertebral column. In its least severe form, spina bifida occulta, the gap is merely a gap in the vertebral arches. It does not impair functioning and may never even be discovered. The most severe form of spina bifida, though, and the focus of this review, is spina bifida aperta, or open spina bifida. Commonly referred to as myelomeningocele, this is a form of spina bifida where the neural tube itself fails to close during neurulation. In cases like these, neural tissue from the spinal cord and meninges are pushed through the open vertebral arches, muscle, and skin into a sac of cerebrospinal fluid protruding from the fetus's body (Sacco et al., 2019).

The exposed neural tissue, in turn, degenerates further with increased exposure to the intrauterine environment. Thus, myelomeningocele is often considered a "two-hit" process, as damage occurs first due to the open neural tube and secondly, and more progressively, due to prolonged exposure of the neural tissue to the amniotic fluid environment. Based on the severity of the defect, the infant will be afflicted with lifelong disabilities such as impaired bladder and bowel function, paralysis, and neurological deficits, and will be at risk for hydrocephalus and hindbrain herniation (Copp et el., 2015).

The etiology is not fully understood, especially considering the various types of spina bifida; various factors are often at play in such a situation. It is understood, however, that the predominant cause of spina bifida worldwide is insufficient blood folate concentrations among women of childbearing age (Oakley, 2020) – a problem easily preventable in many cases, though folate intake is not a cure-all.

Up until the late 1990's, myelomeningocele was repaired postnatally: the defect was surgically closed at birth and the various associated health issues managed with standard medical procedures and therapies. In 1997, though, the first successful in-utero repair of myelomeningocele was performed, which paved the way for many more successful prenatal surgeries. Prenatal repair of myelomeningocele exhibits several distinct advantages over standard postnatal repair; chiefly, the fact that it actively reduces the need for shunting for hydrocephalus and results in better mental and motor function at 30 months of age (Adzick et al., 2013).

As miraculous as it may seem, prenatal surgery still comes with its own set of risks. This paper will discuss the current methods of treating myelomeningocele as well as examine new research and modern advances in the field, and evaluate the risks involved to the best course of action regarding myelomeningocele repair.

Methods

The articles and journals used in this review were found mostly on ProQuest, PubMed, and the National Institute of Health. Among the key phrases used were "spina bifida," "myelomeningocele," "in-utero repair," "stem cell therapy," and "folic acid."

Discussion of Spina Bifida

In a normally developing embryo, primary neurulation begins at the beginning of the third week of gestation. This process is characterized by the formation of the neural plate, a thickened portion of ectoderm—the very beginning of the central nervous system. Through cell division and cell migration, the neural groove is formed in the

center of the neural plate while the sides of the plate form the neural folds. These folds rise, come together, and fuse to form the neural tube; closure begins in the cervical region and extends both cranially and caudally. By the end of the fourth week of gestation, the neural tube is closed and primary neurulation is complete (Fichter et al., 2008.

The problem arises when the neural tube fails to close properly. Researchers are still uncertain as to what precisely causes this to happen, but what is clear is the outcome: an open posterior neuropore. The end result, therefore, is a neural tube defect characterized by an open vertebral arch and open meninges, fused to the skin, that forms a sac containing parts of the spinal cord (Fichter et al., 2005).

Individuals with spina bifida may experience a multitude of difficulties in various aspects of life—specifically with regard to mobility, though much of it is dependent upon the severity and location of the lesion. Though lower limb weakness, lack of sensation, or paralysis below the level of the lesion are frequent, many individuals do achieve independent ambulation as adults, approximately 57% with an L4 lesion and as many as 93% with a sacral lesion (Sacco et al., 2019).

Bladder and bowel dysfunction are common secondary conditions of spina bifida; these are normally managed with catheterization, enemas, laxatives, and the like. Some experience sexual dysfunction as well, specifically with regard to erectile dysfunction in men. In addition, leakage of cerebrospinal fluid through the spinal lesion often causes brain changes such as the Chiari II malformation which causes hindbrain herniation. The herniation impairs development of the cerebrospinal fluid pathways in the brain; this causes hydrocephalus, or a buildup of excess fluid. Hydrocephalus is typically managed with a ventriculoperitoneal shunt, though shunt complications may and do occur (Sacco 2019).

Moreover, children with spina bifida often have significant medical expenses as well as learning disabilities and lower IQ's than average, and many cannot live independently as adults (Adzick, 2013).

Historical Background

In the early 1970's, the advent of prenatal biochemical screening techniques first made it possible to diagnose neural tube defects such as spina bifida; the presence of alpha-fetoprotein (AFP) in a sample of blood or amniotic fluid was a good indicator. As the use of ultrasound technology to detect anomalies became more widespread, the use of biochemical screening techniques, though still useful in some cases, became less relevant, since sonograms are more accurate and specific (Copp et al., 2015).

Still now, the standard traditional treatment for myelomeningocele is postnatal repair and closure of the defect within two days after birth. Among other reasons, this helps avoid the risk of the open wound leading to an infection that can cause meningitis (Copp et al., 2015). The treatment includes the placement of a ventriculoperitoneal shunt to treat the hydrocephalus that will probably occur (Grivell, RM; Andersen, C; Dodd, JM, 2014). The shunt drains the excess fluid from the brain into the peritoneal cavity and needs lifelong monitoring (Adzick et al, 2013).

The main argument for in-utero repair of myelomeningocele can be made as follows. The "two-hit hypothesis" (Joyeux et al., 2018) states that a good deal of the damage caused by myelomeningocele is not due to a failure in neurulation. Rather, the development of neurological damage is progressive; that is to say, exposure of the neural tissue to the amniotic fluid in the intrauterine environment, as well as other mechanical damage, serves to exacerbate the issue and is responsible for much of the loss of function (Fichter et al., 2008). As a result of exposure to the toxicity of the amniotic fluid, the exposed spinal cord may hemorrhage and neural connections may be interrupted, leading to neural death (Copp et al., 2015). This hypothesis is supported by observations such as in cases where spontaneous leg movement was observed early on during a pregnancy, and the same leg was seen to be paralyzed or deformed later on (Grivell et al., 2014). In-utero surgical closure of the lesion, while unable to completely repair the condition, goes a long way toward preventing further damage and worsening an already unfortunate situation.

MOMS Trial

In 1997, the first in-utero myelomeningocele repair by uterine hysterotomy was performed; by 2003, more than 200 fetuses had undergone the surgery (Adzick et al., 2013). However, its efficacy was not yet proven. In 2003, the MOMS Trial, or Management of Myelomeningocele Study, was started; this was a randomized controlled trial aimed at investigating and comparing the outcomes of prenatal vs postnatal repair of myelomeningocele (Kabagambe et al., 2017).

The trial was conducted at three maternal-fetal surgery centers in the United States and went on for seven years (Grivell et al., 2014). The standardized procedure across all three maternal-fetal centers included a maternal laparotomy and stapled hysterotomy; the neurosurgical repair of the lesion was performed as it would have been postnatally (Sacco et al., 2019).

The trial was evaluated for two main outcomes, at 12 and 30 months of age. At 12 months, patients underwent

radiography and magnetic resonance imaging to determine the current state of the lesion. The outcome was based firstly on the patients surviving past birth and infancy, as well as the need for a shunt. At 30 months of age the babies were evaluated once more and given scores of infant development, specifically with regard to motor and mental development, while adjusting for the anatomical level of the lesion (Adzick et al., 2013).

The overall results were arguably and overwhelmingly in favor of the prenatal procedure. In-utero repair of the lesion reduced the need for a ventriculoperitoneal shunt by almost half and drastically improved the rate of hindbrain herniation (Sacco et al., 2019). The patients who underwent in-utero repair also demonstrated substantially better motor skills at 30 months of age—and this was despite the fact that the lesions in the prenatal group were, on average, worse than those in the postnatal group (Copp et al., 2015).

The MOMS Trial was the first of its kind, but it paved the way for other similar non-randomized studies in the years to come, many of which reported similar short-term outcomes. In addition, it was found that in cases where the procedure was performed at an earlier gestational age, the risk of chorioamniotic membrane separation, premature rupture of membranes, and premature birth increased. Therefore, it is now recommended that the procedure should not be performed before 23 weeks of gestation (Sacco et al., 2019).

New Research

In-utero closure of myelomeningocele goes a long way towards reducing spina bifida related challenges, but what it cannot do is reverse the neurological damage that has already been done. A promising course of treatment may lie in the field of stem cell therapy, which when used in conjunction with the standard course of treatment aims to improve neurological function by facilitating spinal cord regeneration and even seeking to prevent the damage in the first place (Biancotti et al., 2020.)

Type 1 stem cell therapies, which are capable of replacing damaged tissue, seem not to be the answer in the case of prenatal spina bifida repair; the ultimate goal here is to prevent the tissue from becoming damaged in the first place, and while regeneration of damaged tissue is certainly useful, it is only helpful after the fact.

Type 2 therapies, on the other hand, create an environment of protection and can minimize damage to the developing spinal cord. These therapies show more promise for in-utero treatment of spina bifida in the long run, because they seek to prevent the damage from ever happening at all (Long, C; Lankford, L; Wang, A., 2019).

Experimental results, specifically with rodent and ovine models, have already shown potential for great change. One study experimented with five different types of stem cells: human embryonic stem cells, neural stem cells, induced pluripotent stem cells, human amniotic fluid stem cells, and mesenchymal stem cells. The results indicated that mesenchymal stem cells were the best candidate for myelomeningocele repair because they were easy to obtain in large amounts, they could enable recovery from spinal cord injuries, and they demonstrated the biggest improvement in motor function (Dugas et al., 2020). Additionally, bone marrow-derived mesenchymal stem cells have the ability to specifically differentiate into the various types of defective tissue, and they were found to induce skin repair in fetuses, reducing the skin lesion area by almost 30%. Transamniotic fluid injection was found to be the most effective method of delivering stem cells (Wei et al., 2020).

However, the use of animal models has its shortcomings: the size of fetal rats and other small rodents presents difficulties in reliably and accurately performing in-utero repair. There is a risk of postoperative death, and often they do not survive long enough postnatally to examine the results properly. Larger animals have the added concern of being too expensive to work with regularly (Biancotti et al., 2020).

As of now, stem cell therapies for NTD's, specifically for myelomeningocele, are still in experimental stages; there have not been any human test subjects yet. However, promise for great change seems to lie in this relatively new field.

Maternal Mortality/Risks

As with any surgical procedure, in-utero repair of myelomeningocele carries inherent risks for both the mother and the fetus simply by virtue of opening the mother's abdomen and uterus mid-pregnancy (Grivell et al., 2014). Possible obstetrical complications associated with the procedure include placental abruption, oligohydramnios, and chorioamniotic membrane separation, as well as the risk of premature rupture of membranes and preterm delivery (Kabagambe et al., 2017). The risk of pulmonary edema and the need for a blood transfusion at birth was slightly higher in the prenatal group as well (Sacco et al., 2019). The average delivery in the prenatal group was 34 weeks while the average delivery in the postnatal group was at 37 weeks.

Additionally, 25% of the women in the MOMS trial experienced thinning and partial or complete tissue edge separation at the hysterotomy site, though none experienced a complete hysterotomy rupture. There were no deaths, but the side effects show that the procedure is not without its risks (Copp et al, 2015).

Because of this, it was necessary for the MOMS trial to

implement strict guidelines regarding maternal health prior to the procedure. Among the requirements for participation were a singleton pregnancy, a gestational age of 19-26 weeks, and myelomeningocele of particular severity as well as evidence of hindbrain herniation. Mothers had to be at least eighteen years of age and United States citizens, as well as have no contraindications for surgery (Adzick et al., 2013). Over the years, the MOMS trial criteria became standard, and most maternal-fetal research centers offering the procedure still use these criteria to determine eligibility for surgery (though some centers will not consider a body mass index of over 40 or carefully managed diabetes to be contraindications for the procedure) (Sacco et al., 2019).

Prevention

Both genetic and non-genetic causes play a role when it comes to spina bifida, or neural tube defects in general. In most instances, the cases are sporadic and do not occur in conjunction with any other syndrome, though in an approximate 10-20% of the cases the NTD is associated with a chromosomal abnormality such as trisomy 13 or 18 (Copp et al., 2015).

Maternal obesity and diabetes as well as certain anticonvulsant drugs have been shown to contribute to NTD's (Fichter et al., 2005), but the role of folic acid has been the most widely investigated (Sacco et al., 2019). Folate deficiency among women of childbearing age is currently the best-known non-genetic cause of neural tube defects (Copp et al., 2015). Therefore, the World Health Organization currently recommends that women take a supplement of 400 µg of folic acid daily from before they conceive until 12 weeks gestation (Sacco et al., 2019); however, many women do not keep to these guidelines, which has led some countries to implement mandatory folate fortification of certain basic food staples. In 2017, for instance, 59 countries mandated fortification of wheat and maize flour with folate, and the incidence of spina bifida that year was significantly reduced Sacco et al., 2019).

According to Oakley, every country should mandate fortification of food staples such as rice and flour with folate to decrease to frequency of spina bifida; inaction, he feels, is unethical (2020). This approach has validity, but it may not be practical on a global level. Additionally, ethical concerns cannot be determined by one man.

The long-term solution is unclear, but it is evident that proper folate intake goes a long way towards preventing neural tube defects.

Discussion and Conclusion

In-utero repair of myelomeningocele is still a relatively new procedure, as it has only been developed within the past twenty years. Though it has been extensively studied, researched, and documented, and though new advances in the field are constantly emerging, there is still room for extensive studies and research to further improve the process.

Nevertheless, based on the evidence from the studies that have already been performed, it appears that because of the reduced need for shunting, potential for reversal of hindbrain herniation, and vastly improved neurologic function, in-utero repair is the most effective method of treatment for myelomeningocele. True, there are inherent risks. However, as demonstrated by numerous studies, both the maternal and fetal risks are relatively low (Sacco et al., 2019). Additionally, the procedure is only performed in some of the safest settings possible in order to minimize risk.

The benefits of the procedure are evident and undeniably advantageous. It is not yet standard medical care by any means; however, with continued research, particularly with regard to stem cell therapies which seek to restore function in addition to halting neurodegeneration, in-utero repair may and possibly should become the new normal for fetuses afflicted with myelomeningocele.

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