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Questioning the rationale and conduct of the management of myelomeningocele study

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ABSTRACT

Surgical intervention in fetal spina bifida developed from the belief that amniotic fluid damages the spinal cord in utero and low spinal pressure from failure of neural tube closure causes hindbrain herniation leading to hydrocephalus after birth for many infants with open spinal lesions. Intrauterine intervention is undergoing a randomised human trial known by the acronym MOMS. It is hoped that randomisation and long-term follow up will demonstrate whether benefits to the infant may result from closure of the vertebral defect before birth. It is argued here that the premise upon which the pathogenesis of neural injury in human spina bifida used to launch this study is mistaken. This has implications for the conduct and conclusions of the trial.

It is proposed that fetal surgery improves central nervous system outcome by improving cerebrospinal fluid flow at the foramen magnum. Successful intervention results in a more normal development of both neural and skeletal components of the neuraxis. Closure of the defect is required before signs of hindbrain herniation and ventriculomegaly are evident on ultrasound imaging as these are indicators of the presence of fetal hydrocephalus.

Introduction

The currently supported theory of neural injury in dysraphism and the hypothesis that assisted the launch of the randomised comparison of prenatal versus postnatal myelomeningocele repair is a theory of low spinal pressure resulting from failure of neural tube closure [1–4]. The theory describes egress of cerebrospinal fluid (CSF) from the spinal lesion and low pressure in the immature embryonic and fetal ventricles leading to small head size, reduced posterior fossa and cerebral deformity, including craniolacunia [1,2]. Low spinal pressure caused by the open defect leads to desent of the brainstem and cerebellum which form the hindbrain [2,5]. Failure of neural tube closure allows exposed neural elements to be damaged by the intrauterine environment [6] caused by amniotic fluid toxicity and impact with the uterine wall. Intrauterine closure of the defect has been stated to cause 'backpressure' that improves hindbrain herniation [3] and the potential for decreased shunt requirement after birth [4,6,7]. Hydrocephalus with spina bifida is widely believed to occur only after birth [2,6]. These existing concepts and early disappointing outcomes from human maternal–fetal surgery have contributed to uncertainties regarding justification for current techniques and support for the randomisation of fetal intervention versus neonatal repair which is known as the management of myelomeningocele study (MOMS).

An alternative theory proposes that the mechanism of neural injury in spina bifida is obstruction to CSF pathways in the posterior fossa, and the goal of fetal surgery is improvement in the Chiari malformation, with an associated improvement in posterior fossa CSF spaces [8]. That by addressing the Chiari malformation maternal–fetal surgery can potentially offer improved neurological outcome in cerebral and spinal functions for the neonate. This new theory argues that obstruction to CSF flow at the foramen magnum causes raised pressure by decreasing central nervous system compliance and thereby damages the spine, making neural injury in Chiari II analogous to that of Chiari I [8].

Ideas are developed in this work to suggest how the vertebral defect contributes to the development of foramen magnum obstruction and raised central nervous system (CNS) pressure in the fetus. This theory indicates how Chiari II surgery may prevent progressive spinal cord injury, as with successful Chiari I surgery, albeit with differing techniques. It is proposed that with a better understanding of the pathology of Chiari II related deformities a randomisation could have been avoided and that advancements in surgical techniques and improved patient selection should be the focus of current efforts.

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; ICP, intracranial pressure; MOMS, management of myelomeningocele study.

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Discussion

Several conceptual requirements are necessary for the formulation of this progression of the hypothesis presented thus far, they include that;

1. Pressure peaks in the CNS represent mechanical energy. Pressure waves within fluid allow transmission of kinetic energy from areas of high pressure to low pressure within the fetus. Mechanical energy within the CNS promotes the growth of bone.
2. The pressure profile in the ventricles of a fetus with reduced skull size and open spina bifida with progression of Chiari malformation is of elevated mode pressure and decreased pulsatility, so that average pressure rises and high energy pressure peaks are attenuated.
3. Successful fetal intervention will reduce cerebral deformity associated with elevated mean pressure which includes aqueduct stenosis and mantle thinning.

The normal CNS pressure profile is pulsatile as demonstrated by continuous monitoring. This pulsatility is generated by fluctuating blood volume caused by physical movements. Cardiac and body movements combine with vascular tone to alter total CNS volume so that pressure in the CNS of a healthy individual is constantly fluctuating. The pressure attained depends upon the volume that enters the CNS and the volume displaced during the phase of any physical exertion in a live subject. Energy in the form of kinetic energy may also be imparted on CNS structures by pressure waves. A common experience of this phenomenon is coughing in the presence of viral meningism; the greater the force of the cough the more headache is likely to be felt. In the absence of body movements CNS pressure will be tend to be dictated by atmospheric pressure. The energy imparted by any movement depends upon the speed and volume of the influx into the CNS which depends on the strength of muscle contractions. The most forceful movements that will propel fluid into the CNS will be the combined actions of skeletal muscles including the diaphragm abdominal and thoracic muscles that cause retrograde flow of blood from the body cavities into the spinal venous plexus. Valsalva manoeuvre demonstrates a CNS pressure effect that may raise initial pressures measured at lumbar puncture (opening pressure) to levels that mimic those of hydrocephalus [9].

Spinal fluid volume fluctuations will send pressure waves towards the head in an upright individual because gravity allows lower pressure in the head than the spine. Normal pressure wave transmission has been demonstrated experimentally; it appears to depend upon continuous fluid pathways. With Chiari I malformation pressure wave transmission is reduced [10]. Failure of spinal pressure waves to transmit to the ventricles of the neonate with open spina bifida has also been demonstrated in humans prior to repair of the open lesion [5] and this is likely to be caused by interruption of CSF pathways between the head and spine. In the fetus with patent CSF pathways it is reasonable to suppose that pressure waves are also directed towards the head because the skull has fontanelles which will dampen intracranial pressure, and wave energy by implication moves from higher to lower pressure zones.

A vertebral defect allows CNS pressure peaks in the fetus to be dissipated by transmission into the uterine cavity, in the same way that a skull defect can reduce pressure in underlying brain tissue. The proximity of the defect to the source of pressure pulsations will encourage the loss of mechanical energy. In the normal fetus influxes of venous volume from the abdomen and thorax transmit energy, CSF spaces are continuous, they 'communicate' and therefore allow transmission of pressure waves. Body movements that are easily visible in an eight week fetus on ultrasound will generate small impulses throughout the embryonic CNS and stimulate proportionate bone growth. In unison with normal bone growth there will be space for growing neural tissue. According to this theory in the fetus with spina bifida aperta the cranial fossae are deprived of the normal pressure peaks that would occur in the head because of the presence of the vertebral defect and because posterior fossa CSF spaces are reduced at an early stage [11]. As posterior fossa CSF spaces are reduced there will be elevated mean (and mode) pressure within the ventricles particularly with active production of CSF at the choroid plexus. Hindbrain crowding is perpetuated as there is elevated pressure from above and reduced posterior fossa. With increasingly forceful body movements abnormally high peaks of pressure in the spine splay the vertebrae and stretch nerves, vessels and membranes [8]. Lateral ventricle enlargement and progression of Chiari malformation in utero is usually interrupted by either fetal demise or birth.

It is proposed that with successful fetal intervention there will be improvement of posterior fossa CSF spaces. This will avert much of the elevation of mean CSF pressure that would otherwise advance relentlessly during gestation [8] and also enhance the transmission of high energy pressure pulsations which will then be detectable within the ventricles. This predicted pattern of elevated mode pressure with attenuation of pressure peaks within the ventricles in the presence of an open lesion which is then transformed into a profile with lower mode pressure and enhanced pulsatility following surgical repair has been recorded in a single case. A 12 year old boy who had never been shunted demonstrated mild ventriculomegaly and a back lesion of 'basket-ball size' with no cord function below L2. Pre-operative intracranial pressure was measured to range from 1 to 14 mm Hg with most pressures occurring between 9 and 12 mm Hg. Postoperatively the range was 3–25 mm Hg with most pressures between 5 and 10 mm Hg. These readings demonstrate a significant reduction in mode pressure and a wide broadening in the range of recorded pressures. The results are shown graphically in Fig. 1. The disparity and duration of measurement of the readings in this case gave a p value for the likelihood of a chance rather than a causal effect of surgery of <0.001 [12]. After repair the child was reported to remain well with stable ventricle size.

The implication of this case is that a spinal repair that is timed appropriately in a fetus with minimal ventricle enlargement and no visible hindbrain herniation will result in a similar change in the pressure profile within the cranium. This will result directly from increased energy transmission in the form of pressure waves that impact the skull. It is arguable that the pressure change in the fetus may be less dramatic than that measured in this case; however it may also be argued that such improvement may be sustained by preventing hindbrain herniation and aqueduct stenosis.

Low intracranial pressure at birth and the variable postnatal course of hydrocephalus in spina bifida aperta has contributed to the misunderstanding that hydrocephalus is not a feature of dysraphism in utero. The precipitous decrease in chest cavity pressure that occurs with expansion of the lungs, and that the skull with open sutures and fontanelles, external jugular veins, and abdomen are exposed to atmospheric pressure will lead to a dramatic drop in CNS pressure by improving venous drainage such that neonatal opening pressure approximates atmospheric pressure. Increased arterial oxygen saturation as metabolic requirements increase will also tend to have a favourable effect on CNS pressure.

Normal intraventricular pressure for the human fetus in utero is unknown; it is unlikely to be lower than that measured in non-human primates which have been found to be in the range of 50–60 mm Hg [13]. Cerebrospinal fluid within enlarged ventricles in the fetus has been found to be under raised pressure, with very

high pressure in the third trimester. Pressures of 250 mm Hg or more towards the end of gestation have been measured in animal studies [14] with similar readings in human observations [14,15]. Although reduced skull size is a feature of fetal spina bifida an enlarged skull can occur in utero with cephalopelvic disproportion requiring caesarean section [16]. These infants will represent the most severe cases of hydrocephalus and will be the manifestation of a high disproportion between normal and abnormal mean intracerebral pressures as the middle and anterior fossae enlarge against pressure imposed by the uterus and its contents. Obstruction to CSF flow is a reliable cause of hydrocephalus particularly when it occurs at the foramen magnum [17]. In the severely affected fetus reduced CSF spaces in the posterior fossa including the basal cisterns and fourth ventricle may be detectable by ultrasound in spina bifida at the end of the first trimester [11]. This means that a mechanism by which cerebral pressure may increase is established in these cases.

Robust evidence for aqueduct stenosis as a consequence of ventriculomegaly has been generated by sequential anatomical studies of viral encephalitis in mice [18]. Obstruction to contrast flow through the aqueduct has been demonstrated with ventriculography in hydrocephalus, with re-opening of the aqueduct to contrast medium following lateral ventricle shunting [19], demonstrating that as pressure is reduced aqueduct flow may resume. Spina bifida infants at autopsy demonstrate that large ventricles are associated with mantle thinning and highly correlated with compression and inferior displacement of the aqueduct, without anatomical occlusion [20]. The implication of these cases is that as lateral ventricle size increases in human fetal spina bifida it causes pressure on the midbrain and progressively reduces flow through the aqueduct. Aqueduct attenuation will tend to further elevate intraventricular pressure in the fetus as in children or adults and lead to mantle thinning.

In the severely affected neonate the period of reduced CNS pressure following birth may be brief. Closure of the spinal defect fails to improve any deformities that cause CSF obstruction and CSF can no longer drain from the placode, hydrocephalus may therefore redevelop rapidly. Where the skull and brain have a more normal configuration there will be lesser degrees of pressure elevation following birth [21,22]. In the most favourable cases of minimal hydrocephalus related cerebral deformity, spinal closure will lower intracranial pressure as in the case illustrated in Fig. 1.

In the earliest stages of gestation there will be little discrepancy in embryonic cavity and amniotic fluid pressure. In a live embryo of less than 1 cm in length there will be pulsatility within fluid filled cavities as the heart starts to beat. Later in gestation pressure is enhanced with fluid production by active metabolism in the choroid plexus. With increasingly strong movements, energetically generated fluid pressure and obstruction to flow, the deformities that occur as a consequence of Chiari malformation will demonstrate variability between cases. Gross pathology may be found throughout the central nervous system with the exceptions of the retina and cochlea, as a greater part of their development occurs in the postnatal period and some protection is afforded by their anatomical relations to bone.

Surgical implications

An imperative of intrauterine repair will be that it achieves mechanical closure of the defect before hindbrain herniation, ventriculomegaly and aqueduct attenuation become established as these deformities obstruct CSF flow and elevate pressure.

The aim will be preventing hindbrain herniation in fetuses that are otherwise destined for hydrocephalus and paraplegia. Ventriculomegaly is known to correlate with posterior fossa signs [23] and following intervention skull growth and ventricle size would be markers for surgical success. Ventriculomegaly is prone to becoming a self perpetuating problem; this is in part because of its tendency to attenuate the aqueduct. Small degrees of ventricle enlargement prior to repair imply the potential for surgical failure. In humans the degree of medullary herniation relates to the size of the spinal defect [24]. The larger the defect and the longer that the gestation proceeds in the presence of posterior fossa crowding the greater will be the risk of irreversible neural deformity. Pregnancies affected by lesions with absent or advanced hindbrain changes will be unsuitable for intrauterine intervention because they will expose women to the risks of surgery and the fetus to adverse outcomes related to prematurity without the opportunity for gain. Timed early delivery where lung maturity is established will suitable for these cases [16,25] and caesarean section may almost

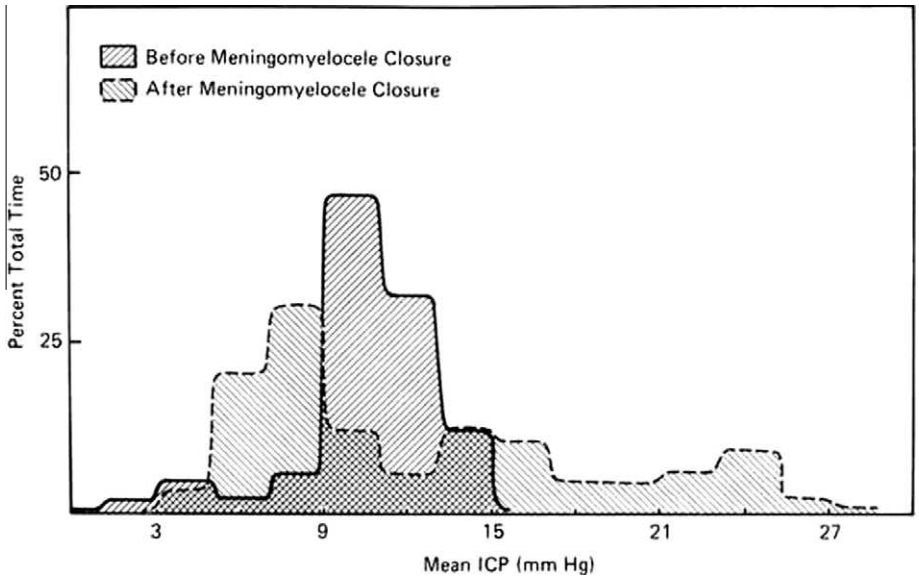

Fig. 1. Time (%) versus mean ICP (mm HG) before and after meningomyelocele closure. ICP data were averaged over 3-min intervals. Reproduced with permission from Karger Basel [12].

always be advisable when dealing with infants with reduced posterior fossa. Safe maternal-fetal surgery will require a minimally invasive technique that allows for prolonged gestation after intervention with a mechanically stable repair as the strength of fetal movements increase with age.

Evidence indicates that mantle thickness and ventricle size are not significantly improved with the MOMS trial methods of maternal–fetal intervention [26]. This may be symptomatic of inadequate case selection, as MOMS made no requirements related to brain morphology [6]. Patient selection based on criteria outlined in this work have however been used at the Bonn centre for minimally invasive fetal surgery [27] and evidence in the form of improved neurological outcome for the spine is emerging from this work [28] that supports this approach.

Evidence indicates that neural injury is a progressive intrauterine phenomenon in open spina bifida. The MOMS intervention group patients were more likely to deliver prematurely than the non intervention group [6]. This means that comparisons between cases, or the group as a whole, is of questionable validity. Despite this reservation it is possible that the MOMS trial patients will show neurological benefit within the subgroup that demonstrate improved hindbrain herniation shortly after intrauterine intervention. Dividing subjects into subgroups following results leads to the requirement for further evaluation.

Theoretical implications

There is no doubt that the hindbrain herniation caused in experimental models of spina bifida by laminectomy and dural incision is related to loss of spinal CSF, but a phase of lowered pressure may be extremely transient. It is possible that the generation of hindbrain obstruction with raised pressure and lack of support from vertebral mesodermal tissue generates a placode [8]. Evidence to support this proposal comes from experiments on the spinal cord of adult cats. Thoracic laminectomy was compared between animals previously made hydrocephalic by intra-cisternal kaolin and non hydrocephalic controls. Control animals showed cords that remained structurally and functionally normal whereas hydrocephalic animals developed extensive hydromyelia and bulging of the cord through the spinal lesion [29]. It is not logical to conclude that opening of the fetal spine in an experimental animal that then causes CSF obstruction at the hindbrain provides evidence for spina bifida as a neural tube defect rather than a re-opening of the neural tube related to high pressure.

Whether there might be phase of low spinal pressure in open human spina bifida is uncertain. If a genetically linked failure of neural tube closure in humans can be demonstrated to be a separate entity to the genetic abnormalities that lead to Chiari I, or if vertebral insufficiency can be separated from posterior fossa hypoplasia on a genetic basis then a theory with low spinal pressure as an initiating force will have validity. If spina bifida is inherited with primary posterior fossa hypoplasia as an identifiable trait then a theory of secondary opening of the spine related to high pressure will be favoured. Alternatively, and in the concept that I favour, both primary fetal posterior fossa hypoplasia and failure of neural tube closure are represented in instances of human disease, and Chiari malformations involve a complex abnormality of pressure profile with periods of abnormally raised and low pressure in the CNS as illustrated by the case represented in Fig. 1.

Conclusion

The pressure effects described in this hypothesis are amenable to laboratory investigation and it could be argued that such studies should have been undertaken before human surgical trials. If demonstrated in animal models it can be concluded that the mechanism by which fetal neurological injury occurs in utero in spina bifida is related to elevation of mean CNS pressure and progressive elevation of pressure during gestation. Amniotic fluid toxicity to the spine would then be understood to be a secondary phenomenon. Intervention may be justified for selected fetuses on the basis of improved neurological outcome. Advances in maternal intrauterine techniques that reduce the risk of premature delivery are hoped for and will assist in justification for the technique.

Competing interests

I declare that I have no competing interests. The author has read and approved the final version of the manuscript.

Author contributions

This is the work of one author.

Conflict of interest statement

I declare that I have no conflicts of interest. No funding has been received in support of this work.

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