The Spinal Cord Lesion in Human Fetuses With Myelomeningocele: Implications for Fetal Surgery

By Martin Meuli, Claudia Meuli-Simmen, Grover M. Hutchins, Mary J. Seller, Michael R. Harrison, and N. Scott Adzick

Zurich, Switzerland; Baltimore, Maryland; London, England; San Francisco, California; and Philadelphia, Pennsylvania

● **Recently produced experimental evidence suggests that secondary traumatic injury and degenerative changes, acquired in utero, to the openly exposed neural tissue may be primarily responsible for the massive neurological deficit associated with myelomeningocele (MMC). The goal of this study was to examine the morphology of human fetuses with MMC to determine if acquired trauma to the spinal cord could be identified. The MMC lesions with surrounding tissues from 10 human fetuses ranging in gestational age between 19 and 23 weeks were prepared with serial histological sections. The MMC lesions were characterized by an open vertebral arch, an open dura mater fused laterally to the dermis, and an open pia mater fused laterally to the epidermis. The spinal cord was exposed, without any meningeal, bony, or cutaneous covering, and was resting on the dorsal aspect of the abnormal arachnoid sac created by the fusion of the meninges to the cutaneous tissues. The exposed neural tissue had undergone varying degrees of recent traumatic injury as a result of its exposed position, ranging from nearly complete preservation of neural elements in four cases to nearly complete loss in two cases. The neural tissue remaining in the MMC with partial loss contained hemorrhages and abrasions from recent injury, suggesting that injury occurred during passage through the birth canal. The presence of dorsal and ventral parts of the cord with nerve roots and ganglia demonstrated that these structures had formed during development and that the loss of tissue by injury was a secondary change. The results support the concept that performing in utero surgery could protect the exposed but initially well-developed and uninjured cord, prevent secondary neural injury, and preserve neural function in the human fetus with myelomeningocele.**

INDEX WORDS: Autopsy, fetal diseases, in utero surgery, myelomeningocele, spinal dysrhaphism, spina bifida, neural tube defects, congenital malformation.

MYELOMENINGOCELE (MMC), or spina bifida aperta/cystica, is one of the most common and devastating birth defects. Most children born with this malformation survive, but their lives are plagued by crippling disabilities such as paraplegia, incontinence, hydrocephalus, and often impaired mental development. The affected part of the spinal cord is destroyed and the neurological function is lost before birth; thus, there is no therapy to restore neurological function postnatally.

In a recently reported series of experiments we demonstrated in fetal sheep that exposure of the normal lumbar spinal cord to the amniotic cavity for the second half of the gestation results in dramatic secondary alterations of the unprotected neural tissue and a human-like MMC at birth.[1,2] Furthermore, we have shown that in utero repair of such evolving MMC lesions at an intermediate stage stops the neural destruction processes and preserves neurological function at birth.[2-4] Even though these experiments strongly suggest that in utero repair may be the only way to rescue neurological function in patients with MMC, we must learn more about the prenatal natural history of human MMC before considering fetal surgery for human MMC fetuses. In particular, we need to corroborate our hypothesis of preventable neural damage at a time point where human fetal surgery is currently feasible.[5] This study was designed to examine the morphology of the cord lesion of human fetuses with MMC and to specifically address the question of whether there is evidence for secondary damage to the pathologically exposed spinal cord tissue.

MATERIALS AND METHODS

Ten specimens were selected for study from a large collection of human fetuses with spinal or cranial dysrhaphia. The specimens were collected between 1981 and 1991 from therapeutic abortions after prenatal diagnosis. Specimens were carefully preserved in formaldehyde solution. Selection criteria included a gestational age within the window in which human fetal surgery is currently being performed,[5] and a thoracic-sacral MMC exhibiting partially or well-preserved neural tissue on gross inspection. On some of the selected fetuses a partial necropsy, not involving the cord lesion, had been performed immediately after abortion.

The pertinent data (medical history, gestational age, crown-rump length) of the fetuses were entered on a form, the gross pathological findings were recorded, and a standard set of photographs was taken.

From the Department of Surgery, University Children's Hospital, Zurich, Switzerland; the Division of Hand, Plastic, and Reconstructive Surgery, University Hospital, Zurich, Switzerland; the Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, MD; the Division of Medical and Molecular Genetics, Guy's Hospital, London, England; The Fetal Treatment Center, University of California, San Francisco, CA; and the Department of Surgery, The Children's Hospital of Philadelphia, Philadelphia, PA.

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Address reprint requests to Martin Meuli, MD, Department of Surgery, University Children's Hospital, Steinwiesstr. 75, 8032 Zurich, Switzerland.

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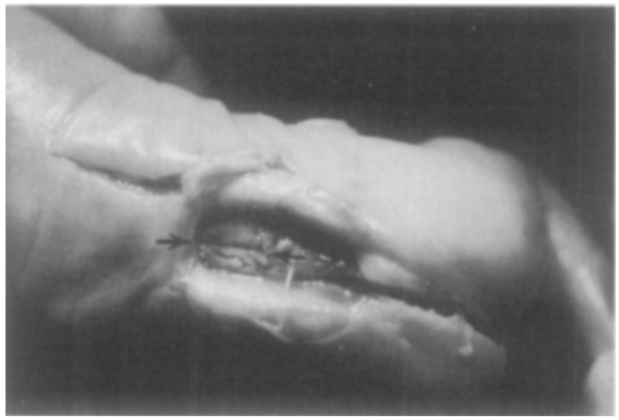

Fig 1. Case 3. Twenty week-old fetus with lumbosacral MMC. The cystic sac has been partially removed at necropsy, however, the neural tissue was left intact. The exposed spinal cord demonstrates an open central canal (arrow), but otherwise it appears relatively well preserved (also see histology in Figs 3A and B).

Thereafter, the entire spine, including soft tissues, was cut transversely into 1-cm thick blocks. The blocks were processed for histology, and serial sections of 8-μm thickness were taken at an interval of 50 μm throughout the blocks. Additionally, arms and legs were sectioned and assessed for nerve degeneration and muscle atrophy. All sections were stained with the Gomori trichrome method.

RESULTS

The major features of the 10 fetuses with myelomeningocele are summarized in Table 1. In general, the gross morphology of the MMC was similar in all specimens (Fig 1). Histologically, in the mid portion of the MMC, the dorsal aspect of the skin and the bony arch of the vertebral column were open. The dura mater was open and fused to the deep dermis of the skin on the lateral aspect of the lesion. Similarly, the open pia mater did not cover the neural tissue on its dorsal aspect but extended laterally to fuse with the layer consisting of the epidermis and a thin portion of the superifical dermis. The exposed neural tissues had no meningeal covering and were directly exposed to the amniotic cavity. The abnormally configured arachnoidal sac at the level of the MMC was formed by the open dura on the ventral aspect and the open pia on the dorsal aspect.

The spinal cord showed varying degrees of preservation within the MMC. In four instances the neural tissues resting on the dorsal aspect of the pia were well preserved with, at most, small areas of loss of neural elements. In two cases the spinal cord tissue was completely or nearly completely lost. Those portions of the cord that had partial loss showed focal hemorrhages within the neural tissues and abrasions of the dorsal aspect of the cord that had been very recently acquired (Figs 2 and 3). The histological appearance of the cord injury was consistent with it having occurred during delivery of the fetus. That the cord had been present, even in those cases with extensive loss of neural tissue, was demonstrated by the presence of the connective tissues that lay in the ventral median fissure of the spinal cord and by the presence of nerve roots and dorsal root ganglia within the MMC.

Other changes within the spinal cord were the presence of duplication of the cord, open central canals, and

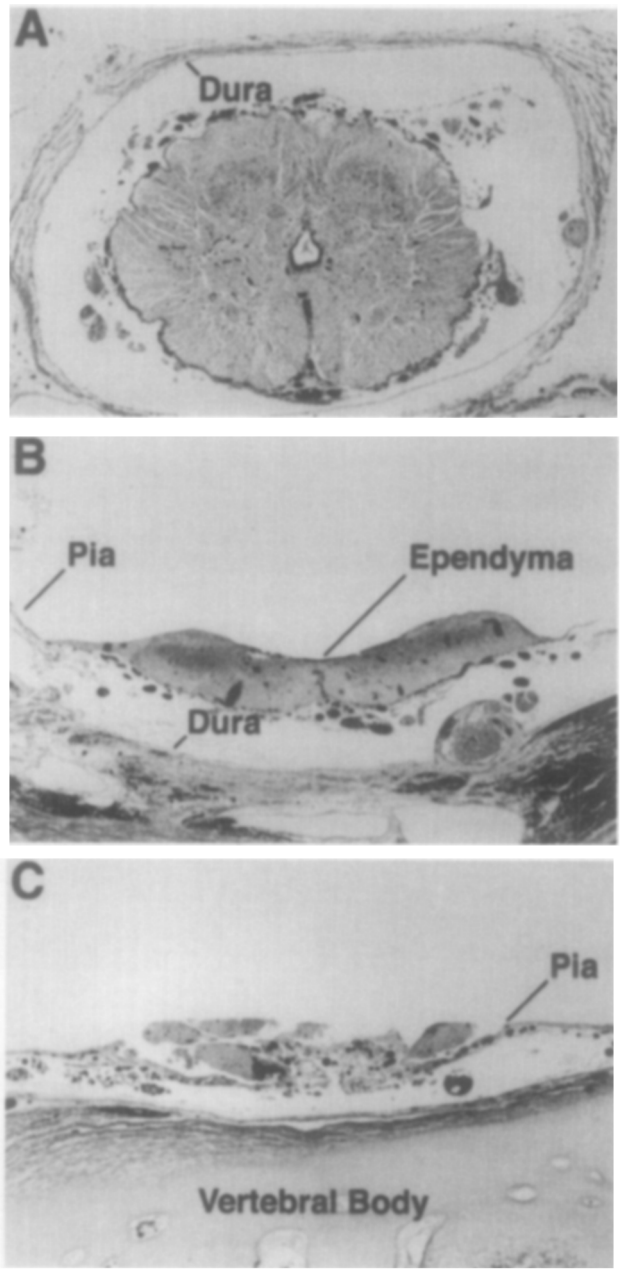

Fig 2. Case 7. (A) Spinal cord proximal to the MMC showing normal structure and normal meningeal relationships. (B) The spinal cord at the MMC has an open central canal. The dorsal horns of the cord are rotated laterally but give rise to nerve roots in a normal manner. The spinal cord rests on the open pia mater and is exposed to the amniotic cavity. (C) At the distal end of the MMC the spinal cord passes over the bodies of the sacral vertebrae and has focal hemorrhage and partial loss of tissue by abrasion [Gomori trichrome, original magnification (A) ×40, (B) ×20, (C) ×20].

Table 1. Features of Human Fetuses with Myelomeningocele

Case	Sex	Gestational Age (wk)	CRL (MM)	Head Circumference (MM)	MMC Location	Proximal Cord	Cord at the Defect	Distal Cord	Other Pathology
1	F	23	190	200	Lumbosacral	Focal hemorrhage	30% loss	Filum terminale	—
2	M	21	180	190	Lumbosacral	Syringomyelia	Open canal 0% loss Focal hemorrhages	Filum terminale	CHD
3	M	20	165	185	Lumbosacral	Focal hemorrhage	20% loss	Diplomyelia	A-C
4	F	19	155		Thoracolumbo-sacral	Small	Open canal 5% loss	Diplomyelia	A-C
5	M	21	172	165	Lumbosacral	Focal hemorrhage	95% loss	Conus medullaris	A-C
6	F	22	185	205	Lumbosacral	Normal	100% loss	Conus medullaris	A-C Triploid (69 XXX)
7	M	20	152	188	Thoracolumbo-sacral	Normal	Open canal 75% loss	Filum terminale	A-C, hypospadias Lumbar kyphus
8	M	20	175	170	Lumbosacral	Hydrosyringo-myelia	Open canal 80% loss Vernicomyelia	Filum terminale	A-C
9	M	20	170	170	Thoracolumbo-sacral	Normal	Partial duplication 15% loss	Diplomyelia	Meckel's diver-ticulum
10	M	19	155	150	Lumbosacral	Diplomyelia	Open central canal 5% loss	Conus medullaris	A-C

Abbreviations: A-C, Arnold-Chiari malformation; CHD, congenital heart disease; CRL, crown rump length.

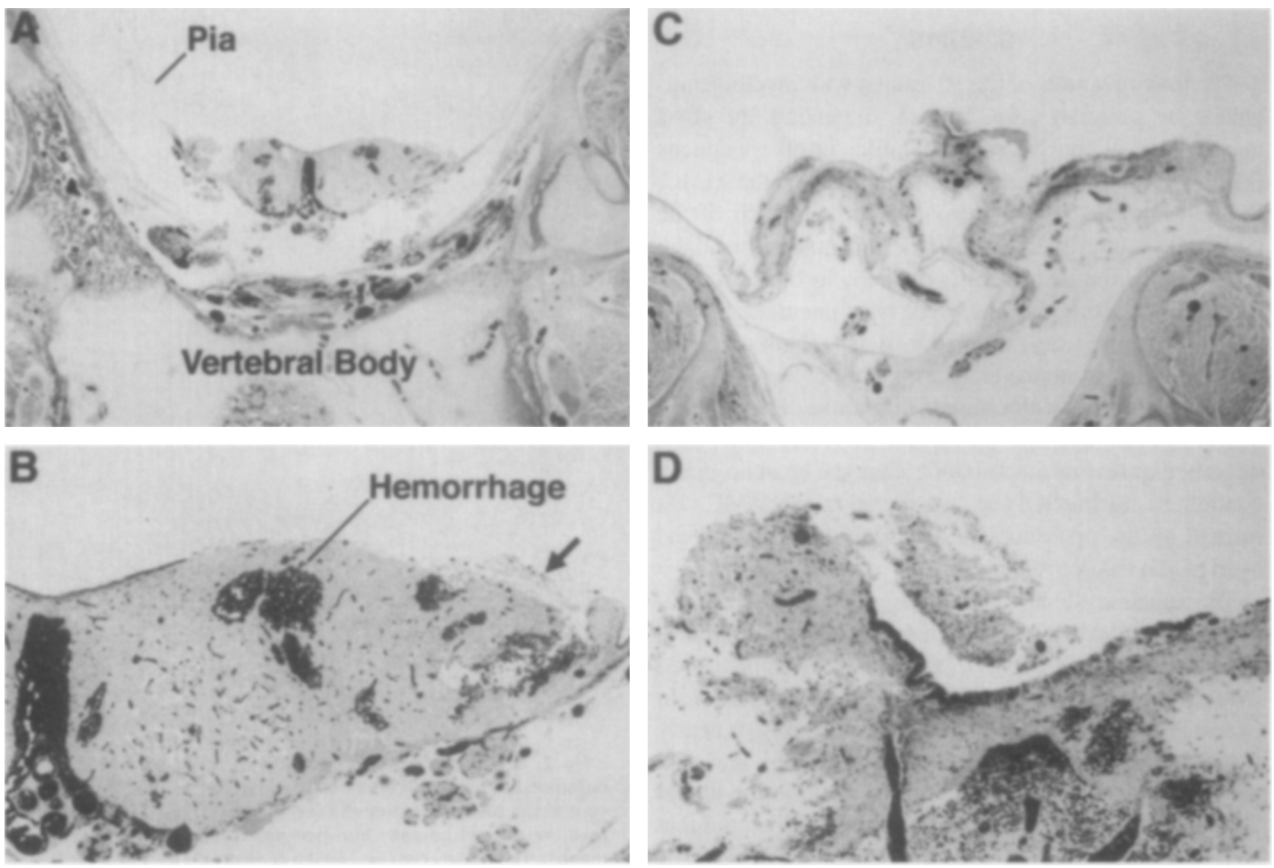

Fig 3. Case 3. (A & B). The exposed spinal cord in the MMC has an open central canal, focal hemorrhage, and slight abrasion with loss of neural tissue (arrow). Case 5. (C & D). The exposed spinal cord in the MMC has an open central canal, marked hemorrhage, and extensive avulsion of neural tissue [Gomori trichrome, original magnification (A & C) ×10, (B & D) ×40].

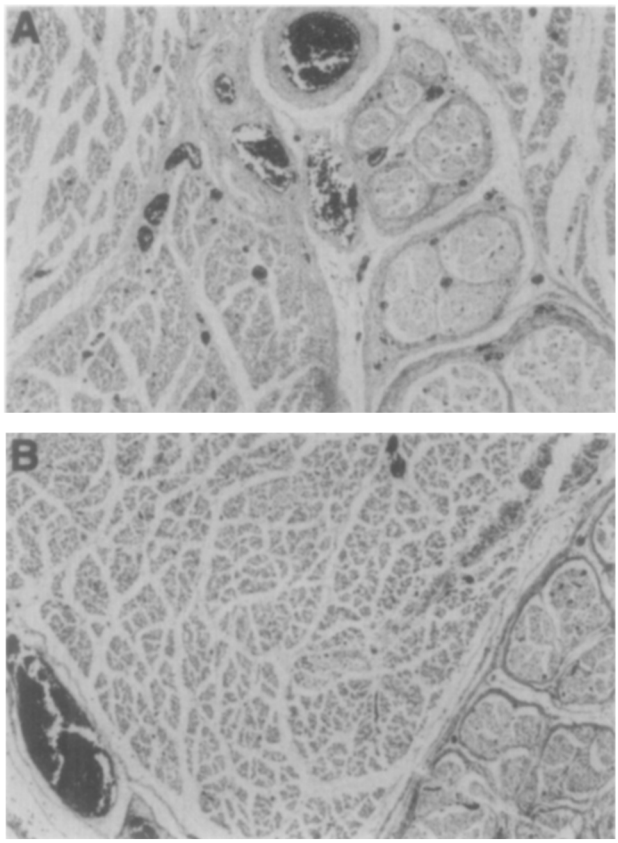

Fig 4. Case 5. Comparison of the nerves (right) and skeletal muscle (left) in the arm (A) and leg (B). There are no discernible differences between the tissues of the arm and leg (Gomori trichrome, original magnification ×100).

hydrosyringomyelia in the cord proximal to the plaque of the MMC.

Examination of the cross-sections of the upper and lower extremities did not show any differences between the arms and legs with respect to the morphology of the nerves or muscles (Fig 4).

DISCUSSION

This study shows that there is good development of spinal cord tissue, nerve roots, and ganglia within the area of the MMC. The various degrees of injury to the neural tissues and the nature of injury, hemorrhage, and abrasion or avulsion, is most consistent with injury to the cord during the process of delivery. Although these fetuses were the product of therapeutic abortions, it is not difficult to envision that the exposed neural tissue would have sustained additional traumatic or degenerative damage during the remainder of gestation. Also, further injuries to the MMC lesion would probably have occurred during labor and delivery of a living fetus.

Thus, this study shows that although there may be abnormal configurations (such as open central canal or diplomyelia) of the otherwise well-developed spinal cord in MMC, the phenomenon that accounts for the loss of neurological function is most likely a traumatic destruction of the neural tissue during gestation, labor, and delivery because it is not protected by its usual meningeal, vertebral, and cutaneous coverings.

This interpretation is further supported by a previous study of an unselected sequential series of human fetuses that had at autopsy more severe injury to the exposed neural tissues than that observed here.[6] It is important to stress that the fetuses investigated here do not represent a random cohort of spinal dysrhaphism patients, but were selected according to gestational age, location of the lesion, and macroscopic aspect of the exposed neural tissue. Thus, the findings reported cannot be translated to all cases of spinal dysrhaphism without reservation.

Furthermore, there are a few older reports of cord lesions examined postnatally in newborn babies and infants (some after surgery, some without).[7,8] In most of these instances, signs of trauma to the plaque were also evident. However, it remains uncertain to what degree these traumatic damages were caused by labor, passage through the birth canal, postnatal handling, or surgery.

What are the implications of this study regarding eventual repair of human MMC in utero? Even though we have shown in a fetal lamb model that exposure of the normal lumbar spinal cord to the intrauterine environment leads to progressive secondary alterations of the neural tissue with total loss of neurological function at birth,[1,2] and even though timely fetal surgery in this experimental setting rescues neurologic function,[2-4] we cannot conclude from morphological evidence alone that secondary neural trauma is exclusively or mainly responsible for loss of function. Nor can we conclude that timely prenatal coverage would salvage function in humans. On the other hand, our results are consistent with the hypothesis that secondary damage does occur and that it is potentially preventable by prenatal intervention.

Additional functional investigations are needed to demonstrate in vivo that progressive cord alterations correlate with progressive loss of neurological function. Electrophysiological studies investigating the functional integrity of the spinal cord in early gestational human fetuses with MMC are currently underway.

Another issue regards the time point of eventual fetal surgery. Currently, open prenatal interventions are feasible beginning at the 18th week of gestation.[5] It remains to be seen whether there are human fetuses with MMC in which neurological function around midgestation is preserved to an extent that would justify fetal surgery.

Of note, there are other important factors to be considered such as associated hydrocephalus, associated spinal cord anomalies outside the actual lesion, severe orthopedic deformations (eg, kyphus, club feet), chromosomal aberrations, or other relevant malformations. Al-

though it appears obvious that karyotype anomalies or additional potentially life-threatening malformations preclude fetal surgery, the impact of associated hydrocephaly or spinal cord anomalies remains unclear.

We have been able to gather morphological information in human fetuses that corroborates our hypothesis of both well-developed neural tissue within the MMC as well as significant secondary trauma, acquired in utero, to the exposed neural tissue. These two elements are the crucial components of the rationale for in utero repair of MMC. Even though these results represent an important step toward understanding the prenatal natural history of human fetuses with MMC, several important questions still need elucidation before human fetal surgery for this devastating malformation can be performed.

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