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Lower Extremity Neuromotor Function and Short-Term Ambulatory Potential following in utero Myelomeningocele Surgery

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Key Words
Myelomeningocele · Spina bifida · Neuromotor function · Fetal surgery · Ambulation

Abstract
Objective: To evaluate lower extremity neuromotor function (LENF) and short-term ambulatory potential following fetal myelomeningocele (fMMC) closure. ***Methods:*** Retrospective chart review of 54 children that underwent fMMC closure at our institution prior to the NIHCD-MOMS trial. Neonatal LENF was compared to predicted function based on spinal lesion level assigned by prenatal ultrasound. Ambulatory status was classified as independent walkers (walks without assistive appliances), assisted walker (requires walking aid), and non-ambulatory (wheelchair bound). ***Results:*** Thoracic, lumbar, and sacral level lesions were present in 4, 44 and 6 fMMC infants, respectively. 31/54 of fMMC children (57.4%; median: 2 levels, range: 1–5) had better than predicted, 13/54 (24.1%) same as predicted and 10/54 (18.5%; median: 1 level, range: 1–2) worse than predicted LENF at birth. At a median follow-up age of 66 months (36–113), 37/54 (69%) walk independently, 13/54 (24%) are assisted walkers, and 4/54 (7%) are wheelchair dependent. The strongest factors predicting a lower likelihood to walk independently were higher-level lesion (>L4, p = 0.001) and the development of clubfoot deformity after fetal intervention (p = 0.026). Despite the observed improved ambulatory status, structured evaluation of coordinative skills revealed that the majority of independent ambulators and all children that require assistive devices to walk experience significant deficits in lower extremity coordination. ***Conclusions:*** We observed that fMMC surgery in this highly selective population results in better than predicted LENF at birth and short-term ambulatory status. However, fMMC toddlers continue to demonstrate deficits in movement coordination that are characteristic for children with spina bifida.

Introduction

Myelomeningocele (MMC) is a severe form of open spina bifida characterized by defective fusion of the caudal neural tube and exposure of the meninges and neural tissue to the intrauterine environment, leading to lifelong physical disabilities including paraplegia, fecal and urinary incontinence, hydrocephalus and variable cognitive impairment.

Compelling experimental and clinical evidence shows that the neurological deficits associated with MMC are acquired early in development and progress in severity throughout gestation. Lower extremity movement seen on sonograms in affected fetuses before 17–20 weeks is

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Table 1. Selection criteria for fMMC repair

Less than 26 weeks of gestation
Confirmed normal karyotype
Absence of associated congenital malformations
Maximum lateral ventricular diameter of <17 mm
Severe Arnold-Chiari II malformation
S1-level lesion or higher
Normal leg movement and absence of talipes deformity

Table 2. Postnatal LENF requirements for functional lesion level assignment

T8–T12	Complete lower extremity paralysis, trunk control due to innervation of abdominal muscles
L1	Hip flexion due to innervation of psoas (lumbar plexus L1,2,3,4) and ilacus (femoral nerve L1,2,3,4)
L2	Hip adduction due to innervation of adductor magnus (obturator nerve L2,3,4) adductor longus (obturator nerve L2,3), adductor brevis (obturator nerve L2,3,4) gracilis (obturator nerve L2,3,4)
L3	Knee extension due to innervation of quadriceps femoris (femoral nerve L3,4)
L4	Ankle dorsiflexion due to innervation of tibialis anterior (deep peroneal nerve L4,5,S1) and knee flexion due to innervation of medial hamstring (sciatic nerve L4,5,S1,2)
L5	Ankle eversion (and weak plantar flexion) due to innervation of peroneus longus and brevis (superficial peroneal nerve (L5,S1), ankle inversion due to tibialis posterior (tibial nerve L5,S1), hip abduction due to gluteus medius and minimus (superior gluteal nerve L4,5,S1), hip extension due to biceps femoris (tibial nerve L5,S1), toe flexion due to innervation of flexor hallucis longus (tibial nerve L5,S1,2) and great toe flexion due to innervation of flexor hallucis longus (tibial nerve L5,S1,2)
S1	Hip extension due to innervation of gluteus maximus (inferior gluteal nerve (L4,S1,2) and ankle plantar flexion due to gastrocnemius and soleus (tibial nerve L4,5,S1,2)

commonly lost with development of talipes by the third trimester [1–3]. While fetal leg movements noted early in gestation can be secondary to spinal arc reflexes, such movements can also be of cerebral origin and their absence later in gestation and at birth may be the result of spinal cord damage caused by secondary trauma or prolonged exposure to amniotic fluid [4, 5]. Animal studies, in which a model of open spina bifida is created surgically, show that function can be retained if the defect is covered before birth [6]. Therefore, in utero repair of MMC may protect the structural defect at a time when significant neuronal damage either has not yet occurred or still has the potential to recover. Early human clinical experience suggests that fetal intervention reverses hindbrain herniation associated with the Arnold-Chiari II malformation and reduces the mortality related to posterior fossa compression syndrome, reduces the need for ventriculoperitoneal shunting by restoring normal cerebrospinal fluid hydrodynamics, and may improve neurodevelopmental outcome [7–13]. However, whether fetal intervention for MMC will reduce neuromotor deficits to the lower extremities and impacts on postnatal leg function and ambulatory potential remains unclear. We therefore followed a selected population of children that underwent midgestation MMC closure at our institution prior to the NIH-sponsored Management of Myelomeningocele Study (MOMS) and examined the lower extremity neuromotor function (LENF) and ambulatory potential in infancy and early childhood.

Material and Methods

This study was approved by the Committee for Protection of Human Subjects Institutional Review Board (IRB# 2005-7-4417).

Patient Population

Between January 1998 and February 2003, 54 patients met our inclusion criteria (table 1) and underwent fetal MMC (fMMC) closure. All infants were subsequently delivered by cesarean section and received neonatal care at our institution. Details of the preoperative evaluation, surgical approach, and postnatal management have been described previously [8, 10, 11]. Data collected retrospectively from maternal prenatal charts, postnatal hospital charts, and follow-up records included gestational age at fetal intervention, anatomical lesion level, and clinical outcomes. Operative reports of shunt placement, if performed, were reviewed to determine timing and indications for shunt placement. Neurosurgical criteria for ventriculoperitoneal (V-P) shunt placement have been previously described [10].

Assessment of Anatomical and Functional Level

Since high-resolution ultrasonography (US) remains the standard for prenatal imaging and patient counseling [14], the anatomic lesion level for fMMC patients was defined by the highest vertebral level at which the spinal dysraphism was visualized at initial evaluation. In all cases that underwent fMMC surgery, normal leg function was preoperatively defined as the presence of flexion and extension movements at the hips, knees, ankles and toes over a course of a 45- to 60-min detailed sonographic evaluation.

Table 3. Patient demographics

	fMMC (n = 54)
GA at initial prenatal evaluation, weeks	22 ± 1.5*
GA at fetal surgery, weeks	23.1 ± 1.4*
GA at delivery, weeks	34.7 ± 2.5*
Birth weight, g	2,482.6 ± 586.5*
Median APGAR 1 min	7
Median APGAR 5 min	9
Level of lesion, n (%)	
Thoracic	4 (7.4)
Lumbar	44 (81.5)
Sacral	6 (11.1)

* Data presented as mean ± SD.

At time of pre-discharge newborn examination, the neuromotor functional level was determined by a physical therapist specialist on the basis of best functional myotome. Table 2 summarizes the requirements of neuromotor function for level assignment. Muscle strength was graded on a scale of 0–5 as follows: (0) no spontaneous muscle contractions, (1) trace of contraction, (2) active movement with gravity eliminated, (3) active movement against gravity, (4) active movement against gravity and resistance, and (5) normal movement. A muscle strength score of at least 3/5 in the lower extremity was required for a myotome level to be assigned [15]. For patients with different neuromotor levels on the left and right, the higher (worse) level was assigned. Testing was performed on all children who could follow commands and actively participate in the testing process. For newborns, clinical observation was used to determine which muscle groups were functional. Neurofunctional levels were compared by subtracting the US level from the functional level, as previously described [16]. A negative value indicated that the functional level was worse (more cephalad) than the anatomic lesion level and a positive value indicated that the functional level was better than the prenatally assigned level. For comparison purposes, fMMC infants were grouped into high- (T–L2), mid- (L3–L4), and low (L5–S1)-level lesions.

Ambulatory Status

Ambulatory status was classified as independent walkers (walks without assistive appliances), assisted walker (walk with appliances, i.e. walker, crutches), and non-ambulatory (wheelchair bound). Patients that were ambulatory without any assistance indoors or for short distances, but required a walking aid or wheelchair for outdoor or long-distances, were classified into the lower category. Ambulatory status assigned at the latest available follow-up was used for evaluation.

Assessment of Coordinative Skills and Deficits

fMMC patients were asked to return for follow-up evaluation at 1, 2 and 3 years of adjusted age as part of a specific neurodevelopmental follow-up program for children with in utero MMC repair (IRB# 2000-11-2081). fMMC children were evaluated using the Bayley Scales of Infant Development (BSID 2nd ed). The BSID yields two scores: the Mental Developmental Index (MDI) assesses the child's level of cognitive, language, personal-social skills, and the Psycho-Motor Index (PDI) assesses the child's fine and gross motor skills. BSID-PDI results obtained for lower extremity gross motor function were analyzed to describe ambulation deficits and skills.

Statistical Analysis

The two-sided t test, median test, and multiple regression analysis were used for statistical comparisons as appropriate and $p < 0.05$ was considered statistically significant.

Results

Patient Population

Fifty-four patients underwent in utero neurosurgical repair. Selected patient characteristics of fMMC (n = 54) neonates are summarized in table 3. All fMMC patients were delivered at or before 36–37 weeks of gestation because of preterm rupture of membranes, preterm labor, or the obstetrical risks associated with the maternal hysterotomy [10]. High (T–L2), mid (L3–L4), and low (L5–S1) level lesions were found in 10 (19%), 24 (44%), and 20 (37%), respectively. Talipes deformity was absent in all fetuses at the time of in utero repair. Thirteen fMMC newborns (24.1%) had talipes at birth (unilateral, n = 9; bilateral n = 4).

Lower Extremity Neuromotor Function

In 31/54 (57.4%) fMMC neonates LENF at birth was better than predicted by a median of 2 functional levels (range, 1–5 levels). In 13/54 (24.1%) fMMC patients LENF was the same as predicted, and in 10/54 (18.5%) fMMC newborns LENF was worse than prenatally predicted by a median of 1 functional level (range, 1–2). Table 4 illustrates LENF stratified by high-, mid- and low-level lesions in fMMC newborns at birth. While fMMC infants with high-level (T–L2) and mid-level lesions (L3–L4) demonstrated better than predicted LENF of up to 5 and 3 levels, respectively, in fMMC patients with low-level lesions (L5–S1), LENF was better than predicted by one level as there was less potential for improvement (table 5).

Ambulatory Status of fMMC Children

Follow-up ambulatory status was available in all 54 fMMC children. At a mean age of 67.0 ± 18.2 months (median, 66; range, 36–113) 37/54 (69%) walk independently, 13/54 (24%) are assisted walkers, and only 4/54 (7%) are wheelchair dependent. Seventeen (46%) of fMMC

Table 4. LENF outcomes by anatomic lesion level at birth for fMMC children

	T12–L2			L3–L4			L5–S1		
	better	same	worse	better	same	worse	better	same	worse
fMMC children, n (%)	10 (91)	1 (9)	0 (0)	15 (65)	7 (31)	1 (4)	6 (30)	5 (25)	9 (45)

Table 5. Median difference in level between observed and predicted LENF after fMMC closure

	T–L2		L3–L4		L5–S1	
	better	worse	better	worse	better	worse
fMMC children	4 levels (2–5)	–	2 levels (1–3)	1 level	1 level	1 level (1–2)

Data presented as median (range).

children that ambulate independently and all children that require assistive devices to ambulate need lower extremity bracing for support. All 4 wheelchair-bound children developed significant complications postnatally precluding these patients to ambulate (i.e. complicated syrinx requiring syringo-meningeal shunt placement, n = 2; severe spinal cord tethering, n = 1; severe intraventricular hemorrhage n = 1). When stratified by lesion level (table 6), in utero MMC closure showed the greatest improvement in ambulation for children with mid and low-level lesions.

Table 6. Ambulatory status for fMMC children stratified by high-level, mid-lumbar, and low-lumbosacral lesions

	T12–L2 (n = 10)	L3–L4 (n = 24)	L5–S1 (n = 20)
Independent walker	3 (30)	15 (63)	19 (95)
Assisted walker	4 (40)	9 (27)	0 (0)
Wheelchair bound	3 (30)	0 (0)	1 (5)

Data presented as n (%).

Predictors of Independent Walking after fMMC Repair

The strongest factors predicting a lower likelihood to walk independently were higher-level lesion (>L4, p = 0.001) and the development of clubfoot deformity (p = 0.026). Early fetal intervention (<22 weeks' gestation, p = 0.33), later gestational age at birth (p = 0.68), higher birth weight (p = 0.36), LENF at birth (p = 0.46), need for V-P shunt placement (p = 0.26), and improved LENF at birth (p = 0.45) did not significantly correlate with independent ambulation.

Assessment of Coordinative Skills and Deficits

Detailed neurodevelopmental assessment data were available in 26/37 independent walkers, 6/13 assisted walkers and 2/4 wheelchair-dependent fMMC children. Due to the small number of patients in the wheelchair-reliant group, neurodevelopmental outcome data were compared only between children that walk independently and children that require assistive devices for ambulation after fMMC closure. No statistically significant differences in neurocognitive outcome (MDI scores) were found between independent walkers (MDI: 91 ± 16; range, 50–114), and assisted walkers (MDI: 97 ± 8; range, 87–107) (p = 0.37). The mean PDI score of assisted walkers (PDI: 59 ± 7; range, 50–68) tended to be lower than the independent walkers (PDI: 66 ± 15; range, 50–97), but did not reach statistical difference (p = 0.059). Subanalysis of specific coordinative tasks revealed that despite the ability to walk independently, the majority of fMMC children continue to demonstrate deficits in lower extremity coordinative skills (table 7).

Table 7. Coordinative skills of fMMC children that walk independently or using assistive devices to ambulate

	Independent walkers (n = 26)	Assisted walkers (n = 6)
Walks with good coordination	18 (69)	0 (0)
Runs with good coordination	4 (15)	0 (0)
Walks stairs up, alone, both feet on each step	5 (19)	0 (0)
Walks stairs down, alone, both feet on each step	3 (12)	0 (0)
Walks forward on line	11 (42)	0 (0)
Walks backward on line	10 (38)	0 (0)
Walks stairs up, alone, alternating feet	2 (8)	0 (0)
Walks stairs down alone, alternating feet	2 (8)	0 (0)
Tiptoes	4 (15)	0 (0)

Data presented as n (%).

Discussion

In a highly selective cohort of children that underwent maternal-fetal surgery for MMC prior to the NIH-sponsored MOMS trial, we studied the impact of prenatal intervention on distal neuromotor function and ambulatory status. The present data suggests that fMMC closure may result in better than expected LENF at birth. These findings are different from the previous reports of Tulipan et al. [17] and Tubbs et al. [18] in which the average level of LENF closely matched the average anatomic level of the bony lesion defect after fetal surgery. The reason for this difference may reflect patient selection, evidence of neuromotor deficits before fetal intervention, and the gestational age at surgery. In the present study, children were operated earlier in gestation and all patients had normal leg movement and absence of clubfoot deformity prior to in utero treatment.

Our results are in accordance with previously reported data obtained in laboratory animals [6, 19]. In an elegant series of studies, Meuli et al. [6] demonstrated near-normal motor function in the fetal sheep model of human MMC after in utero repair. Furthermore, Stiefel et al. [19] reported more recently in the curly-tail mouse model of spina bifida that the observed neurofunctional deficits in MMC arise following secondary destruction of the exposed spinal cord and loss of function during pregnancy. These experiments show preventable neurologic deterioration in MMC supporting the hypothesis that prenatal coverage decreases neurologic damage (2nd hit) to the exposed spinal cord.

In addition to the better than expected LENF at birth, we observed that the majority (93%) of fMMC children are ambulatory at follow-up. Data from previously published case series showed that at a similar follow-up age, approximately 50% of postnatally repaired MMC children are ambulatory [20–22]. Also, while our data suggest that 69% of fMMC children ambulate independently, less than 25% of children with postnatal spina bifida repair are able to walk without aids [21–23]. Despite these compelling observations, we recognize that due to the lack of appropriate controls combined with the relative young age of our population, caution has to be taken in the interpretation of our data. First, the differences in ambulation rates could be explained in part by our strict selection criteria for fetal intervention (i.e. normal leg movement and absence of talipes) which may have preselected a more favorable group of patients than other studies. Second, due to the relatively young age at follow-up, our results may not reflect long-term LENF and ambulatory status. Studies suggest that as MMC children get older and heavier, their power/weight ratio may decrease and independent ambulation becomes more difficult [22–24]. Third, parental and family attitudes and motivation can impact on long-term outcomes. Finally, some patients eventually choose a wheelchair for mobility later in life with the advantage that they expend much less energy to get around and are able to carry their belongings with them [25]. Therefore, reevaluation during adolescence and early adulthood will be critical to assess whether fMMC surgery results in better than expected long-term LENF and ambulatory status.

Between 2000 and 2005, 36 additional women had their pregnancy care, delivery, and postnatal neurosurgical MMC repair at our institution. Although all had undergone evaluation for possible fetal intervention, only 14 had normal leg movement and absence of talipes at the time of prenatal evaluation and were subsequently excluded from fetal surgery due to maternal issues only (e.g. no interest in fetal surgery, evaluation after 26 weeks' gestation, maternal health problems). Of these 14 patients, at a median follow-up of 45 months (range, 30–72), 36% walk independently, 57% are assisted walkers, and 7% are wheelchair dependent. Because of the small sample size and the significant younger age at follow-up, meaningful comparisons between the postnatal repaired children and the fMMC group were not possible. As it is unlikely that a suitable control group can be assembled outside a randomized trial, completion of the NIH-sponsored

MOMS study will be necessary to validate or disprove our current observation.

In accordance with previous studies of postnatally repaired MMC children [14, 25, 29], our study also suggests that prenatally assigned lesion level is the most important predicator of ambulatory status in children that underwent fetal surgery. When the upper level of the defect was ≥L4, the likelihood of walking independently was significantly decreased (T–L3: 37% vs. L4–S1: 86%). However, contrary to previous reports of postnatally repaired children suggesting that 80–100% of high-level lesions are non-ambulatory [20, 25, 27], 70% of fMMC toddlers with high-level lesions (≥L2) in our population were able to ambulate.

The next most significant predictor of ambulatory status was the presence or development of talipes. Only 46% of fMMC children with talipes deformity at birth were able to walk independently, compared to 76% of fMMC infants without talipes at birth. These results are in direct contrast to previous studies by Biggio et al. [20] who reported that for MMC patients repaired after birth, the presence or absence of clubfoot deformity did not influence ambulatory status. The disparity with our findings may be explained by the fact that we subclassified the ambulatory status as independent versus non-independent (assisted ambulation) while Biggio et al. [20] classified their cohort of postnatally repaired MMC patients as only ambulatory or nonambulatory.

Similar to reported data [28–30], we found that the results of newborn neuromotor assessment do not necessarily correlate with the ambulatory status later in childhood. Sival et al. [28] evaluated the LENF in newborns with postnatal MMC repair and found that the presence of neonatal leg movements does not necessarily indicate functional integrity of distal neuronal innervation. These investigators postulated that the lack of correlation of LENF and ambulatory status might be related to the difficulties in assigning a reliable motor functional level in newborns and very young infants, since reflexive movements can occasionally be mistaken for voluntary motor function [28, 29]. Whether LENF assessments beyond the newborn period at a time when children are able to actively participate in the physical evaluation might demonstrate a potential relationship between LENF and long-term ambulatory potential in patients with fMMC closure remains unknown.

Despite the observed improvement of the ambulatory status after fMMC surgery, we found that the majority of independent ambulators and all children that require assistive devices to walk continue to experience deficits in coordinative skills. In MMC, lower extremity motor impairment can have central (hydrocephalus, Arnold-Chiari II malformation) as well as spina nerve root etiologies (neural damage along the spinal cord) [28, 31]. Schoenmakers et al. [31] studied early motor development in children with MMC and lipomyelomeningocele (a closed neural tube defect). They found that although the lesion levels were comparable in both patient groups, motor performance was significantly lower in the children with MMC than in those with lipomyelomeningocele. As intracranial abnormalities are usually absent in lipomyelomeningocele, they suggested that the presence of hydrocephalus and Arnold-Chiari II malformation may contribute more to the gross motor and functional problems than previously recognized [31]. Coordinative deficits and gait disturbances are components of normal pressure hydrocephalus syndrome in adults, and are attributed to stretching and injury of the corticospinal fibers around the enlarged ventricles, with the relatively greater involvement of the lower extremities being due to the longer course of the paracentral leg fibers [32]. It is possible that even though our shunted children no longer have active hydrocephaly, ventricular distension during early brain development may have injured or developmentally altered the corticospinal pathways leading to coordinative skill deficits. As these gross motor and coordinative problems might impact muscle strength, motor performance and mobility, and therefore daily activities, further investigation of these associations would provide important information regarding the prognosis for neuromotor outcome in this group of children.

In summary, this review of our initial nonrandomized cohort of children has offered some compelling insights into the impact of fMMC closure on neurofunctional outcome. We observed that children that underwent maternal-fetal surgery for MMC have better than expected LENF at birth and ambulatory status in early childhood. However, ambulating toddlers continue to demonstrate deficits in movement coordination that are characteristic for children with spina bifida. Further investigation of longer-term outcome of our cohort will be critical to provide more details regarding their ambulatory status and skills during adolescence and early adulthood.

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