OBSTETRICS

Long-term neurofunctional outcome, executive functioning, and behavioral adaptive skills following fetal myelomeningocele surgery

Enrico Danzer, MD; Nina H. Thomas, PhD; Allison Thomas, MA; Karen B. Friedman, PhD; Marsha Gerdes, PhD; Jamie Koh; N. Scott Adzick, MD; Mark P. Johnson, MD

BACKGROUND: Myelomeningocele (MMC) represents the first nonlethal anomaly to be treated by prenatal intervention. Case series and a prospective, randomized study show that fetal surgery for MMC before 26 weeks' gestation may preserve neurological function. Long-term follow-up is a fundamental component to evaluate the overall efficacy of any new medical or surgical procedure. To further delineate the long-term impact of fMMC surgery, we continued to follow children treated in our institution before the Management of Myelomeningocele Study trial by the means of parental questionnaires to assess changes in functional, developmental, and cognitive status as these unique patients grow older.

OBJECTIVE: The objective of the study was to evaluate the long-term neurological outcome, executive functioning (EF), and behavioral adaptive skills (BAS) following fetal myelomeningocele (fMMC) surgery.

STUDY DESIGN: Prior to the Management of Myelomeningocele Study trial, 54 patients underwent fMMC surgery at our institution. Parents of 42 children (78%) participated in structured questionnaires focusing on neurofunctional outcome. EF and BAS were measured by the Behavior Rating Inventory of Executive Function (BRIEF) and the Adaptive Behavioral Assessment System II. The BRIEF is organized into 3 primary indices including the following: Global Executive Composite, Metacognition Index, and Behavioral Regulation Index. The Adaptive Behavioral Assessment System II results in a general adaptive composite score. Based on SD intervals, EF and BAS were categorized as being average, borderline, or impaired.

RESULTS: At a median follow-up age of 10 years (range, 8-14 years), 33 (79%) are community ambulators, 3 (9%) are household ambulators, and 6 (14%) are wheelchair dependent. Preschool ambulation was predictive of long-term ambulation ($P < .01$), whereas the need for tethered cord surgery was associated with persistent deterioration of ambulatory status ($P = .007$). Normal bladder function was found in 26%. Although the majority scored within the average range for the Behavioral Regulation Index, Metacognition Index, and Global Executive Composite indices, significantly more children who had fMMC surgery had deficits in EF in all 3 BRIEF indices compared with the population norms. The general adaptive composite scores were also more likely to fall below average following fMMC surgery. Normal early neurodevelopmental outcomes were predictive of normal EF and BAS ($P < .01$). Need for shunting was associated with a significant impairment of BAS ($P = .02$).

CONCLUSION: The present study suggests that fMMC surgery improves long-term functional outcome. The majority of fMMC children can successfully complete everyday tasks at home and at school. Abnormalities of BAS appear to be more common than impairments in EF and therefore offer an area for early screening and interventional therapy for these at-risk children. Non-shunted fMMC children with normal early neurodevelopmental outcome are less likely to experience problems with EF and BAS. fMMC surgery improves long-term ambulatory status. Symptomatic spinal cord tethering with or without intradural inclusion cyst is associated with functional loss. More than expected fMMC children are continent, but bowel and bladder control continue to be an ongoing challenge for the fMMC children.

Key words: Adaptive Behavioral Assessment System, Behavior Rating Inventory of Executive Function, fetal surgery, myelomeningocele, neuromotor function

Myelomeningocele (MMC) is a congenital malformation with complex physical and neurological sequelae. MMC represents the first nonlethal anomaly to be treated by prenatal intervention. The application of an invasive fetal procedure was felt to be justified because of both the significant lifelong neurological disabilities (eg, lower extremity motor and sensory deficits, incontinence, hindbrain herniation, and hydrocephalus) and the development and validation of the 2-hit hypothesis.[1]

Early clinical experience suggested that ongoing damage to the exposed spinal cord might be alleviated by in utero closure and that fetal intervention potentially improves hindbrain herniation, ventriculoperitoneal shunt rate, and neurofunctional outcome.[2-8] These promising, preliminary results culminated in the Management of Myelomeningocele Study (MOMS), a National Institutes of Health–sponsored, randomized, controlled, prospective, multicenter trial, comparing prenatal surgery to standard postnatal repair.[9]

The MOMS trial demonstrated that fetal MMC (fMMC) surgery improves the short-term neurological outcomes during infancy when compared with postnatal neurosurgical repair.[9] These nonrandomized and randomized studies, however, also showed that the potential benefits of fMMC surgery must be balanced against the risks of fetal and maternal morbidity.

Long-term follow-up is a fundamental component to evaluate the overall efficacy of any new medical or

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surgical procedure. We previously reported 5 year follow-up on the cohort of infants treated in our institution before the MOMS trial. Most fMMC children had functional scores in the average to high average range and were at an age-appropriate level in their schooling.[8]

To further delineate the long-term impact of fMMC surgery, we continued to follow up these children by the means of parental questionnaires to assess changes in functional, developmental, and cognitive status as these unique patients grow older. Executive functioning was measured by having the parents complete the Behavior Rating Inventory of Executive Function (BRIEF), which in turn allows the assessment of a heterogeneous group of higher-order cognitive abilities including self-regulation, inhibition, planning, mental flexibility, and others. Behavioral adaptive functioning, the ability to adapt to and independently complete tasks of daily living skills at an age-appropriate level, was assessed using the Adaptive Behavior Assessment System, second edition (ABAS-II).

The results of the study will help us to better understand the long-term neurodevelopmental and neurofunctional outcomes and problems that children who underwent fetal MMC surgery may have later in life so that we can develop and/or define surveillance and treatment strategies to improve the long term outcome of these children into adulthood.

Material and Methods

Ethical statement

The Institutional Review Board, Committee for Protection of Human Subjects of The Children's Hospital of Philadelphia, approved this study, and all parents or legal guardians gave written informed consent for their children (institutional review board number 2011-007977).

Patient population

Between January 1998 and February 2003, 58 patients met our institutional inclusion criteria described previously and underwent fMMC surgery, with 54 survivors.[1-8] All infants were subsequently born by cesarean delivery and received standardized neonatal care at our institution. Details of the preoperative evaluation, selection process, surgical approach, and postnatal management have been extensively described elsewhere.[1,4,8]

Data collected 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 shunt placement have been previously described.[1,4,8]

Short-term follow-up assessment

As previously reported, families were asked to return for follow-up at 1, 2, 3, and 5 years of adjusted age.[4,8] Each visit included evaluations by a pediatrician, physical therapist, developmental psychologist, radiologist, neurosurgeon, and urologist. During the first 3 years, neurodevelopmental outcome was assessed by the Bayley Scales of Infant Development-II (BSID, second edition) and the Preschool Language Scales-III for cognitive development.[8]

At 5 years of adjusted age, the Wechsler Preschool and Primary Scale of Intelligence, third edition (WPPSI-III), was administered to assess cognitive function.[8] Overall, 37 (68%) returned for follow-up evaluation at 1 year, 30 (56%) at 2 years, 29 (54%) at 3 years, and 30 (56%) at 5 years.[8] These short-term results were used to evaluate potential correlations between early and long-term outcome.

Long-term follow-up assessment

Given that the most common reasons that precluded fMMC families to return for an onsite neurodevelopmental assessment during the first 5 years of life were travel distance and financial costs combined with our goal to capture long-term information of as many patients possible, we opted to mail out structured questionnaires.

The first questionnaire, designed by the authors, contained questions related to the overall ambulatory status, bladder and bowel function, the need for additional neurosurgical and/or orthopedic intervention, and the need for additional therapy and support (eg, enrollment in physical therapy, occupational therapy, etc).

The overall ambulatory status was classified according the Hoffer Functional Ambulation scale into community ambulators (ie, walks indoors and outside), household ambulators (ie, able to walk indoors only but requires equipment and/or wheelchair for outside mobility), and nonambulatory (ie, wheelchair dependent).[10] The questions required mostly yes/no answers. If questions were answered with yes, we encouraged comments on the age of onset, severity, potential intervention, and follow-up. Families were contacted by phone if additional clarification was required.

In addition to the above-mentioned questionnaire, parents were also asked to complete the BRIEF and the ABAS-II. Both are standardized and validated parental questionnaires to assess executive function and behavioral adaptive skills, respectively.[11,12]

The BRIEF is a questionnaire for parents of schoolage children (5−18 years) that enables professionals to assess executive function behaviors in the everyday home and school environments.[11] The parent form contains 86 items within 8 theoretically and empirically derived clinical scales that measure different aspects of executive functioning (inhibit, shift, emotional control, initiate, working memory, plan/organize, organization of materials, and monitor) as well as 2 validity scales (inconsistency and negativity). Parents rate each behavior as occurring never, sometimes, or often.

Raw scores for each scale are converted to T-scores (mean, 50, SD, 10). Scores between 60 and 69 fall in the at-risk range, and scores of 70 or higher fall in the clinically significant range. The clinical scales form 2 broader indexes, the Metacognition Index (MCI; summarizes skills that are essential for self-regulation of cognitive processes) and the Behavioral Regulation Index (BRI; represents skills essential for self-regulation of behavior) as well as an overall score, the Global Executive Composite (GEC).[11]