



Hydrocephalus and school-age neurodevelopmental outcomes in the management of myelomeningocele prenatal surgery trial: a secondary analysis

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OBJECTIVE The purpose of this secondary analysis was to assess the role of hydrocephalus on neurodevelopmental outcomes in a cohort of school-age children enrolled in the Management of Myelomeningocele Study (MOMS) clinical trial.

METHODS The sample analyzed in this report consisted of 150 of 183 children aged 5–10 years (mean \pm SD 7 years 8 months \pm 1.2) who were randomly assigned between 20 and 26 weeks of gestational age to undergo either prenatal or postnatal surgery and were enrolled in the school-age follow-up study of MOMS. These 150 children (76 prenatal and 74 postnatal) were placed into three groups: no hydrocephalus ($n = 22$), unshunted hydrocephalus ($n = 31$), and shunted hydrocephalus ($n = 97$). Comparisons were made on the basis of measures of adaptive behavior, intelligence, reading and math skills, verbal and nonverbal memory, fine motor dexterity, and sensorimotor skills. Parent ratings of executive functions, inattention, and hyperactivity-impulsivity were also compared.

RESULTS There were no statistically significant differences in neurodevelopmental outcomes between the groups with no hydrocephalus and unshunted hydrocephalus, or between the prenatal and postnatal groups with shunted hydrocephalus, so these groups were combined (no/unshunted vs shunted hydrocephalus). The no/unshunted group showed significantly better performance ($p < 0.05$) than the shunted group in terms of adaptive behavior, intelligence, verbal and nonverbal memory, reading skills (but not math), fine motor dexterity, sensorimotor skills (but not visual-motor integration), and inattention (but not hyperactivity-impulsivity or executive function ratings). An assessment of the prenatal surgery group showed that the combined no/unshunted group performed better than the shunted group in terms of adaptive behavior and verbal memory skills. Both the prenatal and postnatal surgery subgroups with unshunted hydrocephalus performed as well as the group with no hydrocephalus despite significantly enlarged ventricles.

CONCLUSIONS Although the primary assessment of school-age outcomes in the MOMS clinical trial did not show better adaptive behavior and cognitive skills in the prenatal group, hydrocephalus and shunting were associated with poorer neurodevelopmental outcomes (both prenatal and postnatal groups). Disease severity and dynamic changes in hydrocephalus status may be the primary factors in the need for shunting and a major determinant of adaptive behavior and cognitive outcomes after prenatal surgery.

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KEYWORDS spina bifida; hydrocephalus; myelomeningocele; MOMS trial; neurodevelopmental outcomes; adaptive behavior; congenital

ABBREVIATIONS ADHD = attention-deficit/hyperactivity disorder; BRIEF = Behavior Rating Inventory of Executive Function; CMS = Children's Memory Scale; CNS = central nervous system; CSF = cerebrospinal fluid; CVLT-C = California Verbal Learning Test for Children; FRESNO = Functional Rehabilitation Evaluation of Sensori-Neurological Outcomes; KBIT-2 = Kaufman Brief Intelligence Test, Second Edition; MOMS = Management of Myelomeningocele Study; MOMS2 = follow-up of MOMS; SBM = spina bifida myelomeningocele; SNAP-IV = Swanson, Nolan and Pelham-IV; WJ-III = Woodcock-Johnson Tests of Achievement, Third Edition.

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SPINA bifida myelomeningocele (SBM) is the most common congenital birth defect affecting the central nervous system (CNS), with a prevalence rate of roughly 1 in 1500 births in the United States.¹ SBM results from a failure of primary neurulation that leads to a typical spinal abnormality, as well as secondary anomalies that can affect brain development, especially in the cerebellum and corpus callosum.^{1,2} Additional injury results from exposure of the developing CNS to a toxic intrauterine environment and hydrocephalus.³ Virtually all children with myelomeningocele develop the Chiari II malformation, representing a spectrum of brain malformations primarily affecting the cerebellum and medulla as well as the midbrain. Many children with myelomeningocele develop hydrocephalus, which often requires cerebrospinal fluid (CSF) diversion. With the advent of prenatal diagnosis, fetal surgery has been developed in an effort to prevent secondary injury to the brain and hydrocephalus.^{1,3-5}

The Management of Myelomeningocele Study (MOMS) was a prospective randomized controlled trial that compared the effects of prenatal repair of myelomeningocele between 20 and 26 weeks gestational age with traditional postnatal repair. The trial was initiated in 2003 and stopped in 2011 after 183 maternal/fetal dyads had been randomly assigned to treatment and a statistically significant reduction in the need for shunting and improved motor function were identified in the prenatal group at 12 months of age.^{4,6} At 30 months of age, 91 children in the prenatal surgery group were compared with 92 children the postnatal surgery group.⁷ Although there was continued evidence for improved motor functioning, there was no difference in the cognitive skills between the two groups.

The most recent follow-up of the MOMS participants (MOMS2) occurred when the children reached 5–10 years of age.⁸ This report replicated the earlier findings of fewer CSF diversionary procedures, as well as better ambulation, sensorimotor, and fine motor skills, in the prenatal group. The prenatal and postnatal surgery groups did not differ in terms of the primary outcome, a measure of adaptive behavior administered with a semi-structured interview of the primary caregiver that assessed everyday habitual performance of activities in the communication, daily living, and socialization domains. However, caregivers in the prenatal group reported less overall family burden and higher quality of life for the child and family, which was related to improved motor functioning and reduction in the need for neurosurgical procedures. There was no strong evidence of improved cognitive function. The prenatal group generally had higher levels of performance than the postnatal group, but only comparisons of reading skills and nonverbal memory achieved statistical significance. The prenatal group scored reliably and significantly higher on a measure of fine motor dexterity.

We hypothesized that heterogeneity in hydrocephalus status among the prenatal group, i.e., variations in hydrocephalus severity and the subsequent need for a CSF diversionary procedure, was responsible for the largely null results in terms of cognitive outcomes at school age. In addition, there is a unique opportunity to evaluate children with myelomeningocele who did not develop hydrocephalus,

who were uncommon prior to prenatal surgery but are representative of a group that is becoming larger as more centers adopt prenatal surgical interventions. In a study before the advent of prenatal surgery,⁹ only 4/24 children with various types of spina bifida and without hydrocephalus had myelomeningocele, with this group largely representing closed lesions such as meningocele and lipoma; a group with ventricular dilation but no shunt consisted almost entirely of children with myelomeningocele (15/18). In the MOMS study, there was also a group of children with myelomeningocele who did not receive a shunt because ventricular dilation did not meet the pre-established criteria or because they met the established criteria but the treating neurosurgeon and family opted not to proceed with a shunt. This group may mimic the current neurosurgical practices at some centers that monitor hydrocephalus before shunt implantation.¹⁰

In the MOMS study, specific criteria were used to determine whether children met the threshold to receive a CSF shunt (Table 1). At 12 months of age, most children in the postnatal surgery group (98%) met the criteria for shunting, compared with 73% of the children in the prenatal group.⁶ However, the actual rates of shunting were 84% and 44% in the postnatal and prenatal groups, respectively. Thus, about 20% of the study cohort met the criteria for shunting but did not receive a CSF shunt. In additional analyses based on the 12-month MRI findings, 25% of the prenatal group had evidence of ventricular dilation and met the predetermined criteria, with another 27% not meeting the criteria for hydrocephalus.⁶

Using data from 30-month visits, Houtrow et al.¹¹ divided the 171 children from the MOMS trial who survived and were not lost to follow-up into three groups on the basis of the MOMS criteria for hydrocephalus (Table 1) and their actual shunt status at 12 months of age: no hydrocephalus, unshunted hydrocephalus, and shunted hydrocephalus. There were no significant differences among the three groups in terms of cognitive and language measures. However, additional analyses of the children who had unshunted or shunted hydrocephalus revealed that children with more severe hydrocephalus, defined by the number of hydrocephalus criteria met, performed more poorly on language and motor measures.¹¹

The present analysis followed the procedures used by Houtrow et al.¹¹ and grouped school-age children on the basis of the same criteria (Table 1), with the primary analysis comparing the three groups (no hydrocephalus, unshunted hydrocephalus, and shunted hydrocephalus) regardless of initial randomization. A secondary analysis compared outcomes according to hydrocephalus status in only the prenatal repair group to clarify the influence of hydrocephalus status on the overall 5–10 year follow-up results of the MOMS2 study. All comparisons used the neurodevelopmental measures from the school-age follow-up⁸ that are sensitive to the long-term effects of SBM and hydrocephalus status.^{9,12,13}

Methods

The MOMS2 follow-up was conducted at the three centers that participated in the original MOMS trial (Chil-

TABLE 1. MOMS criteria for the presence of hydrocephalus indicating need for shunt

<i>Criterion 1</i> At least 2 of the following:	An increase in the greatest occipital-frontal circumference adjusted for gestational age defined as crossing percentiles (if a plateau was reached this did not qualify)
	Bulging fontanelle or split sutures or sunsetting sign
	Increasing hydrocephalus on consecutive imaging studies determined by increase in ratio of biventricular diameter to biparietal diameter according to the method of O'Hayon et al. ³⁴
	Head circumference > 95 percentile for gestational age; or
<i>Criterion 2</i>	Presence of marked syringomyelia with ventriculomegaly; or
<i>Criterion 3</i>	Ventriculomegaly with symptoms of Chiari malformation (stridor, swallowing difficulties, apnea, bradycardia); or
<i>Criterion 4</i>	Persistent CSF leakage from the myelomeningocele wound or bulging at the repair site

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dren's Hospital of Philadelphia, Vanderbilt University, and the University of California, San Francisco), along with the independent data-coordinating center at the George Washington University Biostatistics Center and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Institutional Review Board approval was obtained at each clinical site and the data-coordinating center. Caregivers gave written informed consent and children gave assent per local regulations.

Study Procedures

Families who participated in the original MOMS clinical trial were offered the opportunity to participate in the MOMS2 school-age follow-up study, with data available for 161 of the 183 original MOMS participants (Fig. 1).⁸ There were some missing data on specific measures due to examiner error, lack of cooperation, or inability to understand directions for some tasks.

For this study, we excluded 4 participants who received a CSF shunt despite not meeting the study criteria and 6 participants who underwent shunt implantation after the MOMS study was completed at 30 months, thereby leaving a total sample of 151 children. These participants were excluded because we wanted to assess children who met predetermined criteria for shunting (thus excluding the 4 cases) and because the 6 participants who subsequently underwent shunt implantation had symptomatic hydrocephalus and did not clearly fit into the groups. Of these 151 children, 1 child was missing Vineland Adaptive Behavior Scales data and all neuropsychological measures, leaving a final cohort of 150 children for these secondary analyses (76 in the prenatal group and 74 in the postnatal surgery group). To create the groups for the primary analysis, we combined children across the prenatal and postnatal groups into groups categorized as no hydrocephalus ($n = 22$), hydrocephalus and no shunt (i.e., unshunted hydrocephalus) ($n = 31$), and shunted hydrocephalus ($n = 97$). Four children who underwent third ventricle ventriculostomy were placed in the shunted group. Within the shunted group, 59% of children required a shunt revision. Comparing these patients with those who underwent no revisions and 1–6 revisions revealed no significant differences in neurodevelopmental outcomes ($p > 0.05$). There was a trend for the group that received a shunt revision to

score lower than the shunted group. Fisher's exact test revealed no significant difference in the frequencies of shunt revisions between the prenatal (46%) and postnatal (65%) surgery groups ($p = 0.089$).

Because the MOMS2 follow-up study took place over several years, older children were evaluated first. We tried to evaluate all children when they were 6 years or older, but we had to evaluate some just before 6 years (youngest was 5 years 9 months of age). Participation consisted of a single comprehensive study visit at one of the clinical centers or at home for a partial evaluation (neuropsychological and physical evaluations) if the parent/caregiver did not wish to travel. Although the center visit was comprehensive and included urological, physical, and radiological evaluations over a 2-day period, the focus of this paper is the neurodevelopmental evaluation completed by study-designated psychologists at the clinical center or at home. The psychologist also completed the Vineland Adaptive Behavior Scales semi-structured interview with the parent/caregiver at the center or by telephone for home visits. For quality control, all psychologists were trained centrally and certified by submitting videotapes to the central site. Videotapes of study participants were randomly solicited and reviewed to maintain certification. All psychologists were blinded to the treatment group, and parents/caregivers were instructed not to identify the type of surgery.

Neurodevelopmental Measures

The primary outcome was the composite score from the Vineland Adaptive Behavior Scales, Second Edition, interview schedule.¹⁴ Adaptive behavior represents habitual performance of activities needed for communication, socialization, and daily living in the everyday environment. Secondary neuropsychological outcomes included the composite IQ score from the Kaufman Brief Intelligence Test, Second Edition (KBIT-2);¹⁵ Woodcock-Johnson Tests of Achievement, Third Edition (WJ-III), reading and math subtests;¹⁶ California Verbal Learning Test for Children (CVLT-C), a multi-trial list verbal learning and memory test;¹⁷ Children's Memory Scale (CMS) nonverbal memory subtests (dot learning and faces);¹⁸ Beery-Buktenica Developmental Test of Visual-Motor Integration;¹⁹ Purdue Pegboard Test, a measure of fine motor dexterity;²⁰ and a word generation test.²¹ To evaluate sensorimotor and

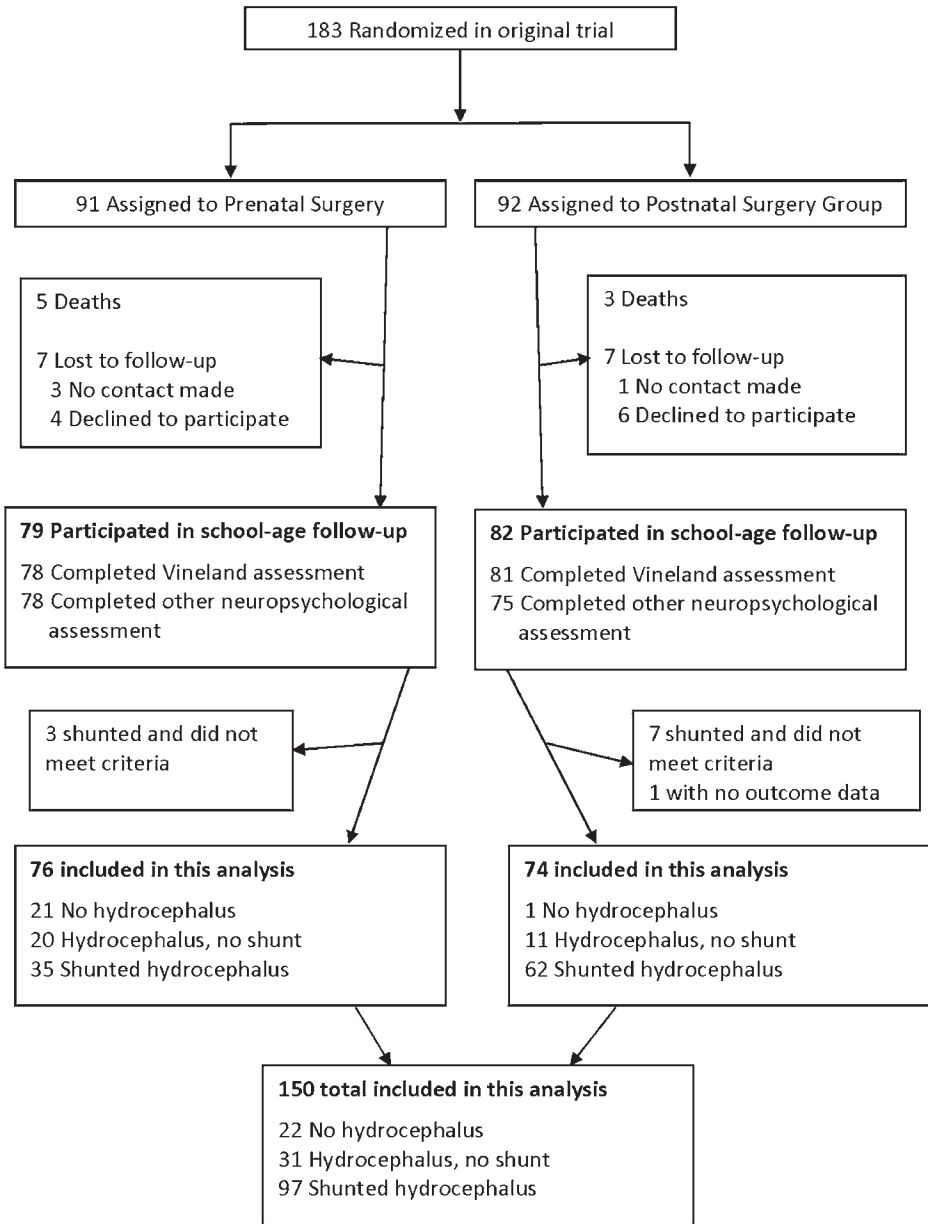


FIG. 1. Enrollment flowchart.

lower-limb improvements, items from the Functional Rehabilitation Evaluation of Sensori-Neurological Outcomes (FRESNO) scale were included.^{22,23} These items evaluated the amount of assistance needed by the child to complete motor activities related to daily living and advanced motor skills. Parents completed rating scales for attention-deficit/hyperactivity disorder (ADHD) behavior (Swanson, Nolan and Pelham-IV [SNAP-IV] rating scale)²⁴ and the Behavior Rating Inventory of Executive Function (BRIEF) to assess executive functions.²⁵

Statistical Analysis

For the Vineland, neuropsychological, and the BRIEF

evaluations, we calculated mean ± SD according to study group by using the norm-referenced scores. For the Purdue Pegboard test, the number of pegs with the preferred hand, nonpreferred hand, and pairs of pegs with both hands were separately converted into z-scores by using normative data and the average z-score of the three conditions reported. The FRESNO score was the percentage of the maximum possible score, while the SNAP score was the raw score averages for the inattention and hyperactivity-impulsivity items. Lower scores indicated fewer problems in the rated domains.

Each outcome variable was separately analyzed. We initially compared the two groups with no hydrocephalus

TABLE 2. Demographic and baseline clinical characteristics (n = 150)

Characteristic	No Hydrocephalus (n = 22)	Unshunted Hydrocephalus (n = 31)	Shunted Hydrocephalus (n = 97)
Age at MOMS2 visit*	8,3 ± 1.2	7,6 ± 1.1	7,8 ± 1.3
Female sex†	6 (27)	20 (65)	54 (56)
Gestational age at birth, wks	35.1 ± 2.8	35.5 ± 2.3	36.2 ± 2.2
Gestational age at surgery‡§			
≤23 wks	10 (48)	14 (70)	7 (21)
≥24 wks	11 (52)	6 (30)	27 (79)
Child race or ethnic group¶			
White non-Hispanic	21 (95)	29 (94)	84 (87)
Black non-Hispanic	0 (0)	0 (0)	1 (1)
Hispanic	0 (0)	0 (0)	5 (5)
Other/not reported	1 (5)	2 (6)	7 (7)
Anatomic lesion level‡			
Thoracic	0 (0)	1 (3)	1 (1)
L1–2	0 (0)	5 (16)	17 (18)
L3–4	12 (55)	15 (48)	50 (52)
L5–S2	10 (45)	10 (33)	29 (30)
Cerebellar herniation level at 12 mos‡**	9 (41)	19 (62)	79 (83)
Corpus callosum dysgenesis at 12 mos‡†	4 (18)†	19 (63)‡	69 (72)‡
Ventricle size on prenatal ultrasound, mm‡			
<10	16 (73)	10 (32)	29 (30)
10–15	6 (27)	17 (55)	50 (52)
≥15	0	4 (13)	18 (19)

Data are presented as mean ± SD or number (%) unless indicated otherwise.

* Age is shown as mean (in years, months) ± SD (years).

† The proportion of patients with no hydrocephalus was significantly less than the proportion with unshunted hydrocephalus, which was equal to the proportion with shunted hydrocephalus ($p < 0.05$).

‡ The proportion of patients with no hydrocephalus was equal to the proportion with unshunted hydrocephalus and less than the proportion with shunted hydrocephalus ($p < 0.05$).

§ The postnatal group was set to missing.

¶ Race or ethnic group was self-reported. The statistical comparison was between White and all other groups.

** C1, C2, or below C2 vs normal.

†† Yes vs no.

and unshunted hydrocephalus in terms of neurodevelopmental outcomes to determine whether these groups could be combined. These comparisons yielded no significant results. In addition, to evaluate whether prenatal surgery had an effect on neurodevelopmental outcomes even if shunting was required, we compared the prenatal and postnatal groups with the shunted hydrocephalus groups. There were no significant differences except in terms of FRESNO scores, so the shunted groups were combined, thereby leaving two groups for comparison (no/unshunted vs shunted hydrocephalus). In the subsequent analysis, we maintained randomization and compared the prenatal groups with the no hydrocephalus, unshunted hydrocephalus, and shunted hydrocephalus. Nominal two-sided p values less than 0.05 were considered to indicate statistical significance; no adjustments were made for multiple comparisons because it was more important in this secondary analysis to detect a potentially significant difference than to miss a difference (i.e., more protection for type II errors than type I errors).

Results

Demographic and Clinical Characteristics

The group with no hydrocephalus was less likely to be female and had lower-level spinal lesions, lower frequency of callosal hypogenesis, less cerebellar herniation, and smaller ventricles than the other unshunted and shunted hydrocephalus groups (Table 2). There were no significant differences in age, ethnicity (White vs other), or gestational age at birth.

Neurodevelopmental Outcomes

Hydrocephalus Groups

There was a consistent pattern showing higher performance for the combined no/unshunted hydrocephalus group compared with that of the shunted hydrocephalus group (Table 3, Fig. 2). These differences were statistically significant for the Vineland composite score ($p = 0.002$). On the neuropsychological tests, the group with no/unshunted hydrocephalus, compared with the shunted group,

TABLE 3. Mean ± SD values and results of significance tests for neurodevelopmental outcomes by hydrocephalus groups (combined prenatal and postnatal groups)

Characteristic	No Hydrocephalus (n = 22)		Unshunted Hydrocephalus (n = 31)		p Value (No vs Unshunted Hydrocephalus)	Shunted Hydrocephalus (n = 97)		p Value (Shunted vs No/Unshunted)
	NT	Value	NT	Value		NT	Value	
Vineland Adaptive Behavior Scales II*	22	92.4 ± 10.6	31	92.2 ± 9.8	0.918	96	86.7 ± 10.8	0.002
Communication	22	95.9 ± 12.1	31	100.8 ± 13.1		96	91.2 ± 13.4	
Daily living	22	92.0 ± 11.8	31	89.1 ± 9.5		96	84.2 ± 11.7	
Socialization	22	97.5 ± 12.9	31	98.7 ± 10.9		96	95.3 ± 11.6	
KBIT-2*								
Composite score	22	100.5 ± 15.4	30	103.5 ± 15.5	0.494	93	94.6 ± 17.7	0.010
Verbal learning	22	102.2 ± 14.5	30	105.8 ± 14.3		93	98.7 ± 16.9	
Nonverbal reasoning	22	98.3 ± 15.7	30	99.9 ± 16.3		93	91.3 ± 17.7	
CVCLT-2 (trials 1–5)†	22	45.1 ± 9.5	30	46.3 ± 10.5	0.511	87	38.8 ± 9.7	<0.001
WJ-III*								
Reading composite‡	22	100.8 ± 14.8	30	105.3 ± 17.3	0.333	92	97.1 ± 16	0.026
Math calculations	22	92.6 ± 21.3	30	98.1 ± 18.6	0.330	90	90.6 ± 21.6	0.161
CMS§								
Dot learning	22	8.6 ± 3	30	8.5 ± 2.8	0.912	90	7.4 ± 2.9	0.031
Faces immediate	22	7.5 ± 2.6	30	8.6 ± 3.3	0.223	80	7.4 ± 3.4	0.190
Beery Visual-Motor Integration*	22	83.8 ± 12.1	30	89.3 ± 7.4	0.068	92	84.8 ± 11	0.254
Purdue Pegboard total pegs¶	22	-1.8 ± 1.2	30	-1.9 ± 0.9	0.852	91	-2.6 ± 1.3	<0.001
NEPSY-II word generation§	22	8.6 ± 2.3	30	8.8 ± 2.6	0.721	92	7.6 ± 2.9	0.028
SNAP—inattention**	22	1.0 ± 0.7	30	0.8 ± 0.5	0.328	93	1.2 ± 0.6	0.021
SNAP—hyperactivity/ impulsivity**	22	0.5 ± 0.5	30	0.5 ± 0.4	0.771	93	0.6 ± 0.5	0.102
BRIEF—global executive composite†	20	51.7 ± 11.6	30	51.4 ± 9.0	0.591	93	54.2 ± 10.9	0.169
FRESNO percentage	22	94.1 ± 10.0	30	93.8 ± 7.1	0.086	91	86.4 ± 14.8	0.001

NEPSY = A Developmental Neuropsychological Assessment; NT = number tested.

Values are shown as number or mean ± SD unless indicated otherwise.

* Normative mean ± SD 100 ± 15.

† Normative mean ± SD 50 ± 10.

‡ Average of the Letter Word Identification and Passage Comprehension tests.

§ Normative mean ± SD 10 ± 3.

¶ Z-score average.

** Raw score.

had higher IQ scores ($p = 0.01$), stronger verbal learning and memory ($p = 0.001$) and nonverbal learning and memory ($p = 0.031$), better reading scores ($p = 0.026$), better fine motor coordination ($p = 0.006$), and better ability to generate words to a category ($p = 0.028$). On the SNAP-IV ADHD scale, the combined no/unshunted group had lower inattention scores (less inattention) than the shunted group ($p = 0.021$), but the difference on the hyperactivity-impulsivity scale was not significant. FRESNO scores showed better sensorimotor skills and walking in the combined no/unshunted hydrocephalus group than the shunted group ($p = 0.001$).

Prenatal Group

To help understand these results relative to the original randomization into surgical groups, the prenatal group was divided into no hydrocephalus ($n = 21$), unshunted hydrocephalus ($n = 20$), and shunted hydrocephalus groups ($n = 35$) (Table 4). There were no significant differences

between the prenatal no hydrocephalus and unshunted hydrocephalus groups, so these groups were combined. Statistical comparisons within the prenatal group between no/unshunted hydrocephalus patients and those with a shunt showed significantly better Vineland composite ($p = 0.035$) and verbal learning ($p = 0.012$) test scores among those with no/unshunted hydrocephalus.

These two prenatal groups and the shunted ($n = 64$) and unshunted ($n = 12$) postnatal groups were compared in Fig. 3. There was a consistent trend for the postnatal unshunted group to score higher than the other groups, but we did not test for differences because the sample size of the unshunted postnatal group was small and highly selected and any comparison was not motivated by a hypothesis. The mean values of the two shunted groups (prenatal shunted and postnatal shunted) paralleled one another even more closely than shown in Table 3 and Fig. 2, reflecting the influence of the higher scores of the postnatal unshunted group.

Analysis of lateral ventricle volumes based on MRI

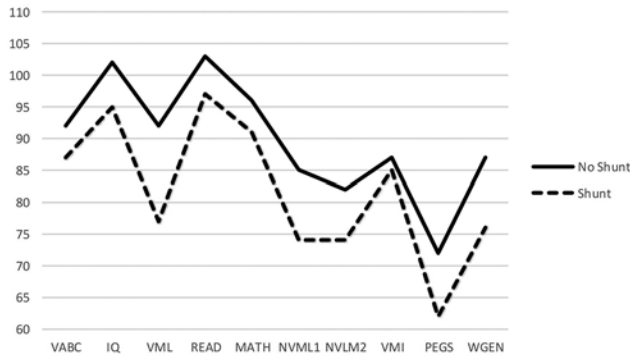


FIG. 2. Plot of the mean values for the unshunted (no hydrocephalus/unshunted hydrocephalus) and shunted hydrocephalus groups, showing neurodevelopmental outcomes. All scores were standardized to a common normative mean \pm SD 100 ± 15 . IQ = Kaufman Brief Intelligence Test composite; MATH = Woodcock-Johnson math computations; NVML1 = Children’s Memory Test Dot Learning; NVML2 = Children’s Memory Test Faces; PEGS = Purdue Pegboard; READ = Woodcock-Johnson reading composite; VABC = Vineland Adaptive Behavior Scales composite; VMI = Beery Visual-Motor Integration; VML = California Verbal Learning Test; WGEN = word generation.

measurements demonstrated that the prenatal and postnatal surgery groups with unshunted hydrocephalus had significantly larger ventricles ($p < 0.001$) than the shunted groups (Fig. 4) and the prenatal group with no hydrocephalus. This finding supports the hydrocephalus grouping.

Discussion

This secondary analysis permitted a more nuanced interpretation of the results of the MOMS trial in relation to

the neurodevelopmental outcomes assessed at school age. In contrast to the largely null results for adaptive behavior and cognitive functions based on the original randomization into the prenatal and postnatal repair groups,⁸ the outcomes of the children with no hydrocephalus and unshunted hydrocephalus (analyzed as a single group because of the null results in the statistical comparisons) showed stronger adaptive behavior (the primary outcome) and cognitive skills compared with the children in the combined prenatal and postnatal groups who required a CSF diversionary procedure. In addition, the results show that in comparison with the outcomes of a traditionally treated postnatal group,^{9,13} neurobehavioral outcomes were generally higher in the unshunted groups. Because children with myelomeningocele who did not receive a CSF shunt were infrequently studied prior to the advent of prenatal surgery, these comparisons show that outcomes are better if the child does not meet the clinical criteria or judgment for shunting. It will be important to continue to study outcomes in this unique group of children with myelomeningocele.

In children with myelomeningocele who develop hydrocephalus, the mechanism is widely understood to be the development of the Chiari II malformation, which obstructs the flow of CSF and necessitates a diversionary procedure.^{26–28} In the McLone-Knepper model,²⁶ Chiari II malformation results from an open neural tube that leads to a spectrum of embryological events that then lead to disturbances of ventricle growth, reduction in the size of the posterior fossa, and exposure of the fetus to CSF. Prenatal surgery is designed to prevent these events and to prevent or reduce the impact of Chiari II malformation.¹ This should result in reduced hindbrain herniation and the spectrum of anomalies associated with Chiari II malformation. Reductions in the incidence and severity of hydro-

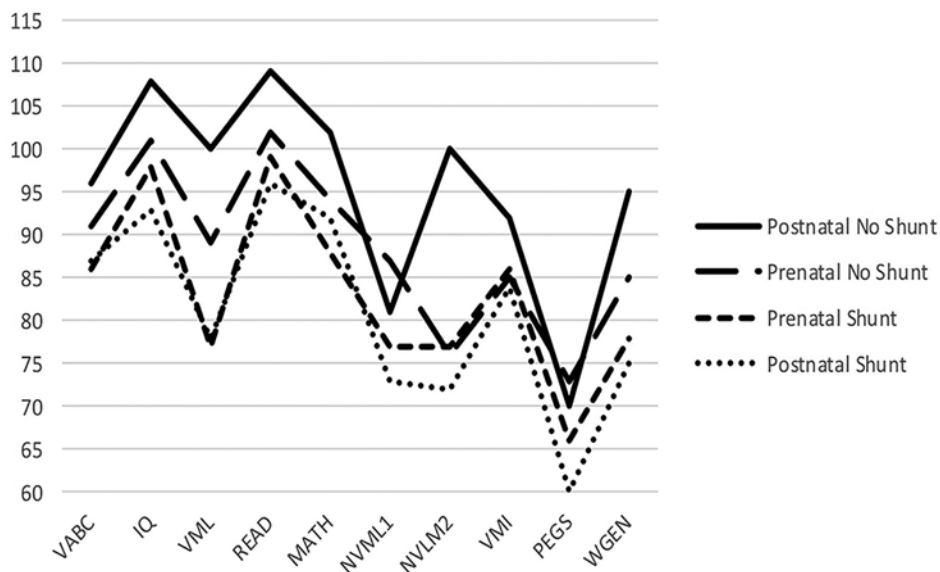


FIG. 3. Plot of the mean values for the unshunted and shunted prenatal and postnatal hydrocephalus groups for neurodevelopmental outcomes. All scores were standardized to a common normative mean \pm SD 100 ± 15 .

TABLE 4. Means ± SD values and results of significance tests for neurodevelopmental outcomes by hydrocephalus groups (prenatal group only)

Assessment	No Hydrocephalus (n = 21)		Unshunted Hydrocephalus (n = 20)		p Value (No vs Unshunted Hydrocephalus)	Shunted Hydrocephalus (n = 35)		p Value (Shunted vs No/Unshunted Hydrocephalus)
	NT	Value	NT	Value		NT	Value	
Vineland Adaptive Behavior Scales II*	21	92.5 ± 10.9	20	89.7 ± 9	0.379	34	86.4 ± 8.9	0.035
Communication	21	95.9 ± 12.4	20	98.4 ± 12.3		34	91.4 ± 11.8	
Daily living	21	92.4 ± 11.9	20	88 ± 9.5		34	84.4 ± 10.4	
Socialization	21	97.3 ± 13.2	20	96.7 ± 9.1		34	94.4 ± 10.4	
KBIT-2*								
Composite score	21	99.9 ± 15.5	19	101.5 ± 15.2	0.749	35	97.8 ± 17.3	
Verbal learning	21	101.7 ± 14.7	19	104.1 ± 13.4		35	100.3 ± 16.3	
Nonverbal reasoning	21	97.7 ± 15.8	19	98 ± 16.6		35	95.0 ± 19	
CVCLT-2 (trials 1–5)†	21	44.6 ± 9.5	19	44.4 ± 11.7		34	38.3 ± 10.1	0.012
WJ-III*								
Reading composite‡	21	100.7 ± 15.1	19	103.2 ± 17.6	0.633	35	99.1 ± 20.5	
Math calculations	21	92.6 ± 21.9	19	95.5 ± 20.9	0.676	35	88.7 ± 25.6	
CMS§								
Dot learning	21	8.6 ± 3.1	19	8.8 ± 2.9	0.818	35	7.7 ± 3	
Faces immediate	21	7.7 ± 2.5	19	7.5 ± 2.7	0.774	30	7.7 ± 2.7	
Beery Visual-Motor Integration*	21	83.4 ± 12.3	19	87.7 ± 6.8	0.174	35	86.2 ± 11.9	
Purdue Pegboard total pegs¶	21	-1.8 ± 1.2	19	-1.8 ± 1.1	0.957	35	-2.3 ± 1.3	
NEPSY-II word generation§	21	8.4 ± 2.2	19	8.6 ± 2.9	0.807	34	7.8 ± 2.9	
SNAP—inattention**	21	1.0 ± 0.6	19	1.0 ± 0.6	0.765	35	1.3 ± 0.7	
SNAP—hyperactivity/impulsivity**	21	0.5 ± 0.5	19	0.6 ± 0.4	0.731	35	0.7 ± 0.5	
BRIEF—global executive composite†	19	52.0 ± 11.8	19	53.6 ± 8.8	0.245	34	56.7 ± 10.6	
FRESNO percentage	21	94.3 ± 10.2	19	92.9 ± 7.7	0.635	33	90.2 ± 9.4	

* Normative mean ± SD 100 ± 15.

† Normative mean ± SD 50 ± 10.

‡ Average of the Letter Word Identification and Passage Comprehension tests.

§ Normative mean ± SD 10 ± 3.

¶ z-score average.

** Raw score.

cephalus, and therefore in the need for shunting, should also stem from prenatal surgery.^{27,28}

From the original school-age follow-up, it could not be concluded that prenatal surgery per se resulted in improved adaptive behavior and cognition.⁶ The present analyses show that hydrocephalus and shunting were associated with poorer adaptive behavior and cognition in both the prenatal and postnatal groups. However, because prenatal surgery reduced the likelihood and severity of hindbrain herniation and Chiari II malformation, there was an indirect effect on adaptive behavior and cognition. The prenatal group with no/unshunted hydrocephalus had stronger adaptive behavior and verbal learning and memory compared with the shunted prenatal group (Table 4).

Stronger adaptive behavior is most likely related to better semantic language and reading, as well as daily living skills, in the unshunted groups. Although language and reading are typical strengths associated with spina bifida,¹² better daily living skills are likely related to the stronger gross and fine motor skills associated with prenatal surgery in general.⁸ The results were more pronounced in the

unshunted prenatal groups relative to both shunted groups, suggesting better ambulation as well as practical skills involving buttoning, zipping, and use of utensils. This improvement in motor ability did not extend to perceptual motor skills, as evidenced by similar low average performance across groups on the Beery test.

In addition to adaptive behavior, the largest differences favoring the no/unshunted group were the results on the fine motor skills and the verbal learning tests. The primary paper reported that fine motor dexterity (Purdue Pegboard) was greater in the prenatal surgery group.⁶ In the present secondary analysis, fine motor dexterity was stronger in the no/unshunted group. We hypothesize that stronger fine motor dexterity was related to reduced cerebellar impairment secondary to reduced hindbrain herniation.

Studies of verbal learning typically show significant impairment in patients with myelomeningocele and hydrocephalus.^{8,9,29,30} The spectrum of abnormalities associated with hydrocephalus often leads to displacement and dysmorphology of the hippocampi, which are key structures for verbal and nonverbal learning and memory.^{30,31}

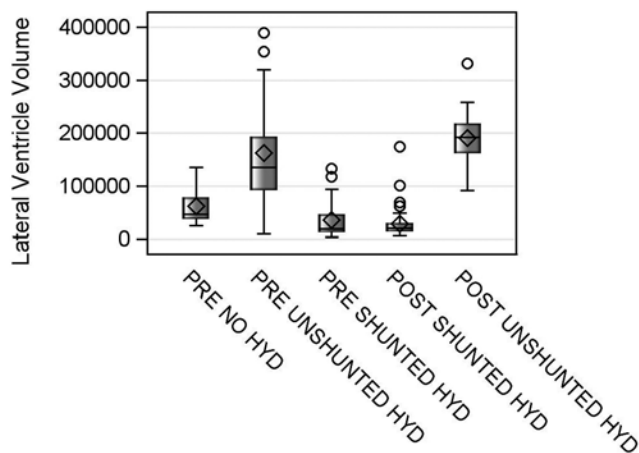


FIG. 4. Lateral ventricle volumes for the prenatal and postnatal groups with no hydrocephalus, unshunted hydrocephalus, and shunted hydrocephalus (HYD). The median is represented by the *straight horizontal line*, and the mean is represented by the *diamond* (both located within the *rectangle*). The *whiskers* around the mean indicate variability outside the upper and lower quartiles (based on Tukey's fencing rule for outlier detection). The *bubbles* represent univariate outliers (i.e., children with very enlarged ventricles).

This process may have been reduced by prenatal surgery because of the reduction of hindbrain herniation. Chiari II malformation may extend to the midbrain, a critical area for the control of involuntary attention (arousal and alerting). In large studies of children with myelomeningocele, most of whom underwent shunt implantation, about one-third met the rating scale criteria on SNAP for ADHD (predominantly inattentive type).¹³ The lower scores on the inattention scale of the unshunted group are consistent with the beneficial effects on the posterior attention system, which is impaired in many patients with myelomeningocele and shunted hydrocephalus.^{31,32} The absence of differences on the hyperactivity-impulsivity scale is also consistent with these prior studies.¹³

It would be inappropriate to attribute the current results to the presence of shunting. The improved outcomes associated with the absence of a shunt despite enlarged ventricles do seem to support the practice of monitoring hydrocephalus prior to shunt insertion at some centers.¹⁰ An assessment from the National Spina Bifida Patient Registry showed that about 80% of children with myelomeningocele across 28 centers identified between 2009 and 2016 underwent shunt implantation or other diversionary procedure in the 1st year of life.^{2,33} However, it is unclear to what extent ventriculomegaly should be permitted before shunting.³⁴ In the present cohort, about 48% of the prenatal surgery sample received a shunt. Prenatal surgery reduced hindbrain herniation in all prenatal groups, although the reduction tended to be greater in the no hydrocephalus group than the unshunted hydrocephalus group. In general, the group with no hydrocephalus was at lower risk for adverse neurobehavioral outcomes. At prenatal MRI screening, this group had no cases with ventricular size > 15 mm and most were less than 10 mm, with no cases involving spinal lesion levels above L3. On MRI evaluations

of school-age children, ventricular volumes were greatest in the unshunted groups with hydrocephalus. Despite larger ventricle volumes, the prenatal and postnatal groups with unshunted hydrocephalus had similar outcomes as the prenatal hydrocephalus group. These data do not provide information on how or when the decision to implant a shunt or not was made, which was left to the clinicians caring for the child.

The subgroup with no hydrocephalus (all but 1 case was in the prenatal group) also had fewer cases of callosal hypogenesis at 12 months than any other group. This finding is important because it may indicate less injury from the primary deficit in neurulation. Previous studies found that over half of traditionally treated children with myelomeningocele had callosal hypogenesis,¹³ consistent with the proportion (66%) reported in Table 2. The corpus callosum develops in the first 20 weeks of gestation in a rostral to caudal direction beginning with the genu; the most anterior portion of the corpus callosum (rostrum) develops around 18–20 weeks. This sequence implies prolonged disruption of neural development in spina bifida myelomeningocele.² The absence of callosal hypogenesis and the lower lesion levels may indicate less disruption of neurulation and could be a predictor of outcomes associated with prenatal surgery. The overall picture is that it is not shunting per se that is related to outcomes, but the severity of the initial disease manifested by ventricular dilation, cerebellar herniation, and callosal hypogenesis. The need for a CSF shunt may reflect the greater severity of disease in those with a shunt.

Limitations

The limitations of this study include the small sample sizes for the hydrocephalus subgroups and the decision not to aggressively control for type I errors in the secondary analysis. We felt that it was more important to not miss a clinically important difference given the small sample sizes. As such, the results should be seen through a hypothesis-generating lens.

The sample of the MOMS study was highly selected and more stringent than the criteria of many current clinical centers, so the results may not generalize to other centers, especially if participants have higher-level lesions and identify as other ethnicities for whom spina bifida is prevalent and are subject to varying genetic and environmental contributors (e.g., individuals of Hispanic origin).

There are important domains that were not formally tested because of the need for a short assessment battery. In particular, attention and executive functions were not assessed with performance tasks.¹² These domains generally require experimental tasks that would be difficult to implement in a multicenter study but would be fruitful for future studies. More assessments of the risk factors, especially from prenatal data, that may predict neurobehavioral outcomes are important for future studies.

There was a subgroup of children with hydrocephalus who did not undergo CSF diversion despite meeting predetermined clinical criteria for shunting. Patients with unshunted hydrocephalus met predefined criteria for hydrocephalus and some met criteria for shunting, but we recognize that there may have been overlap with varying

degrees of ventriculomegaly. There is no information on the nature of the decision-making process between clinicians and parents, or the decision to use third ventricle ventriculostomy instead of a shunt. However, there is also no evidence of adverse cognitive outcomes associated with these decisions.

Conclusions

The primary assessment of school-age outcomes comparing the prenatal and postnatal groups showed no significant differences between the prenatal and postnatal groups in terms of the primary outcome, adaptive behavior, and no robust evidence of stronger cognitive functions. However, there were better sensorimotor, fine motor, and orthopedic outcomes in the prenatal surgery group. This secondary analysis shows that hydrocephalus and shunting were associated with poorer adaptive behavior and cognitive skills in the shunted groups (both prenatal and postnatal). However, it is unlikely that shunting per se explains the better outcomes. Rather, disease severity and dynamic changes in hydrocephalus status seem to be the primary factor in the development of hydrocephalus and the need for shunting,⁶ which are the major determinants of adaptive behavior and cognitive outcomes after prenatal surgery.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Conception and design: Fletcher, Houtrow, MacPherson, Thomas, Adzick, Thom. Acquisition of data: Fletcher, Houtrow, Thomas, Adzick, Thom. Analysis and interpretation of data: Fletcher, Houtrow, MacPherson, Gupta, Adzick, Thom. Drafting the article:

Fletcher, Houtrow, MacPherson, Thomas, Gupta. Critically revising the article: Fletcher, Houtrow, MacPherson, Thomas, Gupta, Adzick. Reviewed submitted version of manuscript: Fletcher, Houtrow, MacPherson, Thomas, Gupta, Adzick. Approved the final version of the manuscript on behalf of all authors: Fletcher. Statistical analysis: MacPherson, Thom.

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