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ARTICLE

Does Cerebellar Injury in Premature Infants Contribute to the High Prevalence of Long-term Cognitive, Learning, and Behavioral Disability in Survivors?

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ABSTRACT

OBJECTIVE. Although cerebellar hemorrhagic injury is increasingly diagnosed in infants who survive premature birth, its long-term neurodevelopmental impact is poorly defined. We sought to delineate the potential role of cerebellar hemorrhagic injury in the long-term disabilities of survivors of prematurity.

DESIGN. We compared neurodevelopmental outcome in 3 groups of premature infants (N = 86; 35 isolated cerebellar hemorrhagic injury, 35 age-matched controls, 16 cerebellar hemorrhagic injury plus supratentorial parenchymal injury). Subjects underwent formal neurologic examinations and a battery of standardized developmental, functional, and behavioral evaluations (mean age: 32.1 ± 11.1 months). Autism-screening questionnaires were completed.

RESULTS. Neurologic abnormalities were present in 66% of the isolated cerebellar hemorrhagic injury cases compared with 5% of the infants in the control group. Infants with isolated cerebellar hemorrhagic injury versus controls had significantly lower mean scores on all tested measures, including severe motor disabilities (48% vs 0%), expressive language (42% vs 0%), delayed receptive language (37% vs 0%), and cognitive deficits (40% vs 0%). Isolated cerebellar hemorrhagic injury was significantly associated with severe functional limitations in day-to-day activities. Significant differences were noted between cases of cerebellar hemorrhagic injury versus controls on autism screeners (37% vs 0%) and internalizing behavioral problems (34% vs 9%). Global developmental, functional, and social-behavioral deficits were more common and profound in preterm infants with injury to the vermis. Preterm infants with cerebellar hemorrhagic injury and supratentorial parenchymal injury were not at overall greater risk for neurodevelopmental disabilities, although neuromotor impairment was more severe.

CONCLUSIONS. Cerebellar hemorrhagic injury in preterm infants is associated with a high prevalence of long-term pervasive neurodevelopment disabilities and may play an important and underrecognized role in the cognitive, learning, and behavioral dysfunction known to affect survivors.

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Key Words
cerebellar injury, prematurity, MRI, developmental, outcome

Abbreviations
CHI— cerebellar hemorrhagic injury
SPI—supratentorial parenchymal injury
MSEL—Mullen Scales of Early Learning
PDMS—Peabody Developmental Motor Scales
VABS—Vineland Adaptive Behavior Scale
CBCL—Child Behavior Checklist
M-CHAT—Modified Checklist for Autism in Toddlers
SCQ—Social Communication Questionnaire

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CEREBELLAR INJURY IN the premature infant is an increasingly recognized problem in recent years.[1–6] Innovations in neuroimaging have advanced the diagnostic sensitivity for cerebellar injury in the living infant.[7–9] The signal characteristics of these lesions suggest a prominent hemorrhagic component, justifying the term cerebellar hemorrhagic injury (CHI). In addition, the impact on survival of advances in neonatal critical care has been greatest among infants at highest risk for CHI,[1–3,5,6] namely extremely premature infants.[10,11] In fact, the incidence of CHI may be as high as 19% among infants born weighing <750 g.[2] Together, these trends have resulted in a growing population of infants who survive premature birth with the diagnosis of CHI.

Despite the growing recognition of this problem, current data regarding the long-term neurodevelopmental consequences of CHI in ex-premature infants remain very limited. To date, outcome studies have been limited to case reports or small case series with widely distributed ages at follow-up, often with outcome based on medical chart reviews or informal neurodevelopmental assessments.[6,9,12,13] Significant neurologic sequelae were recently reported among a selected group of infants with a particularly extensive form of cerebellar injury, associated with widespread supratentorial parenchymal injury (SPI).[5,6,13] To date, no study has systematically used comprehensive and standardized outcome measures to characterize the spectrum of neurodevelopmental outcome across the range of CHI severity in ex-premature infants.

Prematurity is a well-established cause of long-term motor deficits, including cerebral palsy.[14–17] In addition, more recent reports of long-term outcome in survivors of prematurity have emphasized a high prevalence of deficits outside the motor domain, including cognitive, learning, and behavioral disturbances, in some studies reaching as high as 25% to 50%.[10,18–21] Traditionally, the cerebellum has been regarded as a central component of the motor system, with little if any nonmotor functions.[22] However, recent studies in adults[22–25] and children[26–29] demonstrated an important role for the cerebellum in nonmotor functions, including cognition, learning, and behavior. In fact, clinical descriptions of the nonmotor deficits after cerebellar injuries have prompted the term "cerebellar cognitive affective syndrome."[22] To date, there are very limited data regarding the potential role of prematurity-related cerebellar injury in the high prevalence of cognitive, language, and behavioral disturbances in ex-preterm infants. In this study, we hypothesized that CHI in premature infants would be associated not only with long-term motor deficits but also significant disturbances in the development of cognition, communication, and social function.

The effects of both premature birth and prematurity-related brain injuries are important determinants of long-term outcome in survivors.[30–32] To test our overall hypothesis within this context, we set out to address 3 objectives. First, we begin to characterize the neurodevelopmental impact of CHI by comparing the outcome between ex-premature infants with isolated CHI (ie, without supratentorial injury) and age-matched infants with normal neuroimaging studies. Second, we further delineate the developmental impact of CHI by comparing the long-term outcome between ex-preterm infants with isolated CHI and those with combined CHI and supratentorial injury. Our third objective was to describe the structure-function relationship of CHI by comparing the topography of isolated CHI with neurodevelopmental outcome.

METHODS

In a retrospective, case-control design, we used a systematic electronic database search of all neonatal cranial ultrasound reports performed in the NICUs of the Brigham and Women's Hospital and Beth Israel Deaconess Medical Center between January 1998 through December 2003. We identified all preterm infants (<32 weeks' gestational age) with an ultrasonographic diagnosis of CHI. We excluded infants with known or suspected brain malformations, dysmorphic features or congenital anomalies suggestive of a genetic syndrome, metabolic disorders, or central nervous system infections. For each preterm infant with isolated CHI (ie, absence of associated supratentorial parenchymal lesions), we identified, from previous prospective research studies,[33] an infant for the control group with normal cranial ultrasound and MRI studies throughout their stay in the NICU, matched on the basis of gestational age, gender, and year of birth.

Procedures

All neonatal cranial ultrasound studies that included a mastoid view of the posterior fossa were reviewed blindly by an experienced ultrasonologist (Dr Benson) to confirm the diagnosis of CHI and to distinguish between parenchymal and extra-axial hemorrhage.[2] CHI was defined as a unilateral or bilateral echodense lesion in the cerebellar hemispheres or vermis. All infants with CHI underwent clinically indicated MRI scans during early childhood. These conventional MRI studies were reviewed to confirm the diagnosis of cerebellar injury, to exclude infants with isolated extra-axial (ie, nonparenchymal) posterior fossa hemorrhage, and to localize precisely the topography of the lesions. Once infants met the established inclusion criteria, we obtained informed written consent for enrollment. The study was approved by the institutional review boards of Children's Hospital, Brigham and Women's Hospital, and Beth Israel Deaconess Medical Center. Written informed consent was obtained from the children's parents.

MRI Abnormalities

The MRI findings were categorized independently by an experienced neuroradiologist (Dr Robinson) by using conventional, spin-echo T1-weighted and fast spin-echo T2-weighted MRI scans. This neuroradiologist was blinded to the infants' perinatal history, ultrasonographic findings, and outcome data. Lesions were categorized as infratentorial, supratentorial, or combined lesions. Infratentorial lesions consisted of hemorrhagic intraparenchymal cerebellar lesions that were categorized as follows: unilateral hemispheric lesions, unilateral hemispheric plus vermis lesions, and bilateral hemispheric plus vermis lesions, the latter further categorized by severity into partial infero-medial and profound near-complete cerebellar injury (Fig 1). Supratentorial parenchymal lesions included cystic or diffuse periventricular leukomalacia (defined as diffuse, excessive, high signal intensity in the periventricular white matter on T2-weighted scans)[34–36]; periventricular hemorrhagic infarction (defined as a unilateral or asymmetric lesions of increased T2 signal in the periventricular white matter associated with ipsilateral parenchymal germinal matrix-intraventricular hemorrhage); and ventriculomegaly. Infants were categorized as having either isolated CHI (ie, confined to the cerebellar parenchyma), or combined CHI/SPI (Fig 2).

Neurodevelopmental Outcomes

Clinical measures of neurodevelopmental status comprised a battery of standardized instruments listed below. Age at testing was adjusted for prematurity for all infants <24 months of age. All testers were blinded to past medical history, imaging findings, and each other's clinical findings.

A formal neurologic examination was performed by a pediatric neurologist (Dr du Plessis or Dr Bassan), which included assessment of cranial size, cranial nerves, special senses, and motor function (ie, deep tendon reflexes, muscle tone, muscle strength, coordination, and gait). The findings in each of these domains were categorized as normal or abnormal. Microcephaly was defined as a head circumference below the second percentile for corrected age.

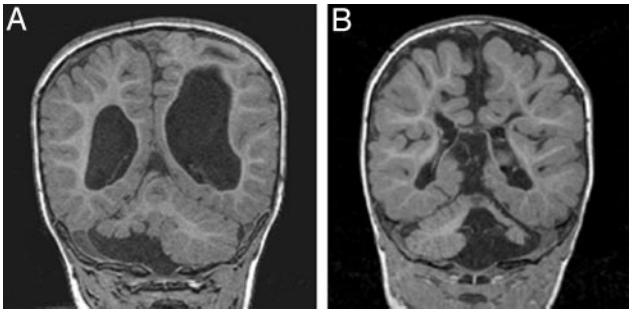

FIGURE 2
Follow-up brain MRIs (coronal spoiled gradient recalled T1-weighted) of infants with combined cerebellar hemorrhagic injury and supratentorial parenchymal injury on neonatal cranial ultrasound. A, Small right cerebellar hemisphere and disorganized cerebellar vermis plus bilateral, asymmetric ventriculomegaly with marked decrease in white matter volume and ex vacuo lateral ventricular dilatation (left more than right). B, Asymmetrically small cerebellar hemispheres (left more than right) plus reduced cerebral white matter volume and gyral crowding.

The Mullen Scales of Early Learning (MSEL)[37] was administered by a pediatric licensed psychologist (Dr Sullivan or Dr Avery). The MSEL is a standardized developmental assessment for children 0 to 69 months of age and consists of 5 subscales: gross motor, fine motor, visual reception, receptive language, and expressive language. For each of these scales, a *t* score (mean: 50; SD: 10) was obtained. A summary measure of general cognitive function underlying all cognitive performances (early learning composite) was also derived and expressed as a standard score (mean: 100; SD: 15). A score of <2 SD of the normative mean was defined as abnormal.

The Peabody Developmental Motor Scales (PDMS) was administered by a pediatric occupational therapist (Dr Limperopoulos). The PDMS objectively evaluates gross motor and fine motor abilities in children by using standardized procedures. A developmental motor quotient for each motor domain was derived.[38] The PDMS was also administered given that the ceiling level of the MSEL Gross motor scales is 33 months and a proportion of our infants were older than 33 months of age. A score of <2 SD of the normative mean was defined as abnormal.

The Vineland Adaptive Behavior Scale (VABS) was

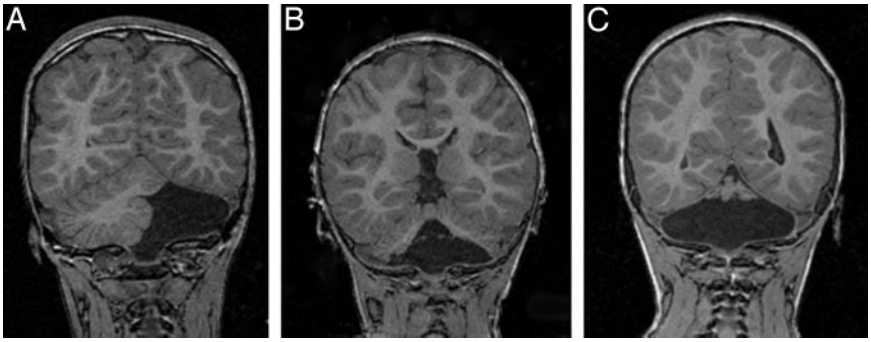

FIGURE 1
Follow-up brain MRIs (coronal spoiled gradient recalled T1-weighted) of infants with isolated cerebellar hemorrhagic injury on neonatal cranial ultrasound. A, Complete absence of the left cerebellar hemisphere with preservation of the right cerebellar hemisphere and vermis. B, Absence of the inferior cerebellar vermis and inferior portions of both cerebellar hemispheres. C, Near-total cerebellar destruction with only a small amount of superior cerebellar vermis present.

completed by a pediatric occupational therapist (Dr Limperopoulos). The VABS is a discriminative norm-referenced measure of functional status in communication, daily living, socialization, and motor skills in children 0 to 18 years of age.[39] Standard scores were generated by using a mean of 100 and a SD of 15. A score of <2 SD of the normative mean was defined as abnormal.

The Child Behavior Checklist (CBCL) includes 113 items, and caregivers report on the frequency of behavioral problems. Externalizing and internalizing problem behavior scores are derived.[40] Internalizing behavior consists of the withdrawn, somatic complaints, and anxious and depressed syndromes scales, and externalizing behavior consists of the delinquent and aggressive behavior syndrome scales. The clinical range is defined as *t* scores of ≥64, the borderline range as *t* scores from 60 to 63, and the reference range as *t* scores of <60.

The Modified Checklist for Autism in Toddlers (M-CHAT) was used to screen all children's behaviors for early signs of autism by parental report. The M-CHAT is a 23-item yes/no parent-report screening instrument for autistic spectrum disorders. Critical items include items concerning joint attention, interest in other children, responding to name, and imitation.[41] Cutoff scores of at least 2 critical items or 3 total items on the checklist are used.

The Social Communication Questionnaire (SCQ) is a parent-report screening measure for autism spectrum disorders based on the Autism Diagnostic Interview-Revised.[42] The SCQ was completed by parents for children ≥4 years old. The SCQ is a 40-item questionnaire that evaluates reciprocal social interaction, language and communication, and repetitive, stereotyped patterns of behavior. A cutoff score of ≥15 is used for this screening.

Socioeconomic Status and Medical History

We used the modified, 2-factor index Hollingshead Scale for socioeconomic status evaluation consisting of both parental highest level of education and type of occupation.[43] We also administered a medical history questionnaire to ascertain the presence of ongoing medical problems.

Statistical Analysis

Continuous perinatal, developmental, and MRI characteristics were summarized by using the mean and SD, ordinal characteristics by using the median and range, and categorical factors with percentages. Characteristics of infants with isolated CHI were compared with those of preterm infants in the control group matched on gestational age, gender, and year of birth by using paired data techniques. The paired *t* test was used for continuous variables, the Wilcoxon signed-rank test for ordinal variables, and McNemar's test for dichotomous variables. Characteristics of preterm infants with CHI with and without associated injury were compared by using the 2-sample *t* test for continuous measurements, the Wilcoxon rank sum test for ordinal variables, and Fisher's exact test for categorical variables. For subgroups of infants categorized by topography, differences in continuous variables were evaluated by using 1-way analysis of variance; ordinal variables were compared by using the Kruskal-Wallis test, and categorical variables by using Fisher's exact test. Additional analyses controlling for gender and birth weight were performed by using multiple linear and logistic regression analysis.

RESULTS

Characteristics of the Overall Cohort

We identified 60 premature infants with a diagnosis of CHI born between the years 1998 and 2003 that met our inclusion criteria. Of these, 7 died in early infancy (4 with CHI and 3 with combined CHI/SPI), and 2 families were lost to follow-up (1 each of CHI and CHI/SPI). All remaining 51 infants (35 had isolated CHI and 16 had combined CHI/SPI) were successfully recruited (96% enrollment rate). Table 1 summarizes the perinatal characteristics of preterm infants with isolated CHI and matched controls, as well as preterm infants with combined CHI/SPI. There were no differences between infants with CHI and their age-matched controls. Premature infants with isolated CHI were more likely to be boys and of lower birth weight compared with those with combined CHI/SPI.

The MRI studies in infants in the control group were

TABLE 1 **Perinatal Characteristics of the Preterm Infants With Isolated CHI, Combined CHI/SPI, and Age-Matched Controls**

Characteristic	Isolated CHI (*n* = 35)	Controls (*n* = 35)	*P*[a]	CHI/SPI (*n* = 16)	*P*[b]
Gestational age, mean ± SD, wk	25.8 ± 1.9	25.8 ± 1.8	.82	26.4 ± 2.1	.32
Birth weight, mean ± SD, g	764 ± 185	784 ± 187	.27	999 ± 342	.019
Male gender, *n* (%)	25 (71.4)	25 (71.4)	.99	6 (37.5)	.031
Singleton, *n* (%)	26 (74.3)	26 (74.3)	.99	13 (81.3)	.73
Apgar score at 5 min, median (range)	6 (2–9)	6 (4–9)	.37	6 (4–8)	.47
Age tested, mean ± SD, mo	32.2 ± 11.6	32.1 ± 11.1	.82	31.3 ± 12.9	.82

[a] Comparison of isolated CHI versus controls.
[b] Comparison of isolated CHI versus combined CHI/SPI.

performed at term-equivalent age. In infants with either isolated CHI or combined CHI/SPI, MRI studies were performed at a mean age of 26 ± 11.6 months (range: 12–46 months). All infants diagnosed with CHI by posterior fossa ultrasound during the neonatal period had cerebellar injury confirmed by follow-up MRI.

We present our results in the context and order of our 3 overall objectives described earlier.

Objective 1

Our first objective was to begin characterizing the developmental impact of CHI by comparing long-term outcome between ex-preterm infants with isolated CHI and age-matched ex-preterm infants in the control group.

There were no significant differences in the age at neurologic and developmental testing between the 35 infants with isolated CHI and the 16 age-matched controls (Table 1). In addition, there was no difference in socioeconomic status on the Hollingshead Scale between the 2 groups on the basis of education and occupation.

Neurologic Outcomes

Twenty-three (65.7%) preterm infants with isolated CHI demonstrated neurologic abnormalities. Hypotonia was present in all cases, with regional/focal hypertonia (11.4%) or without. In addition, abnormal deep tendon reflexes (40%), abnormal gait patterns (37.1%), abnormal eye alignment (37.2%), extraocular abnormalities (22.9%), visual field defects (17.1%), microcephaly (17.1%), abnormal mental status (ie, lethargy/irritability; 14.3%), and motor asymmetries (5.7%) were detected. Neurologic examinations in infants in the control group were normal, with the exception of 2 infants who demonstrated abnormal eye position and mild hypotonia, and 1 infant with an immature gait pattern.

Developmental Outcomes

Developmental performance on the MSEL and PDMS is summarized in Table 2. Mean gross and fine motor, expressive, and receptive language and overall early learning composite scores were significantly lower in preterm infants with CHI ($P < .001$, for all subscales). Fourteen (48.3%) infants with CHI demonstrated significant (<2 SD below the mean) gross and fine motor delays, visual receptive deficits (40.0%), and expressive and receptive language delays (42.9% and 37.1%, respectively) on the MSEL. Similarly, significant gross (40.0%) and fine (54.3%) motor deficits were noted on the PDMS. None of the preterm infants in the control group demonstrated motor, language, or cognitive deficits that were >2 SD below the mean on either assessment.

Functional Outcomes

Infants with isolated CHI had significantly lower standard scores than infants in the control group on all the VABS subsets, including communication, daily living, socialization, and motor functioning ($P < .001$ for all; Table 2). Forty percent of infants with isolated CHI demonstrated severe functional limitations (scores < 70) in motor and daily living skills, whereas 34.3% had communication deficits and 25.7% experienced socialization difficulties. All preterm infants in the control group were free of major functional disabilities (ie, of scores < 70).

TABLE 2 Comparison of Mean ± SD Scores of the MSEL, PDMS, and VABS Between Infants With CHI and Controls

Outcome Measure	Isolated CHI ($n = 35$)	Preterm Controls ($n = 35$)	*P*
MSEL			
Gross motor	29.2 ± 7.2	37.6 ± 3.3	<.001
Fine motor	29.9 ± 10.1	42.1 ± 6.1	<.001
Visual reception	32.7 ± 10.2	45.1 ± 7.3	<.001
Receptive language	33.9 ± 11.2	42.8 ± 5.9	<.001
Expressive language	30.3 ± 9.1	45.0 ± 7.1	<.001
Early learning composite	69.3 ± 16.3	90.1 ± 7.8	<.001
PDMS			
Gross motor	74.1 ± 7.4	84.7 ± 6.3	<.001
Fine motor	73.0 ± 8.6	87.5 ± 6.4	<.001
VABS			
Communication	76.5 ± 10.2	91.1 ± 7.4	<.001
Daily living	72.7 ± 11.2	86.7 ± 5.5	<.001
Socialization	75.2 ± 11.1	89.6 ± 6.9	<.001
Motor	74.6 ± 11.4	86.9 ± 5.3	<.001

Behavioral and Social Outcomes (Table 3)

Children with isolated CHI were much more likely to demonstrate internalizing behavioral problems than infants in the control group (34.3% vs 8.6%; $P = .007$); however, there were no differences in externalizing behavioral problems (11.4% in both groups; $P = .96$). Significant differences were found between infants with isolated CHI versus infants in the control group on the following CBCL subscales: withdrawn (40.0% vs 2.9%; $P < .001$), decreased attention (37.1% vs 11.5%; $P = .03$), affective problems (28.5% vs 2.9%; $P = .003$), and pervasive difficulties (34.3% vs 2.9%; $P < .001$) (Table 4).

TABLE 3 Comparison of Performance on the CBCL, M-CHAT, and SCQ Between Infants With CHI and Controls

Social Behavioral Outcome	Isolated CHI ($n = 35$)	Preterm Controls ($n = 35$)	*P*
CBCL, *n* (%)			
Internalizing normal	23 (65.7)	32 (91.4)	.007
Borderline	8 (22.9)	3 (8.6)	
Clinical range	4 (11.4)	0 (0.0)	
Externalizing normal	31 (88.6)	31 (88.6)	.96
Borderline	4 (11.4)	3 (8.6)	
Clinical range	0 (0.0)	1 (2.9)	
M-CHAT			
Median (range)	2 (0–10)	0 (0–3)	<.001
Abnormal, *n* (%)	13 (37.1)	0 (0.0)	<.001
SCQ ($n = 15$)			
Median (range)	13 (2–26)	2 (1–7)	<.001
Abnormal, *n* (%)	5 (33.3)	0 (0.0)	.063

TABLE 4 **Association Between Topography of Isolated CHI and Outcome**

Variable	Unilateral CHI ($n = 21$)	Unilateral CHI Plus Vermis ($n = 5$)	Bilateral CHI ($n = 9$)	*P*
Male gender, *n* (%)	15 (71.4)	4 (80.0)	6 (66.7)	.99
Birth weight, mean ± SD, g	841 ± 171	677 ± 202	632 ± 113	.006
Age at testing, mean ± SD, mo	31.5 ± 13.2	40.2 ± 10.3	29.3 ± 5.7	.23
PDMS				
Gross motor, mean ± SD	77.7 ± 6.5	69.6 ± 6.1	68.3 ± 4.7	<.001
<70, *n* (%)	3 (14.3)	4 (80.0)	7 (77.8)	<.001
Fine motor, mean ± SD	76.4 ± 9.4	68.0 ± 4.8	67.9 ± 3.0	.013
<70, *n* (%)	8 (38.1)	4 (80.0)	7 (77.8)	.079
MSEL				
Gross motor, mean ± SD	32.1 ± 6.9	27.3 ± 6.4	24.4 ± 5.5	.024
<30, *n* (%)	5 (29.4)	1 (33.3)	8 (88.9)	.009
Fine motor, mean ± SD	34.4 ± 9.7	24.0 ± 5.5	22.7 ± 6.9	.003
<30, *n* (%)	6 (28.6)	3 (60.0)	8 (88.9)	.006
Visual reception, mean ± SD	37.7 ± 9.2	28.0 ± 7.8	23.4 ± 4.9	<.001
<30, *n* (%)	3 (14.3)	3 (60.0)	8 (88.9)	<.001
Receptive language, mean ± SD	39.9 ± 8.7	27.2 ± 10.9	23.8 ± 7.0	<.001
<30, *n* (%)	2 (9.5)	4 (80.0)	7 (77.8)	<.001
Expressive language, mean ± SD	35.3 ± 7.6	24.0 ± 6.9	22.0 ± 4.3	<.001
<30, *n* (%)	3 (14.3)	4 (80.0)	8 (88.9)	<.001
Early learning composite, mean ± SD	78.9 ± 12.8	58.2 ± 11.4	53.2 ± 7.0	<.001
<70, *n* (%)	4 (19.1)	4 (80.0)	8 (88.9)	<.001
VABS				
Communication, mean ± SD	82.4 ± 6.7	71.8 ± 7.4	65.3 ± 7.3	<.001
<70, *n* (%)	1 (4.8)	4 (80.0)	7 (77.8)	<.001
Daily living, mean ± SD	79.5 ± 7.7	62.2 ± 9.1	62.8 ± 6.7	<.001
<70, *n* (%)	3 (14.3)	4 (80.0)	7 (77.8)	<.001
Socialization, mean ± SD	82.2 ± 5.9	63.8 ± 7.8	65.1 ± 9.0	<.001
<70, *n* (%)	0 (0.0)	4 (80)	5 (55.6)	<.001
Motor, mean ± SD	80.5 ± 9.3	68.2 ± 9.6	64.6 ± 7.7	<.001
<70, *n* (%)	4 (19.1)	3 (60.0)	7 (77.8)	.005
M-CHAT, median (range)	2 (0–3)	6 (2–8)	8 (5–10)	<.001
Abnormal, *n* (%)	0 (0.0)	4 (80.0)	9 (100)	<.001
SCQ ($n = 15$), median (range)	8.0 (2–13)	16.0 (15–19)	18.5 (13–26)	.006
Abnormal, *n* (%)	0 (0.0)	2 (66.7)	3 (75.0)	.01

Infants with isolated CHI scored significantly higher on both autism screening tests (M-CHAT and SCQ) than infants in the control group ($P < .001$, for both). Surprisingly, of the infants with isolated CHI, 42.9% had abnormal M-CHAT scores, whereas 40.0% scored in the abnormal range on the SCQ. One (2.9%) infant in the control group screened positive on the M-CHAT, and none of the infants in the control group had an abnormal SCQ score.

Associated Conditions

Two (5.7%) infants with isolated CHI developed epilepsy, and 34.3% had significant health problems, including significant feeding problems requiring gastrostomy tube placement (20.0%), recurrent respiratory problems (eg, asthma, bronchiolitis; 11.4%), and allergies (5.7%). The only significant medical problem among preterm infants in the control group was respiratory illness (8.6%).

There was no difference in socioeconomic status between the 2 groups on the basis of education and occupation.

Objective 2

Our second objective was to compare the long-term outcomes between ex-preterm infants with isolated CHI and ex-preterm infants with combined CHI and supratentorial parenchymal injury.

Of the 16 infants with combined CHI/SPI, the cerebral lesions were unilateral periventricular hemorrhagic infarction in 6, diffuse periventricular leukomalacia in 8, and atrophic ventriculomegaly in 2. None of these infants developed cystic periventricular leukomalacia. There was no significant difference in gestational age (25.8 ± 1.9 vs 26.4 ± 2.1 weeks; $P = .31$) or age at testing (32.2 ± 11.6 vs 31.3 ± 12.9 months; $P = .82$) between preterm infants with isolated CHI versus those with CHI/SPI. However, preterm infants with isolated CHI had significantly lower birth weights (764 ± 185 vs 999 ± 342 g; $P = .019$), and a higher proportion were boys (71.4% vs 37.5%; $P = .031$).

Neurologic Outcomes

Although the overall prevalence of neurologic abnormalities did not differ between the 2 groups, infants with combined CHI/SPI were more likely to have abnormal eye position (50.0% vs 37.2%; $P = .058$), abnormal posture (37.5% vs 11.4%; $P = .054$), motor asymmetries (25.0% vs 2.9%; $P = .027$), and hypertonia (68.8% vs 11.4%; $P < .001$) than those with isolated CHI.

Developmental Outcomes

Although there were no differences between the 2 groups on all other developmental subscales, infants with combined CHI/SPI experienced greater gross motor deficits (by the PDMS and the MSEL) than did infants with isolated CHI (Table 5). On multivariate analysis, the magnitude of the differences in outcome for gross and fine motor disabilities between the 2 groups became more pronounced after controlling for gender and birth weight. However, combined CHI/SPI was not associated with greater impairments in language and communication, cognitive abilities, daily living skills, socialization, or a positive autism screening (M-CHAT).

Objective 3

Our third objective was to describe the structure-function relationship of CHI by comparing the topography of isolated CHI with neurodevelopmental outcome.

In the 35 infants with isolated CHI, the MRI studies showed a unilateral right CHI in 16 (13 hemispheric injury only, 3 hemispheric plus vermis), left CHI in 10 (8 hemispheric only, 2 hemispheric plus vermis), and bilateral hemispheric plus vermis injury in 9 (2 severe near complete). The relationships between subject characteristics, topography of isolated CHI, and outcome are presented in Table 4. There was a significant association between birth weight and topography of CHI; a lower birth weight was associated with more extensive bilateral isolated CHI ($P = .006$). Developmental and functional disabilities were significantly more prevalent and profound (>2 SD below the normative mean) in infants with bilateral isolated CHI, followed by infants with unilateral CHI (plus vermis involvement), compared with those infants with unilateral isolated CHI without vermis involvement. It is noteworthy that socialization difficulties (VABS) and positive autism screening (M-CHAT and SCQ) were almost exclusively associated with injury to the vermis ($P < .001$). We also performed subgroup analyses of infants with unilateral isolated CHI (without involvement of the vermis) and found no significant difference between right versus left isolated CHI and developmental, functional, social, and behavioral deficits. Finally, we analyzed the association between topography of injury and outcome after removing the 2 infants with extensive, near-complete bilateral isolated CHI from the analysis. Although the overall means of the infants in the bilateral CHI group increased slightly, the differences between the 3 diagnostic groups remained statistically significant. For our comparisons of lesion topography (unilateral with and without vermis

TABLE 5 Comparison of Preterm Infants With Primary CHI Versus Infants With CHI and Associated SPI

Outcome Measure	Isolated CHI ($n = 35$)	CHI/SPI ($n = 16$)	*P*
MSEL			
Gross motor ($n = 29, 14$), mean ± SD	29.2 ± 7.2	23.3 ± 5.2	.004
Score <30, *n* (%)	14 (48.3)	12 (85.7)	.023
Fine motor, mean ± SD	29.9 ± 10.1	30.1 ± 10.8	.96
Score = 0, *n* (%)	17 (48.6)	10 (66.7)	.36
Visual reception, mean ± SD	32.7 ± 10.2	30.7 ± 8.7	.49
Score < 30, *n* (%)	14 (40.0)	7 (46.7)	.76
Receptive language, mean ± SD	33.9 ± 11.2	32.2 ± 10.8	.61
Score < 30, *n* (%)	13 (37.1)	7 (46.7)	.55
Expressive language, mean ± SD	30.3 ± 9.1	35.5 ± 10.5	.11
Score < 30, *n* (%)	15 (42.9)	5 (33.3)	.75
Early learning composite, mean ± SD	69.3 ± 16.3	69.1 ± 14.8	.97
Score < 70, *n* (%)	16 (45.7)	9 (60.0)	.54
PDMS			
Gross motor, mean ± SD	74.1 ± 7.4	69.4 ± 7.4	.045
Score < 70, *n* (%)	14 (40.0)	11 (68.8)	.075
Fine motor, mean ± SD	73.0 ± 8.6	70.3 ± 5.7	.19
Score < 70, *n* (%)	19 (54.3)	10 (62.5)	.76
VABS			
Communication, mean ± SD	76.5 ± 10.2	79.1 ± 15.3	.55
Score < 70, *n* (%)	12 (34.3)	4 (25.0)	.75
Daily living, mean ± SD	72.7 ± 11.2	74.6 ± 11.9	.61
Score < 70, *n* (%)	14 (40.0)	6 (37.5)	.99
Socialization, mean ± SD	75.2 ± 11.1	78.1 ± 14.9	.49
Score < 70, *n* (%)	9 (25.7)	5 (31.3)	.74
Motor, mean ± SD	74.6 ± 11.4	69.8 ± 1.6	.17
Score < 70, *n* (%)	14 (40.0)	7 (43.8)	.99
CBCL, *n* (%)			
Internalizing	12 (34.3)	3 (18.8)	.37
Externalizing	4 (11.4)	2 (12.5)	.99
M-CHAT abnormal, *n* (%)	13 (37.1)	5 (31.3)	.76
SCQ abnormal ($n = 15, 7$), *n* (%)	5 (33.3)	1 (14.3)	.62

and bilateral CHI), differences in outcomes detected in univariate analysis remained statistically significant after controlling for gender and birth weight.

DISCUSSION

In this study, we showed that preterm infants with CHI are at significantly increased risk for subsequent neurodevelopmental disabilities when compared with preterm infants in the control group. However, the most striking finding of this study is the particular prominence of dysfunction in nonmotor domains, specifically the high prevalence of significant deficits in cognition, communication (both receptive and expressive), and social-behavioral function. Moreover, our data show that the prevalence of sequelae after CHI was not dependent on the presence of associated SPI. Although the severity of motor impairment was greater in infants with combined CHI/SPI, the cognitive, language, and social sequelae were no worse in infants with combined CHI/SPI than in infants with isolated CHI.

In this study, premature infants were diagnosed with cerebellar injury in the neonatal period using cranial ultrasound through a mastoid approach to the posterior fossa.[44] In all cases, the presence of cerebellar injury by cranial ultrasound was confirmed by subsequent MRI studies, which were also used to delineate the precise topography of cerebellar injury, to identify associated cerebral injury, and to exclude as well as possible brain injury in age-matched controls. To our knowledge, this is the first large-sample case-control study in which CHI was identified by focused posterior fossa ultrasound views, confirmed and delineated by MRI, and in which the neurodevelopmental outcome of survivors was examined by a wide spectrum of standardized neurodevelopmental, functional, behavioral, and social measures.

The cerebellum has long been known to play a central role in the coordination of movement. However, more recent studies in adults and older children have suggested an important role for the cerebellum in the development of language, cognitive, and social function, thereby calling for a broader investigation of the functional consequences of cerebellar pathology.[22–25] In children with cerebellar tumors, severe disturbances in language (eg, mutism, dysarthria) and visual-spatial function, as well as personality regression with emotional lability, have been described.[26–29] Interestingly, over 90% of neuropathological studies in persons with autism have shown well-defined cerebellar anatomic abnormalities, particularly hypoplasia of selective vermian lobules.[45–48] Furthermore, quantitative and functional MRI studies have recently corroborated these pathologic findings in autistic children.[45,49]

Despite this radical revision of the "conventional wisdom" regarding cerebellar function, there are very limited data regarding the overall neurodevelopmental outcome of survivors of preterm CHI. Existing reports have described a selected subgroup of ex-preterm infants with an extensive and symmetric form of cerebellar injury that is invariably associated with pontine hypoplasia and supratentorial parenchymal injury.[4,6,13] These infants demonstrated a high prevalence of profound neurologic impairment including microcephaly, spastic quadriplegia, dystonia, ataxia, and seizures. However, these studies have been limited by the use of small samples, widely distributed age ranges at testing, and the lack of standardized assessments. Combining the superior spatial resolution of MRI with a comprehensive battery of neurodevelopmental outcome measures has allowed us to begin to describe the structure-function relationship of CHI over a broad topographic spectrum of cerebellar injury and functional outcome. Overall, these CHI lesions ranged from a more prevalent and milder form that is primarily focal and unilateral, to a less common but more diffuse bihemispheric and vermian injury. Bihemispheric CHI ranged from partial inferomedial injury to near-total destruction of the cerebellum, similar to that previously described.[5,6] Our outcome data show that long-term neurodevelopmental, functional, and social behavioral deficits are significantly higher in preterm infants with isolated CHI compared with age-matched controls. Importantly, we show that the cognitive and social-behavioral disturbances associated with isolated CHI are not exacerbated in infants with additional cerebral injury, although neuromotor impairment is worse in the latter group. These findings support our hypothesis that cerebellar injury in premature infants plays an important role in the high prevalence of nonmotor deficits described in survivors of prematurity. Furthermore, we demonstrate in our cohort a high rate of positive tests on initial screening for autism spectrum disorders. It is also noteworthy that global pervasive developmental deficits were far more common in preterm infants with injury to the vermis ($P < .001$).

The precise pathophysiology of CHI in the preterm infant remains unknown; both primary hemorrhage into the germinal matrices of the cerebellum and vaso-occlusive hemorrhagic infarction have been proposed.[6,13] Regardless of the underlying mechanism(s) of CHI, we and others have described a clear relationship between cerebellar lesions identified early in preterm life and impairment of subsequent cerebellar growth using quantitative MRI studies. In previous work, we demonstrated that cerebellar development is particularly rapid during the third trimester, and that the cerebellum in premature infants is particularly vulnerable to disturbed development during this critical period.[3] Furthermore, we have shown that unilateral cerebellar injury in premature infants is associated with subsequent impaired development of the contralateral cerebral hemisphere, possibly because of trophic withdrawal in cerebral projection areas of the developing cerebellum.[1] The role of these remote supratentorial effects in the subsequent

structural and functional neurologic development of these infants is an exciting area of ongoing research.

We have discussed the strengths of our study above. However, there are several limitations of this study that warrant mention. First, we used a retrospective design and examined the neurodevelopmental outcome of these children at a relatively young age. Because we recognize that some neurodevelopmental disabilities may be transient whereas others continue to evolve, longitudinal follow-up studies are planned to establish whether these deficits are enduring. These studies are underway. Second, although we used directed posterior fossa cranial ultrasound views for our case detection, it is possible that smaller cerebellar lesions were missed by ultrasound and that our study did not capture the mildest forms of CHI. Similarly, it is possible that more subtle forms of supratentorial parenchymal injury (particularly in the cerebral white matter) may have gone undetected. Finally, although the apparent association between CHI and autism spectrum risk is of great interest, the tests for autism risk were screening tools, and data from more specific and diagnostic testing instruments are required to confirm this association. These studies are in progress.

CONCLUSIONS

We report that CHI in premature infants is associated with significant risk for adverse neurodevelopmental sequelae, a finding that is currently underappreciated in the clinical setting. We have also begun to delineate the structure-function relationship between the topography of cerebellar injury and subsequent neurodevelopmental profiles. Based on our findings, we postulate that cerebellar injury in premature infants may play an important and underrecognized role in the high prevalence of long-term cognitive, learning, and behavioral dysfunction known to affect survivors of preterm birth. The findings of this study underscore the importance of diagnosing CHI with the increasingly sensitive imaging techniques now available. Specifically, we believe that our results justify the inclusion of posterior fossa views as part of routine clinical ultrasound studies in premature infants with follow-up MRI to evaluate subsequent cerebellar growth and development. Given the major and pervasive impact of CHI in preterm infants, early identification of cerebellar injury by these imaging techniques would facilitate timely, focused, and comprehensive interventions aimed at minimizing these sequelae.

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REFERENCES

1. Limperopoulos C, Soul JS, Haidar H, et al. Impaired trophic interactions between the cerebellum and the cerebrum among preterm infants. *Pediatrics.* 2005;116:844–850
2. Limperopoulos C, Benson CB, Bassan H, et al. Cerebellar hemorrhage in the preterm infant: ultrasonographic findings and risk factors. *Pediatrics.* 2005;116:717–724
3. Limperopoulos C, Soul JS, Gauvreau K, et al. Late gestation cerebellar growth is rapid and impeded by premature birth. *Pediatrics.* 2005;115:688–695
4. Bodensteiner JB, Johnsen SD. Cerebellar injury in the extremely premature infant: newly recognized but relatively common outcome. *J Child Neurol.* 2005;20:139–142
5. Messerschmidt A, Brugger PC, Boltshauser E, et al. Disruption of cerebellar development: potential complication of extreme prematurity. *AJNR Am J Neuroradiol.* 2005;26:1659–1667
6. Johnsen SD, Bodensteiner JB, Lotze TE. Frequency and nature of cerebellar injury in the extremely premature survivor with cerebral palsy. *J Child Neurol.* 2005;20:60–64
7. Mercuri E, Atkinson J, Braddick O, et al. Basal ganglia damage and impaired visual function in the newborn infant. *Arch Dis Child Fetal Neonatal Ed.* 1997;77:F111–F114
8. Merrill JD, Piecuch RE, Fell SC, Barkovich AJ, Goldstein RB. A new pattern of cerebellar hemorrhages in preterm infants. *Pediatrics.* 1998;102(6). Available at: www.pediatrics.org/cgi/content/full/102/6/e62
9. Miall LS, Cornette LG, Tanner SF, Arthur RJ, Levene MI. Posterior fossa abnormalities seen on magnetic resonance brain imaging in a cohort of newborn infants. *J Perinatol.* 2003;23:396–403
10. Marlow N, Wolke D, Bracewell MA, Samara M. Neurologic and developmental disability at 6 years of age after extremely preterm birth. *N Engl J Med.* 2005;352:9–19
11. Markestad T, Kaaresen PI, Ronnestad A, et al. Early death, morbidity, and need of treatment among extremely premature infants. *Pediatrics.* 2005;115:1289–1298
12. Williamson WD, Percy AK, Fishman MA, et al. Cerebellar hemorrhage in the term neonate: developmental and neurologic outcome. *Pediatr Neurol.* 1985;1:356–360
13. Johnsen SD, Tarby TJ, Lewis KS, Bird R, Prenger E. Cerebellar infarction: an unrecognized complication of very low birthweight. *J Child Neurol.* 2002;17:320–324
14. Hagberg B, Hagberg G, Beckung E, Uvebrant P. Changing panorama of cerebral palsy in Sweden. VIII. Prevalence and origin in the birth year period 1991–94. *Acta Paediatr.* 2001;90:271–277
15. Weber C, Weninger M, Klebermass K, et al. Mortality and morbidity in extremely preterm infants (22 to 26 weeks of gestation): Austria 1999–2001. *Wien Klin Wochenschr.* 2005;117:740–746
16. Mikkola K, Ritari N, Tommiska V, et al. Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996–1997. *Pediatrics.* 2005;116:1391–1400
17. Hintz SR, Kendrick DE, Vohr BR, Poole WK, Higgins RD. Changes in neurodevelopmental outcomes at 18 to 22 months' corrected age among infants of less than 25 weeks' gestational age born in 1993–1999. *Pediatrics.* 2005;115:1645–1651
18. Aylward GP. Cognitive and neuropsychological outcomes: more than IQ scores. *Ment Retard Dev Disabil Res Rev.* 2002;8:234–240
19. Hack M, Flannery DJ, Schluchter M, Cartar L, Borawski E,

Klein N. Outcomes in young adulthood for very-low-birth-weight infants. *N Engl J Med.* 2002;346:149–157
20. Wood NS, Costeloe K, Gibson AT, Hennessy EM, Marlow N, Wilkinson AR. The EPICure study: associations and antecedents of neurological and developmental disability at 30 months of age following extremely preterm birth. *Arch Dis Child Fetal Neonatal Ed.* 2005;90:F134–F140
21. Tyson JE, Saigal S. Outcomes for extremely low-birth-weight infants: disappointing news. *JAMA.* 2005;294:371–373
22. Schmahmann JD. Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. *J Neuropsychiatry Clin Neurosci.* 2004;16:367–378
23. Riva D, Giorgi C. The cerebellum contributes to higher functions during development: evidence from a series of children surgically treated for posterior fossa tumours. *Brain.* 2000;123:1051–1061
24. Riva D, Giorgi C. The contribution of the cerebellum to mental and social functions in developmental age. *Fiziol Cheloveka.* 2000;26:27–31
25. Leiner HC, Leiner AL, Dow RS. Cognitive and language functions of the human cerebellum. *Trends Neurosci.* 1993;16:444–447
26. Levisohn L, Cronin-Golomb A, Schmahmann JD. Neuropsychological consequences of cerebellar tumour resection in children: cerebellar cognitive affective syndrome in a paediatric population. *Brain.* 2000;123:1041–1050
27. Beebe DW, Ris MD, Armstrong FD, et al. Cognitive and adaptive outcome in low-grade pediatric cerebellar astrocytomas: evidence of diminished cognitive and adaptive functioning in National Collaborative Research Studies (CCG 9891/POG 9130). *J Clin Oncol.* 2005;23:5198–5204
28. Nagel BJ, Delis DC, Palmer SL, Reeves C, Gajjar A, Mulhern RK. Early patterns of verbal memory impairment in children treated for medulloblastoma. *Neuropsychology.* 2006;20:105–112
29. Robertson PL, Muraszko KM, Holmes EJ, et al. Incidence and severity of postoperative cerebellar mutism syndrome in children with medulloblastoma: a prospective study by the Children's Oncology Group. *J Neurosurg.* 2006;105:444–451
30. Huppi PS, Murphy B, Maier SE, et al. Microstructural brain development after perinatal cerebral white matter injury assessed by diffusion tensor magnetic resonance imaging. *Pediatrics.* 2001;107:455–460
31. Thompson DK, Warfield SK, Carlin JB, et al. Perinatal risk factors altering regional brain structure in the preterm infant. *Brain.* 2007;130:667–677
32. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *N Engl J Med.* 2006;355:685–94
33. Huppi PS, Warfield S, Kikinis R, et al. Quantitative magnetic resonance imaging of brain development in premature and mature newborns. *Ann Neurol.* 1998;43:224–235
34. Volpe JJ. Cerebral white matter injury of the premature infant: more common than you think. *Pediatrics.* 2003;112:176–180
35. Maalouf EF, Duggan PJ, Counsell SJ, et al. Comparison of findings on cranial ultrasound and magnetic resonance imaging in preterm infants. *Pediatrics.* 2001;107:719–727
36. Volpe JJ. Neurobiology of periventricular leukomalacia in the premature infant. *Pediatr Res.* 2001;50:553–562
37. Mullen EM. *Mullen Scales of Early Learning (AGS Edition)*. Circle Pines, MN: American Guidance Service; 1995
38. Folio RM, Fewell RR. *Peabody Developmental Motor Scales and Activity Cards*. Austin, TX: DLM Teaching Resources; 1983
39. Sparrow S, Balla D, Cicchetti D. *Vineland Adaptive Behavior Scales (Interview Edition) Survey Form Manual: A Revision of the Vineland Social Maturity Scale*. Circle Pines, MN: American Guidance Service; 1984
40. Achenbach TM, Rescorla L. Manual for the Child Behavior Checklist. *Preschool Forms and Profiles*. Burlington VT: University of Vermont Department of Psychiatry; 2000
41. Robins DL, Fein D, Barton ML, Green JA. The Modified Checklist for Autism in Toddlers: an initial study investigating the early detection of autism and pervasive developmental disorders. *J Autism Dev Disord.* 2001;31:131–144
42. Berument SK, Rutter M, Lord C, Pickles A, Bailey A. Autism screening questionnaire: diagnostic validity. *Br J Psychiatry.* 1999;175:444–451
43. Hollingshead AB. *Four Factor Index of Social Status*. New Haven, CT: Yale Station; 1965
44. Di Salvo DN. A new view of the neonatal brain: clinical utility of supplemental neurologic US imaging windows. *Radiographics.* 2001;21:943–955
45. Courchesne E, Yeung-Courchesne R, Press GA, Hesselink JR, Jernigan TL. Hypoplasia of cerebellar vermal lobules VI and VII in autism. *N Engl J Med.* 1988;318:1349–1354
46. Bauman M, Kemper TL. Histoanatomic observations of the brain in early infantile autism. *Neurology.* 1985;35:866–874
47. Bauman ML, Kemper TL. Neuroanatomic observations of the brain in autism: a review and future directions. *Int J Dev Neurosci.* 2005;23:183–187
48. Beversdorf DQ, Manning SE, Hillier A, et al. Timing of prenatal stressors and autism. *J Autism Dev Disord.* 2005;35:471–478
49. Courchesne E. Abnormal early brain development in autism. *Mol Psychiatry.* 2002;7(suppl 2):S21–S23

Does Cerebellar Injury in Premature Infants Contribute to the High Prevalence of Long-term Cognitive, Learning, and Behavioral Disability in Survivors?

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