Cerebellar Hemorrhage in Extremely Low Birth Weight Infants: Incidence, Risk Factors, and Impact on Long-Term Outcomes

Patricia Maddalena, RN, MHSc, NNP
Sharyn Gibbins, RN, PhD, NNP

Abstract

Improvements in neuroimaging technology and techniques have contributed to the increased recognition of cerebellar hemorrhage (CBH) in the preterm infant. Studies have indicated that the extremely low birth weight (ELBW) infant (<1,000 g) is at highest risk for this injury. Associated risk factors include a constellation of antenatal, intrapartum, and neonatal factors, with immaturity, fetal distress, and cardiorespiratory instability in the early neonatal course as significant contributors. The long-term impact of CBH for the ELBW infant is not fully understood, but recent reports suggest that, in addition to motor impairments, deficits in cognitive, language, and social-behavioral function are also apparent. This article reviews the current state of knowledge of cerebellar development, risk factors for injury, and long-term developmental consequences of injury. Implications for nursing practice, education, and research are discussed.

THE ADVENT AND IMPROVEMENT OF NEUROIMAGING technology and techniques in magnetic resonance imaging (MRI) and cranial ultrasound (CUS) images of the hindbrain with improved transducer head size and frequencies have contributed to increased recognition of cerebellar injury in the preterm infant.[1] During the third trimester, the cerebellum undergoes rapid growth; consequently, infants born before or during the third trimester are particularly susceptible to cerebellar injury. Articles published in the past few years suggest that the extremely low birth weight (ELBW) infant (<1,000 g) is at highest risk for cerebellar hemorrhage (CBH).[1–3] Knowledge of risk factors for this type of injury and its impact on long-term development is currently limited but steadily increasing. This growing body of knowledge suggests that injury to the cerebellum may have significant impact on motor, language, cognition, and social-behavioral functions for the ELBW infant.[1] This article provides an overview of cerebellar development and the factors that contribute to CBH. Nursing implications and directions for future research are discussed. Descriptive terms for structures within the central nervous system are defined in the glossary. (See: Glossary of Terms).

CEREBELLAR DEVELOPMENT

The cerebellum is located within the hindbrain. The hindbrain is separated from the forebrain and midbrain by the *tentorium*. The cerebellum is dorsal to the pons and inferior to the occipital lobe of the cerebral cortex. It is grossly divided into two hemispheres, with the cerebellar *vermis* located between the hemispheres (Figures 1 and 2).

An understanding of the timing of cerebellar development provides some insights into the impact of disruptions that may occur as a result of preterm birth. Cerebellar development begins during the embryonic stage of fetal development (weeks 4 to 8 of gestation) and continues well into childhood. It is this prolonged time course of development that makes the cerebellum particularly vulnerable to a variety of insults including preterm birth.[3–6]

During the embryonic stage of human development, the brain forms in three segments: the prosencephalon, the

Accepted for publication February 2008. Revised April 2008.

Glossary of Terms

Germinal matrix: A highly cellular and highly vascular structure in the brain from which nerve cells proliferate and migrate during fetal development. The capillary network of the germinal matrix is very fragile and prone to bleeding. Involution of the germinal matrix occurs by 36 weeks gestation.

Infratentorial: Having to do with the infratentorium, posterior fossa, or hindbrain.

Infratentorium: *See* **Posterior fossa**.

Neuroepithelium: A cell-dense, proliferative matrix that lines the ventricular system of the developing brain and spinal cord. The neuroepithelium is the precursor to the germinal matrices.

Periventricular hemorrhagic venous infarction (PVHI): A hemorrhagic lesion usually found ipsilateral to a large IVH. Compression of the terminal vein draining the periventricular white matter results in hemorrhagic venous infarction. This lesion is usually unilateral and asymmetric.

Periventricular leukomalacia (PVL): A nonhemorrhagic, cystic area in the periventricular white matter. These lesions are usually small, multiple, bilateral, and fairly symmetric.

Posterior fossa: Structures include the cerebellar hemispheres and the vermis, the tentorium, the cisterna magna, and the fourth ventricle. The posterior fossa is also referred to as the hindbrain or infratentorium.

Spinocerebellar tract: A set of axonal fibers originating in the spinal cord and ending in the ipsilateral cerebellum that transmits information about joint and limb position (also known as proprioception).

Subependymal germinal matrix: Germinal matrices in the third, fourth, and both lateral ventricles that are located beneath the ependymal lining of the ventricles. The most commonly reported subependymal germinal matrix hemorrhages are those within the lateral ventricles; they are also referred to as Grade I IVHs. The extension of the hemorrhage into the lateral ventricles is a Grade II IVH.

Subpial germinal matrix: The external granular layer of the cerebellum.

Supratentorial: Having to do with parts of the brain that are above the tentorium.

Supratentorial parenchymal injury (SPI): Periventricular leukomalacia (PVL) and periventricular hemorrhagic infarction (PVHI).

Supratentorium: Parts of the brain that are above the tentorium (cerebral hemispheres).

Tentorium: Extension of the dura mater that separates the cerebrum and the cerebellum.

Vermis: A wormlike structure located midline between the hemispheres of the cerebellum that receives information from the spinal cord about touch and proprioception.

mesencephalon, and the rhombencephalon. The cerebellum develops from the rhombencephalon, which is the most caudal segment of the embryonic brain. The basic structure of the cerebellum is established by the eighth week of gestation.[6] Further development of the cerebellum evolves from a primary and a secondary *neuroepithelium*, both of which give rise to *germinal matrices*, which are active sites of neuronal proliferation. The primary neuroepithelium is located adjacent to the fourth ventricle (see Figure 2). This gives rise to the *subependymal germinal matrix* of the fourth ventricle. Between 8 and 13 weeks gestation, cells migrate from the primary neuroepithelium in two directions to form the deep cerebellar nuclei and the Purkinje cell layer.

From approximately 12 weeks of gestation, a second stage of neuronal migration occurs over the subpial surface of the developing cerebellum. This migration forms the secondary neuroepithelium, or external granular layer, also known as the *subpial germinal matrix*. From there, neurons migrate inward to form the internal granular cell layer. This process continues until 15 months postnatal age, at which point the subpial germinal matrix disappears. Accelerated growth of the cerebellar vermis occurs during the third month of gestation and is complete by 18 weeks gestation. Further development of the cerebellum continues by five discrete but overlapping processes: neuronal proliferation, neuronal migration and differentiation, formation of synapses, organization, and myelinization.[7,8]

Although the processes of cerebellar development begin early in gestation and continue well into childhood, these processes accelerate from 28 weeks gestation to term. Limperopolous and colleagues compared the MRI findings of preterm and term infants. Fifty-one of the preterm infants had MRI studies at a mean age of 32.8 weeks (± 2.6 weeks) and again at term equivalent age. Mean cerebellar volume and mean intracranial volume measurements were taken at both time points. The results demonstrated that, from 28 weeks to term, the cerebellum grows proportionally faster than the other brain structures. In addition, the cerebellar volumes of the preterm infants at term equivalent age, even in the absence of direct cerebellar injury, were significantly smaller than those of infants born at term gestation ($p<.001$).[5] This finding suggests that prematurity alters the normal development of cerebellar structures, which may have long-term implications.

ROLE OF THE CEREBELLUM

The cerebellum is known to play a major role in the integration of sensory perception and motor control. A number of neural pathways connect the cerebral motor cortex, the cerebellum, and the *spinocerebellar tract*. Studies in adults and older children have suggested that, in addition to coordination of motor functions, the cerebellum may play a broader role in facilitating adaptive behavior and mechanisms that affect a variety of motor and nonmotor skills.[9,10]

Schmahmann and Sherman performed a number of neuroimaging and neurocognitive assessments on a cohort of 20 adults with injury isolated to the cerebellum. They coined the term "cerebellar cognitive affective syndrome" to describe the constellation of deficits seen in the study population. Cerebellar cognitive affective syndrome is characterized by disturbances of executive function including abstract reasoning and working memory, impaired visuospatial cognition and memory, linguistic difficulties, and personality changes including blunting or flattening of affect and inappropriate behavior. The net effect of cerebellar cognitive affective syndrome was an overall lowering of intellectual function. The authors concluded that the array of deficits suggests a "disruption of the cerebellar modulation of neural circuits that link prefrontal, posterior parietal, superior temporal and limbic cortices with the cerebellum" (p. 561).[11]

PATHOPHYSIOLOGY OF CEREBELLAR INJURY

Injury to the cerebellum can be a direct result of hemorrhage or infarction. Distinguishing cerebellar venous infarction from CBH is difficult, even with microscopic examination.[8] However, the signal characteristics of both types of lesions using the current neuroimaging techniques and technologies suggest a major hemorrhagic element.[1] Although the precise mechanisms of injury have not been fully delineated for the preterm infant, and in particular the ELBW infant, CBH is felt to result from immaturity and/or instability of a number of extravascular, vascular, and intravascular factors. The pathogenic mechanisms of CBH are similar to those of intraventricular hemorrhage (IVH) in the preterm infant. Essentially, the pressure-passive cerebral and cerebellar circulation (intravascular factor) exposes the rich but immature capillary beds of the subependymal and subpial germinal matrices (vascular factor) to both hypo- and hypertensive fluctuations in arterial pressure and potentially leads to rupture. In the ELBW infant, the likelihood of rupture of the immature capillary network is amplified by the poorly supported subpial germinal matrix (extravascular factor).[8]

Cerebellar atrophy has also been noted as a consequence of premature birth.[12,13] Atrophy may result from direct injury (hemorrhage) or arrested development, or it may occur secondary to the effect of damage in a distant but connected part of the brain (called "diaschisis" and discussed below). A study by Messerschmidt and associates demonstrates the concept of arrested development as the cause of cerebellar atrophy. This study reported decreased cerebellar volumes on MRI studies performed between the second month and sixth year of life on a cohort of 28 infants. All infants were born between 24 and 30 weeks gestational age. Initial CUS reported no posterior fossa abnormalities, although the ultrasound technique was not described. All infants had some degree of *supratentorial* injury and demonstrated bilateral and symmetric reduction in cerebellar volumes. Because this phenomenon is not observed in infants born after 32 weeks gestation, the authors postulated that the reduced cerebellar volumes may have resulted from a disruption in the rapid developmental processes of the cerebellum between 24 and 32 weeks gestation, leading to an arrest in its growth and development.[5]

Crossed cerebellar diaschisis has also been reported as a cause of cerebellar atrophy. Diaschisis is a phenomenon that results in a loss of or decrease in metabolic activity in a portion of the brain that is distant from the site of injury but neuronally connected to it. Crossed cerebellar diaschisis is observed following a supratentorial lesion as a decrease in blood flow to and metabolism in the contralateral cerebellar hemisphere. Limperopolous and coworkers demonstrated a "significant crossed trophic effect between the developing cerebral and cerebellar structures among preterm infants" (p. 847).[4] The investigators reviewed MRI studies performed at term gestational age equivalent for 74 preterm

FIGURE 1 ■ Location of the hindbrain and the cerebellum.

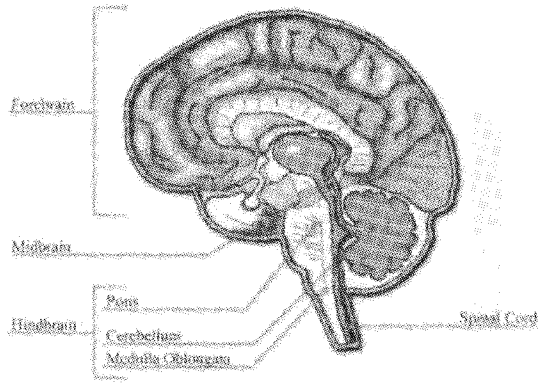
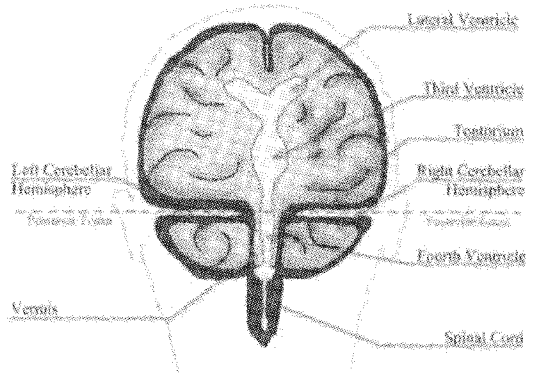


FIGURE 2 ■ Location of the ventricular system.



infants. There were no significant differences in birth weight or gestational age among the infants. All were born at <30 weeks gestation and weighed <1,500 g. Thirty infants had normal MRI studies, 20 had diffuse *periventricular leukomalacia (PVL)*, 14 had *periventricular venous hemorrhagic infarction (PVHI)*, and 10 had CBH. No infants had combined direct injury to both the cerebrum and the cerebellum. Overall, infants with injury to the cerebrum or to the cerebellum had significantly reduced total cerebral volumes ($p<.01$) and total cerebellar volumes ($p<.001$) compared to infants with normal MRI studies. A direct relationship between unilateral cerebral injury and reduced volume of the contralateral cerebellar hemisphere was demonstrated. Additionally, infants with bilateral injury to the cerebral hemispheres showed bilateral decreases in cerebellar volumes. Interestingly, the reverse situation was also demonstrated; unilateral CBH was associated with a decrease in the contralateral cerebral hemisphere, and bilateral CBH was associated with a bilateral reduction in cerebral volumes.[6] This study highlights the important interactions that occur during development between the cerebrum and the cerebellum and may provide further insights into the constellation of cognitive, motor, and behavioral morbidities associated with prematurity.

NEUROIMAGING TECHNIQUES

The incidence of cerebellar injury is likely underreported with the use of conventional CUS techniques. The traditional technique involves imaging via the anterior fontanel and is useful for identifying abnormalities involving the supratentorial anatomy but has limited use in detecting abnormalities inferior to the tentorium. Images of the posterior fossa (infratentorial) structures, which include the cerebellum, are suboptimal with the use of the anterior fontanel views, primarily because of the long distance between the cerebellum and the ultrasound probe as well as the presence of the highly echogenic tentorium.[14,15]

Advances in CUS technology, including transducer head size and available frequencies, as well as increased experience using the posterolateral fontanel view, have enhanced visualization of structures in the posterior fossa. Imaging via the posterolateral fontanel provides improved visualization of the brainstem, subarachnoid cisterns, and cerebellum and improves detection of hemorrhage into these structures, as well as Dandy-Walker variants. The posterolateral fontanel, also known as the mastoid fontanel, is located at the junction of the lambdoidal, occipital, and squamosal sutures (Figure 3). Since the mid-1990s, many NICUs have incorporated images via this fontanel into routine cranial ultrasonography.[14,16] Merrill and colleagues reported a more-than-sixfold increase in identification of posterior fossa hemorrhage after implementation of routine imaging via the posterolateral fontanel compared with previous use of the anterior fontanel only.[15] Figure 4 depicts CBH as seen on CUS using the posterolateral fontanel view.

Although CUS is both practical and noninvasive, MRI provides more detailed anatomic and volumetric information for most brain lesions.[17] Despite this fact, there are still several advantages to performing high-quality CUS. CUS is much less expensive than MRI and can be repeated frequently to follow the progression of cerebral or cerebellar lesions. It can be performed at the bedside and usually takes only 10–15 minutes. MRI is expensive and more disruptive to the care of the infant. The infant may require sedation to obtain good-quality images. MRI requires transfer to another location or unit and takes 30 minutes or more to complete. Usually only one or two MRI studies are performed during an infant's NICU stay. Use of a combined approach, with CUS employed early in the course of stay followed by MRI closer to term, is becoming more common. Further development of neuroimaging techniques as well as timing of application of these techniques are required.[17]

CEREBELLAR HEMORRHAGE AND INJURY: INCIDENCE AND TYPE

The true incidence of CBH is difficult to estimate because it has been underdiagnosed and overlooked as a complication of premature birth.[8] Historically, autopsy studies have reported an incidence of between 10 percent and 25 percent in very low birth weight (VLBW) infants.[18] More recent studies suggest a lower overall incidence, but these reports may be affected by selection biases and imaging techniques. Miall and associates reviewed a cohort of 558 preterm (<36 weeks gestation) and term infants who underwent MRI during a five-year period (1996–2001). The overall incidence of posterior fossa abnormalities was reported as 3.6 percent; however, the report did not specify the incidence in the preterm population. For the term infant, abnormalities of the posterior fossa included predominately subarachnoid hemorrhage and were associated with hypoxic-ischemic encephalopathy, structural abnormalities of the central nervous system, and metabolic disorders. Mortality rates were 40 percent for the term cohort. Of the 10 preterm infants with posterior fossa abnormalities, 80 percent were <30 weeks gestational age at birth and were treated for a number of complications secondary to prematurity. All demonstrated some degree of intracerebellar hemorrhage, and 75 percent also demonstrated supratentorial abnormalities. The remaining 2 infants, born at 34 and 36 weeks gestation, were both diagnosed with cardiac abnormalities and were found to have decreased cerebellar size as well as associated supratentorial abnormalities. The mortality rate for the preterm cohort was zero. This study did not include a control group, and the results may have been influenced by selection bias because many of the infants had clinical or ultrasonographic evidence of neurologic abnormalities.[19]

Perhaps the most comprehensive study to date that reported incidence of and risk factors for CBH in the preterm population was conducted by Limperopolous and coworkers. This was a retrospective case-control study of VLBW

infants (<1,500 g) born between January 1998 and December 2002 at one U.S. tertiary care center. During the study period, 1,242 infants were identified, of whom 35 were diagnosed with CBH by CUS. This study used a CUS protocol that included a view of the posterior fossa. Each of the 35 infants with CBH was matched with two control infants on the basis of sex, year of birth, and gestational age at birth. The matched control group had normal cranial ultrasounds throughout their course of stay in the NICU. Over the five-year period, the incidence of CBH by birth weight category was as follows: <750 g: 8.7 percent; 750–999 g: 0.7 percent; 1,000–1,499 g: 2.7 percent. This demonstrates a statistically significant increase in CBH for infants <750 g compared with more mature infants ($p<.001$). Interestingly, this study also demonstrated an increasing incidence of CBH by approximately 44 percent per year over the five-year period. This increase could have resulted largely from the increased number of preterm infants with birth weights <750 g and the increased detection of CBH as a result of improved neuroimaging techniques over the study period.[2]

Limperopolous and colleagues also noted that CBH was identified later than IVH or PVHI. On average, CBH was identified at a mean age of 5.2 days, whereas IVH and PVHI were identified at a mean age of 1.7 days. Because this was a retrospective study, the timing of CUS was based on unit protocol, with additional ultrasounds based on clinical decision making; it was therefore difficult to ascertain the exact timing of the CBH. It may be that supratentorial lesions precede the onset of CBH, but further studies are needed to determine this. It is also interesting to note that infants with birth weights between 750 and 999 g (who represented 48 percent of the total sample) were less likely to have CBH than were those with birth weights between 1,000 and 1,499 g. Severity of illness might have accounted for the difference in the incidence of CBH between the two groups, although this was not reported in the study.[2]

Historical reports describing the location and extent of CBH have been inconsistent.[18,19] The study by Limperopolous and colleagues reported that unilateral CBH occurs more frequently (almost twofold higher) in the right hemisphere than in the left. Hemorrhage involving the vermis occurred in 29 percent of cases, although bilateral CBH also involving the vermis was relatively uncommon, occurring in 3 (9 percent) of the 35 cases. This study also reported on the association between CBH and other brain lesions. Isolated CBH occurred in 23 percent of the cases; there was associated supratentorial bleeding in 77 percent of cases and infratentorial extra-axial blood in 57 percent of cases.[2] In the past, CBH was reported to be associated with massive supratentorial hemorrhage.[18,20] However, current findings suggest otherwise. The study by Limperopolous and colleagues reported that, of the 27 infants with CBH and associated supratentorial hemorrhage, the incidence of lesser hemorrhage (Grades I and II) versus more significant hemorrhage (Grade III, PVHI) was fairly equal (44 percent versus 52 percent, respectively). One infant in the cohort had PVL.[2] Although the studies to date provide some insight into the incidence and type of CBH, more research is needed to confirm these findings.

FIGURE 3 ■ Location of the posterolateral, or mastoid, fontanel.

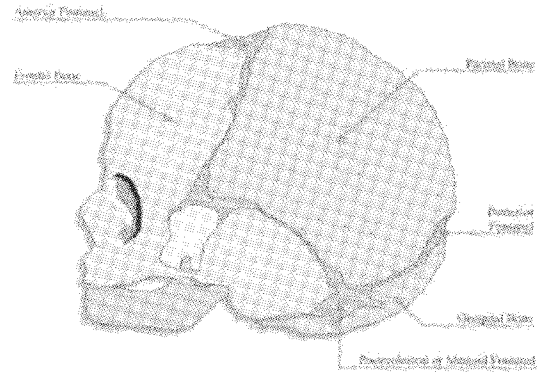


FIGURE 4 ■ CUS depicting CBH using posterolateral fontanel view.

A 24-week-gestation infant on day 9 of life with a left CBH as noted by CUS using the posterolateral fontanel view. This infant did not have a traumatic birth but did demonstrate cardiorespiratory instability during the first ten days of life, requiring high-frequency jet ventilation and inotropic support to maintain blood pressure.

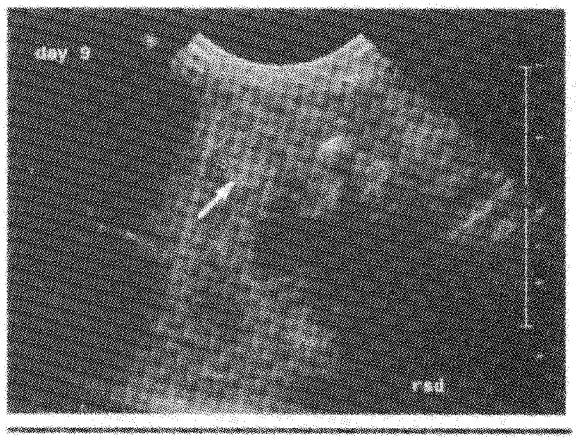


TABLE 1 ■ Risk Factors Associated and Not Associated with Cerebellar Hemorrhage

Category	Associated	Not Associated
Maternal factors	Assisted conception	Pregnancy-induced hypertension
		Antenatal infections
		Chorioamnionitis
		Prenatal abnormal fetal heart rate
Intrapartum factors	Abnormal fetal heart rate	Maternal fever
	Emergent cesarean section ($p = .002$)	Vaginal bleeding
	Lower 1-minute Apgar score	Vaginal delivery
	Lower 5-minute Apgar score	Respiratory resuscitation (including intubation)
		Cardiac compressions
		Medication for resuscitation
Early postnatal factors	High-frequency ventilation	Surfactant
	Pressor support	Reintubation
	Volume expanders	Pneumothorax
	Patent ductus arteriosus ($p<.001$)	Infection
	Pulmonary hemorrhage	5-day maximum PCO_2
	5-day minimum pH ($p<.001$)	5-day minimum PO_2
	5-day minimum plasma bicarbonate concentration	
	5-day minimum white blood cell count	
	5-day minimum hematocrit	
	5-day minimum platelet count	

Note: Items printed in **bold type** are identified as independent risk factors.

Adapted from: Limperopoulos, C., Benson, C. B., Bassan, H., DiSalvo, D. N., Kinnamon, D. D., Moore, M., et al. (2005). Cerebellar hemorrhage in the preterm infant: Ultrasonographic findings and risk factors. *Pediatrics, 116,* 717–724.

RISK FACTORS FOR CEREBELLAR HEMORRHAGE

The underlying mechanisms that contribute to CBH are not yet well defined. Historically, intracerebellar hemorrhage has been associated with traumatic delivery[21] and mask continuous positive airway pressure devices with tight-fitting occipital straps used to secure the mask.[22,23] More recent studies suggest a new model for cerebellar injury that may be clinically silent, not associated with traumatic delivery or extensive supratentorial hemorrhage or mortality.[15,19]

Prematurity has been defined as a risk factor for CBH.[2,8,19] As previously noted, the incidence is inversely related to birth weight. The retrospective case-control study by Limperopolous and colleagues suggest a multifactorial array of risk factors (Table 1) that includes maternal, intrapartum, and early postnatal cardiorespiratory instability. Although many risk factors were identified, only three independent risk factors were predictive for CBH: emergent cesarean section, patent ductus arteriosus (PDA), and five-day minimum mean pH (mean 7.11 ± 0.13).[2] This constellation of independent risk factors suggests that fetal distress and hemodynamic compromise during the first five days of life may be important markers for CBH.

These findings have implications for caregivers in the NICU, specifically nurses, who are in an optimal position to monitor infants for changes in status and intervene with supportive care when appropriate. The presence of a large PDA may contribute to poor cerebellar perfusion, and although the mechanisms of action are unclear, they are most likely related to changes in hemodynamic stability. Ongoing nursing assessment for the presence of a PDA and prompt medical and/or surgical management may minimize the risk of CBH; further prospective studies are required to verify this connection. Acidosis that may be associated with fetal distress and cardiorespiratory instability in the first five days of life impairs cerebral autoregulation and leaves the brain vulnerable to hemodynamic fluctuations.[24] The independent risk factors for CBH are also associated with IVH and PVHI.[25,26] These lesions are also highly correlated with CBH.

Early studies of infants with CBH report mortality rates of close to 100 percent.[18,20] These are in direct contrast with more recent studies reporting 100 percent survival to discharge for infants with CBH.[15,19] Limperopolous and colleagues reported a higher mortality rate of 14 percent for infants with CBH versus 1 percent for the control group ($p = .04$). In the short term, morbidity rates were higher for survivors of CBH than for infants in the control group with normal CUS. Infants with CBH were more likely to require longer periods of assisted ventilation ($p < .001$) and supplemental oxygen ($p < .004$), and they were also more likely to require PDA ligation or to develop necrotizing enterocolitis, bronchopulmonary dysplasia, and Stage 3 or greater retinopathy of prematurity.[2]

LONG-TERM OUTCOMES

Preterm birth is associated with a number of neurologic, cognitive, and behavioral deficits. Major deficits increase with decreasing gestational age and include cerebral palsy, blindness, sensorineural hearing loss, and moderate to severe mental retardation.[27–29] IVH and periventricular white matter injury, which includes PVHI and PVL, are reported as major contributors to adverse neurodevelopmental outcomes.[30,31] Although strategies such as the administration of indomethacin have been shown to reduce the incidence of severe IVH, their application has not resulted in improvements in long-term neurocognitive outcomes.[32–34] These data suggest that the presence of an IVH is not the sole factor for poor neurocognitive outcomes and that other types of more subtle or diffuse brain injuries may be involved.[35]

Laptook and coworkers performed developmental assessments on 1,749 ELBW infants (mean ± SD GA: 26 ± 2 weeks; mean ± SD BW: 792 ± 134 g) who had normal

early and late CUS. The investigators reported that 30 percent of these infants had either cerebral palsy or low Mental Developmental Indexes (<70) on the Bayley Scales of Infant Development–II.[36] The rate of major impairments has remained fairly stable over the past decade.[37] But there is growing awareness and concern regarding an increase in the prevalence of attention deficit/hyperactivity disorders, difficulties with self-regulation and inhibition, learning disabilities, impairment of visual motor integration, speech and language deficits, and borderline mental retardation. These deficits are estimated to occur in 50–70 percent of preterm infants, with increasing prevalence among infants of lower gestational age and birth weight, and contribute to an overall decrease in school performance.[27,28] The constellation of deficits seen in the preterm population—and particularly among ELBW individuals—bears striking similarities to the adult "cerebellar cognitive affective syndrome" described by Schmahmann and Sherman.[11] These similarities have resulted in an increasing awareness of and interest in the role of CBH in the long-term developmental outcomes of preterm infants.

Although the impact of CBH on long-term outcome is not yet fully understood, recent studies of preterm infants with CBH have demonstrated significant deficits in cognitive, language, and social-behavioral functions that persist into adolescence, in addition to motor impairments.[5,12,13,38] The major limitation of these studies was the lack of an age-matched preterm control group.

A recent retrospective study reviewed the CUS of all infants born at <32 weeks gestational age from two tertiary level NICUs between 1998 and 2003. Isolated CBH was identified in 35 infants, and combined CBH and *supratentorial parenchymal injury (SPI)* was identified in 16 infants. Each infant with isolated CBH was matched 1:1 with a control infant on the basis of gestational age, sex, and year of birth. All infants in the control group had normal CUS and/or MRI studies during their NICU stay. Formal neurologic assessments and a number of standardized developmental assessments were completed. Infants with isolated CBH had significantly greater impairment in cognitive, motor, language, and social-behavioral measures than those in the control group ($p<.001$ on all measures). Infants with CBH/SPI had worse neuromotor outcomes but no increased impairment in cognitive, language, or social-behavioral measures. In addition, all infants who suffered CBH, and particularly those with injury to the vermis, were noted to have significantly more positive results on autism screening tests than those in the control group ($p<.001$). Although this was a retrospective study with a relatively small sample size ($n = 86$), the results suggest an association between cerebellar injury and a wide range of long-term neonatal morbidities.[1]

NURSING IMPLICATIONS

The pathophysiology of and risk factors for cerebellar injury require further study, but it would seem prudent for care practices to address maternal, intrapartum, and early postnatal cardiorespiratory instability. Astute antenatal monitoring and ongoing communication between obstetric and neonatal staff regarding the hemodynamic stability of the pregnant mother and the fetus are paramount, and prompt delivery is recommended in the event of fetal distress. A collaborative, family-centered approach to the management of high-risk situations begins with obstetric management and continues into the neonatal unit, where developmentally supportive care must be provided. Ensuring that an experienced team is present in the delivery room to provide resuscitation measures and maintenance of a neutral thermal environment to minimize physiologic stress may help to reduce cerebrovascular changes that contribute to the development of CBH.[39]

Additional potentially better practices that could reduce overall brain injury during the intrapartum and early postnatal periods are outlined by McLendon and colleagues. These include appropriate and individualized ventilation strategies, timely and accurate recognition of hypotension, indomethacin prophylaxis for patent ductus arteriosus, facilitation of thermoregulation, and strategies to minimize pain and stress.[39] Appropriate pharmacologic management, as recommended by evidence-based practices such as the Neonatal Resuscitation Program, may also minimize physiologic disturbances surrounding birth and the resuscitation process.[40]

As primary caregivers, nurses are in an optimal position to assess infants' responses to handling, minimize the number of unnecessary procedures performed, and intervene when they observe signs of stress. Irrespective of gestational age, infants demonstrate adverse physiologic (heart rate, oxygen saturation, blood pressure) and behavioral (body movement, facial expression, tone) responses to varying degrees of stimuli.[41–44] It is essential that nurses observe these responses and stop the caregiving activity whenever possible to allow the infant to regain stability. The avoidance of practices such as routine suctioning or weighing should be advocated, and cue-based care should be the norm.

Fetuses as early as 20 weeks gestation have the cortical capacity to interpret varying levels of painful stimuli, but do not have the inhibitory mechanisms to modulate pain impulses.[45] There are reports that infants as immature as 25 weeks gestational age demonstrate this cortical activity in response to stimuli by changes in hemoglobin concentration in the cortex.[46,47] These findings support the need to reduce stimulation—in particular, painful stimulation—to minimize potentially negative changes in cortical activity.

In an attempt to reduce brain injury, neonatal nurses need to minimize environmental stressors such as bright lights, excessive noise, and multiple, painful procedures in the delivery room. The concept of a "developmentally supportive resuscitation" needs to be explored with the health care team so that the philosophy can be exercised with each high-risk delivery. The literature supporting developmental care suggests that it decreases length of hospitalization, improves

weight gain, and improves neurodevelopmental outcomes at 9–12 months.[58] No studies, however, have determined when developmental care should be instituted. It is plausible that implementation of developmental care, defined as minimal environmental stressors and caregiving activities that are tailored to the physiologic and behavioral stability of the infant, from the moment of birth will reduce the likelihood of CBH in high-risk infants.

Because most of the CBHs appear to occur within the first week of life, nursing interventions in the early postnatal period that target the developmental needs of high-risk infants are crucial. Avoiding activities that alter cerebral blood flow in infants with poor autoregulation may reduce the risk of CBH. Management of acute or procedural pain has been shown to reduce physiologic disturbances; therefore, it is essential that neonatal nurses accurately assess pain and advocate for early and appropriate interventions. Other caregiving activities include the avoidance of rapid movement, such as what occurs during transfer from bed to incubator and with diaper changes. Close attention must br paid to symptoms of changes in hemodynamic stability, such as the presence of a PDA or alterations in the pH. Nurses need to continuously assess their patients, communicate their findings to other members of the health care team, intervene where appropriate, and involve families in all decisions that pertain to their infant.

Nurses can prepare parents for many of the routine events, such as CUSs, that occur in the NICU. An understanding of brain anatomy and the rationale for early CUSs will enable nurses to provide clear and concise information to parents. Because posterior views are relatively new, teaching packages that include the rationales for the practice and pictures of the brain anatomy may alleviate some of the stress associated with testing and further promote open and honest communication with families. Nurses can take the lead in identifying parental needs and referring parents to appropriate resources.

If any brain injury has occurred, it may be even more important to optimize developmental care practices, especially given the intricate relationship between cerebral and cerebellar injury and the impact on overall brain development. The overlapping processes of brain development are neuronal proliferation, neuronal migration and differentiation, formation of synapses, and myelinization. The effect of brain injury on these processes is unclear; however, the infant's interaction with the NICU environment shapes the developing central nervous system, suggesting that brain structure and function are intimately connected. Attention to handling and positioning techniques and pain management strategies, as well as reduction of environmental stressors, not only promote better physiologic stability, but may also augment neural maturation.[59]

Nurses also need to address counseling of families of infants with CBH. Although the impact of this injury is emerging as a potentially significant contributor to adverse neurodevelopmental outcomes, especially for the ELBW infant, more studies are required to quantify the nature and extent of CBH effects on this population. The uncertainty with respect to long-term outcomes should be discussed at each center, and outcomes in the literature should be compared with center-specific outcomes for this type of injury. This information should be presented to families in a comprehensive and sensitive manner, recognizing that the uncertainty surrounding the long-term impact of CBH is likely to cause increased stress and anxiety for the family unit. This highlights the need for comprehensive follow-up programs that can not only help clarify the long-term impact of CBH for the ELBW infant, but also provide ongoing support and service to these infants and their families.

FUTURE RESEARCH

There are numerous opportunities for future nursing research with respect to CBH and the ELBW infant. First, more adequately powered, prospective studies are required to precisely define the incidence of and risk factors associated with CBH. Second, neuroimaging techniques and protocols need to be refined to accurately detect CBH in preterm infants. Third, because the current state of knowledge suggests that cardiorespiratory instability around the time of birth and in the early neonatal period may contribute to CBH, especially in the ELBW infant, protocols to enhance cardiorespiratory stability (such as a developmentally supportive resuscitation) require further improvement, and their effectiveness needs to be validated. Because data regarding the immediate and long-term outcomes of infants with CBH are limited, longitudinal studies are required. Postdischarge follow-up programs that report the long-term impact of CBH on the ELBW infant and family should be a mandatory component of all tertiary care centers. Nurses need to explore parental concerns surrounding the diagnosis of CBH and identify strategies to promote positive parent-infant relationships following discharge.

CONCLUSION

CBH and its consequences are increasingly being recognized as an important contributor to neonatal mortality and morbidity, especially for the ELBW infant. To date, few comprehensive studies exist that describe CBH incidence, risk factors, and long-term outcomes. To improve care practices and outcomes for this population, further studies are required to increase our understanding of this significant complication. Nurses are in an optimal position to ensure that the NICU is a developmentally supportive and family-centered environment that enhances the continual processes of neural development for the ELBW infant.

REFERENCES

1. Limperopoulos, C., Bassan, H., Gauvreau, K., Robertson, R. L., Sullivan, N. R., Benson, C. B., et al. (2007). Does cerebellar injury in preterm infants contribute to the high prevalence of long-term cognitive, learning and behavioral disability in survivors? *Pediatrics, 120,* 584–593.

2. Limperopoulos, C., Benson, C. B., Bassan, H., DiSalvo, D. N., Kinnamon, D. D., Moore, M., et al. (2005). Cerebellar hemorrhage in the preterm infant: Ultrasonographic findings and risk factors. *Pediatrics, 116,* 717–724.

3. Limperopoulos, C., Soul, J. S., Gauvreau, K., Huppi, P. S., Warfield, S. K., Bassan, H., et al. (2005). Late gestation cerebellar growth is rapid and impeded by preterm birth. *Pediatrics, 115,* 688–695.

4. Limperopoulos, C., Soul, J. S., Haidar, H., Huppi, P. S., Bassan, H., Warfield, S. K., et al. (2005). Impaired trophic interactions between the cerebellum and the cerebrum among preterm infants. *Pediatrics, 116,* 844–850.

5. Messerschmidt, A., Brugger, P. C., Boltshauser, E., Zoder, G., Sterniste, W., Birnbacher, R., et al. (2005). Disruption of cerebellar development: Potential complication of extreme prematurity. *American Journal of Neuroradiology, 26,* 1659–1667.

6. Moore, K. L., & Persaud, T. V. N. (2003). *Before we are born: Essentials of embryology and birth defects* (6th ed.). Toronto: W.B. Saunders.

7. Limperopoulos, C., & du Plessis, A. (2006). Disorders of cerebellar growth and development. *Current Opinion in Pediatrics, 18,* 621–627.

8. Volpe, J. (2001). *Neurology of the newborn* (4th ed., pp. 401–412). Philadelphia: W.B. Saunders.

9. Exner, C., Koschack, J., & Irle, E. (2002). The differential role of the premotor frontal cortex and basal ganglia in motor sequence learning: Evidence from focal basal ganglia lesions. *Learning & Memory, 9,* 376–386.

10. Leiner, H. C., Leiner, A. L., & Dow, R. S. (1991). The human cerebro-cerebellar system: Its computing, cognitive and language skills. *Behavioral Brain Research, 44,* 113–128.

11. Schmahmann, J. D., & Sherman, J. C. (1998). The cerebellar cognitive affective syndrome. *Brain, 121,* 561–579.

12. Peterson, B. S., Vohr, B., Staib, L. H., Cannistraci, C. J., Dolberg, A., Schneider, K. C., et al. (2000). Regional brain volume abnormalities and long-term cognitive outcome in preterm infants. *Journal of the American Medical Association, 284,* 1939–1947.

13. Srinivasan, L., Allsop, J., Counsell Boardman, J. P., Edwards, A. D., & Rutherford, M. (2006). Smaller cerebellar volumes in very preterm infants at term-equivalent age are associated with the presence of supratentorial lesions. *American Journal of Neuroradiology, 27,* 573–579.

14. Di Salvo, D. N. (2001). A new view of the neonatal brain: Clinical utility of supplemental neurologic US imaging windows. *RadioGraphics, 21,* 943–955.

15. Merrill, K. D., Piecuch, R. E., Fell, S. C., Barkovich, A. J., & Goldstein, R. B. (1998). A new pattern of cerebellar hemorrhages in preterm infants. *Pediatrics, 102,* E62.

16. Luna, L. A., & Goldstein, R. B. (2000). Sonographic visualization of neonatal posterior fossa abnormalities through the posterolateral fontanelle. *The American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine, 174,* 561–567.

17. de Vries, L. S., & Groenendaal, F. (2002). Neuroimaging in the preterm infant. *Mental Retardation and Developmental Disabilities Research Reviews, 8,* 273–280.

18. Martin, R., Roessmann, U., & Fanaroff, A. (1976). Massive intracerebellar hemorrhage in low birthweight infants. *The Journal of Pediatrics, 89,* 290–293.

19. Miall, L. S., Cornette, L. G., Tanner, S. F., Arthur, R. J., & Levene, M. I. (2003). Posterior fossa abnormalities seen on magnetic resonance brain imaging in a cohort of newborn infants. *Journal of Perinatology, 23,* 396–403.

20. Perlman, J. M., Nelson, J. S., McAlister, W. H., & Volpe, J. J. (1983). Intracerebellar hemorrhage in a premature newborn: Diagnosis by real-time ultrasound and correlation with autopsy findings. *Pediatrics, 71,* 159–162.

21. Huang, L. T., & Lai, C. C. (1995). Tentorial hemorrhage associated with vacuum extraction in a newborn. *Pediatric Radiology, 25*(Suppl. 1), S230.

22. Pape, K. E., Armstrong, D. L., & Fitzhardinge, P. M. (1976). Central nervous system pathology associated with mask ventilation in the very low birthweight infant: A new etiology for intracerebellar hemorrhages. *Pediatrics, 58,* 473–483.

23. Tuck, S., & Ment, L. R. (1980). A follow-up study of very low birthweight infants receiving ventilatory support by face mask. *Developmental Medicine and Child Neurology, 22,* 633–641.

24. du Plessis, A. J., & Volpe, J. J. (2002). Perinatal brain injury in the preterm and term newborn. *Current Opinion in Neurology, 15,* 151–157.

25. Bass, W. T., Schultz, S. J., Burke, B. L., White, L. E., Khan, J. H., & Karlowicz, M. G. (2002). Indices of hemodynamic and respiratory functions in premature infants at risk for development of cerebral white matter injury. *Journal of Perinatology, 22,* 64–71.

26. Osborn, D. A., Evans, N., & Kluckow, M. (2003). Hemodynamic and antecedent risk factors of early and late periventricular/intraventricular hemorrhage in premature infants. *Pediatrics, 112,* 33–39.

27. Marlow, N., Hennessy, E. M., Bracewell, M. A., & Wolke, D. (2007). Motor and executive function at 6 years of age after extremely preterm birth. *Pediatrics, 120,* 793–804.

28. Aylward, G. P. (2002). Cognitive and neuropsychological outcomes: More than IQ scores. *Mental Retardation and Developmental Disabilities Research Reviews, 8,* 234–240.

29. Bhutta, A. T., Cleves, M. A., Casey, P. H., Cradock, M. M., & Anand, K. J. (2002). Cognitive and behavioral outcomes of school-aged children who were born preterm: A meta-analysis. *Journal of the American Medical Association, 288,* 728–737.

30. Bassan, H., Limperopoulos, C., Visconti, K., Mayer, D. L., Feldman, H. A., Avery, L., et al. (2007). Neurodevelopmental outcome in survivors of periventricular hemorrhagic infarction. *Pediatrics, 120,* 785–792.

31. Bassan, H., Feldman, H. A., Limperopoulos, C., Benson, C. B., Ringer, S. A., Veracruz, E., et al. (2006). Periventricular hemorrhagic infarction: Risk factors and neonatal outcome. *Pediatric Neurology, 35,* 88–92.

32. Ment, L. R., Vohr, B., Oh, W., Scott, D. T., Allan, W. C., Westerveld, M., et al. (1996). Neurodevelopmental outcome at 36 months' corrected age of preterm infants in the multicenter indomethacin intraventricular hemorrhage prevention trial. *Pediatrics, 98,* 714–718.

33. Schmidt, B., Davis, P., Moddemann, D., Ohlsson, A., Roberts, S., Saigal, S., et al. (2001). Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. *The New England Journal of Medicine, 344,* 1966–1972.

34. Vohr, B. R., Allen, W. C., Westerveld, M., Schneider, K. C., Katz, K. H., Makuch, R. W., et al. (2003). School-age outcomes of very low birth weight infants in the indomethacin intraventricular hemorrhage prevention trial. *Pediatrics, 111,* e340–e346.

35. Dyet, L. E., Kennea, N., Counsell, S. J., Maalouf, E. F., Ajayi-Obe, M., Duggan, P. J., et al. (2006). Natural history of brain lesions in extremely preterm infants studied with serial magnetic resonance imaging from birth and neurodevelopmental assessment. *Pediatrics, 118,* 536–548.

36. Laptook, A. R., O'Shea, T. M., Shankaran, S., Bhaskar, B., & NICHD Neonatal Network. (2005). Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: Prevalence and antecedents. *Pediatrics, 115,* 673–680.

37. Wilson-Costello, D., Friedman, H., Minich, N., Siner, B., Taylor, G., Schluchter, M., et al. (2007). Improved neurodevelopmental outcomes for extremely low birth weight infants in 2000–2002. *Pediatrics, 119,* 37–45.

38. Allin, M., Matsumoto, H., Santhouse, A. M., Nosarti, C., AlAsady, M. H., Stewart, A. L., et al. (2001). Cognitive and motor function and the size of the cerebellum in adolescents born very pre-term. *Brain, 124,* 60–66.

39. McLendon, D., Check, J., Carteaux, P., Michael, L., Moehring, J., Secrest, J. W., et al. (2003). Implementation of potentially better practices for the prevention of brain injury in very low birth weight infants. *Pediatrics, 111*, e497–e503.

40. Kattwinkel, J. (Ed.). (2006). *Textbook of neonatal resuscitation* (5th ed., pp. 6-1–6-21). Elk Grove Village, IL: American Academy of Pediatrics and American Heart Association.

41. Gibbins, S., Stevens, B., McGrath, P. J., Yamada, J., Beyene, J., Breau, L., et al. (2007). Comparison of pain responses in infants of different gestational ages. *Neonatology, 93*, 10–18.

42. Grunau, R. E., Holsti, L., Whitfield, M. F., & Ling, E. (2000). Are twitches, startles, and body movements pain indicators in extremely low birth weight infants? *The Clinical Journal of Pain, 16*, 37–45.

43. Holsti, L., Grunau, R. E., Whitfield, M. F., Oberlander, T. F., & Lindh, V. (2006). Behavioral responses to pain are heightened after clustered care in preterm infants born between 30 and 32 weeks gestational age. *The Clinical Journal of Pain, 22*, 757–764.

44. Holsti, L., Grunau, R. E., Oberlander, T. F., Whitfield, M. F., & Weinberg, J. (2005). Body movements: An important additional factor in discriminating pain from stress in preterm infants. *The Clinical Journal of Pain, 21*, 491–498.

45. Anand, K. J., & Craig, K. D. (1996). New perspectives on the definition of pain. *Pain, 67*, 3–6, 209–211.

46. Bartocci, M., Bergqvist L. L., Lagercrantz, H., & Anand, K. J. (2006). Pain activates cortical areas in the preterm newborn brain. *Pain, 122*(1-2),109–117.

47. Slater, R., Boyd, S., Meek, J., & Fitzgerald, M. (2006). Cortical pain responses in the infant brain. *Pain, 123*, 332–334.

48. Symington, A., & Pinelli, J. (2006). Developmental care for promoting development and preventing morbidity in preterm infants. *Cochrane Database of Systematic Reviews*, CD001814.

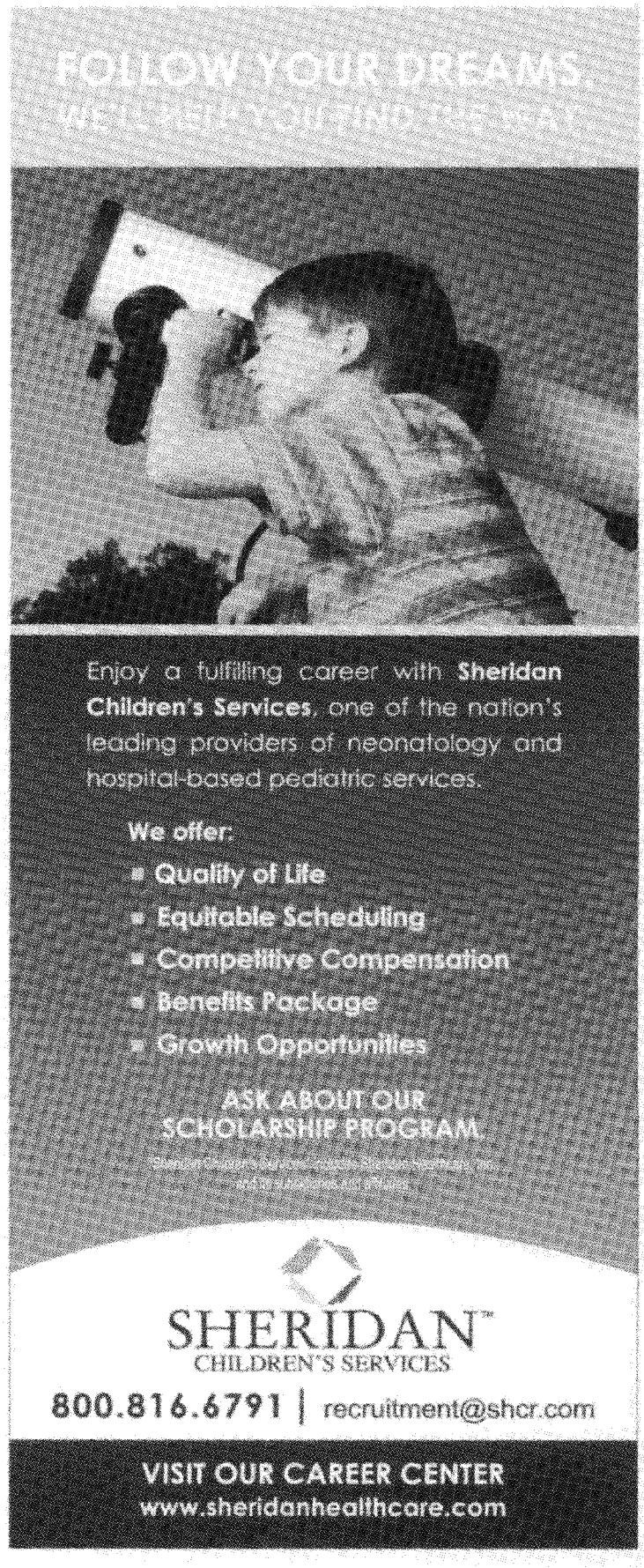
49. Aucott, S., Donohue, P. K., Atkins, E., & Allen, M. C. (2002). Neurodevelopmental care in the NICU. *Mental Retardation and Developmental Disabilities Research Reviews, 8*, 298–308.

About the Authors

Patricia Maddalena is a neonatal nurse practitioner at Sunnybrook Health Sciences Centre. She practices in both the NICU and the Neonatal Follow-Up Clinic. Her area of interest is long-term outcomes for the ELBW infant.

Sharyn Gibbins is the head of interdisciplinary research at Sunnybrook Health Sciences Centre. She also practices clinically in the NICU. Her program of research includes the assessment and management of pain in the ELBW infant.

For further information, please contact:
Patricia Maddalena
Sunnybrook Health Sciences Centre
76 Grenville Street, Room 466
Toronto, Ontario, Canada
M5S 1B2
E-mail: patricia.maddalena@sunnybrook.ca



Copyright of Neonatal Network is the property of Neonatal Network and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.