Intraventricular hemorrhage and posthemorrhagic hydrocephalus

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In this issue, Dr. Robinson provides a comprehensive overview of intraventricular hemorrhage (IVH) of prematurity and posthemorrhagic hydrocephalus (PHH).1 The article covers epidemiology, pathophysiology, management, and current research in these fields. Relevant background material is obtained from a comprehensive MEDLINE database search and from additional references found in the identified articles.

There is little to add to this excellent overview, but I would like to highlight and expand on several points raised by the author. The article describes stability in the number of preterm infants in the neonatal intensive care unit of the author’s institution, but a 3-fold drop in surgical intervention for PHH. As suggested, there are probably many factors contributing to this decrease, but changing attitudes among surgeons is probably one of them. In the Hydrocephalus Clinical Research Network (HCRN), we have documented significant variation in the management of these patients from one center to another across 4 centers (Riva-Cambrin et al., unpublished data). Among 110 neonates surgically treated for IVH, the strongest factor predicting whether they needed treatment was the center at which they were treated. As a result, we have developed standardized protocols for making decisions about treatment of these children and are now applying these prospectively.

The pathophysiology of both IVH and PHH are described by Dr. Robinson. In addition to the biomarkers discussed in the article, some new data are relevant. In a mouse model of intracranial hemorrhage, the brains of mouse embryos were exposed to lysophosphatidic acid (LPA). This exposure resulted in the development of fetal hydrocephalus, which was dependent on the expression of the LPA1 receptor. Administration of an LPA antagonist blocked the development of fetal hydrocephalus.8 The LPA signaling pathway therefore appears to have a role in causing fetal hydrocephalus associated with hemorrhage.

It is interesting to note that Dr. Robinson’s group has seen a reduced incidence of CSF shunting with serial lumbar punctures. This topic was the subject of a Cochrane database review4 in 2002 that identified 4 controlled trials, 3 of which were randomized. Two of these studies evaluated lumbar punctures and 2 evaluated reservoir tapping. The relative risks for shunt placement, death, and disability in the pooled data were very close to 1.0, with no significant effect. These measures have not been formally reconsidered in the last 10 years, so it is interesting to see that Dr. Robinson’s group has had success with serial lumbar punctures.

The recent work by Whitelaw et al.6 on drainage, irrigation, and fibrinolytic therapy (DRIFT) is described by Dr. Robinson. As noted in the section on nonsurgical treatment, a Phase I trial7 suggested a benefit compared with historical controls, but a randomized trial7 was stopped early because of an increased hemorrhage rate. It should be emphasized, as mentioned later in the section on neuropsychological outcome, that the delayed follow-up of those patients demonstrated a clear benefit from the therapy.6,7 This trial6 was conducted at 3 centers, but most of the patients were from a single center, and further experience with this technique is required before it is more universally adopted.

The temporary treatment option of subgaleal shunt versus subgaleal reservoir is discussed. This has been studied by Wellons et al.,3 whose results appeared to favor the use of a reservoir, although the variability in baseline factors did not allow strong conclusions. Within the HCRN, further prospective work is leading to a randomized trial to compare these 2 treatment options.

Dr. Robinson describes an increased shunt infection rate in patients in the PHH group compared with those with other causes of hydrocephalus. Our data have demonstrated an increased risk of shunt failure in addition to the risk of infection. Among 554 children with various causes of hydrocephalus, IVH was an independent risk factor for shunt revision.2

Intraventricular hemorrhage and PHH continue to provide significant challenges for children, their families, and their surgeons. The field is broad, and there are many areas of active investigation. We are indebted to Dr. Robinson for this comprehensive review of the current status of this condition.

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Disclosure

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References


Response

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Dr. Kestle highlights several key points relevant to the evolving field of the biology and treatment of neonatal PHH, and I thank him for his kind comments. The optimal management of hydrocephalus in these infants and children remains a challenging problem.

As Dr. Kestle mentions, we recently reviewed the outcomes of all very preterm infants born with a weight less than 1500 g and an estimated gestational age less than 30 weeks who were treated within 3 days of birth at Rainbow Babies and Children’s Hospital over the past decade (Alan et al., unpublished data). We found a stable cohort of neonates, with a consistent referral pattern, survival rate, and set of neonatal risk factors, who were treated by a consistent team with a consistent management approach to symptomatic hydrocephalus. The incidence of severe IVH and periventricular leukomalacia, as detected by serial cranial ultrasound imaging, was also stable. Comparison of outcomes from the early part of the past decade (2000–2003) to the most recent period for which data were available (2005–2008) revealed a significant decline in the incidence of bronchopulmonary dysplasia and sepsis. Notably, there was also a significant reduction in the need for temporary ventriculostubgaleal (VSG) and permanent ventriculoperitoneal (VP) shunt insertion in these infants. The infants with ventriculomegaly were all followed over the long term by physicians from multiple disciplines to confirm that late symptomatic hydrocephalus was appropriately detected and treated. As Dr. Kestle notes, data from the HCRN showed that the strongest predictor for surgical treatment of IVH in preterm infants was the treating center (Riva-Cambrin et al., unpublished data). The differences in shunt rates among various neonatal ICUs (NICUs) may be due in part to differences in surgeons’ clinical paradigms, but also may reflect genetic and demographic variations in the neonatal population served by the NICUs and variations in NICU practices that affect neonatal outcomes.

From a neurosurgical perspective, the current overall goal for these children is avoidance of a permanent VP shunt and optimal neurodevelopmental outcome. After many decades of slow progress for this subpopulation of children with hydrocephalus, the pace of improvement has started to evolve more rapidly. For example, since this review was submitted, at least 3 novel lines of investigation have appeared. As noted above, a single institution study found a marked reduction in the need for surgical intervention in these neonates during the past decade, which may be related to improved NICU practices that impact outcomes. Multicenter trials with more detailed analysis of NICU parameters are clearly needed. Second, combined endoscopic third ventriculostomy with choroid plexus cauterization may be an effective alternative to insertion of a permanent VP shunt in selected patients. Third, as Dr. Kestle described above, the recent work by Yung et al. found that the formation of congenital hydrocephalus is dependent on lipid LPA signaling through the receptor LPA1, as shown by both genetic deletion of the LPA1 receptor in mice and use of a small molecule receptor antagonist. Excess LPA was associated with the development of hydrocephalus and has also been implicated in abnormal neurodevelopment. Removal of excessive levels of molecules such as LPA may in part explain the improved neurodevelopmental outcomes observed in the late follow-up of the patients in the DRIFT trial, and I agree with Dr. Kestle that further study of this technique is warranted before it is widely adopted. All of these lines of investigation may decrease the need for permanent VP shunt insertion in infants with posthemorrhagic hydrocephalus, as well as other challenging populations, such as infants with postmeningitic or posttraumatic hydrocephalus.

As part of the management protocol in the recent Rainbow study, a trial of serial lumbar punctures was used as the initial treatment for infants with symptomatic hydrocephalus, defined as clinical symptoms and signs of increased intracranial pressure associated with progressive ventriculomegaly on serial cranial ultrasound examinations. If the serial LPs failed to stabilize the infants within 2 days, we inserted a temporary VSG shunt. This

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