Fuzzy Images: Ethical Implications of Using Routine Neuroimaging in Premature Neonates to Predict Neurologic Outcomes

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Intraventricular hemorrhage (IVH) is a worrisome complication of premature birth affecting roughly 20% of very low birth weight infants (birth weight <1500 g).[1] Neonatal IVH is associated with neurologic impairments that include cerebral palsy (CP), developmental delay, and hearing loss.[2] For over 30 years, nearly all neonates born less than 32 weeks have undergone routine neuroimaging, principally head ultrasound (HUS), typically within the first days or weeks of life to evaluate for IVH.

Neonatal neuroimaging studies were initiated "in the hope of better prediction of neurologic and developmental outcome, and to provide a more rational basis for decision making in the provision or exclusion of life support systems."[3] It is believed that routine neonatal neuroimaging benefits premature infants, aiding in the prediction of neurodevelopmental impairment (NDI)[4-6] and directing discussion between neonatal practitioners and families regarding goals of care when substantial IVH is present.[4] We present a historical examination of neurodevelopmental prediction in neonatology, with focus on the clinical and ethical challenges raised by routine and widespread early HUS screening. We encourage neonatal practitioners to reconsider whether the perceived screening benefits are valid and the prediction of NDI definitive.

Neonatal Neuroimaging Origins

Increasing survival of very low birth weight infants starting in the late 1960s challenged neonatologists' thoughts about viability limits in neonates.[7] At the same time, a perceived rising prevalence of neurologic compromise for survivors of premature birth tempered optimism for neurodevelopmental outcomes in extreme prematurity.[8] Prevention and prediction of NDI became a central aim for neonatologists as an emphasis on survival free of significant neurologic disability (ie, "intact survival") caused some providers to question neonatal resuscitation at certain gestational ages and birth weights.[9] A thoughtful and ethical approach to the care of these neonates was needed.

CP	Cerebral palsy
CT	Computerized tomography
HUS	Head ultrasound
IVH	Intraventricular hemorrhage
MDI	Mental Developmental Index
MRI	Magnetic resonance imaging
NDI	Neurodevelopmental impairment
QoL	Quality of life
WMI	White matter injury

Prior to the first neonatal neuroimaging studies, clinical outcomes of infants with posthemorrhagic hydrocephalus, a complication of IVH, were published in 1975.[8] Many neonates had highly symptomatic bleeding with acute clinical and neurologic deterioration, a group for which the authors stated "resuscitation maneuvers and mechanical ventilatory assistance [were] not indicated." Others had no clinical change that would generate suspicion for IVH prior to their development of hydrocephalus. The prognostic uncertainty of those latter infants presented an ethical dilemma and "carefully considered judgment in each individual case" regarding continuation of care was suggested.[8] Without neuroimaging, clinicians faced significant challenges to implementing these approaches given the great difficulty in determining which neonates in fact had IVH, and whether an acute clinical deterioration was related to IVH or had other cause.

With anticipation that it would "eventually become clear which infants are so hopelessly brain-damaged that intensive care can, if the parents wish it, be ethically withheld,"[10] neonatal providers turned to new neuroimaging technologies to better delineate the clinical course of IVH. Krishnamoorthy et al used computerized tomography (CT) to evaluate neonates for IVH in 1977.[11] Although a large spectrum of bleeding patterns were found, survivors had less extensive hemorrhages. Noting that "withdrawal of life support has been suggested when diagnosis of ICH [intracranial hemorrhage] is strongly suspected," the authors cautioned that "the presence of massive IVH alone should not be used as the basis for discontinuing life support because we do not know the natural history of the disease."[11]

A classification system for IVH was created by Papile et al in a 1978 study of neonates with birth weights less than 1500 g.[12] Hemorrhages, as visualized on CT, were graded based upon location and presentation from I to IV, a system that remains universally used today. Survivors were reported for each of the 4 grades of hemorrhage. Troublingly, IVH incidence, roughly 40%, was much higher than previously recognized and for most neonates was a clinically silent event.[12] An editorial response accompanying that study reminded readers that the "major unanswered question in

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The authors declare no conflicts of interest.

 http://dx.doi.org/10.1016/j.jpeds.2013.03.055

the acute management of the infant with periventricular hemorrhage is how to identify those with a hopeless prognosis."[13]

The use of CT to diagnose IVH had significant limitations, however, including risks of radiation to the neonate and transportation of sick infants to a scanner. Therefore, soon after the initial reports of CT scanning of neonates, a new technology, bedside HUS, gained the attention of neonatologists for its advantages in safety and convenience.[14]

Early Investigation of IVH Outcomes

Widespread adoption of neuroimaging in neonatology was followed by numerous studies of IVH outcomes. Follow-up for neonates with graded IVH was first reported in 1979.[15] Notably, that study showed the neurologic prognosis at a mean age of 24 months old was not "uniformly hopeless." A range of outcomes were seen for all grades of IVH and patients with grades I and II hemorrhages had normal development or mild developmental impairments. Given these variable outcomes, the practice of withdrawal of support from neonates with grades I and II IVH was discouraged, and the authors expressed concern that "based on previous information stating that the prognosis after IVH was uniformly poor, physicians have doubted the wisdom of continuing intensive care for such infants and reflected pessimism in the discussion with other staff as well as with the parents."[15]

Outcomes were further clarified in a 1983 study comparing neonates with and without an IVH history.[16] In that cohort, infants with grades I and II hemorrhages had comparable risks of developing major NDI to infants without. Outcomes for grades III and IV hemorrhages were less encouraging. Although those grades represented only 16% of infants, they contributed 51% of the major neurologic impairments for the population.[16]

Neurologic disability was not certain, though, for the higher grades of IVH. A 1987 report demonstrated a limited predictive value for grades III and IV IVH in neurologic outcomes of infants with birth weights less than 1750 g.[17] A striking trend toward less NDI was seen between visits at 1 and 2 years of age. Over one-half were functioning within normal ranges of development at 2 years of age. Presciently, the authors hypothesized that this "limited prediction may be due to remarkable CNS [central nervous system] plasticity in young infants, abnormalities in the brain that may not be adequately imaged by ultrasound or computer scanning, or the nature of the outcome measures."[17]

A relationship between timing of HUS and accuracy of neurodevelopmental prediction in neonates born less than 32 weeks gestation was explored in a 1988 study.[18] The positive and negative predictive value of HUS improved with increasing postnatal age and was most accurate once infants reached 40 weeks postmenstrual age. The authors attributed this to an improved detection of evolving cystic periventricular leukomalacia and its resultant impact on neurodevelopment. Even at 40 weeks, HUS only correctly identified 58% of infants with future moderate to severe NDI.[18]

Practice Standardization and Intensive Care Limitations

The clinical practice and predictive abilities of neonatal HUS testing were reviewed by Levene in 1990.[19] Physicians were encouraged to clarify what diagnostic information they sought from ultrasonography given that with the exception of posthemorrhagic hydrocephalus, no immediate treatment was available for cerebral insults. Routine neuroimaging was therefore, in part, a screening test for selective early withdrawal of life support. Levene wrote that this approach had a significant downside given that "the prognostic accuracy of late ultrasound scans is far better than early scans performed in the first week of life and, thus, limits the value of the technique as a reliable method for recognizing the infant in whom selective withdrawal of intensive care is a realistic and honest option."[19]

Pervasiveness of neonatal neuroimaging was evident by 1998 in a cost/benefit analysis of routine ultrasonography.[3] This editorial observed that research efforts to understand neurodevelopmental outcomes for neonates with IVH had been considerably delayed in comparison to advancements in technology to investigate the population. The cost effectiveness of HUS testing was questioned, especially for infants born after 29 weeks gestation, and the authors speculated if ultrasonography had more principle value as a research tool.[3]

Despite such critique, routine HUS screening was encouraged for all infants born less than 32 weeks gestation by the Canadian Paediatric Society in 2001.[5] Neuroimaging of premature neonates was similarly recommended by the American Academy of Neurology and the Child Neurology Society in 2002, which firmly stated that HUS "should be used to predict long-term neurodevelopmental outcome."[6] Detection of intracranial lesions associated with NDI[6] and direction of families to appropriate follow-up for the management and intervention of the chronic neurodevelopmental sequelae[5] were some of the benefits attributed to screening HUS in these statements. The Canadian guideline did recognize that routine HUS could be potentially harmful if parental anxiety was increased by presenting false positive results or if long-term neurodevelopment risks were minimized through studies that were falsely negative.[5] Neither statement addressed the practice of limiting intensive care for neonates with IVH.

Cardiopulmonary vulnerability in many premature infants susceptible to IVH will result in almost certain lethality if mechanical ventilation is discontinued. Throughout this era of routine neonatal neuroimaging, radiography reflective of substantial IVH has led to clinical considerations for withdrawal of life support. Even though clinicians report widely divergent approaches to the clinical scenario of withdrawing support from an extremely preterm neonate with IVH,[20] quantifying the prevalence among neonatologists is difficult as few published studies directly address the practice. One