Neuroimaging in the Evaluation of Neonatal Encephalopathy

WHAT'S KNOWN ON THIS SUBJECT: Computed tomography is commonly used for neuroimaging in newborn infants with neonatal encephalopathy despite concerns over potential harm from radiation exposure. Alternative neuroimaging options include MRI and cranial ultrasound.

WHAT THIS STUDY ADDS: Using a very large, international, multicenter database, we demonstrate utilization rates and compare diagnostic findings of computed tomography, MRI, and cranial ultrasound in the evaluation of neonatal encephalopathy.

abstract

BACKGROUND AND OBJECTIVE: Computed tomography (CT) is still used for neuroimaging of infants with known or suspected neurologic disorders. Alternative neuroimaging options that do not expose the immature brain to radiation include MRI and cranial ultrasound. We aim to characterize and compare the use and findings of neuroimaging modalities, especially CT, in infants with neonatal encephalopathy.

METHODS: The Vermont Oxford Network Neonatal Encephalopathy Registry enrolled 4171 infants (≥36 weeks' gestation or treated with therapeutic hypothermia) between 2006 and 2010 who were diagnosed with encephalopathy in the first 3 days of life. Demographic, perinatal, and medical conditions were recorded, along with treatments, comorbidities, and outcomes. The modality, timing, and results of neuroimaging were also collected.

RESULTS: CT scans were performed on 933 of 4107 (22.7%) infants, and 100 of 921 (10.9%) of those received multiple CT scans. Compared with MRI, CT provided less detailed evaluation of cerebral injury in areas of prognostic significance, but was more sensitive than cranial ultrasound for hemorrhage and deep brain structural abnormalities.

CONCLUSIONS: CT is commonly used for neuroimaging in newborn infants with neonatal encephalopathy despite concerns over potential harm from radiation exposure. The diagnostic performance of CT is inferior to MRI in identifying neonatal brain injury. Our data suggest that using cranial ultrasound for screening, followed by MRI would be more appropriate than CT at any stage to evaluate infants with neonatal encephalopathy. *Pediatrics* 2014;133:e1508–e1517

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KEY WORDS

neonatal encephalopathy, computed tomography, MRI, cranial ultrasound

ABBREVIATIONS

CT—computed tomography
VON—Vermont Oxford Network

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Computed tomography (CT) is a popular neuroimaging modality for diagnosing cerebral injury in children. Approximately 4 to 7 million CT examinations of the head or body are performed annually in children, including infants, in the United States.[1,2] After increasing utilization rates of pediatric head CT in the late 1990s and early 2000s, rates have more recently decreased.[3]

Despite the potential benefits of CT, a disadvantage is the inevitable radiation exposure, of concern for both adults and children. Unique considerations apply to pediatric subjects, and particularly small infants, in relation to radiation exposure from CT scans. Children often receive a relatively higher effective radiation dose in CT scans and are considerably more radiosensitive than adults, as demonstrated in epidemiologic studies of exposed populations. They have a longer life expectancy than adults, thus having a longer time frame to express the effects of radiation damage.[4–8]

Neuroimaging remains vital for the identification, characterization, treatment, and prevention of the brain injury in infants with neonatal encephalopathy. The lack of recognized antecedent events in these infants may have driven increasing use of CT and other imaging modalities for evaluating this condition.[9–12] Besides CT, cranial ultrasonography and MRI are also used for neuroimaging of infants, and each of the modalities has its advantages and disadvantages.[13–16] The goal of all 3 imaging modalities is to identify the presence, nature, and extent of brain injury, thus improving treatment and prognostic guidance. Unlike CT, there is no radiation exposure with ultrasound and MRI. Most experts consider MRI as the "gold standard" for the safe assessment of neonatal brain injury and anomalies of brain development.[15,17] Using a database from a large international registry, we evaluated the pattern of use and findings of the 3 neuroimaging modalities in newborns with encephalopathy.

METHODS

Vermont Oxford Network Registry

The Vermont Oxford Network (VON) established the Neonatal Encephalopathy Registry and began enrolling patients in 2006. In 2006 and 2007, only the VON centers participating in the VON expanded database could participate in the registry. Beginning in 2008, all network centers were eligible to participate in the registry. The registry enrolled newborn infants with encephalopathy, including those treated with therapeutic hypothermia, to identify their demographic characteristics, associated perinatal factors, medical treatments, comorbidities, and outcomes.

Centers collected and submitted data by using VON eNICQ software.[18] VON staff members performed additional data assessment and contacted centers about missing data items, unresolved records, out-of-range values, and appropriate modifications. No interventions or alterations in treatment or parameters for diagnostic testing, imaging, or otherwise, were specified or required for registry entry and only deidentified data were submitted. The institutional review boards at the University of Vermont and at each participating center reviewed and approved registry participation.

Neonatal Encephalopathy Registry Eligibility Criteria

There were 2 paths for entry into the registry. Any infant treated with therapeutic hypothermia, regardless of gestational age, was eligible. Additionally, any infant born ≥36 weeks' gestation with evidence of neonatal encephalopathy within 3 days of birth was eligible. Neonatal encephalopathy was defined as presence of seizures (clinical or electroencephalographic) and/or altered consciousness (stupor, coma). Infants with central nervous system birth defects were excluded from the registry (Fig 1).

For neuroimaging evaluation, the modality (cranial ultrasound, CT, MRI), timing of first and last imaging with each modality, and results of neuroimaging were recorded. Using radiology reports, each center recorded hemorrhages, ventriculomegaly, arterial and venous occlusions, and cystic white matter, deep nuclear gray matter, and cerebellar injury for all 3 modalities. Brainstem injuries were identified for CT and MRIs. Diffuse injury to the white matter, cortical, parasagittal watershed cortical gray matter, and posterior limb of the internal capsule were recorded for MRI only. For all modalities, centers were given the opportunity to describe other abnormalities. Two neonatologists (Drs Barnette and Inder) reviewed and used these descriptions to exclude infants with radiologist reports of congenital intracranial anomalies (eg, polymicrogyria, lissencephaly, Dandy-Walker) and aid consistency in the reported abnormalities (eg, comments of injury to the putamen were used to correctly include deep nuclear gray matter injury).

Information was also collected on obstetric and prenatal history, clinical and neurologic status, hypothermic therapy, and discharge status. Hospital characteristics were obtained from the VON Annual Survey.

Statistical Analyses

Data analysis was generated by using SAS software, version 9.3 (Cary, NC). Data were reported with number of eligible infants (N) and number of observed cases along with unadjusted rates for categorical measures. Means and SDs and medians and quartiles were used to describe continuous variables. McNemar's test and Fisher's

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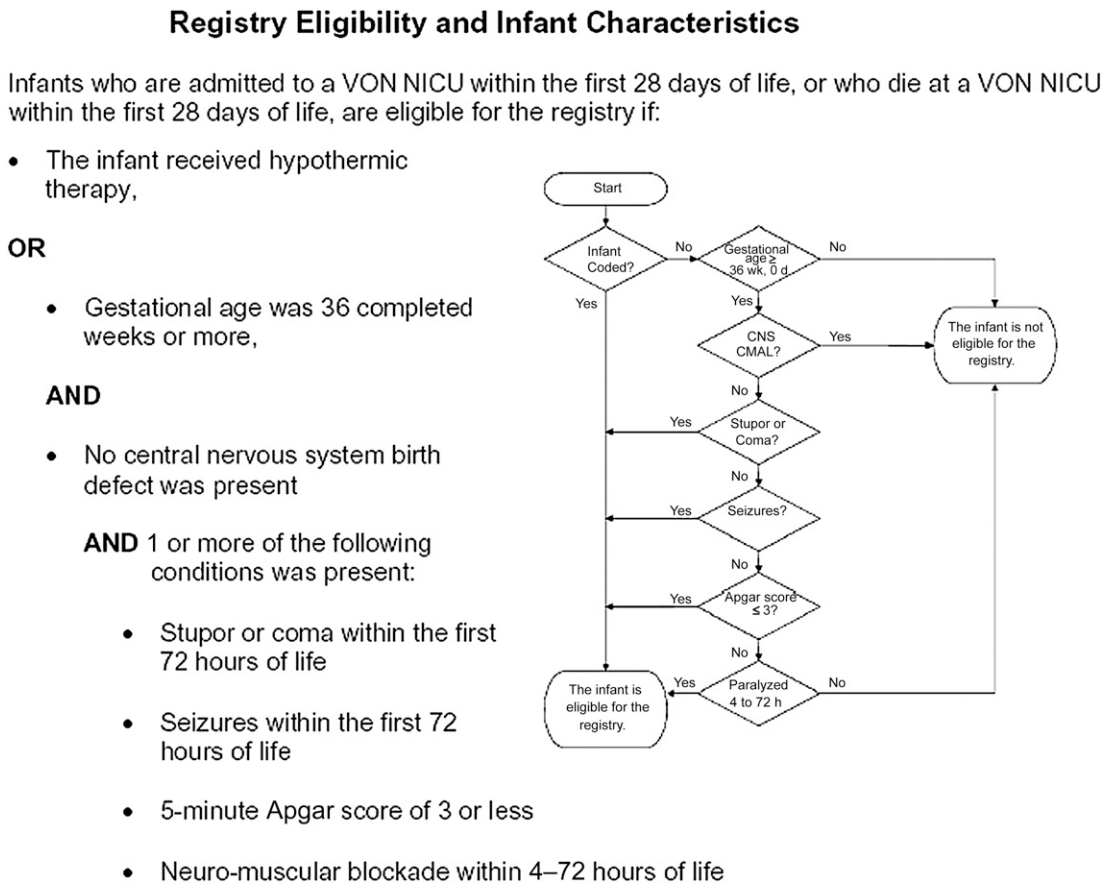

FIGURE 1
Registry eligibility and infant characteristics. CNS CMAL, central nervous system congenital malformation.

exact test were used for comparisons of imaging modality results and conditions associated with CT imaging, respectively.

RESULTS

Subjects

In 2006–2010, there were 4171 infants enrolled in the registry from 95 centers.[18] The Appendix contains a complete list of participating centers. All centers reported access to cranial ultrasound, while CT and MRI were available at 93 of 95 (97.9%) and 92 of 95 (96.8%) centers, respectively. The majority of the infants were admitted to the registry because of seizures (57.4%), with nearly half the infants having a 5-minute Apgar score ≤3 (49.6%). Approximately 38% of these infants received therapeutic hypothermia. The characteristics of the cohort are outlined in Table 1.

Neuroimaging Modalities

Imaging was performed for 2006 patients with cranial ultrasound, 933 patients with CT, and 2690 patients with MRI. The number of patients with zero, 1, 2, and all 3 types of imaging were 678 (16.5%), 1405 (34.3%), 1845 (45.0%), and 170 (4.1%), respectively (N = 4098 patients). One or more imaging status variables were unavailable for 73 (1.8%) infants. Multiple scans were performed by using cranial ultrasound for 560 of 1994 (28.1%), by using CT in 100 of 921 (10.9%), and by using MRI in 300 of 2669 (11.2%) patients. The dates of repeat imaging were unavailable for 12 cranial ultrasound patients, 12 CT patients, and 21 MRI patients. The day of life on which the 3 modalities were performed differed, with ultrasound generally earlier and MRI generally later than CT. Although cranial ultrasound reports identified intraventricular hemorrhage well, they lacked the sensitivity of MRI and CT for identifying other types of hemorrhage and intracranial injury. Abnormalities of the white matter, cerebellum, and deep nuclear gray matter were noted on more of the MRIs than either of the other 2 modalities (Table 2, Fig 2). Infants who died more commonly had no neuroimaging than the surviving infants (23.3% vs 15.5%).

Neuroimaging studies not including cranial ultrasound were performed in 1425 patients. Although most of these patients with an initial CT had a subsequent MRI (383 of 590, 64.9%), the patients with an initial MRI rarely had a CT (18 of 758, 2.4%). The sequence of

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TABLE 1 Infant Characteristics

	2006–2010 (*N* = 4171)	Cranial Ultrasound (*N* = 2006)	CT (*N* = 933)	MRI (*N* = 2690)	No Imaging (*N* = 678)
Inborn	1662/4171 (39.8)	725/2006 (36.1)	316/933 (33.9)	893/2690 (33.2)	400/678 (59.0)
Boy	2420/4168 (58.1)	1144/2006 (57.0)	545/933 (58.4)	1529/2690 (56.8)	414/677 (61.2)
Maternal race, white	2633/4134 (63.7)	1220/1987 (61.4)	628/927 (67.7)	1676/2664 (62.9)	426/672 (63.4)
Maternal race, black	768/4134 (18.6)	386/1987 (19.4)	153/927 (16.5)	474/2664 (17.8)	149/672 (22.2)
Maternal race, Hispanic	569/4134 (13.8)	294/1987 (14.8)	116/927 (12.5)	410/2664 (15.4)	71/672 (10.6)
Maternal race, Other	164/4134 (4.0)	87/1987 (4.4)	30/927 (3.2)	104/2664 (3.9)	26/672 (3.9)
Twin	65/4171 (1.6)	35/2006 (1.7)	8/933 (0.9)	42/2690 (1.6)	12/678 (1.8)
Small gestational age	661/4170 (15.9)	338/2005 (16.9)	115/933 (12.3)	409/2690 (15.2)	117/678 (17.3)
Entry criteria					
Stupor or coma	749/4135 (18.1)	491/1983 (24.8)	118/927 (12.7)	510/2665 (19.1)	71/672 (10.6)
5-minute Apgar score ≤3	2040/4109 (49.6)	948/1969 (48.1)	142/922 (15.4)	1013/2645 (38.3)	613/674 (90.9)
Seizures ≤72 h	2381/4151 (57.4)	1189/1996 (59.6)	836/932 (89.7)	1900/2678 (70.9)	73/675 (10.8)
Paralysis induced	85/4153 (2.0)	67/1996 (3.4)	4/930 (0.4)	25/2678 (0.9)	12/675 (1.8)
Hypothermia initiated	1598/4171 (38.3)	1112/2006 (55.4)	91/933 (9.8)	1329/2690 (49.4)	84/678 (12.4)
Cord pH, median (interquartile range)[a]	*N* = 1904; 7.05 (6.88–7.21)	*N* = 1014; 7.00 (6.84–7.17)	*N* = 276; 7.18 (7.03–7.26)	*N* = 1291; 7.01 (6.85–7.18)	*N* = 329; 7.19 (7.02–7.27)
Any birth injury	581/4145 (14.0)	263/1999 (13.2)	227/925 (24.5)	412/2681 (15.4)	45/670 (6.7)
Skull fracture	68/4145 (1.6)	23/1999 (1.2)	56/925 (6.1)	44/2681 (1.6)	1/670 (0.1)
Limb/clavicle fracture or brachial plexus injury	136/4144 (3.3)	64/1998 (3.2)	41/925 (4.4)	93/2680 (3.5)	14/670 (2.1)
Cephalohematoma	316/4144 (7.6)	142/1998 (7.1)	141/925 (15.2)	243/2680 (9.1)	16/670 (2.4)
Other injury	201/4145 (4.8)	92/1999 (4.6)	64/925 (6.9)	137/2681 (5.1)	18/670 (2.7)
Mode of delivery	*N* = 4167	*N* = 2004	*N* = 932	*N* = 2688	*N* = 678
Spontaneous vaginal	1397 (33.5)	586 (29.2)	401 (43.0)	844 (31.4)	260 (38.3)
Vacuum or forceps	443 (10.6)	218 (10.9)	147 (15.8)	307 (11.4)	48 (7.1)
Cesarean delivery					
After labor	1409 (33.8)	722 (36.0)	213 (22.9)	915 (34.0)	244 (36.0)
After vacuum/forceps	97 (2.3)	46 (2.3)	40 (4.3)	70 (2.6)	8 (1.2)
No labor	821 (19.7)	432 (21.6)	131 (14.1)	552 (20.5)	118 (17.4)
Sentinel event[b]	626/4171 (15.0)	383/2006 (19.1)	52/933 (5.6)	474/2690 (17.6)	62/678 (9.1)
Fetal bradycardia	1224/3613 (33.9)	712/1719 (41.4)	135/808 (16.7)	868/2319 (37.4)	163/601 (27.1)
Inflammatory indicators[c]	976/4170 (23.4)	435/2006 (21.7)	229/933 (24.5)	607/2690 (22.6)	193/678 (28.5)
Mortality	537/4166 (12.9)	310/2004 (15.5)	59/932 (6.3)	151/2688 (5.6)	113/676 (16.7)

Data presented as *n*/*N* (%) unless noted otherwise.

[a] Cord pH was arterial cord blood from 2006 to 2008 and any cord blood from 2009 to 2010.

[b] Antepartum hemorrhage/placental abruption, cord prolapse, uterine rupture, tight nuchal cord, or maternal shock or death.

[c] Clinical chorioamnionitis, maternal fever in labor ≥37.5°C, fetal tachycardia, rupture of membranes >24 hours, early bacterial infection, or toxoplasmosis, other infections, rubella, cytomegalovirus infection, and herpes simplex.

imaging could not be determined for 77 patients.

Six hundred fifty-one patients had both CT and MRI. In these patients, CT scans were obtained earlier, with the first and last scans occurring at mean (SD) 3.2 (4.4) and 4.0 (6.3) days of life, respectively. For MRI, the first and last days of imaging were 5.7 (4.6) and 7.3 (7.4), respectively. Injuries to the deep nuclear gray matter (22.6% vs 7.8%), brainstem (5.3% vs 0.5%), and cerebellum (5.0% vs 2.5%), and arterial and venous occlusions ["strokes"], 11.7% vs 7.2%) were more commonly identified ($P < .001$ for each of the 4 abnormalities) with MRI than CT (Fig 2A). Diffuse white matter, diffuse cortical, and parasagittal gray matter abnormalities were collected for MRI only and were detected in 26.2%, 27.3%, and 12.5%, respectively.

Both CT and cranial ultrasound were obtained in 245 infants. The first and last days of life (mean [SD]) on which these infants were imaged by using ultrasound were 4.1 (5.0) and 8.5 (12.8) and by using CT were 5.5 (9.5) and 8.3 (16.2). Hemorrhages, especially extraaxial (including subdural, epidural, and subarachnoid), were noted with CT more often than ultrasound. Deep nuclear gray matter injuries and strokes were also more commonly identified with CT (Fig 2B). Brainstem injuries were not identified by ultrasound and were detected with CT in 1.2% of these patients.

Multiple types of neuroimaging were performed on the same day of life in 152 infants. For these infants, ultrasound was less sensitive than CT or MRI for all hemorrhages and abnormalities. MRI was superior to both ultrasound and CT in detecting deep nuclear gray matter and cerebellar injury (Table 3).

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TABLE 2 Neuroimaging Results

	Ultrasound	CT	MRI
Number of infants	2006/4111 (48.8)	933/4107 (22.7)	2690/4109 (65.5)
Day of life at first scan, median (interquartile range)	2 (1–3); *N* = 2001	2 (2–3); *N* = 928	6 (4–8); *N* = 2682
Any reported abnormality	642/1985 (32.3)	552/930 (59.4)	1798/2676 (67.2)
Intraventricular hemorrhage	171/2001 (8.5)	110/930 (11.8)	220/2686 (8.2)
Extraaxial hemorrhage	59/2003 (2.9)	321/927 (34.6)	487/2686 (18.1)
Parenchymal hemorrhage	90/2001 (4.5)	125/929 (13.5)	292/2687 (10.9)
Deep nuclear gray matter abnormality	140/1994 (7.0)	65/926 (7.0)	603/2671 (22.6)
Cystic white matter injury	43/1997 (2.2)	24/928 (2.6)	131/2677 (4.9)
Diffuse white matter injury	—	—	628/2674 (23.5)
Venous or arterial occlusion	22/1980 (1.1)	54/925 (5.8)	183/2657 (6.9)
Ventriculomegaly	84/2004 (4.2)	39/929 (4.2)	92/2687 (3.4)
Cerebellar injury	21/1986 (1.1)	29/929 (3.1)	137/2677 (5.1)
Brainstem injury	—	7/927 (0.8)	126/2677 (4.7)
Diffuse cortical signal abnormality	—	—	572/2673 (21.4)
Parasagittal watershed injury	—	—	285/2665 (10.7)
Absent posterior limb of the internal capsule	—	—	114/2659 (4.3)
Other abnormality	329/2000 (16.5)	190/931 (20.4)	588/2686 (21.9)

Data presented as *n*/*N* (%) unless noted otherwise.

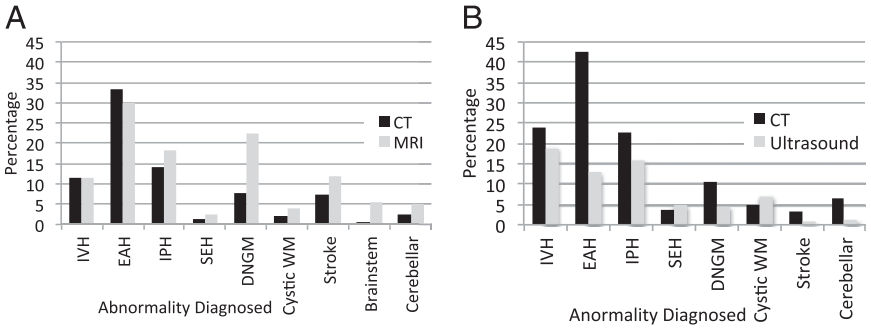

FIGURE 2
Comparison of results of infants imaged with (A) both MRI and CT (*N* = 651) and (B) both cranial ultrasound and CT (*N* = 245). IVH, intraventricular hemorrhage. EAH, extra axial hemorrhage. IPH, intraparenchymal hemorrhage. SEH, subependymal hemorrhage. DNGM, deep nuclear gray matter abnormality. Cystic WM, cystic white matter injury.

Overall, 22.7% of registry infants had at least 1 CT scan. This rate decreased steadily over 5 years (36.2% in 2006, 28.8% in 2007, 23.2% in 2008, 22.3% in 2009, and 15.2% in 2010). During these years, the rates of MRI (53.8% in 2006, 63.8% in 2007, 66.7% in 2008, 67.8% in 2009, and 67.2% in 2010) and ultrasound (36.6% in 2006, 36.6% in 2007, 49.1% in 2008, 53.9% in 2009, and 53.5% in 2010) increased. There was considerable variation among the 95 centers in usage of CT, with a range of imaging of zero to 66.7% and mean (SD) of 22.4 (16.0%). Factors associated with less CT use included the presence of a sentinel event[12] (8.3% vs 25.3%, $P < .001$) and treatment with mechanical ventilation (14.6% vs 38.9%, $P < .001$), whereas more CT imaging were obtained in newborns with birth trauma (39.6% vs 19.9%, $P < .001$).

Six hundred seventy-eight infants in the registry were not evaluated by using any of the 3 neuroimaging modalities. Compared with the imaged infants in the registry, this group was less likely to have received therapeutic hypothermia (12.4% vs 44.0%) and less likely to have seizures in the first 72 hours of life (10.8% vs 67.4%). Yet the mortality rate and frequency of 5-minute Apgar scores ≤3 were higher (16.7% vs 10.8% and 90.9% vs 40.6%, respectively). All 4 of these comparisons were statistically significant with $P < .001$. The surviving nonimaged infants were more likely to have been discharged earlier from the hospital (median [interquartile range], 7 [5–10] vs 13 [9–23] days of life). Additional characteristics are presented in Table 1.

DISCUSSION

Using a large, multicenter database, this study indicates that CT is still commonly used for the evaluation of term and near term infants with suspected brain injury. Our data indicate that CT performs relatively poorly for delineation of the common patterns of brain injury in neonatal encephalopathy, including deep nuclear gray matter and white matter injury. In comparison with MRI, CT detected less than one-third of deep nuclear gray matter injuries and few brainstem or cerebellar lesions. These findings are consistent with previous publications revealing MRI detects brain injuries and malformations in infants that CT misses.[13–15,19,20] Because CT was inferior in detecting pathology in the deep gray matter, white matter, brainstem, and cerebellum, using CT alone for assessing the prognosis may lead to inaccurate counseling.[21,22]

Because CT scanning has inherent risks, one should consider alternative neuroimaging modalities. Physician groups, government organizations, and the media have voiced concerns about the harmful effects of medical radiation and encourage the use of alternative forms of imaging when possible.[4,7,23] Major national and international organizations agree that there is likely no amount of radiation that can be considered absolutely safe.[4] Recent data from irradiated children demonstrate small, but significant increases in cancer risk, even at levels of radiation (25–50 milligray; 1.8–3.8 millisievert) comparable with those produced by

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TABLE 3 Neuroimaging Findings of Infants With 2 Types of Imaging on the Same Day

	Ultrasound Versus CT		Ultrasound Versus MRI		CT Versus MRI	
	Ultrasound	CT	Ultrasound	MRI	CT	MRI
Intraventricular hemorrhage	2/43 (5)	4/43 (9)	3/47 (6)	5/47 (11)	8/70 (11)	9/70 (13)
Extraaxial hemorrhage	2/42 (5)	10/43 (23)	1/46 (2)	11/47 (23)	17/69 (25)	14/70 (20)
Parenchymal hemorrhage	5/42 (12)	7/43 (16)	3/46 (7)	6/47 (13)	10/69 (14)	13/70 (19)
Subependymal hemorrhage	1/42 (2)	2/43 (5)	1/46 (2)	2/47 (4)	0/69 (0)	1/70 (1)
Deep nuclear gray matter abnormality	1/42 (2)	4/42 (10)	4/46 (9)	11/47 (23)	8/69 (12)	18/70 (26)
Cystic white matter injury	0/42 (0)	2/42 (5)	0/46 (0)	4/47 (9)	1/69 (1)	2/70 (3)
Venous or arterial occlusion	0/42 (0)	1/42 (2)	0/46 (0)	2/47 (4)	12/69 (17)	13/70 (19)
Cerebellar injury	1/42 (2)	3/43 (7)	0/46 (0)	4/47 (9)	1/69 (1)	5/70 (7)
Brainstem injury					6/69 (9)	6/70 (9)

Data presented as *n*/*N* (%) unless noted otherwise.

neonatal and pediatric CT scans.[24,25] In addition, radiation may also have harmful cognitive effects. In immature animal models, the cerebellum and cortical migration appear sensitive to damage from radiation.[26,27] In humans, fetal radiation exposures have been linked to neurologic abnormalities,[4,27] whereas infant medical radiation exposures have been associated with impaired cognitive development.[8] The Image Gently campaign promotes reducing the frequency of CT imaging and minimizing medical radiation exposure.[28,29] Further efforts by CT scanner manufacturers, individuals ordering and performing the imaging, the medical education system, and the caregivers of newborns are needed to limit medical radiation exposure in infants.[7,29]

Alternatives to CT for neuroimaging of the neonatal brain are available. Approximately half the registry infants were evaluated with ultrasound in the first week of life. This practice may have been due to the clinical challenges of moving sick infants to either the CT or MRI scanner early during the course of their illness. Prospective trials using cranial ultrasound and MRI in patients with neonatal encephalopathy have demonstrated that, using appropriate technique and equipment, cranial ultrasound detects most injuries.[30–32] However, as used in the registry, the diagnosis with ultrasound of the common patterns of brain injury in neonatal encephalopathy, such as deep nuclear gray matter injury, remains limited. Because cranial ultrasounds were often performed early and deep nuclear injuries may take a few days to be visible on cranial ultrasounds, serial imaging may have improved the sensitivity.

CT use was recommended by the 2002 American Academy of Neurology practice parameters for infants with birth trauma and a low hematocrit or coagulopathy[20] on the basis of interpretation of 2 small studies reporting on CT diagnoses of intracranial hemorrhages leading to interventions.[20,33,34] However, there were no comparisons with cranial ultrasound for these 31 infants. In our patients who underwent 2 imaging modalities, CT was superior to ultrasound for the detection of hemorrhage. Although we were unable to determine the impact of the imaging findings of the infants who needed surgical intervention, only 9 of 933 infants with CT examinations underwent any central nervous system surgery.

Our data support the superiority of MRI in identifying injuries to the deep nuclear gray matter, brainstem, and cerebellum, and perinatal strokes. These lesions are consistent with but not diagnostic of hypoxic-ischemic injury as the major etiology for encephalopathy. Although the respective timing of imaging was not controlled for, assuming an ante- or peri-partum timing to the brain injury in these infants, it appears highly unlikely that the generally later timing of MRI in the registry infants contributes to this superiority. These radiologic findings have major prognostic significance, and thus their identification is valuable to clinicians and caregivers.[21,22]

Despite recommendations for neuroimaging of all infants with neonatal encephalopathy in practice parameters published by the American Academy of Neurology over a decade ago,[20] 16.5% of infants (n = 678) in the registry underwent no neuroimaging. Mortality was higher in this subset, but most of these infants survived (83.3%, n = 563) with relatively short hospitalizations. These apparent paradoxes suggest the group without imaging comprised infants with a heterogeneous mix of severity: either extremely ill or entering into the registry with a low 5-minute Apgar score but rapidly recovering with early discharge. Of additional consideration, in the absence of autopsy, postmortem MRI can be beneficial in determining the etiology of neonatal encephalopathy.[35]

Striving to image all infants with encephalopathy and transitioning from CT to alternative forms of neuroimaging for these newborns are important quality improvement goals. Although our data reveal that the portion of infants in the registry exposed to CT decreased annually from 2006 to 2010, 15.2% in 2010 were still evaluated by using this less sensitive neuroimaging modality with higher risks due to radiation exposure.

Barriers to the transition to MRI include the following: limited data comparing it with other neuroimaging methods, perceptions that sedation is required for successful imaging, difficulty in transporting ill patients to scanners, lack of interpretation expertise, and limited practical understanding of MRI's ability to improve diagnosis and

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delineate brain injury. The safety of nonsedated MRI has been demonstrated.[17] A further concern with MRI has been the length of acquisition time compared with CT scanning for consideration of traumatic or hemorrhagic brain injury. Development of rapid MRI sequences (taking <10 minutes in the MRI room) and new MRI systems located inside intensive care units may reduce these concerns. Although such MRI units are likely to be unavailable in most centers, MRI facilities were available at all units treating patients from this study. Further education and training are needed to enhance the utilization of MRI for newborns with encephalopathy.

CONCLUSIONS

This study has identified key gaps in the implementation of optimal neuroimaging methods to define the nature of brain injury in newborns with encephalopathy. A significant proportion of infants received no neuroimaging evaluation. Many of the cohort infants were exposed to CT scanning, a modality with less sensitivity for brain injury and greater potential harm due to radiation exposures. For infants with neonatal encephalopathy, we conclude that using cranial ultrasound for screening, followed by MRI is more appropriate than CT at any stage of evaluation.

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REFERENCES

1. Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure. *N Engl J Med*. 2007;357(22):2277–2284
2. Frush DP, Applegate K. Computed tomography and radiation: understanding the issues. *J Am Coll Radiol*. 2004;1(2):113–119
3. Miglioretti DL, Johnson E, Williams A, et al. The use of computed tomography in pediatrics and the associated radiation exposure and estimated cancer risk. *JAMA Pediatr*. 2013;167(8):700–707
4. American Academy of Pediatrics. Committee on Environmental Health. Risk of ionizing radiation exposure to children: a subject review. *Pediatrics*. 1998;101(4 pt 1):717–719
5. Brenner D, Elliston C, Hall E, Berdon W. Estimated risks of radiation-induced fatal cancer from pediatric CT. *AJR Am J Roentgenol*. 2001;176(2):289–296
6. Miller RW. Special susceptibility of the child to certain radiation-induced cancers. *Environ Health Perspect*. 1995;103(suppl 6):41–44
7. Amis ES Jr, Butler PF, Applegate KE, et al; American College of Radiology. American College of Radiology white paper on radiation dose in medicine. *J Am Coll Radiol*. 2007;4(5):272–284
8. Hall P, Adami HO, Trichopoulos D, et al. Effect of low doses of ionising radiation in infancy on cognitive function in adulthood: Swedish population based cohort study. *BMJ*. 2004;328(7430):19
9. Adamson SJ, Alessandri LM, Badawi N, Burton PR, Pemberton PJ, Stanley F. Predictors of neonatal encephalopathy in full-term infants. *BMJ*. 1995;311(7005):598–602
10. Badawi N, Kurinczuk JJ, Keogh JM, et al. Antepartum risk factors for newborn encephalopathy: the Western Australian case-control study. *BMJ*. 1998;317(7172):1549–1553
11. Badawi N, Kurinczuk JJ, Keogh JM, et al. Intrapartum risk factors for newborn encephalopathy: the Western Australian case-control study. *BMJ*. 1998;317(7172):1554–1558
12. Nelson KB, Bingham P, Edwards EM, et al. Antecedents of neonatal encephalopathy in the Vermont Oxford Network Encephalopathy Registry. *Pediatrics*. 2012;130(5):878–886
13. Chau V, Poskitt KJ, Sargent MA, et al. Comparison of computer tomography and magnetic resonance imaging scans on the third day of life in term newborns with neonatal encephalopathy. *Pediatrics*. 2009;123(1):319–326
14. Miller SP, Cozzio CC, Goldstein RB, et al. Comparing the diagnosis of white matter injury in premature newborns with serial MR imaging and transfontanel ultrasonography findings. *AJNR Am J Neuroradiol*. 2003;24(8):1661–1669
15. Miller SP, Ferriero DM. From selective vulnerability to connectivity: insights from newborn brain imaging. *Trends Neurosci*. 2009;32(9):496–505
16. van Wezel-Meijler G, Steggerda SJ, Leijser LM. Cranial ultrasonography in neonates: role and limitations. *Semin Perinatol*. 2010;34(1):28–38
17. Mathur AM, Neil JJ, McKinstry RC, Inder TE. Transport, monitoring, and successful brain MR imaging in unsedated neonates. *Pediatr Radiol*. 2008;38(3):260–264
18. Pfister RH, Bingham P, Edwards EM, et al. The Vermont Oxford Neonatal Encephalopathy Registry: rationale, methods, and initial results. *BMC Pediatr*. 2012;12(1):84
19. Hsieh DT, Chang T, Tsuchida TN, et al. New-onset afebrile seizures in infants: role of neuroimaging. *Neurology*. 2010;74(2):150–156
20. Ment LR, Bada HS, Barnes P, et al. Practice parameter: neuroimaging of the neonate: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2002;58(12):1726–1738
21. Martinez-Biarge M, Diez-Sebastian J, Kapellou O, et al. Predicting motor outcome and death in term hypoxic-ischemic encephalopathy. *Neurology*. 2011;76(24):2055–2061
22. Martinez-Biarge M, Diez-Sebastian J, Rutherford MA, Cowan FM. Outcomes after central grey matter injury in term perinatal hypoxic-ischaemic encephalopathy. *Early Hum Dev*. 2010;86(11):675–682
23. Bogdanich W. After Stroke Scans, Patients Pace Serious Health Risks. *The New York Times*. August 1, 2010;Section A1
24. Hall EJ, Brenner DJ. Cancer risks from diagnostic radiology. *Br J Radiol*. 2008;81(965):362–378
25. Pearce MS, Salotti JA, Little MP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet*. 2012;380(9840):499–505
26. Cui L, Pierce D, Light KE, et al. Sublethal total body irradiation leads to early cerebellar damage and oxidative stress. *Curr Neurovasc Res*. 2010;7(2):125–135
27. Schull WJ. Brain damage among individuals exposed prenatally to ionizing radiation: a 1993 review. *Stem Cells*. 1997;15(suppl 2):129–133
28. Goske MJ, Applegate KE, Boylan J, et al; Alliance for Radiation Safety in Pediatric Imaging. Image Gently(SM): a national education and communication campaign in radiology

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using the science of social marketing. *J Am Coll Radiol*. 2008;5(12):1200–1205

29. Amis ES Jr, Butler PF; American College of Radiology. ACR white paper on radiation dose in medicine: three years later. *J Am Coll Radiol*. 2010;7(11):865–870
30. Eken P, Jansen GH, Groenendaal F, Rademaker KJ, de Vries LS. Intracranial lesions in the fullterm infant with hypoxic ischaemic encephalopathy: ultrasound and autopsy correlation. *Neuropediatrics*. 1994; 25(6):301–307
31. Epelman M, Daneman A, Kellenberger CJ, et al. Neonatal encephalopathy: a prospective comparison of head US and MRI. *Pediatr Radiol*. 2010;40(10):1640–1650
32. Rutherford MA, Pennock JM, Dubowitz LM. Cranial ultrasound and magnetic resonance imaging in hypoxic-ischaemic encephalopathy: a comparison with outcome. *Dev Med Child Neurol*. 1994;36(9):813–825
33. Odita JC, Hebi SCT. CT and MRI characteristics of intracranial hemorrhage complicating breech and vacuum delivery. *Pediatr Radiol*. 1996;26(11):782–785
34. Perrin RG, Rutka JT, Drake JM, et al. Management and outcomes of posterior fossa subdural hematomas in neonates. *Neurosurgery*. 1997;40(6):1190–1199, discussion 1199–1200
35. Nicholl RM, Balasubramaniam VP, Urquhart DS, Sellathurai N, Rutherford MA. Postmortem brain MRI with selective tissue biopsy as an adjunct to autopsy following neonatal encephalopathy. *Eur J Paediatr Neurol*. 2007;11(3):167–174

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APPENDIX Hospitals Registering Infants in the VON Neonatal Encephalopathy Registry, 2006–2010

Name	City	State	Country
Cork University Maternity Hospital	Cork	—	Ireland
National Maternity Hospital	Dublin	—	Ireland
Rotunda Hospital	Dublin	—	Ireland
Hospital de S. Joao	Porto	—	Portugal
Hospital Sant Joan de Deu	Barcelona	—	Spain
Latifa Hospital	Dubai	—	United Arab Emirates
Southmead Hospital	Bristol	—	United Kingdom
Arkansas Children's Hospital	Little Rock	Arkansas	United States
University of California Irvine Medical Center	Orange	California	United States
Sharp Mary Birch Hospital for Women	San Diego	California	United States
Santa Clara Valley Medical Center	San Jose	California	United States
The Children's Hospital	Aurora	Colorado	United States
Exempla St. Joseph Hospital	Denver	Colorado	United States
Poudre Valley Health System	Fort Collins	Colorado	United States
Yale New Haven Children's Hospital	New Haven	Connecticut	United States
Christiana Care Health Services	Newark	Delaware	United States
Golisano Children's Hospital of Southwest Florida	Fort Myers	Florida	United States
Baptist Children's Hospital	Miami	Florida	United States
Miami Children's Hospital	Miami	Florida	United States
St. Joseph's Children's Hospital	Tampa	Florida	United States
Tampa General Hospital	Tampa	Florida	United States
The Medical Center at Columbus Regional	Columbus	Georgia	United States
St. Luke's Regional Medical Center	Boise	Idaho	United States
Evanston Hospital	Evanston	Illinois	United States
Edward Hospital and Health Services	Naperville	Illinois	United States
Advocate Children's Hospital, Park Ridge	Park Ridge	Illinois	United States
Rockford Memorial Hospital	Rockford	Illinois	United States
St. John's Hospital	Springfield	Illinois	United States
Carle Foundation Hospital	Urbana	Illinois	United States
Central DuPage Hospital	Winfield	Illinois	United States
St. Luke's Hospital	Cedar Rapids	Iowa	United States
Blank Children's Hospital	Des Moines	Iowa	United States
Overland Park Regional Medical Staff	Overland Park	Kansas	United States
Wesley Medical Center	Wichita	Kansas	United States
Kosair Children's Hospital	Louisville	Kentucky	United States
Woman's Hospital	Baton Rouge	Louisiana	United States
Eastern Maine Medical Center	Bangor	Maine	United States
Barbara Bush Children's at Maine Medical	Portland	Maine	United States
University of Maryland Division of Neonatology	Baltimore	Maryland	United States
Frederick Memorial Hospital	Frederick	Maryland	United States
Massachusetts General Hospital for Children	Boston	Massachusetts	United States
University of Massachusetts Memorial Healthcare	Worcester	Massachusetts	United States
University of Michigan, CS Mott Children's, Brandon NICU	Ann Arbor	Michigan	United States
Henry Ford Hospital	Detroit	Michigan	United States
DeVos Children's, Spectrum Health	Grand Rapids	Michigan	United States
Sparrow Hospital	Lansing	Michigan	United States
University of Minnesota Amplatz Children's Hospital	Minneapolis	Minnesota	United States
North Memorial Medical Center	Robbinsdale	Minnesota	United States
St. Cloud Hospital	Saint Cloud	Minnesota	United States
St. Francis Medical Center, Cape Girardeau	Cape Girardeau	Missouri	United States
Cardinal Glennon Children's Hospital	St. Louis	Missouri	United States
St. Louis Children's Hospital	St. Louis	Missouri	United States
St. Elizabeth Regional Medical Center	Lincoln	Nebraska	United States
Alegent Health Bergan Mercy Medical Center	Omaha	Nebraska	United States
Nebraska Medical Center	Omaha	Nebraska	United States
Albany Medical Center	Albany	New York	United States
Weiler Hospital Montefiore	Bronx	New York	United States

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APPENDIX Continued

Name	City	State	Country
Winthrop University Hospital	Mineola	New York	United States
Columbia University Medical Center	New York	New York	United States
Golisano Children's Hospital at Strong	Rochester	New York	United States
Mission Children's Hospital	Asheville	North Carolina	United States
Duke University	Durham	North Carolina	United States
Cape Fear Valley Medical Center	Fayetteville	North Carolina	United States
Women's Hospital of Greensboro	Greensboro	North Carolina	United States
Vidant Medical Center	Greenville	North Carolina	United States
WakeMed Faculty Physicians, Wake Medical Center	Raleigh	North Carolina	United States
Brenner Children's Hospital at Wake Forest University Baptist Medical Center	Winston-Salem	North Carolina	United States
Akron Children's Hospital	Akron	Ohio	United States
Children's Hospital Medical Center Cincinnati	Cincinnati	Ohio	United States
Henry Zarrow Neonatal ICU	Tulsa	Oklahoma	United States
Rogue Regional Medical Center	Medford	Oregon	United States
Providence St. Vincent Medical Center	Portland	Oregon	United States
Randall Children's Hospital at Legacy Emanuel	Portland	Oregon	United States
Salem Hospital	Salem	Oregon	United States
Sacred Heart Medical Center	Springfield	Oregon	United States
St. Luke's University Hospital	Bethlehem	Pennsylvania	United States
Geisinger Medical Center	Danville	Pennsylvania	United States
Pennsylvania State Children's Hospital	Hershey	Pennsylvania	United States
Thomas Jefferson University Hospital	Philadelphia	Pennsylvania	United States
Magee Women's Hospital	Pittsburgh	Pennsylvania	United States
Palmetto Health Richland	Columbia	South Carolina	United States
Children's Hospital of Greenville	Greenville	South Carolina	United States
University of Tennessee Medical Center	Knoxville	Tennessee	United States
Baptist Memorial Hospital for Women	Memphis	Tennessee	United States
Monroe Carell Jr. Children's Hospital Vanderbilt	Nashville	Tennessee	United States
Cook Children's Medical Center	Fort Worth	Texas	United States
Children's Hospital of San Antonio	San Antonio	Texas	United States
Methodist Children's Hospital	San Antonio	Texas	United States
Vermont Children's at Fletcher Allen Health Care	Burlington	Vermont	United States
Carilion Clinic Children's Hospital	Roanoke	Virginia	United States
Swedish Medical Center	Seattle	Washington	United States
West Virginia University School of Medicine	Morgantown	West Virginia	United States
Gundersen Lutheran Medical Center	La Crosse	Wisconsin	United States
St. Mary's Hospital Medical Center	Madison	Wisconsin	United States
Wheaton Franciscan Healthcare at St. Joseph	Milwaukee	Wisconsin	United States

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