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Position Statement

Canadian Paediatric Society

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Position Statement

Routine imaging of the preterm neonatal brain

Mireille Guillot, Vann Chau, Brigitte Lemyre

Canadian Paediatric Society, Fetus and Newborn Committee, Ottawa, Ontario

Correspondence: Canadian Paediatric Society, 100–2305 St Laurent Blvd, Ottawa, Ontario K1G 4J8. E-mail info@cps.ca, website www.cps.ca

Abstract

Routine brain imaging to detect injuries affecting preterm infants is used to predict long-term outcomes and identify complications that might necessitate an intervention. Although magnetic resonance imaging may be indicated in some specific cases, head ultrasound is the most widely used technique and, because of portability and ease of access, is the best modality for routine imaging. Routine head ultrasound examination is recommended for all infants born at or before 31+6 weeks gestation. For preterm neonates born between 32+0 to 36+6 weeks gestation, routine head ultrasound is recommended only in presence of risk factors for intracranial hemorrhage or ischemia. Brain imaging in the first 4 to 7 days postbirth is advised to detect most germinal matrix and intraventricular hemorrhages. Repeat imaging at 4 to 6 weeks of age is recommended to detect white matter injury. In preterm neonates born before 26 weeks gestation, a repeat HUS at term-equivalent age is recommended.

Keywords: *Computed tomography; Germinal matrix hemorrhage; Head ultrasound; Intraventricular hemorrhage; Magnetic resonance imaging; Periventricular hemorrhagic infarction; Periventricular leukomalacia; Post-hemorrhagic ventricular dilation*

BACKGROUND

The preterm infant's brain is at greater risk of hypoxic, hemorrhagic, or inflammatory injury than the term infant's brain. Intracranial hemorrhage and white matter insult are the two most significant brain injuries that can affect the preterm brain, and both are associated with adverse neurodevelopmental outcomes, including cerebral palsy (CP) (1–6). When interpreted in conjunction with other clinical information, brain imaging can help direct parental counselling on prognosis and possible outcomes.

Head ultrasound (HUS) is the most widely used technique for imaging the neonatal brain. HUS reliably detects intraventricular hemorrhage (IVH) and cystic periventricular leukomalacia (PVL). Magnetic resonance imaging (MRI) has been shown to be superior for detecting noncystic white matter lesions (2–4,7,8).

A previous Canadian Paediatric Society position statement, published in 2001, focused on ultrasound imaging. The wider availability of MRI, improved ultrasound techniques, and increasing rates of survival at very low gestational ages (GA), have changed the clinical picture. This revised statement discusses the most common preterm brain injuries, explains their origins and trajectories, and provides guidance on whom to routinely screen, when, and using what imaging modality, within the capacity and limitations of the Canadian health care system.

METHODS—SYSTEMATIC REVIEW OUTLINE

A comprehensive, systematic search of the literature published between 2000 and 2017 was conducted, using MEDLINE,

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Embase, and the Cochrane Collaboration Registry of Controlled Trials. Search terms included cranial ultrasound (or head ultrasound), head MRI (or brain MRI), head computed tomography (CT) (or head CT scan), germinal matrix (GM) hemorrhage, IVH, brain injury, ventriculomegaly, echodensity, porencephaly, PVL, white matter injury (WMI), and preterm infant (or newborn or neonate). Original articles on diagnosis and prognosis were rated, and strength of recommendations were graded using the classification and levels described in a practice parameter for neonatal neuroimaging published in 2002 by the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (9). Additionally, a targeted literature search (2017–2020) was performed specifically related to IVH and brain injury.

DISEASE PROCESS AND RISK FACTORS

The preterm infant's brain is more vulnerable to both hemorrhagic and ischemic brain injury than the term infant, due to vascular, cellular, and anatomical features of the developing brain. The pathogenesis of IVH is explained by the fragility of the GM and fluctuations in cerebral blood flow during a period of physiological instability and limited cerebral autoregulation (10). Risk factors leading to fluctuations in cerebral blood flow include: variation in systemic blood pressure, anemia, hypo- or hypercarbia, acidosis, patent ductus arteriosus (PDA), severe respiratory distress syndrome (RDS), and pneumothorax (11,12).

The subependymal GM, a highly vascularized region of the brain, is extremely fragile and the primary source of bleeding within the cerebral ventricles, causing IVH. The hemorrhage may be confined to the GM (germinal matrix hemorrhage or GMH) or spread throughout the ventricular system (IVH). Periventricular hemorrhagic infarction (PVHI) is a characteristic parenchymal lesion usually associated with severe IVH (13,14). PVHI represents a venous hemorrhagic infarct in the drainage area of the periventricular terminal veins and typically leads to cystic changes in periventricular white matter (porencephalic cyst) (8). The GM involutes with time and is almost absent by 34 to 36 weeks postmenstrual age. The incidence of IVH is therefore infrequent past that period of brain development (11).

Thirty to 50 per cent of the infants with severe IVH develop post-hemorrhagic ventricular dilation (PHVD), which may stop spontaneously (nonprogressive condition) or continue (progressive condition requiring intervention). PHVD is typically seen 7 to 14 days after an IVH has occurred, and is usually associated with severe IVH (15–17).

More recently, cerebellar injury, which is better assessed using MRI or ultrasound (mastoid view), has also been recognized as a relatively frequent form of brain injury and is associated with a broad spectrum of developmental disabilities (18). Cerebellar injury is reported in 10% to 20% of preterm infants less than 32 to 34 weeks GA (19,20).

Although hemorrhagic and ischemic injuries are caused by different pathophysiological processes, they often occur together. The vascular structure of the cerebral white matter in mid- to late gestation includes long, penetrating arteries that originate from the anterior, middle, and posterior cerebral arteries. These arteries are especially prone to hypoperfusion and ischemia, with increased likelihood of necrotic damage along their course or in their end zones, in the periventricular area. The WMI pattern in the form of cystic PVL has declined significantly in the last decades (21), and shifted to a more subtle, noncystic and diffuse WMI that is better recognized using MRI (22,23).

CLASSIFICATION OF ABNORMAL FINDINGS

Different systems have been suggested for classifying and grading GMH and IVH (13,24,25). The Papile grading system (24), first described in 1978 using CT scan images, has been adapted for other imaging modalities (notably HUS and MRI), and is still the most commonly used IVH grading system in Canadian centres. The Papile grading system is used in this statement because of its prevalence, but a reporting radiologist should always specify the grading system being used, and describe abnormal findings in detail, when interpreting any imaging study.

As per Papile's description, severity of hemorrhage is based on the extent of bleeding, parenchymal involvement, and the presence of ventricular distension: Grade 1 IVH is limited to the GM; Grade 2 IVH involves blood in the ventricles; Grade 3 IVH has blood filling and distending the ventricular system; Grade 4 refers to parenchymal involvement with hemorrhage. The Papile system does not specifically include white matter lesions in brain locations other than periventricular areas, or lesions in the cerebellum, basal ganglia, and brainstem.

Grades 1 and 2 IVH are considered to be mild, while Grades 3 and 4 are considered severe. While this differentiation aids description, it can lead to confusion between PHVD and Grade 3 IVH. The other important limitation of this classification is the wide spectrum of entities that can be considered to be Grade 4 IVH. This definition encompasses bleeding that extends into the parenchyma and is consistent with PVHI, echogenicity in the parenchyma that could be ischemic, and isolated parenchymal bleeding. Depending on the locus and extent of injury, severity and outcomes can vary widely. The Bassan scoring system, which was developed for PVHI specifically, assessed severity

of brain injury and associated abnormal outcomes (25). This scoring system is based on the maximal size of a PVHI (i.e., territories involved), whether it is unilateral or bilateral, and midline shift.

One of the most commonly used grading systems for PVL on HUS describes four grades of severity: Grade 1 involves transient periventricular areas with increased echogenicity for 7 days or more; Grade 2 includes small, localized fronto-parietal cysts; Grade 3 presents with extensive periventricular cystic lesions; and Grade 4 involves areas of increased echogenicity in deep white matter which are evolving into extensive cystic lesions (26).

WHO SHOULD GET NEUROIMAGING?

Because GMH-IVH and ischemic WMI occur more often in preterm infants (and much more often in infants born before 32 weeks GA), routine HUS examinations are most valuable for this group. Both risk and severity of GMH-IVH increase with decreasing GA, as shown in Table 1. Moreover, 25% to 50% of GMH-IVH cases are clinically asymptomatic and are, therefore, only detectable by routine imaging (13).

Although prematurity is the predominant risk factor for IVH, additional risk factors include low birth weight (BW less than 1,000 g), lack of maternal prenatal corticosteroid use, birth outside of a tertiary care centre, and histological chorioamnionitis (11,27,28). Events leading to cerebral blood flow instability (e.g., respiratory distress with acidosis, hypo- or hypercarbia, or rapid changes in blood pressure due to cardiorespiratory instability) in the early postnatal course have also been associated with GMH-IVH.

The risk decreases considerably after 32 weeks GA, with severe anomalies on HUS (Grades 3 and 4 IVH or PVL) being reported in 0.2% to 4% of infants (29,30). In the late and moderately preterm infant, risk factors for abnormal brain imaging include lower GA, head circumference below the third percentile, need for resuscitation at birth or critical care out of keeping with the usual neonatal course (e.g., need for mechanical ventilation or inotropes in the first 24 hours postbirth), complicated monochorionic twin pregnancy (e.g., selective intrauterine growth restriction [IUGR] or fetal demise), and postnatal complications (particularly sepsis, necrotizing enterocolitis [NEC], major surgery, or acute clinical deterioration) (30–32).

HUS should be considered for all infants with abnormal neurological signs (e.g., altered level of consciousness, abnormal tone, or seizures), a critical illness, or other significant risk factors (11,13).

WHAT IMAGING MODALITIES ARE AVAILABLE?

Ultrasound (US)

US has several advantages over computed tomography (CT) and MRI. It is safe (US has no ionizing radiation, unlike CT), portable, easily repeated, usually readily available, economical, and requires no special preparation. In preterm infants, obtaining views through anterior and mastoid fontanels permits good visualization of the ventricular system, white matter, and cerebellum. US is ideal for detecting GMH-IVH, large cerebellar bleeds, and large cysts and echogenic areas in white matter. One disadvantage is that US is operator-dependent, and subtle lesions may be missed in less experienced hands.

Table 1. Head ultrasound findings by GA (Canadian Neonatal Network 2014/2016)

Weeks GA	Number with available imaging	GM hemorrhage Number (per cent) (Grade 1 IVH)	Intraventricular hemorrhage (IVH) (Grade 2 and 3 IVH)	Intraparenchymal lesion (Grade 4 IVH)	PVL
22	29	10 (34%)	14 (48%)	3 (10%)	0
23	218	128 (59%)	114 (52%)	45 (21%)	17 (8%)
24	548	272 (50%)	248 (45%)	103 (19%)	27 (5%)
25	719	303 (42%)	233 (32%)	87 (12%)	40 (5.6%)
26	844	295 (35%)	224 (27%)	68 (8%)	35 (4%)
27	969	282 (29%)	171 (18%)	46 (4.7%)	23 (2.4%)
28	1166	266 (23%)	145 (12%)	34 (2.9%)	29 (2.5%)
29	1286	278 (22%)	150 (12%)	30 (2.3%)	28 (2.2%)
30	1397	243 (17%)	81 (6%)	19 (1.4%)	25 (1.8%)
31	1601	237 (15%)	78 (5%)	19 (1.2%)	20 (1.2%)
32	1303	155 (12%)	56 (4.3%)	18 (1.4%)	14 (1.1%)

Data excludes moribund infants, those with major congenital anomalies, and those with no neuroimaging results. Imaging findings were not mutually exclusive (i.e., a neonate may have had more than one finding).

GA Gestational age; GM Germinal matrix; IVH Intraventricular hemorrhage; PVL Periventricular leukomalacia.

Computed tomography

CT has been used to assess for calcifications, hemorrhage, brain injury, and edema secondary to hypoxia-ischemia, venous sinus thrombosis, masses, and structural abnormalities, but this modality is now largely supplanted by MRI due to the ionizing radiation required for imaging. Except for emergencies, CT scans are now generally avoided for newborn imaging.

Magnetic resonance imaging

MRI offers the highest resolution for detecting and quantifying WMI, low-grade IVH, cerebral malformation, and posterior fossa abnormalities, due to its greater neuroanatomical definition (11,33,34). MRI can also help with diagnosing inborn errors of metabolism (35). WMI is the most common finding seen on MRI in preterm infants. Such injuries include cystic and punctate lesions, delayed myelination, volume loss, thinning of the corpus callosum, and diffuse excessive high signal intensity (DEHSI) (36). MRI is an expensive, time- and resource-consuming technique that is not always available, often requires transport, and may require sedation (2). MRI before term-corrected age can be challenging to organize in critically ill infants (33).

US AND MRI AS PREDICTIVE TOOLS

The strongest predictors of abnormal neuromotor function on US include severe IVH (Papile Grades 3 and 4), cystic PVL, and PHVD (37). For MRI imaging at term-equivalent age, moderate-to-severe WMI, cerebellar injury, and abnormal myelination in the posterior limb of internal capsule (PLIC) are the main predictors of motor impairment (4,36,37). Any combination of these predictors increases risk for adverse motor outcomes. The predictive value of both HUS and MRI for neurocognitive and behavioural impairments is limited (4). One systematic review and meta-analysis showed that moderate-to-severe MRI abnormalities at term-corrected age predicted CP with only moderate sensitivity and specificity (77% sensitivity and 79% specificity). Motor function was predicted with 72% sensitivity and 62% specificity (38). Another study showed that in infants with Grade 4 IVH, absence of myelin in the PLIC was strongly predictive of future hemiplegia (39).

Several studies have compared HUS with MRI as diagnostic and prognostic tools in the preterm population. Limitations when interpreting results from these studies include the lack of serial US and different time points for assessment. In a cohort of 167 very preterm infants (at or under 30 weeks GA), conventional MRI at term age was reported to be superior to early serial (at or under 6 weeks) HUS in predicting motor outcomes at 2 years of age (3). However, studies comparing near-term HUS and MRI at term showed that any substantial abnormalities on MRI were also detected on HUS (2,40). Furthermore, adverse HUS findings at term were associated with adverse neurodevelopmental outcomes, although a significant proportion of patients with an abnormal HUS did not have severe neurodevelopmental impairment at 18 to 20 months (5). One study compared the predictive capability of MRI and/or HUS near-term in a cohort of 445 extremely preterm infants (5). While combining both neuroimaging techniques offered the best predictive value, the improvement with adding MRI was only marginal. The value of routine MRI at term over sequential HUS from birth to term remains an area of active research. Newer MRI classifications and scoring systems seem to yield better predictive values, but their applicability in the clinical setting remains to be determined (38,41-43).

Furthermore, health-related costs and the parental anxiety associated with imaging modalities should be considered. One recent study compared maternal anxiety and cost:benefit ratios of MRI versus HUS when performed at term-equivalent age in infants born less than 33 weeks GA. While maternal anxiety levels decreased after receiving the results of either imaging modality, they were slightly lower after MRI. Meanwhile, health-related costs increased (44).

Neuroimages should always be interpreted with caution, in consultation with experienced HCPs, and in conjunction with other clinical information. Abnormal neuroimaging findings may not necessarily predict severe neurodevelopmental impairment, just as normal brain imaging is no guarantee of normal development (3,5,44). Many risks and protective factors need to be accounted for when predicting neurological outcomes. Risks include the neonatal complications of prematurity (such as bronchopulmonary dysplasia, retinopathy of prematurity, sepsis, and poor growth), genetic conditions, and socio-familial factors (36).

WHEN SHOULD NEUROIMAGING TAKE PLACE?

Among infants who develop GMH or IVH, about 50% present on the first day after birth, 25% on day 2, and 15% on day 3 (13). Approximately 20% to 40% of these infants exhibit progression of hemorrhage over 3 to 5 days (8,13). Table 2 summarizes optimal timelines and modalities, based on GA and risk factors.

Imaging in the first 4 to 7 days postbirth will diagnose most GMH-IVHs and might detect early ventricular dilatation (16,45-47). Brain imaging performed early in life can contribute to identify antenatal brain injury or findings in keeping with metabolic or genetic disorder. For portability and ease of access, HUS is the best imaging modality.

For extremely ill, extremely low (less than 26 weeks) GA infants, when severe bleeding or injury might inform shared decision-making with parents regarding goals and direction of care, an ultrasound in the first few days after birth may be considered.

Table 2. Suggested timelines and modality for routine imaging by GA[1]

GA	First imaging	Repeat imaging*	Term-corrected imaging
≤31+6 weeks	HUS 4 to 7 days postbirth	4–6 weeks postbirth	Routinely for neonates born before 26 weeks Not routinely for neonates born between 26+0 and ≤31+6 weeks[†]
≥32+0 to 36+6 weeks with additional risk factors[‡]	HUS 4 to 7 days postbirth	4–6 weeks postbirth, and only if first image is abnormal	Not routinely

[1]This HUS schedule is for routine surveillance of preterm infants with uncomplicated clinical course and should be intensified if clinically indicated or in the presence of anomalies detected on HUS.

GA Gestational age; HUS Head ultrasound; IVH Intraventricular hemorrhage; NEC Necrotizing enterocolitis; PHVD Post-hemorrhagic ventricular dilation; PVL Periventricular leukomalacia; WMI White matter injury.

*If an abnormality (Grade 2 or higher IVH or WMI) is detected on first imaging, a repeat HUS should be performed 7–10 days later. If ventricular dilation or worsening IVH/WMI is detected, the frequency of HUS should be intensified (at least weekly initially and as clinically indicated thereafter). A repeat HUS should also be conducted in the weeks following acute illness (e.g., NEC or sepsis).

[†]HUS between 37 and 42 weeks corrected GA if previous moderate-to-severe anomalies (Grade 3 or higher IVH, PHVD, or Grade 3–4 PVL) on HUS, or presence of additional risk factors (e.g., critical illness requiring mechanical ventilation or vasopressors, NEC, major surgery).

[‡]Additional risk factors for the late and moderately preterm infant include: need for critical care out of keeping with the usual neonatal course, complicated monochorionic twin pregnancy, microcephaly, complicated postnatal course: sepsis, NEC, major surgery, or abnormal neurological symptoms.

Sequential imaging allows for the detection and, if needed, early treatment of complications, including PHVD (16,45–47). Repeat scans also optimize the diagnosis of WMI. PVL tends to occur 2 to 6 weeks post ischemia or infection/inflammation and to resolve within several weeks (48,49). Some children born at or before 32 weeks GA may develop periventricular cysts beyond 28 days, especially following an acute illness, such as NEC or a severe infection (32). In more than 50% of infants with localized cystic PVL, cysts are no longer seen at term-equivalent age and, in most but not all cases, ventriculomegaly is found instead. A repeat HUS is indicated at 4 to 6 weeks of age to detect WMI. For the same reason, a repeat HUS should also be conducted in the weeks following acute illness (e.g., NEC or sepsis). Additionally, for the more preterm neonates (born before 26 weeks gestation), repeat brain imaging closer to term-equivalent age improves the detection of cystic PVL (48).

When the first brain imaging is abnormal (Grade 2 or higher IVH or in the presence of WMI), a repeat HUS should be performed 7 to 10 days later to detect complications, such as PHVD. If ventricular dilation is present, the frequency of HUS should be intensified: at least weekly initially and as clinically indicated thereafter. These more frequent ultrasounds would avoid the undesirable situations where imaging is needed urgently following a rapid increase in an infant's head circumference or other signs of rising intracranial pressure.

Imaging at 37 to 42 weeks GA can show WMI, ventriculomegaly (following WM disease or secondary to PHVD) and structural anomalies (48). A repeat HUS between 37 and 42 weeks corrected GA is recommended for infants born before 26 weeks gestation and for infants with moderate-to-severe anomalies on HUS (Grade 3 or higher IVH, PHVD, or Grade 3 to 4 PVL) or additional risk factors (e.g., illness requiring mechanical ventilation or vasopressors, NEC, major surgery).

Images provided by MRI are superior in quality and more inclusive. MRI can quantify growth and maturation of brain structures, and detect noncystic WMI, which may be harder to see on US (50). However, the long-term predictive value of such findings remains limited. In infants with moderate-to-severe anomalies on HUS, or when risk for WMI is greater, a term-corrected MRI may be considered, always weighing in cost, need to transport, the infant's clinical stability and the clinical purpose of imaging (e.g., whether it will influence access to specialized medical care).

The following recommendations for practice are based on the best available evidence:

1. Routine head ultrasound (HUS) examinations are recommended for all infants born at or before 31+6 weeks GA in the first 4 to 7 days postbirth to detect GMH-IVH and early ventricular dilatation. Repeat imaging at 4 to 6 weeks is recommended to detect white matter injury (WMI)

(Grade A recommendation). This HUS schedule is for routine surveillance of preterm infants with uncomplicated clinical course and should be intensified if clinically indicated or in the presence of anomalies detected on HUS.

2. If an abnormality (Grade 2 or higher IVH or WMI) is detected on routine imaging, a repeat HUS should be performed 7 to 10 days later. If ventricular dilatation or worsening PHVD is detected, the frequency of HUS should be intensified (at least weekly initially and as clinically indicated thereafter). Additional brain imaging should be considered after episodes of acute illnesses (e.g., sepsis, necrotizing enterocolitis [NEC]). (Grade B recommendation).
3. For preterm infants born before 26 weeks gestation, HUS at term-corrected age is recommended. For infants born between 26+0 and 31+6 weeks GA, HUS at term-corrected age is recommended in the presence of additional risk factors or previous moderate-to-severe anomalies on HUS (Grade 3 or higher IVH, PHVD, or Grades 3 to 4 PVL) (Grade A recommendation.
4. For the late and moderately preterm infant (32+0 to 36+6 GA), HUS examination is not recommended routinely. At the clinician's discretion, an HUS can be considered when risk factors have been identified (e.g., the need for resuscitation or critical care out of keeping with the usual neonatal course for GA, a complicated monochorionic twin pregnancy, microcephaly, or a postnatal course complicated by sepsis, NEC, major surgery, or abnormal neurological signs) (Grade B recommendation).
5. Despite good predictive values, routine term-corrected MRI is not recommended at this time given the limited accessibility and expertise in many Canadian NICUs. However, a brain MRI at term-corrected age may be considered for infants with moderate-to-severe anomalies on HUS (Grade 3 or higher IVH, PHVD, or Grades 3 to 4 PVL), when clinical risk for WMI is increased, or when parental reassurance is needed. Cost, need to transport, the infant's clinical stability, and relevance for treatment are factors to be considered when making this decision (Grade C recommendation).
6. Brain images should be interpreted in consultation with an experienced specialist and in conjunction with other clinical information. In isolation, brain imaging has only moderate predictive value, and multiple factors need to be taken into account when predicting neurodevelopmental outcomes (Grade B recommendation).

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