PEDIATRIC NEWBORN MEDICINE CLINICAL PRACTICE GUIDELINES

Term-Equivalent Brain MRIs For Very Preterm Infants

Clinical Practice Guideline: Term-Equivalent Brain MRIs For Very Preterm Infants

Points of emphasis/Primary changes in practice include:

1. Recommendations for which preterm infants should receive a term-equivalent MRI
2. Expanding knowledge on interpretation of term-equivalent MRIs using a scoring system for abnormal findings
3. Recommendations for discharge coordination and outpatient follow-up if abnormalities are detected

Rationale for change:

Given current controversy on which preterm infants should be offered term-equivalent MRIs and how to best interpret and utilize results, this guideline was created by the MRI working group with a goal to maximize use of best practices.

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This is a clinical practice guideline. While the guideline is useful in approaching the use of term-equivalent brain MRI in very preterm infants, clinical judgment and/or new evidence may favor an alternative plan of care, the rationale for which should be documented in the medical record.

I. Purpose and Background

Preterm delivery is associated with greater risk of poor neurodevelopmental outcomes, including cerebral palsy, intellectual disability, sensory impairments, language delays, visual-perceptual disorders, learning disabilities and behavior problems.[1] While severe intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) detected by head ultrasound (HUS) have been invariably associated with poor outcome,[2-6] many preterm infants without evidence of these injuries go on to have neurodevelopmental impairment after leaving the neonatal intensive care unit (NICU).[7] Other tools to identify patients with less apparent brain injury or dysmaturity are needed.[8]

Although there is an agreement that MRI gives a more detailed picture of brain structure and can identify even minor abnormalities, its role as a predictive tool has been the area of active past and ongoing research. The degree of technical difficulty associated with performing an MRI on a preterm infant has fallen with the development of MRI compatible incubators, monitoring devices, ventilators, and immobilizing devices that decrease the need for sedation.[9-11] Whether term-equivalent MRI (TE MRI) should be utilized as a routine screening for all premature infants has been an area of major controversy.[12-15] However, in a center which offers the resources to perform this study without sedation and allows for accurate interpretation of results, an MRI can provide very valuable information to parents and providers who will care for the infant in the future.

Over the years, many techniques, and scoring systems have been examined. Currently, the most promising practical findings are: white matter injury (WMI), abnormal brain growth, deep grey matter injury, and cerebellar lesions.[16]

1. White Matter Injury (WMI) and Outcome

Overall, white matter injury has been associated with worsened motor and cognitive outcomes.

For motor outcomes, WMI in TE MRI was associated with increased motor delay and cerebral palsy (CP) at 24 months of age.[11] The MRI features that are most strongly related to CP at 30 months of age are severe white matter reduction, cystic lesions, and delayed myelination.[17] At 5 years of age, compared with very premature infants without WMI, those with moderate-to-severe WMA were 19 times more likely to have a significant motor impairment, and those with mild WMA were 5.6 times more likely to have a significant motor impairment.[18]

For cognitive outcomes, WMI was associated with delayed cognitive development on the Bayley Scale of Infant Development at 18 months of age[19]. Cognitive development scores at 24 months of age decreased with increasing severity of WMA.[11] At 6 years of age, with increasing severity of WMI, an increase in general intellectual, language, and executive functioning impairment was also noted.[20] Finally, WMI has also been reported to be associated with language development, learning capacity, attention, and processing speed delays at 7 years of age.[21-23]

2. Abnormal Brain Growth

Kidokoro *et al*. studied 3 very preterm cohorts (n = 325), and proposed the following measurements as helpful indicators of abnormal brain growth. Decreased biparietal width (BPW) was related to lower gestational age, need for inotropic support, patent ductus arteriosus, necrotizing enterocolitis, prolonged parenteral nutrition, and oxygen at 36 weeks. Decreased BPW was also associated with delayed cognitive development. Increased interhemispheric distance (IHD) was related to male gender, postnatal dexamethasone use, and severe brain injury. It was also associated with reduced cognitive development, independent of BPW. The children who had both small BPW and increased IHD had the poorest cognitive and motor development at 24 months of age, even in the absence of high-grade injury.[24]

3. Deep Grey Matter

In 70 infants < 32 weeks GA who had an MRI within 2 weeks of life and at term-equivalent and were followed up to 4 years of age (n= 53), growth of the caudate and globus pallidus predicted visual motor integration. Growth of the caudate and putamen nuclei was associated with IQ and language scores.[25]

4. Cerebellar Lesions

When 35 preterm infants with isolated cerebellar injury were evaluated at a mean age of 32 months, a variety of developmental delays were found: neurologic abnormalities (66%), severe motor delay (48%), expressive and receptive language delay (42% and 37% respectively), general cognitive deficits (40%), elevated rates of autism symptoms (37%) and internalizing behavior problems (34%).[26] In the NEURO study from the Neonatal Research Network (n=480), infants were followed up to 18-22 months. Significant cerebellar lesions (defined as lesions

which are bilateral, cystic, and/or lesions that were >4 mm in size) were independently associated with neurodevelopmental impairment, particularly gross motor delays.[27]

II. Process of obtaining term equivalent brain MRIs for preterm born infants
Criteria for obtaining a term equivalent (TE) MRI for very preterm infants

In light of the information above on the association of early white and grey matter abnormalities on TE brain MRI with later neurodevelopmental challenges, a near term-equivalent study should be considered for the highest risk preterm infants. Please consider obtaining a TE MRI for infants who meet the following criteria:

1. Extremely preterm infants born at < 28 weeks gestational age, OR
2. Very preterm infants (born at GA < 32 weeks) with additional risk factors:
   - Head Ultrasound (HUS) abnormality, including:
     - Any intraventricular hemorrhage grade
     - Any structural abnormality, including ventriculomegaly
     - Any hyperintensity noted after 7 days
     - Any white matter abnormalities, including periventricular leukomalacia (PVL) or other white matter cystic findings
     - Presence of multiple connatal cysts
   - Abnormal physical or neurological exam:
     - altered mental status
     - hypotonia or hypertonia
     - microcephaly
     - severe intrauterine growth restriction/small for GA status
   - One or more major neonatal morbidity:
     - Critically ill neonate, requiring inotrope use for blood pressure instability (*e.g.* Dopamine use of >= 5 mcg/kg/min for > 1 day)
     - Moderate or severe bronchopulmonary dysplasia (BPD), defined as need for supplemental O_2 for first 28 days of life and requiring supplemental O_2 or positive pressure support at 36 weeks corrected GA
     - Any major surgery, including surgical patent ductus arteriosus (PDA) closure or bowel obstruction
     - Necrotizing enterocolitis (NEC), stage II or higher
     - Severe retinopathy or prematurity (ROP) requiring intervention
     - Documented infection: bacteremia, sepsis, central line infection, meningitis, or encephalitis

- Other indications to consider:
  - postnatal steroids/dexamethasone course
  - prolonged or refractory hypoglycemia requiring IVF with high GIR *via* a central line beyond the first week of life for glycemic control
  - severe jaundice requiring an exchange transfusion
  - severe dysphagia (out of proportion for what would be expected for infant's corrected gestational age)

3. Additional referrals for a TE MRI can be made at the discretion of the medical team on a case-by-case basis.

Process for obtaining a neonatal brain MRI at Brigham and Women's Hospital

Please see NICU MRI Guidelines on the Department of Pediatric Newborn Medicine Intranet (under Guidelines and Policies – Neuro) for details.

http://www.bwhpikenotes.org/policies/departments/NICU/documents/NICUBWHMRIGuidelines.pdf

MRI order requisition form:

When ordering an MRI, please provide detailed clinical information regarding the indication for obtaining the study. An example of a template requisition form is presented in Appendix 2.

Subspecialty (Neurology) involvement

Consider requesting a Neurology consultation prior to obtaining a TE MRI for very preterm infants who:

- have a *significant abnormality* on HUS, including
  - IVH grade II or larger, with or without post hemorrhagic hydrocephalus or shunt placement
  - White matter cysts/PVL
  - Cerebellar hemorrhage
  - Other: ventriculomegaly, thinning corpus callosum, loss of volume
- have an abnormal neurological examination

After obtaining near-term brain MRI:

- Consider Neurology consultation if any determinants of white matter injury (white matter signal abnormality, volume loss, cystic lesions, thinning of CC, ventriculomegaly) or gray matter injury are in severe range – *i.e*. have a score of 3 or 4 on the scoring systems as detailed by Kidokoro *et al*.[28]
- Any new concerning finding at the discretion of the medical team.

Timing of obtaining TE MRIs for very preterm babies

It is recommended that TE MRIs for very preterm babies be obtained at least *1 week prior to the anticipated discharge date* (as long as the infant is above 35 weeks postmenstrual age, the study will provide reliable information[29]). This will allow the medical team time to review results with Neurology and Neuroradiology to reach a consensus regarding assessment and recommendations prior to discussing results with families. This will also inform coordination of outpatient follow-up (*i.e* need for referrals to programs such as Early Intervention (EI), Fragile Beginnings, developmental follow-up programs, or outpatient Neurology follow-up).

III. Interpretation of results of term equivalent MRIs, communication with families, discharge planning, and outpatient follow-up referrals.

Interpretation of TE MRI

Once obtained, a near term brain MRI will be formally read by a member of the BCH Neuroradiology department. Comments on the variables designated in the white and gray matter scoring systems proposed in Appendix 1[28] will be provided in the MRI interpretation. Please see Appendix 3 for a sample of a TE MRI report. Notably, the MRI reports will not include global scores. A final impression of the study will be formulated by the primary attending neonatologist, in collaboration with BCH Neurology and Neuroradiology consultants where appropriate. An example of a scoring system that can be used for interpretation of a TE MRI is outlined in Appendix 1 based on Kikodoro et al.[28] A total near term brain MRI abnormality score can be calculated as the sum of regional total scores of white matter, cortical gray matter, deep gray matter, and cerebellum abnormalities using this scoring system. As per the cited scoring system,[28] a global MRI score can be interpreted as follows:

- Negative TE MRI (total score, 0–3)
- TE MRI with mild abnormalities (total score, 4–7)
- TE MRI with moderate abnormalities (total score, 8–11)
- TE MRI with severe abnormalities (total score, ≥12).

Communication of MRI results to families

TE MRI results should be discussed with families by the primary medical team – i.e. attending neonatologist on service with nurse practitioner, physician assistant, fellow and/or resident, in conjunction with Neurology consultants when appropriate. The medical team will describe the process of reviewing the MRI study and reaching a final interpretation. Although a preliminary report may become available shortly after the study is completed, a final interpretation of a study may take up to several weekdays depending on the complexity of the findings. Only final MRI results should be presented to families, after discussion/consensus between the medical team and, possibly, the Neurology and Neuroradiology teams where appropriate. Families should be advised that MRI results will not be provided by overnight or weekend covering teams. For that reason, it is advisable to avoid scheduling a routine TE MRI on a Friday afternoon whenever possible. Lastly, counseling of a family should include the mention that a negative TE MRI study does not entirely exclude the possibility of longer term neurodevelopmental challenges.

Term equivalent MRIs, discharge planning, and outpatient follow-up

In the situation where the TE MRI identifies findings which are thought to place the former preterm infant at high risk for neurodevelopmental delays, the multidisciplinary team is encouraged to consider communicating the results, as well as interpretation of risk and recommendations, through the following mechanisms:

- Direct communication with the primary pediatrician at the time the infant is discharged. If MRI has abnormalities, the attending neonatologist should make efforts to communicate directly with pediatrician what the MRI result is, how it has been presented to the family, and what are the recommendations for follow-up.
- Inclusion of MRI results in the discharge summary, including the scale and scoring system used to determine risk, with concrete recommendations for developmental follow-up.
- Direct communication with the Early Intervention (EI) catchment area office to ensure awareness of the infant's risk for motor and cognitive delays. The developmental therapy team can facilitate this conversation.
- Communication with the outpatient infant follow up program and Neurology clinic the infant is being referred to

In addition, referrals for additional Physical therapy (PT), Occupational therapy (OT) and/or Feeding therapy services as appropriate (above and beyond what will be provided by early intervention) can be explored for the highest risk infants. Medical teams can work with the Care Coordination and the Developmental Therapy team in making these referrals.

Early Intervention Services

Early Intervention (EI) is a federally funded developmental support program available to all qualifying children 0-3 years in the United States. It may carry different names in different states, and aims to *"… provide family-centered services to help children who qualify to develop the skills they will need to continue to grow into happy and healthy members of the community."*[30] Early developmental services for preterm born children have been shown to have a beneficial impact on their early motor and cognitive skills, and these effects are likely to persist into school age.[31]

EI Eligibility for services in Massachusetts:

Children aged 0-3 with developmental concerns or who are at risk for neurodevelopmental delays can be referred for an EI evaluation by either a medical professional (pediatrician, nurse, developmental therapist, *etc.*) or a parent/caregiver. Typically, the regional EI catchment area to which a family belongs geographically conducts a multidisciplinary assessment for each referred child. Children may then qualify for ongoing services of variable frequency, intensity and duration depending on the results of this initial evaluation.

There are four categories of eligibility under which infants and young children can qualify to receive ongoing EI services:

1. Infants with an Established Condition or Conditions:
   - Includes: blindness, retinopathy of prematurity, cerebral palsy, meningitis, encephalitis, epilepsy, IVH grades 3 or 4, chromosomal or metabolic disorders, congenital cytomegalovirus infection, cleft lip. Of note, these have to be established diagnoses and not "at risk" conditions.
2. Infants with Established Developmental Delay (at least 1.5 standard deviations below mean on Batelle Developmental Inventory-II)
3. Infants at Risk for Developmental Delay (need at least 4 risk factors to qualify)
   - Birth weight below 1200 grams
   - Gestational age at birth less than 32 weeks
   - Need to stay in the neonatal intensive care unit (NICU) for over 5 days
   - Apgar score less than 5 at 5 minutes of life
   - Intrauterine growth restriction and/or small for gestational age status
   - Ongoing chronic feeding difficulties
   - Central nervous system abnormalities (infection, IVH, apnea, NAS, abnormal tone)
4. Clinical Judgment – at the discretion of the EI providers, if the EI evaluation team concludes that infant is at high risk for neurodevelopmental delays despite not meeting any of the criteria in the categories above. This is a window of opportunity for preterm infants with TE

MRI abnormalities who may not otherwise qualify for EI services based on GA and other diagnoses criteria, to receive ongoing services.

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APPENDIX 1

Suggested Scoring System for Term-Equivalent MRI[28]

1. **White Matter (WM)Abnormalities**

	WM Score				
	0	1	2	3	4
Cystic Lesions	None	Focal Unilateral	Focal Bilateral	Extensive Unilateral	Extensive Bilateral
Focal Signal Abnormality	None	Focal Punctuate	Extensive Punctuate	Linear	
Myelination Delay	PLIC and Corona Radiata	Only PLIC	Minimal – No PLIC		
Thinning of CC	None	Partial (genu/body< 1.3mm OR Splenium < 2.0 mm)	Global (genu/body< 1.3 mm AND splenium< 2.0 mm)		
Dilated LV	Both sides VD < 7.5 mm	One side 7.5 mm ≤ VD< 10 mm	Both sides 7.5 mm ≤ VD< 10 mm or one side VD ≥ 10 mm	Both Sides VD ≥ 10 mm	
Volume Reduction	cBPW ≥77 mm	77 mm < cBPW ≥ 72 mm	72 mm < cBPW ≥67 mm	67 mm > cBPW	

No (total score, 0-2), mild (total score, 3-4), moderate (total score, 5-6), and severe (total score ≥7)

2. Cortical Gray Matter (GM) Abnormalities

	Cortical GM score				
	0	1	2	3	4
Signal Abnormality	None	Focal Unilateral	Focal Bilateral	Extensive Unilateral	Extensive Bilateral
Gyral Maturation	Delay < 2 weeks	2 ≤ delay < 4 weeks	Delay ≥ 4 weeks		
Increased Extracerebral Space	IHD < 4 mm	4 mm ≤ IHD < 5 mm	5mm ≤IHD < 6 mm	IHD ≥ 6 mm	

No (total score, 0), mild (total score, 1), moderate (total score, 2), and severe (total score ≥3)

3. Deep GM Abnormalities

	Deep GM score				
	0	1	2	3	4
Signal Abnormality	None	Focal Unilateral	Focal Bilateral	Extensive Unilateral	Extensive Bilateral
Volume Reduction	cDGMA ≥ 9.5	9.5 > cDGMA ≥ 8.5	8.5 > cDGMA ≥ 7.5	7.5 > cDGMA	

No (total score, 0), mild (total score, 1), moderate (total score, 2), and severe (total score ≥3)

4. Cerebellum

	Cerebellum score				
	0	1	2	3	4
Signal Abnormality	None	Focal Unilateral	Focal Bilateral	Extensive Unilateral	Extensive Bilateral
Volume Reduction	cTCD ≥ 50 mm	50 mm > cTCD ≥ 47 mm	47 mm> cTCD ≥ 44 mm	44 mm > cTCD	

No (total score, 0), mild (total score, 1), moderate (total score, 2), and severe (total score ≥3)

5. Global brain abnormalities

Score was calculated as the sum of these regional total scores and was classified as

- normal (total score, 0–3)
- mild (total score, 4–7)
- moderate (total score, 8–11)
- severe (total score≥12).

APPENDIX 2.

Term equivalent brain MRI order requisition form template

This is a preterm baby BOY/GIRL born at XX weeks, now corrected to XX GA, NICU course significant for the following major morbidities:

- [ ]IVH grade ---
- [ ] posthemorrhagic hydrocephalus with/without shunt placement
- [ ]PVL
- [ ] cerebellar hemorrhage
- [ ]BPD
- [ ]any surgery (including PDA ligation)
- [ ]infection (sepsis, meningitis, central line infection)
- [ ]NEC
- [ ] abnormal neurological exam --- (please explain)
- [ ] postnatal steroid use
- [ ] twin/multiple gestation infant with high risk sibling
- [ ]other --- (please explain).

APPENDIX 3.

Term equivalent brain MRI report template

HISTORY:

Birth GA /Corrected GA:

TECHNIQUE: The study consists of sagittal moco MEMPRAGE with axial and coronal reformations, axial and coronal T2 FSE, axial DTI, axial SWI additional sequences. 3D PRESS was obtained with TE=35 and TE= 135. Representative voxels in the [Location] were saved. No intravenous contrast was administered.

COMPARISON:

FINDINGS:

The ventricles are [normal in size and configuration], measuring [width on coronal] on the left and [width on coronal] on the right. The subarachnoid spaces are [normal in size] with an interhemispheric distance of [IHD]mm. There are [no] extra-axial collections. There is [no] ependymal or subarachniod hemosiderin staining [to suggest prior IVH].

Overall brain volume appears [normal/decreased] with biparietal diameter of [mm].

Gyral folding is grossly normal for corrected gestational age. [No cortical signal abnormality is identified].

[There is diffuse increased T2 signal in the frontal and parietal white matter that is nonspecific in nature]. There are [number/extensive if >?] white matter foci of increased T1 signal [on right/on left/bilaterally]. There are [number/extensive if >?] cysts [on right/on left/bilaterally]. Myelination [is] seen in the [posterior limb internal capsule] [and in the corona radiata bilaterally].

The corpus callosum is fully formed [but thinned].

The basal ganglia are [normal] in size [and normal in signal]. The thalami are [normal] in size [and normal in signal].

Diffusion imaging shows [no] evidence of decreased diffusion.

There is [no] evidence of cerebral parenchymal hemorrhage including at the caudothalamic notch.

The vermis, brainstem and cerebellar hemispheres are normally formed and normal in size. There is [no] cerebellar increased T1 or T2 signal and [no]cerebellar parenchymal hemorrhage.

MRS shows prominent peaks due to choline, creatine and n-acetyl aspartate with ratios appropriate for age. No lactate identified.

The major intracranial arteries and venous sinuses have normal flow voids.