Seminars in Perinatology 38 (2014) 422–428

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/semperi

Magnetic resonance imaging of bilirubin encephalopathy: Current limitations and future promise

Jessica L. Wisnowski, PhD[a], *Ashok Panigrahy, MD*[a], *Michael J. Painter, MD*[b], *and Jon F. Watchko, MD*[c,*]

[a]*Department of Pediatric Radiology, Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center, University of Pittsburgh School of Medicine, Pittsburgh, PA*
[b]*Division of Pediatric Neurology, Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, PA*
[c]*Division of Newborn Medicine, Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213*

ARTICLE INFO

Keywords:
Kernicterus
Magnetic resonance spectroscopy
Tractography
Myelination

ABSTRACT

Infants with chronic bilirubin encephalopathy often demonstrate abnormal bilateral, symmetric, high-signal intensity on T2-weighted magnetic resonance imaging of the globus pallidus and subthalamic nucleus, consistent with the neuropathology of kernicterus. Early magnetic resonance imaging of at-risk infants, while frequently showing increased T1-signal in these regions, may give false-positive findings due to the presence of myelin in these structures. Advanced magnetic resonance imaging including diffusion-weighted imaging, magnetic resonance spectroscopy, and diffusion tensor imaging with tractography may shed new insights into the pathogenesis of bilirubin-induced brain injury and the neural basis of long-term disability in infants and children with chronic bilirubin encephalopathy.

Introduction

Bilirubin-induced brain injury is distinctive, distinguished by remarkably selective involvement of the globus pallidus, subthalamic nucleus, selected brainstem nuclei, the CA2–CA3 sectors of the hippocampus, the reticular portion of the substantia nigra, and the dentate, roof nuclei, and Purkinje cells of the cerebellum.[1–4] The cerebral cortex, periventricular white matter, CA1 sector of the hippocampus, and putamen are spared.[2,4] This regional distribution of neuropathological changes is very similar across term, preterm, previously well or septic neonates, and the rare adult reported with kernicterus and notably different from that of hypoxic-, ischemic-, or hyperoxic-induced brain injury in the newborn.[1–4] Magnetic resonance imaging (MRI) of infants with chronic bilirubin encephalopathy (kernicterus) often mirrors this pattern

Supported in part by the Children's Hospital of Pittsburgh Foundation—Ian Harrison Family Fund for Neonatal Neurology Research Program, the Mario Lemieux Foundation, and National Institutes of Health, USA (K23NS063371).

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article. Permission for use of clinically acquired neuroimaging data and waiver for informed consent were obtained from the University of Pittsburgh Institutional Review Board.

*Corresponding author.
E-mail address: jwatchko@mail.magee.edu (J.F. Watchko).

http://dx.doi.org/10.1053/j.semperi.2014.08.005
0146-0005/

of involvement demonstrating abnormal bilateral, symmetric, high-signal intensity in the globus pallidus and less consistently in the subthalamic nucleus.[5–12] This review will detail our growing understanding of bilirubin-induced central nervous system (CNS) injury as reflected in MRI studies and suggest how future studies using MRI may help to shed new insights in the pathogenesis of acute and chronic bilirubin encephalopathy.

Terminology: ABE, CBE, and BIND

Before addressing the features of bilirubin-induced CNS injury on MRI, it is important to define the clinical terms used to describe bilirubin effects on the brain and distinguish between acute bilirubin encephalopathy (ABE), chronic bilirubin encephalopathy (CBE), and bilirubin-induced neurologic dysfunction (BIND). ABE defines an encephalopathic state induced by hazardous hyperbilirubinemia during the first days of postnatal life and is characterized by a constellation of abnormal clinical signs typically progressive in their severity. In term ($\geq 37^{0/7}$ weeks gestation) and late preterm ($34^{0/7}$–$36^{6/7}$ weeks gestation) infants, the initial phase of ABE is characterized by stupor (lethargy), hypotonia, and poor sucking.[5,13] These non-specific signs are seen in numerous clinical contexts, but in a hyperbilirubinemic infant should raise the possibility of early ABE. Clinical signs of intermediate to advanced stages of ABE are increasingly more specific to bilirubin-induced neurotoxicity and herald a marked increased risk for permanent injury.[5,13] These include hypertonia often manifested by retrocollis and opisthotonus, fever, and high-pitched cry.[5,13] Inability to feed and apnea may ensue.[14] Infants <34 weeks of gestation less frequently show these classic abnormal neuromotor signs.[15] Recurrent apnea and desaturations may be the only clinical manifestations of ABE in preterm infants during the neonatal period, if any appear at all.[16]

In contrast, chronic bilirubin encephalopathy (CBE) defines the permanent clinical sequelae of bilirubin toxicity that become evident in the first year of life and is synonymous with the term kernicterus.[5,13] The American Academy of Pediatrics (AAP) recommends the term kernicterus be reserved for the chronic and permanent neurologic sequelae of bilirubin toxicity.[17] These include the extrapyramidal movement disorders of dystonia and/or choreoathetosis, hearing loss due to auditory neuropathy spectrum disorders, and the eye movement abnormality of paresis of upward gaze.[5,13]

Bilirubin-induced neurologic dysfunction or BIND is a term whose meaning has evolved over time and thereby sown some confusion in the literature. In its current usage, BIND characterizes a constellation of more subtle neurodevelopmental disabilities without the classical findings of kernicterus, which after careful clinical review appear to be due to bilirubin neurotoxicity.[5] It includes disturbances of central auditory processing, coordination, muscle tone, and sensorimotor integration.[5] BIND and subtle kernicterus are synonymous.[5] The concept of BIND as a clinical entity is an area of ongoing debate that merits intense investigation. Indirect evidence suggests the cerebellum as a possible site of injury relevant to BIND particularly in premature neonates. The latter derives from the considerable overlap in the putative neurophenotype of BIND and other conditions associated with cerebellar injury in preterm neonates. Systematic MRI studies of subjects with BIND are as yet unavailable and urgently needed to help clarify the nature of this disorder. BIND will not be covered in this review.

Original case description of kernicterus on MRI

The seminal MRI description of bilirubin encephalopathy was a case report of a term glucose-6-phosphate dehydrogenase-deficient neonate who developed hazardous hyperbilirubinemia (peak TSB 50 mg/dl) associated with *Escherichia coli* sepsis.[18] MRI studies on day of life 8 and 16 showed abnormal signal intensity in the globus pallidus, internal capsule, thalamus, and hippocampus. These were most prominent as high signal on T1-weighted images but also as subtle increased signal on T2-weighted images.[18] A growing experience with neuroimaging of neonates with kernicterus has refined our understanding of MRI changes in bilirubin encephalopathy.

Conventional structural MRI (T1 and T2 weighted)

Although many studies have reported signal abnormalities in the globus pallidus and subthalamic nuclei, hippocampus, and cerebellum in neonates with CBE, it is now well understood that the nature of these signal abnormalities varies with time. Chronically, bilateral, symmetrically increased T2-signal (or T2-FLAIR signal) in the globus pallidus and subthalamic nucleus of an infant with a history of hyperbilirubinemia and CBE remains the neuroimaging hallmark of kernicterus (Fig. 1).[5–12] Additionally, increased T2-signal may also be seen in the substantia nigra or in the dentate nucleus of the cerebellum, while T1-signal in all of these regions is variable in CBE.

By contrast, early MR studies of infants in the first days to weeks following ABE onset (i.e., subacute phase) who later meet criteria for CBE often demonstrate increased T1-signal in the globus pallidus and subthalamic nucleus, while T2-signal in these regions is most often unremarkable or subtly hyperintense (Fig. 2).[5,6,8,11,18–21] The anatomic loci of increased T1-signal identified in the subacute phase of bilirubin encephalopathy mirror the distinctive topographical pattern observed in CBE, and suggests that increased T1-signal could be used as a diagnostic marker of kernicterus. However, as we demonstrate below, the sensitivity and specificity of T1-signal changes during the subacute phase to predict kernicterus is hindered by both the evolving nature of the signal abnormalities and confounding signal changes associated with normal myelination.

In practice, conventional T1- and T2-weighted sequences are the most heavily utilized MR sequences because they visualize the underlying anatomy. In addition, T1-weighted MR sequences have a high sensitivity for hemorrhage and lipid content while T2-weighted sequences have a high sensitivity for water (CSF and/or tissue edema). As noted above, in infants who later show CBE, early MR images often demonstrate prominent,