

Magnetic resonance imaging of the brain in children with chronic kernicterus

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ABSTRACT

Advances in perinatal monitoring and early treatment for hyperbilirubinemia in high-risk patients have greatly reduced the incidence of kernicterus. Findings on MRI in patients with kernicterus are characteristic. The most characteristic pattern of neuropathological lesions in kernicterus is symmetric and highly selective involvement of the basal ganglia. In this study, we report the MRI findings in 2 infants with clinical and laboratory evidence of kernicterus.

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Bilirubin toxicity remains a significant problem despite recent advances in the care of jaundiced neonates. Traditionally, the term kernicterus (literally yellow kern, with kern indicating the most commonly afflicted region of the brain, namely, the nuclear region) refers to an anatomic diagnosis made at autopsy based on a characteristic pattern of staining found in babies who had marked hyperbilirubinemia before they died. Regions most commonly affected include the basal ganglia, hippocampus, geniculate bodies, and cranial nerve nuclei, such as the oculomotor, vestibular, and cochlear. The cerebellum can also be affected. Acute bilirubin encephalopathy, which refers to the clinical signs associated with bilirubin toxicity, namely, hypotonia followed by hypertonia, opisthotonus or retrocollis, or both, is usually synonymous with kernicterus. An MRI of the brain in this condition has specific findings that aid in the accurate diagnosis of the condition, along with clinical and biochemical criteria. The MRI has shown good sensitivity in kernicterus.¹⁻⁴ We herein describe 2 cases of kernicterus where MR imaging demonstrated bilateral symmetric hyperintensity in the globi pallidi (GP) on T2-weighted images.

Case reports. Patient 1. This male child was born at 39 weeks gestation after an uneventful pregnancy (spontaneous vaginal delivery, birth weight: 2750 gm, length: 49 cm). There was no prolonged rupture of membranes or elevation of maternal temperature. Blood groups were compatible, and Coombs test was negative. One-minute and 5-minute Apgar scores were normal (normal range: 7-10), and there was no history of perinatal asphyxia, symptomatic metabolic abnormalities, infection, or other problems in the neonatal period, except for severe indirect hyperbilirubinemia on the 8th day of life with irritability, severe jaundice, and opisthotonus. The abdominal and trans-fontaneller sonographic examinations were normal. The serum peak indirect bilirubin level was 32 mg/dl. Other laboratory tests (including hypothyroidism, sickle cell anemia, galactosemia and glucose-6-phosphate dehydrogenase deficiency) were within normal limits. An exchange transfusion was not performed because serum indirect bilirubin level decreased to 23 mg/dl within a day of phototherapy. Phototherapy was performed 3 times, and the serum bilirubin level decreased to 8 mg/dL over the following days. Results of a neurologic

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examination during the neonatal period were normal. The patient was discharged to home. His parents noticed that he was flabby during the early months of life, and involuntary abnormal movements were observed after 7 months of age. On examination at 12 months of age, he presented with severe dystonia, and choreoathetosis (mainly involving the head and neck). In addition, he had severe developmental delay and poor head control. These findings were consistent with dyskinetic cerebral palsy. The EEG revealed normal findings.

Patient 2. This female child was born with normal Apgar scores at the 40th gestational week. At birth, her weight was 3050 gm, length was 49 cm. The patient's antepartum course had been unremarkable. There was no history of perinatal asphyxia, symptomatic metabolic abnormalities, infection, or other problems in the neonatal period, except for neonatal indirect hyperbilirubinemia resulting from ABO and Rhesus incompatibilities (maternal blood group: 0, Rh negative; blood group of the boy: A, Rh positive). Jaundice was noticed on the sixth postnatal day, however, her parents were not aware of the seriousness of the disease. When the patient was admitted to our hospital on the 10th day of life, the serum indirect bilirubin level was 38 mg/dl. Other laboratory tests (including hypothyroidism, sickle cell anemia, galactosemia and glucose-6-phosphate dehydrogenase deficiency) were within normal limits. An exchange transfusion was performed, and the serum bilirubin level decreased to 6 mg/dl over the following days. Results of a neurologic examination during the neonatal period were normal. The patient was discharged home. At 15 months old, she was admitted to our hospital because of choreoathetosis, mental and motor retardation, dystonia, and muscle rigidity. The EEG revealed normal findings.

Magnetic resonance findings. After a neurological examination was performed on all patients by a pediatric neurologist, MR imaging of the brain was performed on a 1.5 Tesla MR scanner (Excelart, Toshiba, Japan) with a standard head coil. A T1-weighted spin-echo (SE) (repetition time [TR] = 400-440 msec/echo time [TE] = 10-15 msec) and T2-weighted fast spin-echo (FSE) (TR = 3000-4400 msec/TE = 80-100 msec), fluid attenuated inversion recovery sequence (FLAIR) (TR = 7500-8800 msec/TE = 100-140 msec, time inversion [TI] = 2200 msec) images in axial, coronal and sagittal planes were obtained. No gadolinium-based contrast material was administered. The MRI examinations were carried out at 12 months of age for Patient 1, and at 15 months of age for Patient 2. Both of the patients were sedated, transported and monitored by physicians who remained with the infant throughout

the entire procedure. Both of the patients had abnormal high signal intensity lesions in the bilateral GP, with no evidence of mass effect on T2-weighted and FLAIR images, a finding consistent with kernicterus. The T1-weighted images demonstrated hypointensity bilaterally in the GP. Patient 1 had abnormal signal intensity at the posteromedial border of the GP (**Figures 1a & 1b**). Patient 2 had bilateral signal intensity increase in the GP and subthalamic nuclei (**Figures 2a & 2b**).

Discussion. Kernicterus is a pathologic term meaning the neuropathologic changes of the brain resulting from neurotoxicity of neonatal indirect hyperbilirubinemia. The neurologic manifestations of kernicterus consist of choreoathetoid movements, dystonia, limited eye movements, hearing loss, and developmental delay.⁵ Bilirubin is usually bound to plasma albumin, rendering it nontoxic. However, free bilirubin is toxic and can enter the brain when the concentration of bilirubin exceeds normal albumin binding capacity.⁶ The term kernicterus, first mentioned by Schmorl in 1904, describes the yellow staining of specific areas of the brainstem, basal ganglia, and cerebellum in children with neurological disorders caused by increased access of unconjugated bilirubin to brain tissue.⁷ Microscopic studies reveal the basal ganglia, the inferior olivary nuclei, the hippocampus, the dentate nuclei, the subthalamic nuclei and cranial nerve nuclei at the floor of the fourth ventricle to be areas of pathological bilirubin deposition. On histopathological examination, the bilirubin deposition leads to a loss of neurons, proliferation of astrocytes, gliosis, and demyelination in the affected areas.⁸ With the advent of effective therapies that prevent excessive elevation of bilirubin levels in high-risk patients and screening of maternal and fetal blood groups, kernicterus has become rare in the medical spectrum.

The neurological manifestations of kernicterus appear when serum bilirubin levels rise above 20 mg/dl. This tends to be lower in the premature infant. The characteristic neurological symptoms are somnolence, hypotonia, opisthotonus, rigidity and high-pitched cry. Early in the course of the disease, the symptoms may be subtle, mimicking sepsis, asphyxia or hypoglycemia.⁹ Initially, seizures are uncommon. Once the neurological complications appear, the prognosis is poor.¹⁰ In the early stage of disease, clinical findings suggestive for kernicterus are somnolence and hypotonia, which are reversible to some extent, followed by an irreversible stage characterized by opisthotonus and rigidity.⁷ Early hyperbilirubinemia detection is critical to the

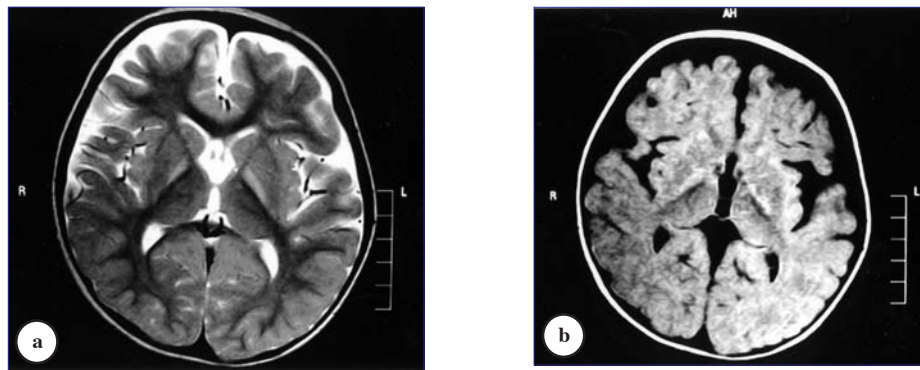


Figure 1 - MRI of 12-month-old male infant with chronic kernicterus. a) Axial T2-weighted, and b) FLAIR image shows the symmetric high-intensity signal in the area of the GP.

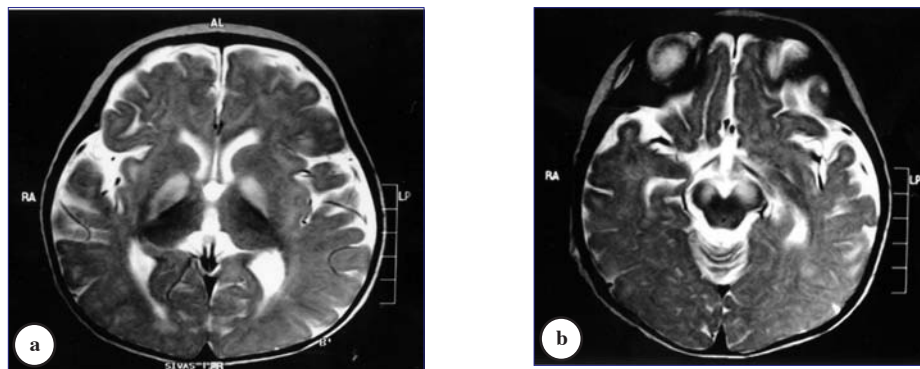


Figure 2 - MRI of 15-month-old female infant with chronic kernicterus. a) Axial T2-weighted image at the level of the basal ganglia shows symmetric, hyperintense GP involvement. b) In addition, she had abnormal signal intensity bilaterally in the subthalamic nucleus.

prevention of the irreversible effects of kernicterus. Health-care providers, parents, and other caretakers should be aware of risk factors for hyperbilirubinemia, and treatment should begin immediately after hyperbilirubinemia is diagnosed.¹¹ The clinical features of chronic bilirubin encephalopathy evolve slowly over the first several years of life in the affected infant. The clinical features can be divided into phases; the first phase occurs in the first year of life and consists of hypotonia, hyperreflexia, and delayed acquisition of motor milestones. The tonic neck reflex can also be observed. In children older than one year, the more familiar clinical features develop, which include abnormalities in the extrapyramidal, visual, and auditory systems. Minor intellectual deficits can also occur.¹² The neuroradiologic findings of kernicterus have been demonstrated by MR imaging. Although kernicterus affects various parts of the central nervous system, only the GP demonstrates

remarkable signal changes with MR imaging. The most commonly reported and characteristic MR imaging finding of kernicterus, after the acute period, is bilateral hyperintense GP lesions on T2-weighted MR images. The posteromedial border of the GP has been shown by MR imaging to be the most sensitive area to kernicterus. High signal intensity in the bilateral GP corresponds to the areas of preferential deposition of unconjugated bilirubin. Signal changes in the thalami, subthalamic nuclei, hippocampus and cranial nerve nuclei (especially III, IV and VI) have also been reported.^{13,14} In the present study, we observed the subthalamic involvement in one patient. To the best of our knowledge, 3 cases with the subthalamic involvement caused by kernicterus have been reported.^{5,7,13} Although MR findings of cases with kernicterus are nonspecific, they may have a role in the diagnosis of kernicterus together with clinical findings. In children, hypoxic, toxic, metabolic,

infectious, and inherited disorders can be responsible for basal ganglia lesions seen on MR imaging studies. Lesions of the GP are especially common in hypoxic-ischemic encephalopathy, hemolytic uremic syndrome, hypoglycemia, encephalitis, carbon monoxide poisoning, glutaric acidemia type II, neurofibromatosis type I, Hallervorden Spatz disease, which demonstrates that they are not a specific finding for kernicterus,¹⁵ however, it is known from pathological studies that in addition to the GP, the subthalamic nucleus and the horn of Ammon are other common sites of bilirubin deposition in patients with kernicterus. In particular, perinatal hypoxic-ischemic encephalopathy involves mainly the putamen, the basal ganglia, and the thalami. These lesions appear on MRI studies as areas of abnormal signal intensity in the posterior putamen and ventrolateral thalamus.¹³ Axial and coronal T2-weighted and FLAIR images are most sensitive and best suited to demonstrate the anatomical location and distribution of findings in the basal ganglia and the mesencephalic nuclei. On T1-weighted images, the lesions appeared iso- and hypointense and could not be delineated clearly; however, if imaging is carried out during the acute phase of kernicterus, the basal ganglia can be bright on T1-weighted images.^{14,16}

In conclusion, in contrast to acute stage kernicterus in which characteristic T1-hyperintense GP involvement is a well-known feature of the disease, GP involvement in chronic kernicterus is demonstrated as increased signal intensity on T2-weighted MR imaging. This is a common and characteristic finding of chronic kernicterus, as we saw in our study. The triad of clinical evaluation, laboratory, and MRI findings helps in the diagnosis of kernicterus.

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