Magnetic Resonance Imaging Findings in Patients With Severe Neonatal Indirect Hyperbilirubinemia

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ABSTRACT

The aim of this study was to document the magnetic resonance imaging (MRI) findings of cases with a history of severe neonatal indirect hyperbilirubinemia. Ten cases (eight cases with neurologic findings, two normal cases) with a history of severe neonatal indirect hyperbilirubinemia were studied. Neurologic findings and MRI results were described and correlated. Seven of eight cases with neurologic findings demonstrated symmetric and uniform increased T_2 signal changes limited to globus pallidi. MRI scans of two cases without neurologic findings showed no abnormality. Severe neonatal indirect hyperbilirubinemia should be considered in the differential diagnosis of bilateral symmetric hyperintense signal changes in the globus pallidus on MRI. However, high levels of unconjugated bilirubin concentrations in the neonatal period may not always cause such lesions of globus pallidus on MRI despite the presence of neurologic findings. (*J Child Neurol* 2001;16:452–455).

Kernicterus is an encephalopathy due to neuronal toxicity of unconjugated bilirubin in the early days of life.[1] Neurologic abnormalities resulting from kernicterus include cerebral palsy, particularly the athetoid-dystonic type, hearing loss, vertical gaze palsies, and developmental delay.[1–4] Diagnosis of the sequelae of neonatal bilirubin toxicity is made based on the clinical examination.

There have been reports about neuroradiologic findings of the neuronal damage due to the toxicity of unconjugated bilirubin during the neonatal period.[5–9] We hereby present the magnetic resonance imaging (MRI) findings of 10 patients to document the neuroradiologic lesions caused by neonatal hyperbilirubinemia. The relationship between neurologic status and the MRI findings of these cases is also discussed.

Subjects and Method

Ten children (six boys, four girls) with a history of severe neonatal jaundice, ages 3½ to 53 months, were studied. All children were born at term and had normal birthweights (mean 3100 g). None had a history of perinatal asphyxia, symptomatic metabolic abnormalities, infection, or other problems except for neonatal indirect hyperbilirubinemia in the neonatal period. There was no history of any medical problems that could interfere with their subsequent neurologic and physical development. Seven cases had hemolytic disease (Rh incompatibility in two cases, ABO incompatibility in five cases), and three cases had idiopathic hyperbilirubinemia.

All children had thorough physical and neurologic examinations, and their developmental status was tested. Auditory function was assessed by brainstem auditory evoked potential examinations in five children. Magnetic resonance imaging examinations were performed under sedation with various MRI devices of 1.0- or 1.5-Tesla field strengths. All examinations consisted of T_1- and T_2-weighted spin echo or fast spin echo sequences in the axial, coronal, and sagittal images. Magnetic resonance imaging scans were interpreted prospectively by two radiologists who were blinded to the neurologic manifestations and the levels of serum unconjugated bilirubin. No significant differences were noted between the evaluations of the two radiologists. Magnetic resonance imaging results, neurologic status, and serum unconjugated bilirubin concentrations of the cases were correlated.

Table 1. Laboratory, Neurologic, MRI, and Brainstem Auditory Evoked Potential Findings of the Cases

Patient No. (Sex)	Peak Level of Serum Unconjugated Bilirubin (mg/dL)	Age at Last Visit (mo)	Age at MRI Examination (mo)	Neurologic Findings at the Last Examination	MRI Findings	Brainstem Auditory Evoked Potential
1 (F)	42	24	10	Axial hypotonia, choreoathetoid movements, limited upward gaze Mild psychosocial, moderate motor delay, language delay	Bilateral symmetric globus pallidus hyperintensity on T_2 images	Not able to perform
2 (M)	17.7*	24	8	Mild choreoathetoid movements and dystonia Moderate motor, severe language, mild psychosocial delay	Bilateral globus pallidus hyperintensity on T_2 images	Bilateral auditory neuropathy
3 (F)	31	18	13	Dystonia, choreoathetosis, limited upward vertical gaze Moderate psychosocial-motor delay	Bilateral globus pallidus hyperintensity on T_2 images	Not able to perform
4 (F)	36	50	36	Mild choreoathetosis and dystonia, limited upward gaze Mild motor and psychosocial delay, language delay	Bilateral globus pallidus hyperintensity on T_2 images	Bilateral auditory neuropathy
5 (F)	30	13	4.5	Dystonia, athetosis Moderate psychosocial-motor delay	Bilateral globus pallidus hyperintensity on T_2 images	Normal
6 (M)	29.4	24	24	Dystonic-choreoathetoid cerebral palsy, limited vertical gaze movements to upward Moderate psychosocial-motor delay, language delay	Bilateral globus pallidus hyperintensity on T_2 images	Not able to perform
7 (M)	40	5	4	Opistotonus, rigidity, athetoid movements, slow saccades Severe psychosocial-motor and language delay	Bilateral globus pallidus hyperintensity on T_2 images	Bilateral auditory neuropathy
8 (M)	35	30	30	Choreoathetosis, limited extraocular eye movements (vertical and horizontal) Severe motor delay, moderate psychosocial delay, language delay	Bilateral globus pallidus hyperintensity on T_2 images	Bilateral auditory neuropathy
9 (M)	30	29	28	Normal	Normal	Not tested†
10 (M)	30	53	51	Normal	Normal	Not tested†

*The patient was born with severe hemolytic anemia due to Rh incompatibility. Although exchange transfusion was performed immediately after birth, jaundice appeared within 2 days.
†Linguistic functions were fully developed.

Results

All patients had neonatal hyperbilirubinemia with serum unconjugated bilirubin levels ranging from 17.7 to 42 mg/dL. Of these, eight cases exhibited neurologic abnormalities. These abnormalities included choreoathetoid movements, dystonia, and developmental delay in eight cases, limited extraocular movements in six, and bilateral auditory neuropathy in four (Table 1).

Magnetic resonance imaging findings in the form of symmetric and uniform increased T_2 signal limited to the globus pallidi could be demonstrated in seven of these cases (Figure 1). One patient had a normal MRI scan, despite a high neonatal serum bilirubin level and severe neurologic findings.

Among the patients included in the study, two had no neurologic abnormalities. The justifications for MRI examinations were high neonatal indirect hyperbilirubinemia in the history and to investigate whether such severe hyperbilirubinemia could cause MRI changes without neurologic findings. MRI did not show any signal abnormalities in these cases. Four cases with bilateral auditory neuropathy exhibited bilateral globus pallidus hyperintensity on MRI. One patient with normal brainstem auditory evoked potential results demonstrated a globus pallidus lesion.

Discussion

Neonatal hyperbilirubinemia, a common medical diagnosis, can represent a benign physiologic process or can result in severe neurotoxicity. With the advent and wide use of exchange transfusion and phototherapy in the management of neonatal hyperbilirubinemia and the use of preventive measures for hemolytic disease, the incidence of severe neurologic damage resulting from neonatal jaundice has been greatly reduced in the last three decades.[1,10,11]

Although kernicterus and related neurologic sequelae have been known since the nineteenth century, the pathophysiology and neuropathology of bilirubin neurotoxicity have not yet been clearly established.[1,10–13] The most characteristic pattern of neuropathologic lesions in kernicterus is symmetric and highly selective involvement of the basal ganglia. The pathologic changes caused by the cytotoxic effect of unconjugated bilirubin consist of discoloration and destruction of the affected neurons. The pallidum, subthalamic nucleus, and hippocampus are the most commonly affected areas with relative sparing of the cerebral cortex, white matter, midbrain, and brain stem. Other structures such as the thalamus, striatum, substantia nigra, cerebellar nuclei, inferior olivary nuclei, and various cranial nerve nuclei, particularly the ocu-

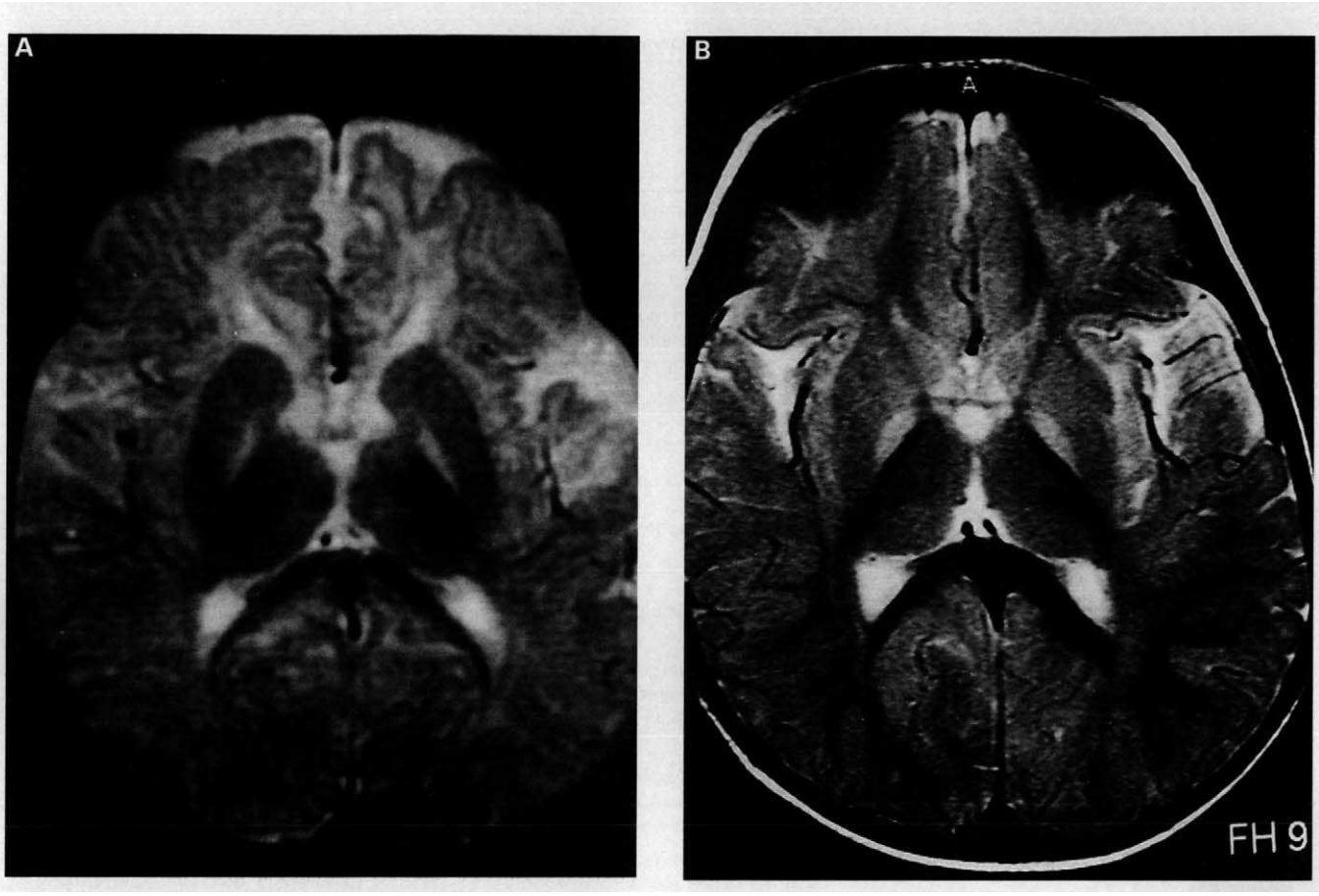

Figure 1. Bilateral symmetric hyperintensity in globus pallidus on T_2-weighted axial MRI scan. *A*, MRI scan of patient 2; *B*, MRI scan of patient 8.

lomotor, vestibular, cochlear, and facial nerve nuclei, may be affected.[1,14–16] The pathogenesis of the selective involvement and susceptibility of specific nuclear groups to unconjugated bilirubin are not well understood.

The neurologic manifestations of kernicterus include choreoathetoid movements, dystonia, limited eye movements, hearing loss, and developmental delay.[2–4,16,17] These neurologic findings are mostly related to basal ganglia involvement. Pathologic studies of patients with athetoid cerebral palsy related to severe neonatal jaundice showed marked astrocytic gliosis with severe loss of neurons and myelin sheaths in the pallidum and subthalamic nucleus.[18]

The advent of MRI has made the demonstration of the neuroradiologic features of these pathologies possible.[5–7,9] In this study, 7 of 10 cases with neonatal severe indirect hyperbilirubinemia had bilateral globus pallidus hyperintensities on T_2-weighted images. The presence of such findings in the globus pallidi correlated

Table 2. MRI Results of the Cases With Neonatal Hyperbilirubinemia in the Literature

Study	*Gestational Age*	*Peak Level of Unconjugated Bilirubin (mg/dL)*	*Neurologic Findings*	*MRI Findings (Age at Examination)*
Martich-Kriss et al[9] (*n* = 1)	Term	49.40	Hypotonia, early signs of choreoathetosis, developmental delay, nystagmus, suspected seizure activity	Bilateral symmetric high signal in the globus pallidus (18 d)
Yokochi[5] (*n* = 3)	39 wk	30.52	Athetoid CP, mild mental retardation	Bilateral symmetric high signal in the globus pallidus (3 yr)
	38 wk	29.53	Athetoid CP	Bilateral symmetric high signal in the globus pallidus (7 yr)
	38 wk	46.02	Athetoid CP, mild mental retardation	Bilateral symmetric high signal in the globus pallidus (12 yr)
Penn et al[7] (*n* = 1)	Term	50.00	Hypertonicity, poor head control, and visual tracking, poor vertical eye movements, inconsistent response to auditory stimulation	High signal intensity in the globus pallidus, capsula interna, thalamus (8 d)
Worley et al[6] (*n* = 1)	Term	46.20	Early signs of athetoid CP, bilateral sensorineural hearing loss	Bilateral symmetric high signal in the globus pallidus (7 mo)

CP = cerebral palsy.

with dystonia, choreoathetoid movements, and developmental delay in these cases. These results suggested that the characteristic neurologic findings of posticteric bilirubin encephalopathy have been correlated with the destruction of the globus pallidus. Despite the fact that kernicterus is known to affect various parts of the brain, particularly the pallidi, subthalamic nuclei, and hippocampus, it is remarkable that only the pallidi demonstrate signal change on MRI scans. Pathologic signal changes of the globus pallidus have been demonstrated in various disorders such as carbon monoxide poisoning, mitochondrial disorders, inborn errors of metabolism, hypoxic-ischemic encephalopathy, hemolytic-uremic syndrome, neurodegenerative disorders, and neurofibromatosis.[8,19–24] The MRI findings of our cases, combined with previous reports (Table 2), suggest that kernicterus should be considered in the differential diagnosis of bilateral, symmetric lesions of the globus pallidus.

One patient with severe neurologic disabilities and serum unconjugated bilirubin level of 36 mg/dL in the neonatal period did not show any signal changes in the globus pallidi on the MRI scans. This finding suggests that the absence of demonstrable MRI signal changes does not rule out the presence of neuropathologic damage and that neurologic symptoms do not necessarily correlate with MRI findings.

Two patients with a neonatal bilirubin level of 30 mg/dL did not show neurologic symptoms, and their MRI scans were normal. It may be postulated that high unconjugated bilirubin levels in the newborn period may not result in neurologic abnormalities or in MRI signal changes.

Conclusion

Patients with neurologic deficits due to bilirubin toxicity can exhibit bilateral symmetric globus pallidus hyperintensities on MRI scans. However, high levels of serum unconjugated bilirubin concentrations may not always result in such lesions of the globus pallidus on MRI scans despite the presence of neurologic symptoms. Although the diagnosis of kernicterus is traditionally made based on clinical findings, MRI may prove to have a conjunctive diagnostic value.

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