PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

This information is current as of November 7, 2006

The online version of this article, along with updated information and services, is
located on the World Wide Web at:
http://www.pediatrics.org/cgi/content/full/112/6/1256

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Changes in Globus Pallidus With (Pre)Term Kernicterus

Paul Govaert, MD, PhD*; Maarten Lequin, MD, PhD‡; Renate Swarte, MD*; Simon Robben, MD, PhD§;
René De Coo, MD, PhD‖; Nynke Weisglas-Kuperus, MD, PhD*; Yolanda De Rijke, MD¶;
Maarten Sinaasappel, MD#; and James Barkovich, MD, PhD**

ABSTRACT. *Objective.* We report serial magnetic resonance (MR) and sonographic behavior of globus pallidus in 5 preterm and 3 term infants with kernicterus and describe the clinical context in very low birth weight preterm infants. On the basis of this information, we suggest means of diagnosis and prevention.

Methods. Charts and MR and ultrasound images of 5 preterm infants and 3 term infants with suspected bilirubin-associated brain damage were reviewed. Included were preterm infants with severe hearing loss, quadriplegic hypertonia, and abnormal hypersignal of globus pallidus on T2-weighted MR imaging (MRI). In 1 infant who died on day 150, the diagnosis was confirmed during the neonatal period. The others were picked up as outpatients and scanned at 12 or 22 months' corrected age. Three instances of term kernicterus were included for comparison of serial MRI in the neonatal period and early infancy: they were caused by glucose-6-phosphate dehydrogenase deficiency, urosepsis, and dehydration plus fructose 1–6 biphosphatase deficiency.

Results. Five preterm infants of 25 to 29 weeks' gestational age presented with total serum bilirubin (TSB) levels below exchange transfusion thresholds commonly advised. Mixed acidosis was present in 3 infants around the TSB peak. The bilirubin/albumin molar ratio was >0.5 in all, in the absence of displacing drugs. All failed to pass bedside hearing screen tests and had severe hearing loss on auditory brain response testing. Symmetrical homogeneous hyperechogenicity of globus pallidus was the alerting feature in 1 infant. Globus pallidus was hyperintense on T1-weighted MR images in this child. The other infants presented with severe developmental delay as a result of dyskinetic quadriplegia and hearing loss. Globus pallidus was normal on T1- but hyperintense on T2-weighted MR images at 12 or 22 months' corrected age. Subthalamic involvement was documented in coronal fluid attenuated inversion recovery MRI in 2 infants. The term infants with classical clinical presentation in the neonatal period had MR behavior similar to the preterms, but pallidal injury was not recognized with targeted sonographic examination. Their neonatal MR images demonstrated pallidal T1 hyperintensity and mild T2 hyperintensity.

Conclusion. Acidotic very low birth weight preterm infants with low serum albumin levels develop MR-confirmed pallidal injury and hearing loss facing "accepted" TSB levels. Serial MRI documents a shift from acute mainly T1 hypersignal to permanent T2 hypersignal in globus pallidus within the late neonatal period. Subthalamic and not thalamic involvement helps to differentiate from ischemic or metabolic disorder. As newborns, these infants are rigid and have severe apnea, before developing hypertonic quadriplegia in infancy. *Pediatrics* 2003;112:1256–1263; *preterm, kernicterus, globus pallidus, albumin, acidosis.*

Free unconjugated bilirubin is toxic to synapses and injures axons and cell body organelles.[1] Kernicterus is a clinical and neuropathologic entity defined by acute yellow discoloration of deep gray nuclei in cerebrum, brainstem, and cerebellum. Affected regions become permanently gliotic. By the late 1950s, the use of exchange transfusion in Rh sensitization had greatly decreased the incidence of typical kernicterus at term, shifting the focus to kernicterus of the preterm.[2] In the 1970s, pathologists found an apparent reduction of preterm kernicterus, probably as a result of better general care and early phototherapy.[3] There is consensus on the absence of a tight correlation between total serum bilirubin (TSB) levels and kernicterus in sick preterm infants. In extremely low birth weight infants, kernicterus has been reported at TSB levels of 150 μmol/L (8 mg/dL), ie, between commonly advised phototherapy and exchange transfusion thresholds. Several components of the pathogenesis of kernicterus indeed bear no relation to the serum bilirubin level: reversible opening of the blood brain barrier,[4,5] reserve binding capacity of albumin and total serum albumin level,[6,7] acidosis,[8] clearance of bilirubin from the brain, and duration of contact between free or bound bilirubin and brain endothelium.[1,9]

In this report, we describe 5 instances of unexpected kernicterus in sick very low birth weight (VLBW) infants. The condition is probably underreported. Pallidal injury was picked up with ultrasound first in 1 infant. The diagnosis is facilitated by the use of magnetic resonance imaging (MRI). The

history and (serial) MR behavior of globus pallidus of 3 term infants with kernicterus is added. The diagnostic challenge of preterm kernicterus is reported in detail, focusing on the acute context.

Case Reports

Patient 1

This girl was delivered at 25 weeks and 4 days postmenstrual age, with Apgar scores of 8 and 10 at 1 and 5 minutes, respectively. She needed high-frequency oscillation for 6 days and conventional ventilation for 30 days thereafter. Initially started on penicillin and tobramycin, antibiotic treatment was stopped on day 3 with negative cultures. On the second day of life, an ultrasound scan revealed subependymal hemorrhage in the right caudothalamic groove with mild intraventricular bleeding (Fig 1, top). A patent ductus arteriosus was closed with fluid restriction and indomethacin on days 2 and 3 (3 doses of 0.2 mg/kg in 30 minutes every 8 hours). Pneumatosis intestinalis presented on day 8. Peritoneal drainage and intravenous meropenem could not prevent deterioration with mixed acidosis (Table 1), leading to subtotal colectomy 30 hours later. The postoperative period was complicated by 1) hypotension requiring expander, dopamine, and noradrenaline; 2) tubular necrosis; 3) cholestasis; and 4) postnatal hydrops. Serum albumin levels were not determined, and albumin was not supplemented in the first 2 weeks. In the fifth week, recurrent staphylococcal bacteremia was treated with vancomycin and rifampicin. With ultrasound, medial striate infarction within the region of the middle cerebral artery was documented postoperatively. During serial brain sonography on day 50, bilateral and symmetric hyperechogenicity was observed in both globi pallidi, in addition to the previous lesions (Fig 1). This subtle aspect of increased pallidal sound reflection persisted without cavitation until demise. Pallidal hyperechogenicity thus spans postmenstrual ages 32 to 47 weeks. At 38 postmenstrual weeks, pallidal hyperintensity was documented on T1-weighted MR images (Fig 2). Facing recurrent central and obstructive apnea refractory to caffeine and doxapram, it was decided not to support ventilation artificially because of severe hypertonia and hearing loss documented with absent reaction on 2 auditory brain response (ABR) tests between days 100 and 140. The electroencephalogram (EEG) was appropriate for age on 2 occasions. The girl died on day 150, permission for postmortem examination not being granted. Bilirubin and albumin values are shown in Table 1. Lactate and pyruvate were normal in plasma and cerebrospinal fluid on postnatal day 60.

Patients 2–5 (Preterm Infants)

Four cases of hearing loss and rigid quadriplegia were detected in VLBW outpatients with cerebral palsy of uncertain cause. Each had pallidal hyperintensity on T2-weighted images beyond the newborn period, with normal signal intensity on T1-weighted images (Fig 3). Pallidal involvement was partial, preferring the inferior and posteromedial area. No definite signal abnormality could be detected in other regions known to be affected by kernicterus, except for the subthalamic nucleus (Fig 4). Their neonatal sonograms were reviewed, but pallidal hyperechogenicity was not observed; sonograms were taken with a 6.5-MHz HP scanhead and not targeted at visualization of pallidal injury. Relevant clinical and biochemical data are in Table 1, focusing on acidosis and bilirubin/albumin ratio. Penicillin, indomethacin, and furosemide were used in the first week in all infants. Albumin supplements were not given during the acute icteric phase. Phototherapy in VLBW infants is started above the threshold line of 85 μmol/L at birth, 115 μmol/L at 24 hours, 150 μmol/L at 48 hours, 170 μmol/L at 72 hours, and 180 μmol/L from 96 hours on. The postnatal clinical course excluded ongoing metabolic disease in these infants.

Patients 6–8 (Term Infants)

Patient 6 was delivered at home at 39 weeks' gestation. She weighed 2280 g and was not depressed at birth. Blood groups were compatible, and the Coombs test was negative. She was admitted at 72 hours of life with lethargy, jaundice, apnea, and hypothermia (34°C). Her TSB level reached 632 μmol/L on admission, with an albumin level of 32 g/L (molar ratio bilirubin/albumin, 1.3). She was not anemic and had maximal reticulocyte counts in the first week of 60%. Bacteremia, galactosemia, and hypothyroidism were excluded. Two exchange transfusions and 5 days of phototherapy were needed. The day after admission, she became opisthotonic and developed increasing apnea necessitating ventilatory support. EEG disclosed brief epileptic discharges over the left side of the brain. ABR documented severe hearing loss of 90 dB. MRI demonstrated T1 hypersignal in globus pallidus and subthalamic nucleus on days 6 and 10 (Fig 5), with mildly increased T2-signal intensity. Diffusion-weighted MRI did not pick up pallidal injury. Pallidal echoreflections appeared normal. At 3 months, the infant was normotonic but deaf. At this time, glucose-6-phosphate dehydrogenase deficiency was diagnosed. T1-signal intensity had returned to normal, whereas T2 signals had increased in globus pallidus.

Patient 7 was born vaginally at 37 weeks of gestation, birth weight 3950 g, Apgar scores 9 and 10 at 1 and 5 minutes, respectively. After discharge home within 24 hours, she was readmitted on day 6 with decreased diuresis and refusal of breastfeeding. Clinically jaundiced from day 2, the first estimated TSB level on admission was 776 μmol/L. She had 1 exchange transfusion and phototherapy. Blood group incompatibility was excluded. *Proteus mirabilis* bacteremia and urinary infection were diagnosed. Epileptiform changes were seen on EEG in the acute stage. MRI (Fig 6) demonstrated T1 hypersignal in globus pallidus on days 6 and 14, with mildly increased T2-signal intensity. Pallidal echoreflections appeared normal. At 3 months, T1-signal intensity was normal,

Fig 1. Coronal and parasagittal 8.5-MHz sonograms (8.5 MHz, Acuson Sequoia) in patient 1 at 50 days of age: cystic old infarct in the left caudothalamic groove; neat homogeneous hyperechoic aspect of globi pallidi (arrows); compare with previous scans on day 7 (top, 6.5 MHz Hewlett-Packard).
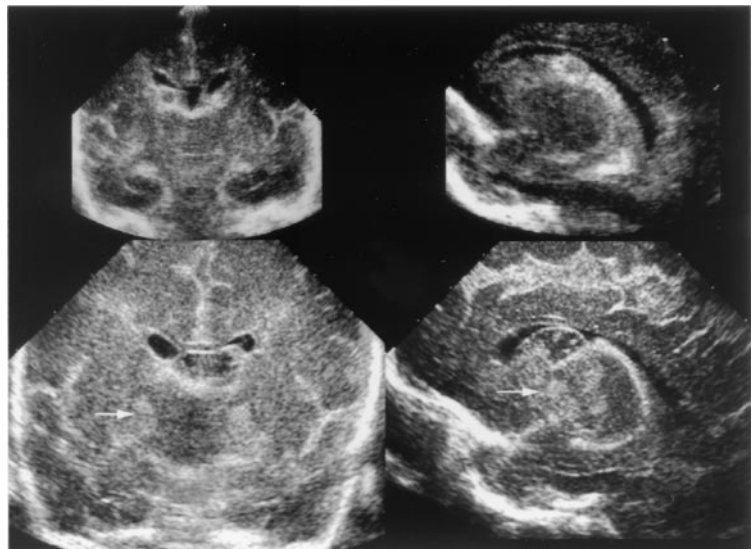
TABLE 1. Serial Clinical and Biochemical Findings in Preterm Infants With Kernicterus

Day	vef:girl °150500 — 25w4d, 900g · Event	TSB	Albumin	de:boy °161298 — 29w, 1320g · Event	TSB	Albumin	sr:boy °090498 — 25w4d, 900g · Event	TSB	Albumin	sl:girl °090498 — 25w4d, 745g · Event	TSB	Albumin	pvd:boy °240301 — 28w5d, 1365g · Event	TSB	Albumin
1	HFO			sIMV			sIMV, HFO			HFO			HFO		
2	IVHgr2, PDA	92		PDA			PDA	82		PDA	84		hypotension	156	23
3		137		left pneumothorax	126			120			128		capillary leak	159	
4	pHa 7.24 [5.9/−8]	158		right pneumothorax	137			142			134		IVH gr 2	172	
5		108		hypoglycemia	122			151			139		pHa 7.21 [7.3/−7]	204 (boxed)	25 (boxed)
6		147					ileostoma	150			145			189	
7	SIMV	148					IVH gr2, irritable	157		PDA clip; IVHgr2	156		gastric bleed, sIMV	173 (boxed)	18 (boxed)
8	NEC, ileostoma				143			161			206 (boxed)			189	
9	pHa 6.98 [10.3/−15]	131 (boxed)	14 (boxed)	pHa 7.09 [8.3/−11]	179		pHa 7.33 [5.7/−3.6]	220 (boxed)	19 (boxed)	pHa 7.17 [7.7/−8.8]	114	18 (boxed)		141	13
10	anuria			irritable	186 (boxed)	21 (boxed)		135			113			154	20
11					139	19								163	22
12							EEG not epileptic hydrocephalus				148			105	
13		52		hypertonia											
14				irritable	22										
B/A peak ratio	0.62			0.58			0.76			0.75			0.54 / 0.63		
evolution	prolonged edema cholestasis mitoch screen neg rigidity obstructive apnea absent ABR exitus d 150 MR at 38 w T1 pallidum Δ+ T2 pallidum = left caudate infarct			mild BPD doxapram, coffeine 12 months: mitoch screen neg choreoathetosis quadriplegia absent ABR MR at 12 months T1 pallidum = T2 pallidum Δ+			3 years: hypertonia choreoathetosis (spastic) quadriplegia abnormal ABR MR at 22 months T1 pallidum = T2 pallidum Δ+ PVL			BPD, dxm d 20 apnea, coffeine 3 years: hypertonia choreoathetosis (spastic) quadriplegia abnormal ABR MR at 22 months T1 pallidum = T2 pallidum Δ+ PVL, left cerebellar infarct			evolution no BPD transient ventriculomegaly 1 year: hypertonia tongue thrusting spastic quadriplegia abnormal ABR MR at 12 months T1 pallidum = T2 pallidum Δ+ mild PVL		

B/A indicates bilirubin/albumin molar ratio, ratio determinants highlighted by borders; BPD, bronchopulmonary dysplasia; HFO, oscillation; IVH, intraventricular hemorrhage; MR, magnetic resonance; NEC, necrotizing enterocolitis; PDA, open ductus arteriosus; pHa, lowest pHart [pCO2, BE]; PVL, periventricular leukomalacia; SIMV, triggered intermittent ventilation.

Fig 2. T1- and T2-weighted MR images at 38 weeks' postmenstrual age in patient 1: hyperintense signal (arrows) in globus pallidus on T1 and not T2 sequences.
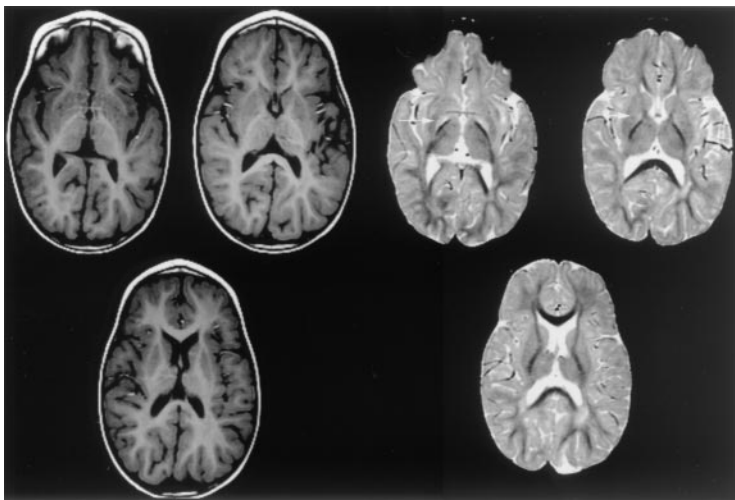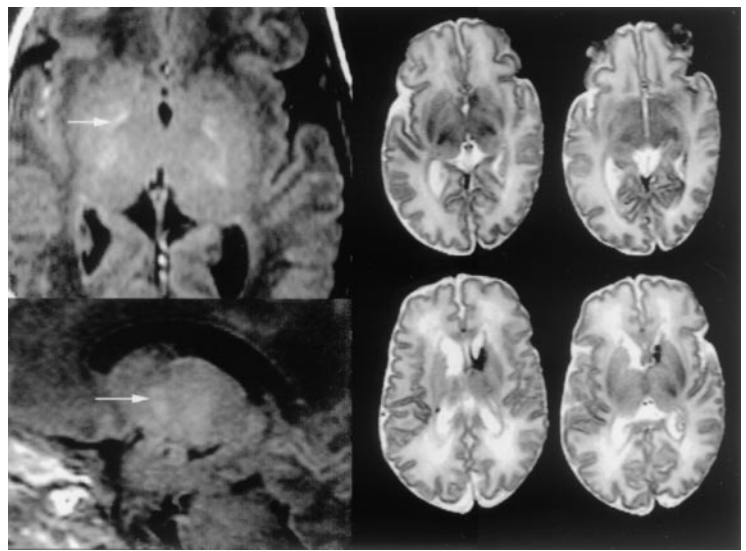

Fig 3. Corresponding axial T1 and T2 MR images at 22 months in patient 4: hyperintense signal in caudal and inferior globus pallidus on T2 is suggestive of permanent gliosis (arrows).

Fig 4. Composite image to show subthalamic nucleus injury. Left, parasagittal T1 in patient 8 at 12 days: high signal in pallidum (horizontal arrow) and especially subthalamus (vertical arrow). Right, coronal fluid attenuated inversion recovery MR at 22 months in patient 3: subthalamic (vertical arrow) and pallidal hypersignal.
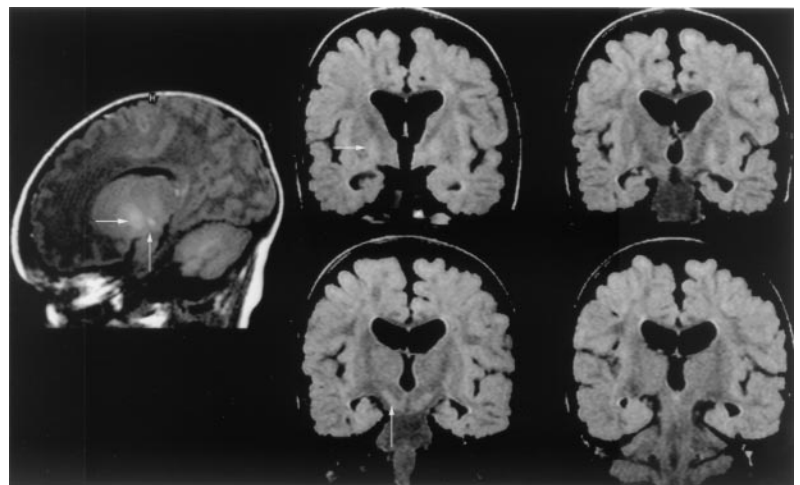
whereas T2 signals had increased in globus pallidus. Hearing loss was confirmed with ABR. The infant was by then hypotonic with repetitive tongue thrusting.

Patient 8 was born at term without asphyxia and with birth weight 3520 g. Her parents were first cousins. She was readmitted after 72 hours because of jaundice (TSB 763 μmol/L), lethargy, and poor feeding after losing 700 g of weight (20%). Other indicators of hypertonic dehydration were fever to 38.6°C, high serum sodium of 158 mEq/L, and urea of 37 mmol/L. After 1 exchange transfusion, she became acidotic (pH 7.05, BE -21) and was referred. She underwent another exchange transfusion at a TSB of 481 μmol/L (direct fraction 37 μmol/l). She was ventilated for (EEG confirmed) seizures with apnea and received phenobarbitone and clonazepam. Opisthotonus was not noted. Cloudy corneae, retinitis pigmentosa, and fructose 1–6 biphosphatase deficiency were diagnosed in infancy during episodes of diarrhea and

ARTICLES **1259**

Fig 5. Axial T1-weighted MR on day 6 in a term infant with kernicterus (patient 6, above) compared with a term newborn with seizures of unknown origin but normal sonogram and MRI; the hypersignal in pallidum is best interpreted at intermediate and inferior sections through pallidum mediale.
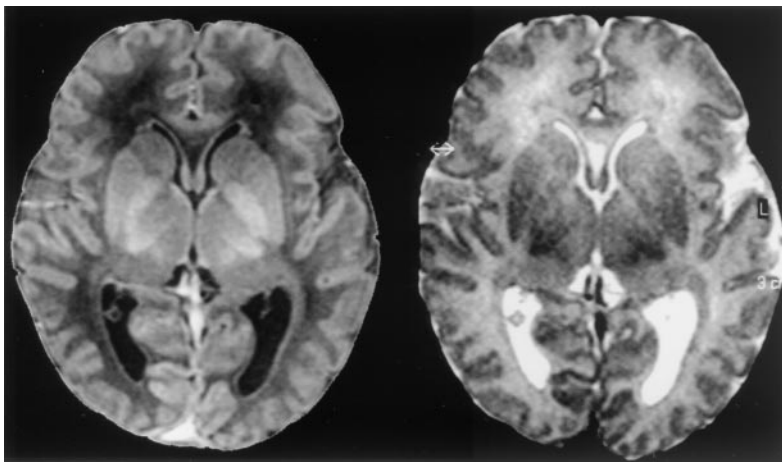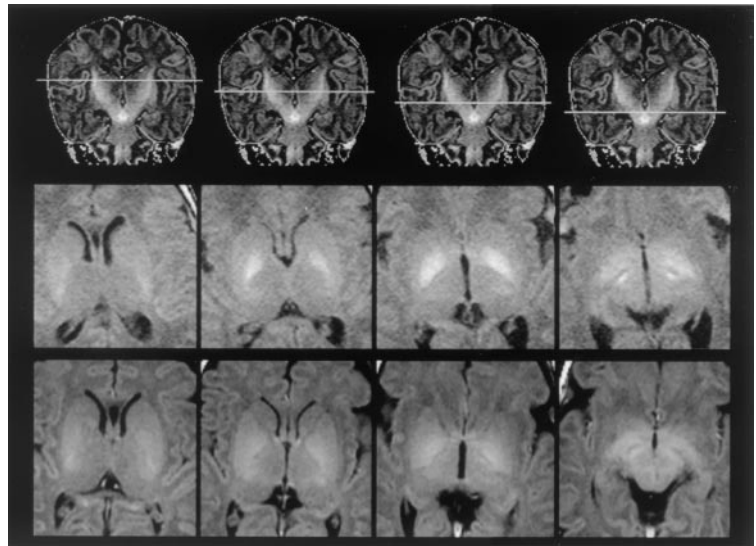

Fig 6. Axial IR-TSE T1-weighted MR on day 6 in patient 7: very high signal in entire globus pallidus on T1, mildly hyperintense aspect on T2 making pallidum just discernible from putamen.

lactacidosis. At 4 years, she has severe hearing impairment and is athetotic and spastic quadriplegic. Her tonic neck reflexes persisted for >1 year. MRI at 12 days of age illustrated hypersignal on T1 in pallidum and subthalamus (Fig 4) and discrete hypersignal in pallidum on T2.

METHODS

MR Images

A 1-Tesla MR scanner (Philips Medical Systems, Best, The Netherlands) was used to obtain T1-weighted spin echo with parameters of 425/20/2 (time to relaxation/time to exatation/excitations) and T2-weighted spin echo images of the brain with parameters of 3000/30/90/1. The section thickness was 4 mm, with an intersection gap of 0.4 mm. The matrix was 256×256, and the field of view was 19 cm.

MRI examination was performed at 38 postmenstrual weeks in patient 1 and at 12, 22, 22, and 12 months in patients 2, 3, 4, and 5, respectively. The term infants were scanned in the first or second week and at 3 months of age. For recognition of the hypersignal in globus pallidus on T1-weighted MRI in the neonatal period, we compared axial sections at several levels through this nucleus with normal term infants (Fig 6). The inferior aspect of the globus pallidus, pallidum mediale, which extends farther inferior than pallidum laterale, is more involved with kernicterus, whereas the T1 shortening that is seen in normals involves both nuclei equally. Regarding the T2 prolongation in the acute phase, we suspect that it represents edema and is transient.

Serum Bilirubin Estimation

Total serum bilirubin was measured with the Wahlefeld method[10] using the colorimetric assay after displacement by detergent and azobilirubin formation with 2,5-dichlorophenyl diazonium ion.

DISCUSSION

On the basis of our experience with 5 preterm and 3 term kernicteric infants, we describe the neonatal and early childhood behavior of globus pallidus on brain imaging. We demonstrate early usefulness of T1- and T2-weighted MRI and, in 1 case, ultrasound and permanent decisive value of T2-weighted MRI. In our preterm infants, molar bilirubin/albumin ratios but not TSB levels were above the exchange transfusion thresholds recommended by Ahlfors in 1994.[7] The neonatal clinical cluster associates a complicated history in a VLBW infant with hypoalbuminemia and/or acidosis during the hyperbilirubinemic period, early hearing loss, hypertonia, and severe apnea before term. This clinical syndrome has to be differentiated from metabolic disorders. Limitations are the absence of data for bilirubin binding capacity or free serum bilirubin levels, postmortem correlation, and serial MRI in the same preterm.

Only postmortem studies could confirm kernicterus before the MR era.[11] Macroscopic staining of brain areas occurs in the absence of neuronal cell loss, troubling the histopathologic diagnosis. Regional exudation of bilirubin should not be equated

with kernicterus. Crucial to the diagnosis is recognition of the pallido-subthalamic type of selective neuronal injury with residual fibrillary gliosis, contrary to the putamino-thalamic type of hypoxic-ischemic injury.[12,13] Pallidal involvement in asphyxia is not obligatory and often is mild.[13–15] In our patients, no definite signal abnormality could be detected in other regions known to be vulnerable in kernicterus (except for the subthalamic nucleus): dentate nucleus, hippocampus, substantia nigra, hypothalamus, cranial nerve nuclei VIII, and inferior olive. Leukomalacia was present in 3 surviving preterm infants but is unlikely to be caused by hyperbilirubinemia. Our experience suggests pallidal injury by bilirubin to be independent of maturation. Thalamic injury, on the contrary, is an outstanding marker for global asphyxia, even in the third-trimester fetus.[14–16] CO intoxication and mitochondriopathy were unlikely as causes of pallidal injury in the infants reported here. Kernicteric injury at term has been confirmed with MRI (Table 2). T2-weighted images permitted recognition of gliosis in globus pallidus[17–25] and subthalamic nucleus[21,24] after 6 months of age. Pallidal involvement, if partial, affects the medial posterior and inferior area of the nucleus. The images fit the description of dense fibrillary cell-poor gliosis as histologic end stage.[26] In neonatally documented cases, pallidal injury was recognized only from T1 hyperintensity.[17,21,22] This may reflect astroglial cell gemistocytic reaction of the acute event[26] and explain hyperechoic features of globus pallidus in 1 of our cases. There is the possibility that edema or bilirubin itself may contribute in the hyperacute stage. Mild hypersignal has already been suspected in globus pallidus on T2 at 16[17] and 18[19] days of age in term infants with classical kernicterus. Change of T1 intensity from hypersignal at 9 days to normal signal at 10 months of age has been reported in a term kernicteric infant with hearing loss and transient hypertonia in early infancy.[22,23]

Our experience suggests that loss of the hyperintense T1 signal already occurs between the first and third weeks. The case by Martich-Kriss et al[19] already carried discrete high T2 signal on day 18. Identical observations of the long-term T2 behavior of globus pallidus and subthalamic nucleus were recently made in 4 preterm infants.[24,27] The discernibility of pallidum on T2-weighted images in the hyperacute stage is unusual and helpful only in association with relative increase of intensity on T1.[28] Manganese intoxication is very unlikely in these newborns and would have caused transient T1 hyperintensity without leaving permanent T2 hyperintensity in case 1 with liver disease.[29–31] A similar finding has been published for transient polycythemia.[32] The switch from easy detectability on T1 in the neonatal period to mainly hypersignal on T2 in early childhood may not be typical of kernicterus, as it is also seen after birth asphyxia.[33] The preterm infants with kernicterus presented in this report were analyzed in view of the current insights on clinical factors that contribute to kernicterus.[1]

Acidosis can influence bilirubin entry into the brain at different levels: 1) promoting precipitation into suitable partially polar lipid membranes[8,34] and 2) increasing cerebral blood flow (respiratory acidosis) and therefore contact time between brain endothelium and bilirubin.[9] It was established early that being a sick (pre)term newborn reduces bilirubin-binding capacity for at least 1 week after birth.[35] This reduction is independent of serum albumin level. Postmortem cohort studies introduced controversy about the role of acidosis.[3,11] Some did correlate free serum unconjugated bilirubin with autopsy-confirmed preterm kernicterus.[36] Focusing on sensorineural deafness without cerebral palsy in preterms of gestational age <34 weeks and TSB peak level >240 μmol/L (14 mg/dL), de Vries et al in 1985[37] correlated bilirubin toxicity with spells of respiratory acidosis and with duration of hyperbilirubinemia (5 of

TABLE 2. MR Descriptions of Kernicterus in the Literature

Author	(Pre)Term	Clinical Condition	Age at MR	MR Findings	
Penn et al[17]	Term	Sepsis	16 d	T1Δ++	T2Δ+
Yokochi[18]	Term ×3	Sepsis, hemolysis	3 y, 7 y, 12 y		T2Δ+
Martich-Kriss et al[19]	Term	Hemolysis	18 d/*6 mo*		T2Δ+
Worley et al[20]	Term	Hemolysis	7 mo		T2Δ+
Steinborn et al[21]	Term	Hemolysis	2.5 y		T2Δ+ subthal
Harris et al[22]	Term ×2	Sepsis	5 d, 9 d	T1Δ+	? T2
			10 mo	normal	normal
Sugama et al[24]	Preterm ×2		1 y, 10 mo, 5 mo	? T1	T2Δ+
	Term ×1		4 y	? T1	T2Δ+ subthal
Okumura et al[27]	Preterm ×2		5 mo, 9 mo	? T1	T2Δ+
Yilmaz et al[25]	Term × 8	Hemolysis × ?	3–53 mo	T1 normal	T2Δ+
This report	Preterm × 5		38 w GA	T1Δ+ subthal	T2−
			12 mo ×2	T1−	T2Δ+ subthal
			22 mo	T1−	T2Δ+
				T1−	T2Δ+
	Term × 3	G6PD deficient	6 d	T1Δ+	T2+
			3 mo	T1−	T2Δ+ subthal
		Sepsis	6 d	T1Δ+	T2+
			3 mo	T1−	T2Δ+ subthal
		Dehydration FDD	12 d	T1Δ+ subthal	T2+

GA indicates gestational age; subthal, subthalamus.
Δ+, increase of signal intensity; −, no change; ?, information unclear; subthal, subthalamus also affected in a way similar to globus pallidus. Serial MRI in italics.

12 deaf children with at least 48 hours of TSB >240 μmol/L, versus 1 of 12 matched control subjects).

A high bilirubin/albumin ratio may have contributed to preterm kernicterus according to the free bilirubin hypothesis.[38] This hypothesis provided a rationale for the albumin-primed exchange transfusion.[39,40] Increasing the albumin level might redistribute bilirubin from healthy into acidotic organs, and albumin leaking out of injured capillaries might retain bilirubin in such organs. For these and other reasons, the use of albumin other than for priming before exchange transfusion did not become popular.[38] Odell[6] modeled the albumin molecule for bilirubin binding sites. At secondary (low-affinity) sites, organic anions such as sulfisoxazole or free fatty acids displace bilirubin even below molar equivalence. High free fatty acid levels may have contributed to an impediment of bilirubin binding in our patients but were not measured. Potential displacing drugs[41] given to our preterm infants, such as indomethacin, penicillin, and furosemide, normally do not achieve serum levels sufficient to displace significant amounts of unconjugated bilirubin, but their combined effect is unknown. Ahlfors[7] lined up arguments for the use of serum bilirubin/albumin molar ratio as an acceptable surrogate for determination of residual binding capacity of albumin or of free serum bilirubin levels. Many sick preterm infants have an optimal molar ratio of bilirubin to albumin <0.7, some drop to approximately 0.4. From these data can be derived the attitude of not allowing sick neonates to exceed molar bilirubin/albumin ratio 0.5. Displacement studies using sulfisoxazole and benzoate established the danger level of free bilirubin for induction of kernicterus between 8.6 and 12 ng/mL (approximately 15 nmol/L; 1 mg bili = 1.71 μmol).[42] The turning point for abnormal ABR maturation in the first week of life in preterm infants of 28 to 32 weeks of gestation is lower, approximately 5 ng/mL.[43] This effect on central auditory pathways is observed at a bilirubin/albumin ratio between 0.3 and 0.4, below the ratios of our preterm infants.

In practice, there seem to be 2 means of preventing preterm kernicterus that can be supported with clinical, laboratory, and experimental findings: 1) correction of acidosis and 2) striving for a low bilirubin to albumin ratio with phototherapy and/or albumin supplements. We still need proof of protection for either method in randomized clinical studies, but on the basis of our experience, will supplement albumin if <20 g/L in an icteric preterm infant and let the bilirubin/albumin ratio guide phototherapy. Other measures may include prevention of bilirubin formation with prophylactic phenobarbitone, early phototherapy,[44] avoidance of displacing drugs, and control of serum free fatty acid levels.

In conclusion, preterm kernicterus can be suspected in the neonatal period on specific clinical, imaging, and laboratory grounds. MRI has crucial value, but as stated by others, the signal changes on both T1- and T2-weighted images are subtle and easily overlooked. Our study confirms the finding of signal abnormality on T1-weighted early MR scans. Only from the late neonatal period, T2-weighted MR images show persistent abnormal hypersignal in globus pallidus. This early lesion pattern may on occasion be identified with ultrasound. The pathophysiologic role of low serum albumin levels must be considered in the jaundiced VLBW infant in the first 2 weeks of life. In term infants with severe hyperbilirubinemia and acidosis, fructose 1–6 biphosphatase deficiency must be excluded.[45]

REFERENCES

1. Hansen TWR. Mechanism of bilirubin toxicity: clinical implications. *Clin Perinatol*. 2002;29:765–778
2. Cashore WJ. The neurotoxicity of bilirubin. *Clin Perinatol*. 1990;17: 437–447
3. Pearlman MA, Gartner LM, Lee KS. Absence of kernicterus in low-birth-weight infants 1971–1976: comparison with 1966–1967. *Pediatrics*. 1978; 62:460–464
4. Levine RL, Fredericks WR, Rapoport SI. Entry of bilirubin into the brain due to opening of the blood brain barrier. *Pediatrics*. 1982;69:255–259
5. Wennberg RP, Hance AJ. Experimental bilirubin encephalopathy: importance of total bilirubin, protein binding, and blood-brain barrier. *Pediatr Res*. 1986;20:789–792
6. Odell GB. *Neonatal Hyperbilirubinemia. Monographs in Neonatology*. Grune and Stratton; 1980
7. Ahlfors CE. Criteria for exchange transfusion in jaundiced newborns. *Pediatrics*. 1994;93:488–494
8. Brodersen R, Stern L. Deposition of bilirubin acid in the central nervous system: a hypothesis for the development of kernicterus. *Acta Paediatr Scand*. 1990;79:12–19
9. Wennberg RP. The blood-brain barrier and bilirubin encephalopathy. *Cell Mol Neurobiol*. 2000;20:97–109
10. Wahlefeld AW, Herz G, Bernt E. Modification of the Maloy-Evelyn method for a simple, reliable determination of total bilirubin in serum. *Scand J Clin Lab Invest*. 1972;29(suppl 126):11–12.
11. Turkel SB, Miller CA, Guttenberg MEA. clinical pathologic reappraisal of kernicterus. *Pediatrics*. 1982;69:267–272
12. Ahdab-Barmada M, Moosy J. The neuropathology of kernicterus in the premature neonate: diagnostic problems. *J Neuropathol Exp Neurol*. 1984; 43:45–55
13. Hayashi M, Satoh J, Sakamoto K, et al. Clinical and neuropathological findings in severe athetoid cerebral palsy: a comparative study of glob-Luysian and thalamo-putaminal groups. *Brain Dev*. 1991;13:47–51
14. Friede RL. Perinatal lesions of gray matter. In: *Developmental Neuropathology*. Berlin: Springer-Verlag; 1989:82–87
15. Friede RL. Kernicterus. In: *Developmental Neuropathology*. Berlin: Springer-Verlag; 1989:115–124
16. Leech RW, Alvord EC. Anoxic-ischemic encephalopathy in the human neonatal period. *Arch Neurol*. 1977;34:109–113
17. Penn AA, Enzmann DR, Hahn JS. Kernicterus in a full term infant. *Pediatrics*. 1994;93:1003–1006
18. Yokochi K. Magnetic resonance imaging in children with kernicterus. *Acta Paediatr Scand*. 1995;84:937–939
19. Martich-Kriss V, Kollias SS, Ball WS Jr. MR findings in kernicterus. *Am J Neuroradiol*. 1995;16(4 suppl):819–821
20. Worley G, Erwin CW, Goldstein RF, et al. Delayed development of sensorineural hearing loss after neonatal hyperbilirubinemia: a case report with brain magnetic resonance imaging. *Dev Med Child Neurol*. 1996;38:271–277
21. Steinborn M, Seelos KC, Heuck A, von Voss H, Reiser M. MR findings in a patient with kernicterus. *Eur Radiol*. 1999;9:1913–1915
22. Harris MC, Bernbaum JC, Polin JR, et al. Developmental follow-up of breastfed term and near-term infants with marked hyperbilirubinemia. *Pediatrics*. 2001;107:1075–1080
23. Newman TB, Maisels MJ. Magnetic resonance imaging and kernicterus. *Pediatrics*. 2002;109:555
24. Sugama S, Soeda A, Eto Y. Magnetic resonance imaging in three children with kernicterus. *Pediatr Neurol*. 2001;25:328–331
25. Yilmaz Y, Alper G, Kilicoglu G, et al. Magnetic resonance imaging findings in patients with severe neonatal indirect hyperbilirubinemia. *J Child Neurol*. 2001;16:452–455
26. Larroche J-C. Kernicterus and posticteric encephalopathy. In: *Develop-

mental Pathology of the Neonate. North-Holland: Elsevier; 1977:447–454

27. Okumura A, Hayakawa F, Kato T, et al. Preterm infants with athetoid cerebral palsy: kernicterus? *Arch Dis Child Fetal Neonatal Ed.* 2001;84: F136–F137

28. Barkovich J. MR of the normal neonatal brain: assessment of deep structures. *Am J Neuroradiol.* 1998;19:1397–1403

29. Malecki EA, Devenyi AG, Barron TF, et al. Iron and manganese homeostasis in chronic liver disease: relationship to pallidal T1-weighted magnetic resonance signal hyperintensity. *Neurotoxicology.* 1999;20: 647–652

30. Pal PK, Samii A, Calne DB. Manganese neurotoxicity: a review of clinical features, imaging and pathology. *Neurotoxicology.* 1999;20:227–238

31. Rose C, Butterworth RF, Zayed J, et al. Manganese deposition in basal ganglia structures results from both portal-systemic shunting and liver dysfunction. *Gastroenterology.* 1999;117:640–644

32. Gikova CG, Zirretta JC, Bezerra JMF, et al. Transient globus pallidus T1 shortening associated with polycythaemia and dystonia. *Neuroradiology* 1999;41:288–291

33. Krägeloh-Mann I, Helber A, Mader I, et al. Bilateral lesions of thalamus and basal ganglia: origin and outcome. *Dev Med Child Neurol.* 2002;44: 477–484

34. Bratlid D, Cashore WJ, Oh W. Effects of acidosis on bilirubin deposition in rat brain. *Pediatrics.* 1984;73:431–434

35. Meisel P, Jährig D, Beyersdorff E, et al. Bilirubin binding and acid-base equilibrium in newborn infants with low birthweight. *Acta Paediatr Scand.* 1988;77:496–501

36. Cashore WJ, Oh W. Unbound bilirubin and kernicterus in low-birth-weight infants. *Pediatrics.* 1982;69:481–485

37. de Vries LS, Lary S, Dubowitz LMS. Relation of serum bilirubin levels to ototoxicity and deafness in high-risk low-birth-weight infants. *Pediatrics.* 1985;76:351–354

38. Brodersen R. Bilirubin transport in the newborn infant, reviewed with relation to kernicterus. *J Pediatr.* 1980;96:349–356

39. Odell GB, Bryan WB, Richmond MD. Exchange transfusion. *Pediatr Clin North Am.* 1962;9:605–615

40. Ebbesen F. Effect of exchange transfusion on serum reserve albumin for binding of bilirubin and index of bilirubin toxicity. *Acta Paediatr Scand.* 1981;70:643–648

41. Robertson A, Karp W, Brodersen R. Bilirubin displacing effect of drugs used in neonatology. *Acta Paediatr Scand.* 1991;80:1119–1127

42. Ahlfors CE. Unbound bilirubin associated with kernicterus: a historical approach. *J Pediatr.* 2000;137:540–544

43. Amin SB, Ahlfors C, Orlando MS, Dalzell LE, Merle KS, Guillet R. Bilirubin and serial auditory brainstem response in premature infants. *Pediatrics.* 2001;107:664–670

44. Epstein MF, Leviton A, Kuban KCK, et al. Bilirubin, intraventricular hemorrhage, and phenobarbital in very low birth weight babies. *Pediatrics.* 1988;82:350–354

45. Buhrdel P, Bohme HJ, Didt L. Biochemical and clinical observations in four patients with fructose-1, 6-diphosphatase deficiency. *Eur J Pediatr.* 1990;149:574–576

ELASTOGRAPHY

"One day, radiologists will screen for tumors by jiggling our innards like plates of jelly. The technique, called elastography, is like the centuries-old method of palpating the body to find odd lumps, except it can feel deep inside the body without an incision. Instead, it measures the elasticity of tissue. Sideways vibrations are applied to the area under investigation, and then magnetic resonance imaging is used to watch the waves moving through it. Tumors will be stiffer than the surrounding tissue and so the waves will diminish as they pass through.

'Every day,' says Richard Ehman, a radiologist at the Mayo Clinic in Rochester, Minnesota, 'surgeons reach in through incisions and feel tumors that we've missed with every one of our existing imaging techniques.'

The key is that stiffness varies so widely between tissue types: tumors are 10 to 100 times as still as healthy tissue. But this variation only shows up as a fourfold difference in density using conventional body imaging techniques."

New Scientist. August 16, 2003

Noted by JFL, MD

Changes in Globus Pallidus With (Pre)Term Kernicterus

Paul Govaert, Maarten Lequin, Renate Swarte, Simon Robben, René De Coo, Nynke Weisglas-Kuperus, Yolanda De Rijke, Maarten Sinaasappel and James Barkovich

This information is current as of November 7, 2006

Updated Information & Services	including high-resolution figures, can be found at: http://www.pediatrics.org/cgi/content/full/112/6/1256
References	This article cites 41 articles, 17 of which you can access for free at: http://www.pediatrics.org/cgi/content/full/112/6/1256#BIBL
Citations	This article has been cited by 6 HighWire-hosted articles: http://www.pediatrics.org/cgi/content/full/112/6/1256#otherarticles
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): **Premature & Newborn** http://www.pediatrics.org/cgi/collection/premature_and_newborn
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.pediatrics.org/misc/Permissions.shtml
Reprints	Information about ordering reprints can be found online: http://www.pediatrics.org/misc/reprints.shtml