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Changes in Globus Pallidus With (Pre)Term Kernicterus

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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.***

ABBREVIATIONS. TSB, total serum bilirubin; VLBW, very low birth weight; MRI, magnetic resonance imaging; ABR, auditory brain response; EEG, electroencephalogram.

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

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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,

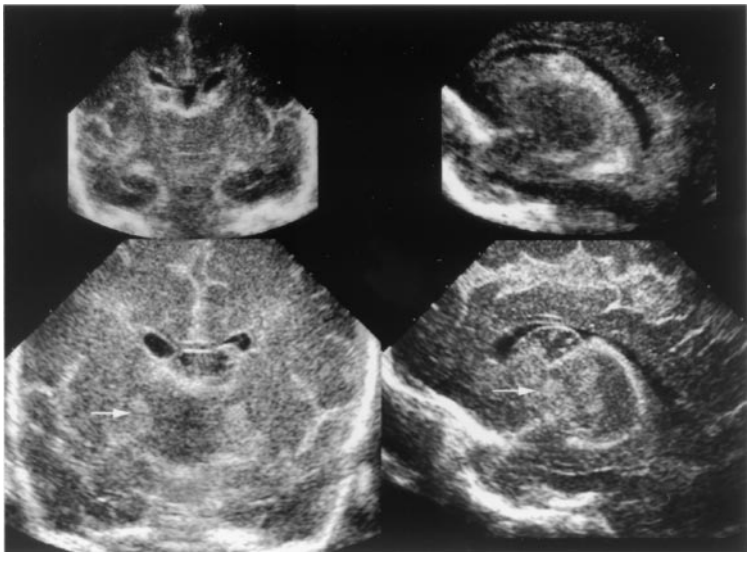

Fig 1. Coronal and parasagittal 8.5-MHz sonograms (8.5 MHz, Acuson Sequoia) in patient 1 at 50 days of age: cystic old infarct in the left caudothalamic groove; neat homogeneous hyperechoic aspect of globi pallidi (arrows); compare with previous scans on day 7 (top, 6.5 MHz Hewlett-Packard).

TABLE 1. Serial Clinical and Biochemical Findings in Preterm Infants With Kernicterus

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

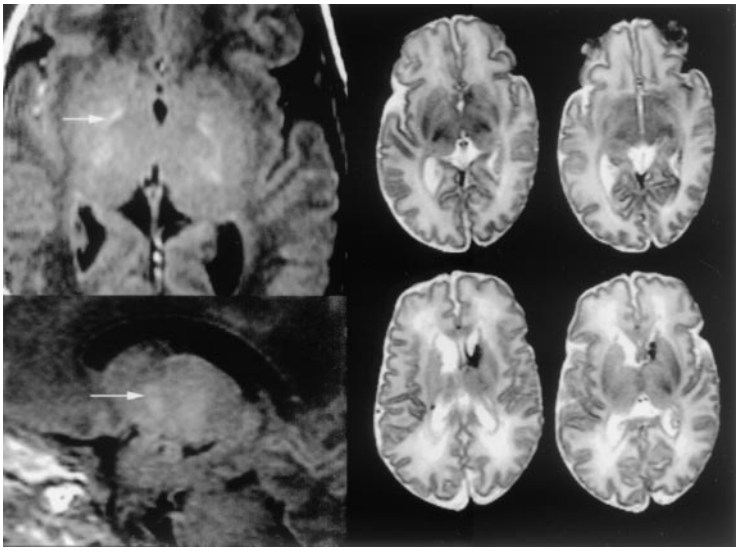

Fig 2. T1- and T2-weighted MR images at 38 weeks' postmenstrual age in patient 1: hyperintense signal (arrows) in globus pallidus on T1 and not T2 sequences.

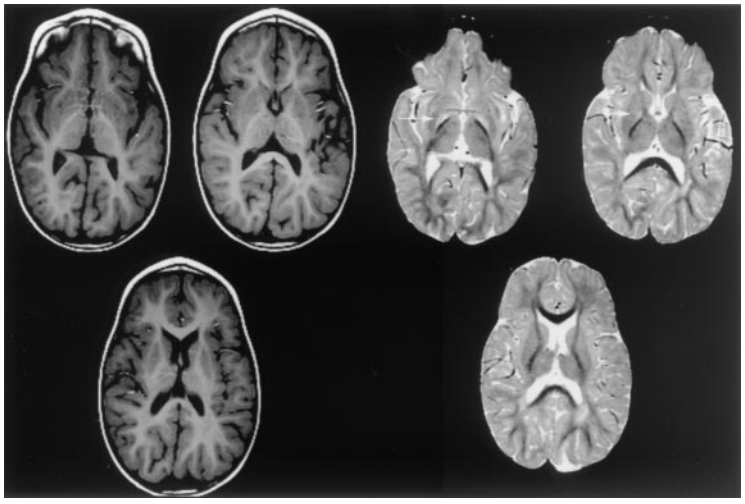

Fig 3. Corresponding axial T1 and T2 MR images at 22 months in patient 4: hyperintense signal in caudal and inferior globus pallidus on T2 is suggestive of permanent gliosis (arrows).

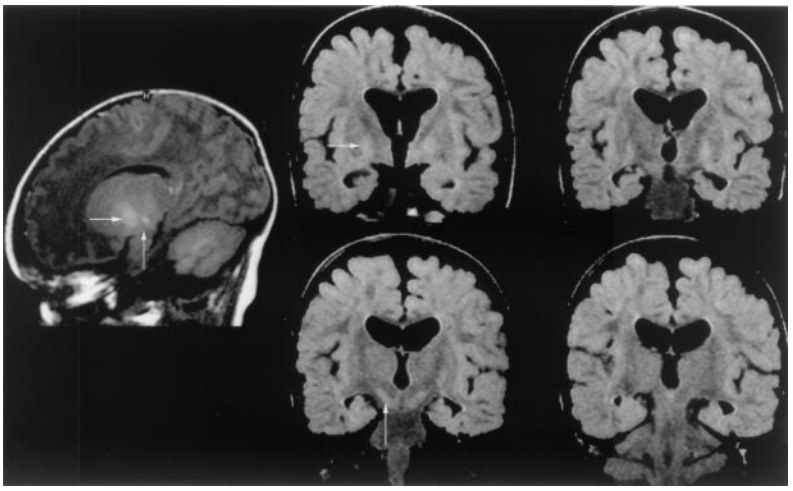

Fig 4. Composite image to show subthalamic nucleus injury. Left, parasagittal T1 in patient 8 at 12 days: high signal in pallidum (horizontal arrow) and especially subthalamus (vertical arrow). Right, coronal fluid attenuated inversion recovery MR at 22 months in patient 3: subthalamic (vertical arrow) 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

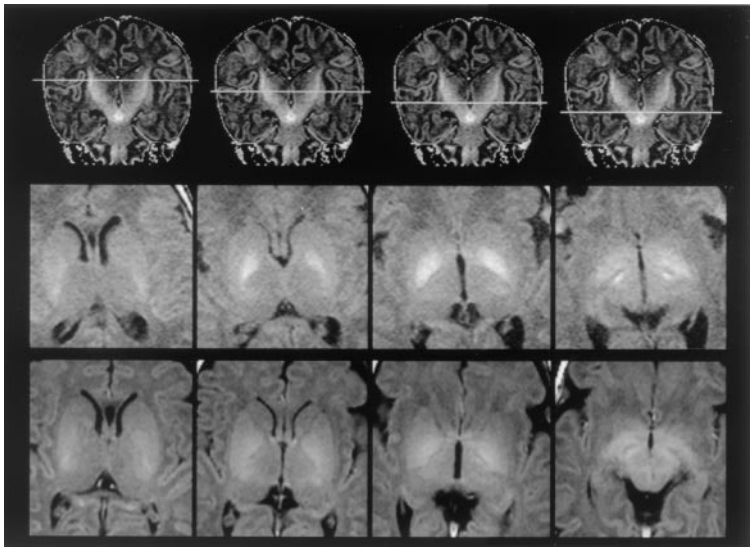

Fig 5. Axial T1-weighted MR on day 6 in a term infant with kernicterus (patient 6, above) compared with a term newborn with seizures of unknown origin but normal sonogram and MRI; the hypersignal in pallidum is best interpreted at intermediate and inferior sections through pallidum mediale.

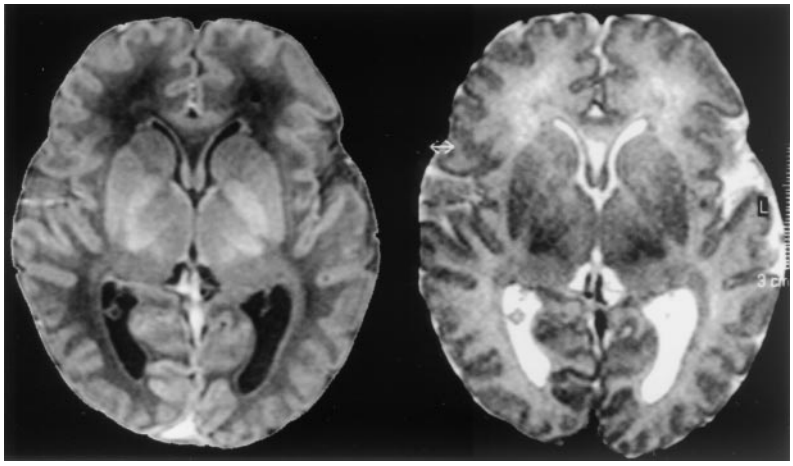

Fig 6. Axial IR-TSE T1-weighted MR on day 6 in patient 7: very high signal in entire globus pallidus on T1, mildly hyperintense aspect on T2 making pallidum just discernible from putamen.

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]

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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