ORIGINAL ARTICLE

Neurological Complications of Kernicterus

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ABSTRACT: ***Objective and Background:*** Prevention of bilirubin encephalopathy relies on the detection of newborns who are at risk of developing serious hyperbilirubinemia. The objective of this study was to reassess the clinical syndrome of kernicterus as neurodiagnostic studies have become more readily available and can be used to evaluate these infants. ***Methods:*** The study population was neonates born at term or near term admitted to The Hospital for Sick Children in Toronto, Ontario, Canada, between January 1990 and May 2000. During the study period, there were 9776 admissions (average number of admissions per year – 888 infants). The inclusion criteria were that patients had total serum bilirubin levels of > 400µmol/L at the time of diagnosis and no evidence of hypoxic ischemic encephalopathy. Records were reviewed to establish neurodevelopment outcomes. ***Results:*** Twelve neonates (nine males) were identified. Bilirubin levels at the time of diagnosis ranged from 405 to 825µmol/L. Causes of these elevated levels included glucose-6-phosphate dehydrogenase deficiency (seven patients), dehydration (three patients), sepsis (one patient), and was undetermined in one patient. Abnormal visual evoked potentials were found in three of nine patients and abnormal brainstem auditory evoked potentials in seven of ten patients. Abnormal electroencephalograms were documented in five patients studied. Brain magnetic resonance imaging results were abnormal in three of four patients. ***Conclusions:*** Magnetic resonance imaging typically showed an increased signal in the posteromedial aspect of the globus pallidus and was, therefore, useful in the assessment of the structural changes of chronic bilirubin encephalopathy after kernicterus.

RÉSUMÉ: Complications neurologiques du kernictère. La prévention de l'encéphalopathie par hyperbilirubinémie est basée sur le dépistage des nouveau-nés qui sont à risque de développer une hyperbilirubinémie sévère. L'objectif de cette étude était de réévaluer le syndrome clinique du kernictère étant donné que les examens neurodiagnostiques sont de plus en plus disponibles et peuvent être utilisés pour évaluer ces enfants. La population à l'étude comprend les nouveau-nés à terme ou près du terme admis au *Hospital for Sick Children* de Toronto, Ontario, Canada, entre janvier 1990 et mai 2000, soit 9776 admissions (moyenne annuelle de 888 nouveau-nés). Les critères d'inclusion étaient un taux de bilirubine sérique total de plus de 400 mmol/L au moment du diagnostic, sans évidence d'encéphalopathie ischémique hypoxique. Les dossiers ont été révisés pour vérifier l'issue neurodéveloppementale. Douze nouveau-nés, dont 9 garçons et 3 filles, ont été identifiés. Les taux de bilirubine au moment du diagnostic étaient de 405 à 825 mmol/L, dont la cause était un déficit en glucose-6-phosphate-déshydrogénase chez 7 patients, une déshydratation chez 3 patients, une septicémie chez 1 patient et indéterminée chez 1 patient. Les potentiels évoqués visuels étaient anormaux chez 3 patients sur 9 et les potentiels évoqués auditifs au niveau du tronc cérébral étaient anormaux chez 7 patients sur 10. Des anomalies à l'ÉEG ont été observées chez 5 patients. L'IRM était anormale chez 3 patients sur 4. La présentation typique à l'IRM était une augmentation du signal dans la région postéro-médiale du globus pallidus et s'est avérée utile dans l'évaluation des changements structuraux de l'encéphalopathie chronique après un kernictère.

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Kernicterus, or bilirubin encephalopathy, is the term used to describe the acute and chronic neurologic conditions shown in Table 1, which are thought to be caused by bilirubin toxicity to the basal ganglia and various brainstem nuclei. Recent reports of kernicterus indicate that this condition, although rare, still occurs; yet most cases are preventable.[1]

Methods

We completed a retrospective review of the charts of all neonates admitted to the neonatal intensive care unit at The Hospital for Sick Children in Toronto, Ontario, Canada, from January 1990 to May 2000. To be included in the study, these neonates had to have a gestational age ≥ 36 weeks, a normal perinatal history, and a total serum bilirubin (unconjugated) level

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Table 1: Neurological features of acute vs. chronic bilirubin encephalopathy

Acute	Chronic
Poor feeding with a feeble suck	Extrapyramidal abnormalities (athetosis)
Lethargy	Gaze abnormalities (upward gaze)
High pitched cry	Auditory disturbance (sensorineural hearing loss)
Hypertonia/hypotonia	Intellectual deficits-minority in mentally retarded range
Decerebrate/opisthotonic posturing	
Seizures	
Sensorineural hearing loss	
Incomplete Moro	
Thermal instability (hypothermia/ hyperthermia)	
Fever	

of > 400µmol/L (23.4mg/dl). Infants were excluded if there was evidence of hypoxic ischemic encephalopathy either clinically and/or laboratory, that is, there was no evidence for fetal distress (fetal heart rate abnormalities, meconium-stained amniotic fluid, acid-base status of the fetus, Apgar scores and pathological placental conditions), depression at birth or systemic organ involvement.

Data recorded included gestational age, sex, ethnicity, birth weight, venous blood gases at birth and findings on neurological examination at presentation and at follow-up, including tone, the presence of athetosis, upward gaze palsy, tremor, and seizures. The results of neurophysiological studies were reviewed, specifically visual evoked potentials, brain auditory evoked potentials (BAEPs), and electroencephalography (EEG), as well as the neuroimaging studies: including cranial ultrasound, computerized tomography (CT), and magnetic resonance imaging (MRI). The duration of follow-up and development assessment results were documented.

Results

Twelve infants (nine boys) were included in this case series. Eleven of the 12 were born at 37 to 40 weeks gestation, and the other infant at 36 weeks gestation. The mean birth weight was 2.93kg (range 1.6 to 3.93kg). Six infants were caucasian, two were African American, and four were Asian. All but one had been discharged home and were readmitted with hyperbilirubinemia. All discharged infants had normal perinatal and neonatal histories and appeared well at the time of the first discharge from referring hospitals.

The infant who was not discharged was diagnosed to have intrauterine growth retardation; this child had been observed in a special care nursery. This infant had a serum bilirubin (unconjugated) level of 405µmol/L of undetermined origin at five days of age. The symptoms that caused the other 11 infants to be admitted to hospital (at three to five days of age) were jaundice (seven patients), poor feeding (two patients), and seizures (two patients). All were lethargic. Only one patient had laboratory evidence of sepsis documented as coagulase-negative staphylococci from the blood culture.

The infants' serum bilirubin levels ranged from 405 to 825µmol/L. The causes of jaundice were hemolysis secondary to a glucose-6-phosphate dehydrogenase (G6PD) deficiency in seven of the infants (four were Asian, two African-American and one Caucasian), dehydration in three, and sepsis in one patient and undetermined in one. One child had galactosemia as well as hemolysis.

Table 2: Bilirubin level at time of admission, chronological age at neurodevelopment assessment, and outcome

				Development Level (months)		
Patient No.	**Bilirubin level (µmol)**	**Diagnosis**	**Chronologic age**	**Gross motor**	**Fine motor**	**Adaptive and social skills**
1	825	*G6PD*	9 months	2	2	6*
2	636	*G6PD*	6 years	N/A	N/A‡	6†
3	650	*G6PD*	7 months	4	4	3
4	767	*G6PD* & Sepsis	8 months	4	4	6
5	405	Undetermined	2 years	12	12	12

*Developmental level in months
†Developmental level in years; age appropriate
‡Developmental level not available; assessed as weak
N/A = not available

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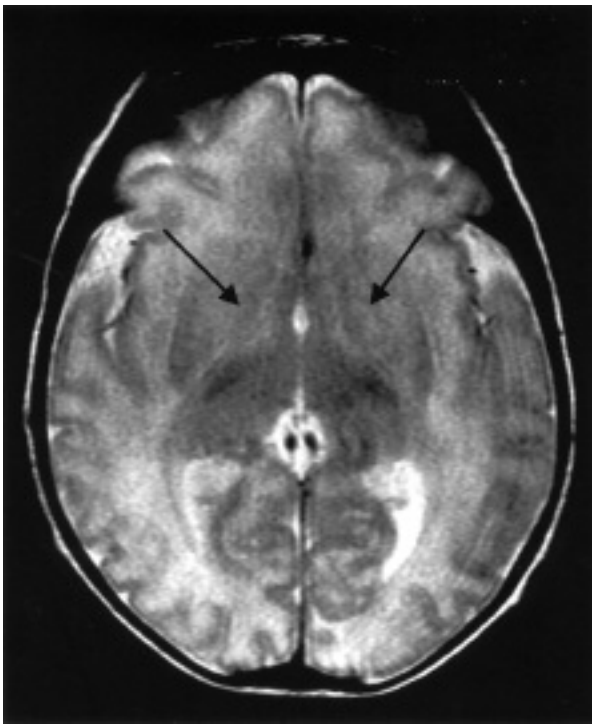

Figure 1: *T1 weighted image reveals increased signal intensity, localized to the globus pallidus (arrows) and lateral thalami. The globus pallidus signal intensity is more than expected for normal signal within this structure in the term neonate.*

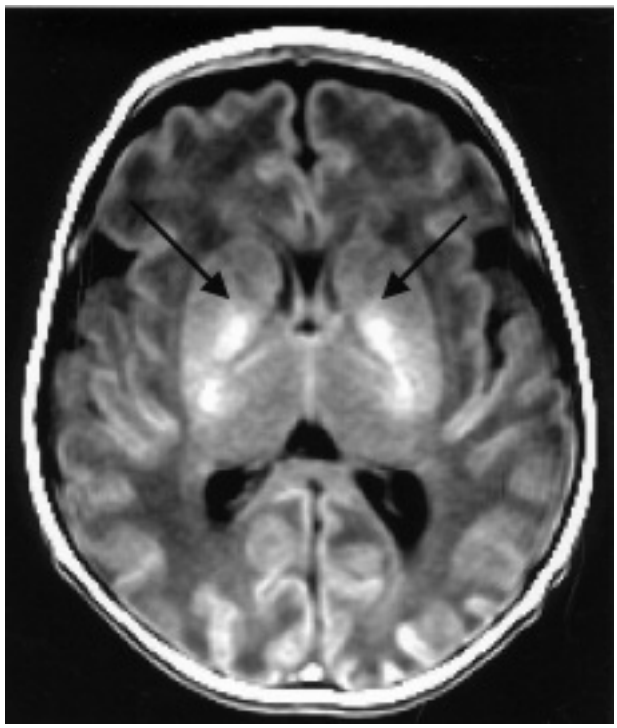

Figure 2: *T2 weighted image demonstrates hazy increased signal intensity of the basal ganglia (arrows). Putamina and globus pallidi are involved bilaterally.*

Of the nine patients who had visual evoked potentials, three had abnormal results. Seven of ten patients who had BAEPs had abnormal results. The most consistently observed abnormalities involved the threshold of all waves, latency for wave I, and conduction times between waves I, III, and V - generally the effects of both peripheral and brainstem disturbances. All five patients who had EEGs had abnormal results including multifocal and generalized spikes and polyspikes, and discontinuous and intermittently asynchronous backgrounds. Of the five patients who had CT scans, only one had abnormal study results. Two of the four patients who had MRI scans had abnormal study results that were consistent with kernicterus (Figure 1, 2). Another patient receiving total parental nutrition had abnormal study results that were inconclusive as it was unclear whether the abnormalities were secondary to elevated bilirubin levels or to total parental nutrition (TPN) as has been reported.[2]

On follow-up neurological examination, four of the 12 patients had hypertonia, five had hypotonia, and three had athetosis. Abnormal upward gaze was seen in only two of the 12 patients. Follow-up developmental assessments were documented between seven months to six years. Three patients developed normally, two were lost to follow-up, and seven had abnormal development.

Among the seven patients who had delayed development, five patients were assessed by either a neurologist or a developmental pediatrician and therefore it was felt accurate data with regard to outcome was available. Table 2 shows the bilirubin levels at time of admission, chronological ages at the time of neuro-development assessment, and outcomes for these five patients. The other two children described as having delayed development had no developmental assessments in their health records.

Discussion

In this study, we describe 12 infants who suffered severe neonatal jaundice and developed neurological sequelae secondary to bilirubin toxicity. The aim of the study was to emphasize the importance of universal and close follow-up of these infants and awareness of the real risk of extreme hyperbilirubinemia and kernicterus.

The recent increase in the number of cases in term and near-term infants with neurologic sequelae related to hyperbilirubinemia may represent a re-emergence of kernicterus in the industrialized world.[3] Possible reasons suggested for this apparent increase have included a combination of decreased concern about jaundice in full-term breast-fed infants and shortened neonatal hospital stay.[4-6]

The average time of discharge from the maternity ward for apparently healthy mature infants has been reduced in recent years. In our current chart review, 11 of 12 infants had been discharged home one day after birth, then returned to hospital with elevated bilirubin levels. This study reinforces the need for consensus about the optimal timing of follow-up after early newborn discharge.

Although seven of the 12 subjects in this study had a G6PD

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deficiency, all our subjects except one patient were otherwise healthy, term and near term newborns who did not have isoimmune or other types of hemolytic disease. G6PD deficiency is a condition that is frequently encountered in practice but is easy to overlook in the absence of a high index of suspicion. In addition, G5PD deficiency has a later onset of significant jaundice compared with other causes of hemolysis in the newborn (day 2-3 vs. day 3-5).[5,8] Maintaining a high index of suspicion is therefore important in the clinical evaluation of infants who have elevated bilirubin levels. Infants of East Asian and Native American descent have higher levels of bilirubin than Caucasian infants.[5,8]

Classic kernicterus has been documented[6] in full-term, otherwise healthy, breast-fed infants. In a review[6] of 22 cases of infants born at 37 weeks' gestation or older, six showed signs of acute bilirubin encephalopathy and its typical neurologic sequelae. One infant had an elevated reticulocyte count (9%), but no other evidence of hemolysis, and no cause was found for the hyperbilirubinemia (other than breastfeeding).

The presence of vertical gaze palsy occurs in 90% of those who have posticteric encephalopathy but in less than 5% of children with other types of cerebral palsy.[7] After athetosis, vertical gaze palsy is the most common finding in the tetrad of symptoms of posticteric encephalopathy, which also includes dental-enamel dysplasia, and abnormalities of auditory processing.[7] In our study, only two patients had these abnormalities. Detection may have been low as gaze palsy is difficult to diagnose with certainty in the first six months of life. After six months, it can be identified with more confidence, if the child has adequate visual acuity.

Because the auditory pathways are frequently affected by hyperbilirubinemia, kernicterus may result in sensorineural hearing loss.[9,10] BAEPs may be helpful in the early detection of bilirubin audiotoxicity. Many studies have documented distinct abnormalities of the evoked responses of patients who have hyperbilirubinemia.[11] These responses improve when bilirubin levels decrease with treatment, including exchange transfusion. BAEP testing, as a measure of the function of the auditory pathway, is an accurate, cost-effective, noninvasive method to assess the possible effects of kernicterus.[9,10,12,13] Diagnosis of the sequelae of kernicterus during childhood is difficult; only BAEPs can detect previous neuronal damage by bilirubin.[11,14,15] Prolongation of the latency of wave I, abnormalities in inter-peak latencies of wave I–II or I–V, and decreased or lost amplitude are suggestive of bilirubin encephalopathy.[5,12]

The abnormal EEG results for the five patients in our study indicate that EEG can be a useful tool for the detection of injury to the brain caused by bilirubin. The striking features of the EEG results in our study included multifocal and generalized spikes and polyspikes, and discontinuous and intermittently asynchronous background. Of the few studies[5,16] reported assessing EEG results for subjects with hyperbilirubinemia, the observations were consistent with the burst suppression–pattern encephalopathy.

Seizures are much less common in posticteric cerebral palsy than in the other forms of cerebral palsy.[5] In the first two to four weeks of life, infants with posticteric cerebral palsy may have extensor spasms that may simulate seizures, but these spasms tend to disappear after the first month of life. During infancy, this group may have more febrile seizures than the population of normal infants.[5] After the second year of life, however, recurrent seizures are much less common than in children with spastic forms of cerebral palsy. Seizures occur in 50% of the hypertonic patients, but in less than 20% of those with posticteric encephalopathy.[17] In our study, six of the patients developed seizures.

The neuropathological lesions of kernicterus are typically of the globus pallidus, subthalamic nucleus, and hippocampus combined.[18,19] The dentate and olivary nuclei, which are stained in the acute phase, show less serious damage. Results of MRI studies have shown that the globus pallidus is the most sensitive region to change, especially the posteromedial border.[19] Attention to the posteromedial border of the globus pallidus on MRI is, therefore, useful in the determination of the causation of perinatal brain damage.[5,17]

The MRI lesions in the globus pallidus have been demonstrated in various other disorders including Leigh syndrome, Hallervorden Spatz disease (pantothenate kinase deficiency), hepatic failure and total parenteral nutrition due to the presence of manganese deposits in the basal ganglia[2].

Only one patient in our study had neuropsychological testing. This child showed average nonverbal intellectual ability. Reports of intelligence testing of post-kernicterus children at follow-up shows that only a small minority have serious deficits. Byers et al[20] found that only 20% of patients who had athetosis had an intelligence quotient of less than 70. This sparing of intellect in these full-term infants is consistent with the pathologic observation that the cerebral cortex is relatively uninvolved in cases of kernicterus.[20,21]

In conclusion, prevention of bilirubin encephalopathy is based on the detection of infants at risk of developing a serious hyperbilirubinemia. The American Academy of Paediatrics recommends that infants discharged from the hospital within 48 hours of birth receive follow-up care within two to three days by their primary care physician. Infants at risk for severe hyperbilirubinemia should receive follow-up care within 48 hours of discharge. The recommendations leave follow-up specifics to the discretion of the physician.[1]

We speculate that inadequate establishment of breastfeeding coupled with early hospital discharge of full-term newborns, may play a role in the occurrence of serious hyperbilirubinemia in these infants; therefore, early discharge of newborns from hospital remains a major concern. Further studies are needed to quantify the risks, benefits, and costs of various strategies aimed at preventing kernicterus.

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