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The role of magnetic resonance imaging in the prediction of the neurodevelopmental outcome of acute bilirubin encephalopathy in newborns

Aim: Magnetic resonance imaging (MRI) is widely used in the diagnosis of acute bilirubin encephalopathy, but the relationship between MRI findings and neurodevelopmental outcome in newborns with acute bilirubin encephalopathy remains unclear. The aim of this study was to investigate the relationship between acute bilirubin encephalopathy, MRI findings, and neurodevelopmental outcome.

Materials and Methods: The study included 13 infants with acute bilirubin encephalopathy. MRI was performed at 11-30 days of age. Infants were evaluated using the Denver Developmental Screening Test at 3 and 6 months of age.

Results: Four of the 13 infants developed well. Five infants had abnormal MRI findings. Two of these 5 infants had good neurodevelopmental outcome. Nine of the 13 patients had poor developmental outcomes.

Conclusion: In newborns with acute bilirubin encephalopathy, neither encephalopathy stage nor MRI findings predicted neurodevelopmental outcome, as measured by the Denver Developmental Screening Test.

Key words: Acute bilirubin encephalopathy, hyperbilirubinemia, magnetic resonance imaging, kernicterus

Manyetik rezonans görüntülemenin akut bilirubin ensefalopatili yenidoğanların nörogelişimsel sonuçlarını tahmin etmedeki rolü

Amaç: Manyetik rezonans görüntüleme (MRG) akut bilirubin ensefalopati tanısında yaygın kullanılan bir tanı yöntemidir. Ancak MRG bulgularıyla akut ensefalopatili yenidoğanların nörogelişimsel sonuçları arasındaki ilişki halen net değildir. Bu çalışmanın amacı akut bilirubin ensefalopatili yenidoğanların nörogelişimsel sonuçlarını önceden tahmin etmede MRG'nin rolünü araştırmaktır.

Yöntem ve Gereç: Akut bilirubin ensefalopatisi olan 13 yenidoğan çalışmaya alındı. MRG yenidoğanların 11 ile 30. günleri arasında çekildi. Hastalar 3. ve 6. aylarında "Denver Developmental Screening Test" ile nörogelişimsel olarak değerlendirildi.

Bulgular: Çalışmaya dahil edilen 13 yenidoğanın 4'ü nörogelişimsel olarak normal, 9'u da anormal olarak bulundu. Toplam 5 hastada da normal olmayan MRG bulguları saptandı. Bu 5 hastanın 2'si nörogelişimsel olarak normal olarak bulundu.

Sonuç: Akut ensefalopatili yenidoğanlarda MRG bulguları ve ensefalopatinin düzeyi "Denver Developmental Screening Test" ile ölçülen nörogelişimsel sonuçları tahmin edememektedir.

Anahtar sözcükler: Akut bilirubin ensefalopatisi, hiperbilirubinemi, manyetik rezonans görüntüleme, kernikterus

Introduction

Acute bilirubin encephalopathy (ABE) refers to the clinical findings caused by bilirubin toxicity to the basal ganglia and various brainstem nuclei. The American

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Academy of Pediatrics recommends that this term be used to describe the acute manifestations of bilirubin toxicity seen during the first weeks after birth and that the term kernicterus be reserved for the chronic and permanent clinical sequelae of bilirubin toxicity (1).

Bilirubin toxicity remains a significant problem despite recent advances in the care of infants with jaundice. Early discharge policies and increased breastfeeding have increased the risk of marked hyperbilirubinemia and kernicterus (2). In recent years there has been an increase in the number of reported cases of kernicterus (3,4).

The pathological changes caused by the cytotoxic effect of unconjugated bilirubin include discoloration and destruction of affected neurons (3). The pallidum, subthalamic nucleus, and hippocampus are the most commonly affected areas, whereas the cerebral cortex, white matter, midbrain, and brain stem are unaffected. Other structures, such as the thalamus, striatum, substantia nigra, cerebellar nuclei, inferior olivary nuclei, and various cranial nerve nuclei may also be involved (5). Recognition of the signs of ABE is vital, as prompt treatment may be successful in reversing the damage. Shapiro has emphasized that the faster and more aggressive the treatment, the more reversible and better the outcome (6).

Pathological changes in affected regions of the brain can be detected as high signal intensity with magnetic resonance imaging (MRI) in infants with kernicterus (7,8). Although MRI is widely used in the diagnosis of kernicterus, the relationship between MRI findings and neurological outcome in newborns with ABE remains unclear. The aim of the present study was to investigate the relationship between ABE, MRI findings, and neurodevelopmental outcome.

Patients and Methods

Newborns with severe jaundice that were admitted to our institution's neonatal intensive care unit were enrolled in this prospective study. Recruitment criteria included the presence of ABE, bilirubin levels ≥ 30 mg dL⁻¹, and gestational age ≥ 37 weeks. Newborns without ABE or those with major congenital malformations or infections were excluded from the study. Our institution's ethics committee approved the study protocol, and informed consent was obtained from the parents of each infant.

All infants were examined by a neonatologist at admission. Clinical signs of ABE, including alteration in consciousness, muscle tone, movement, and brainstem function (lethargy, irritability, poor feeding, abnormal crying, muscle tone abnormalities, arching, opisthotonus, and seizures) were recorded. All patients were classified according to previously described ABE criteria: initial (phase I), moderate (phase II), and severe (phase III) (9). All patients underwent intensive phototherapy and 1 or more exchange transfusions.

Laboratory studies included complete blood count, direct Coombs test, reticulocyte count, Rh compatibility, and serum electrolytes and glucose levels. We were unable to test for glucose-6-phosphate dehydrogenase deficiency due to technical issues.

Cranial MRI was performed between 11 and 30 days (mean 18 days) after the clinical onset of encephalopathy. All patients were scanned using the same 1.5 Tesla scanner (Picker International, Cleveland, Ohio, USA) and all scans were evaluated by the same radiologist.

Complete neurological examinations were made by an experienced pediatrician in all patients when they were 3 months old and again at 6 months of age. Developmental assessment was performed by the same pediatrician using the Denver Developmental Screening Test (DDST) Turkish Modification (10). All patients were referred to our institution's otorhinolaryngology clinic for hearing examinations.

Data were analyzed statistically with SPSS v.11.5 for Windows. The Mann-Whitney U test and Spearman's correlation test were used for comparison of nonparametric values, and Fisher's exact test was used for dichotomous variables. Results were calculated as mean \pm standard deviation (SD). P values < 0.05 were regarded as statistically significant.

Results

The study included 13 patients (9 female, 4 male). Mean age of patients at admission was 5.8 ± 2.4 days (range: 3-13 days). Mean gestational age was 38.5 ± 1.1 weeks (range: 37-40 weeks) and mean birth weight was $2828 \text{ g} \pm 413 \text{ g}$ (range: 2060-3400 g). Mean unconjugated bilirubin level at admission was 40.2 ± 6.7 mg dL⁻¹ (range: 30-52 mg dL⁻¹).

Of the 13 patients, 5 met the criteria for phase I ABE and 8 met the criteria for phase II (Table). Abnormal MRI findings were observed in 5 patients (38.4%), 4 of which had a hyperintense signal in the cerebral white matter and 1 with hyperintensity in the globus pallidus.

Gross motor delay was present in 11 for the 13 infants (85%) at age 3 months and in 9 of the 13 infants (69%) at age 6 months. DDST scores for all parameters improved with age. Neurological examination findings in the patients were as follows: 5 (38%) of the patients had phase I ABE and 8 (62%) of the patients had phase II. Four of the 5 patients (patients 2, 3, 10, and 12) with abnormal MRI findings had moderate (phase II) encephalopathy at admission. Only 1 patient (no: 9) had initial phase (phase I) encephalopathy. There was not a statistically significant correlation between MRI changes and clinical findings. Demographic characteristics, MRI, and DDST results are shown in the Table.

ABE phase was significantly correlated with motor retardation ($P = 0.035$, $r = 0.59$) and language development ($P = 0.042$; $r = 0.57$) at age 3 months, but there were no correlations between ABE phase and DDST score at age 6 months. Four infants were well

developed at 6 months of age. Nine infants showed various developmental handicaps based on DDST scores at 6 months of age.

Of the 4 healthy infants, 2 had phase I ABE and 2 had phase II ABE. Of the 9 handicapped infants, 3 had phase I ABE and 6 had phase II ABE. ABE phase was not statistically significant ($P = 0.51$). Mean total bilirubin levels in healthy infants was lower than in handicapped infants ($P = 0.02$). Only social development at 6 months of age was correlated with opisthotonus ($P = 0.034$; $r = 0.59$), hypertonia ($P = 0.011$; $r = 0.68$), and high pitched crying ($P = 0.034$; $r = 0.59$). Other developmental abnormalities were not correlated with clinical findings at admission. Additionally, there was not a correlation between ABE phase and abnormal MRI findings ($P = 0.32$; $r = 0.3$).

Discussion

There is no doubt about the relationship between elevated total serum bilirubin (TSB) levels and brain damage, or that the ability of a single peak bilirubin level to predict long-term neurodevelopmental outcome is poor. Sick and preterm infants are more likely to be vulnerable to the deleterious neurotoxic

Table. Demographic characteristics, total bilirubin, and MRI and DDST results in the study infants.

No.	Sex	Age (day)	Gestational age	Weight (g)	Maximum TSB (mg dL ⁻¹)	Encephalopathy stage	MRI findings	DDST at 3 months	DDST at 6 months
1	F	4	40	3100	35	1	Normal	Abn	N
2	F	6	38	3300	36	2	↑T2 in WM	N	N
3	M	6	39	2060	30	2	↑T2 in WM	Abn	N
4	F	6	39	3000	34	1	Normal	N	N
5	M	5	38	2700	39	1	Normal	Abn	Abn
6	F	6	40	3100	39	2	Normal	Abn	Abn
7	M	4	37	2500	33	1	Normal	\Abn	Abn
8	F	5	38	3000	50	2	Normal	Abn	Abn
9	F	7	39	3200	40	1	↑T1 in WM	Abn	Abn
10	F	5	37	2500	43	2	↑T1 in WM	Abn	Abn
11	F	13	40	3400	52	2	Normal	Abn	Abn
12	M	3	38	2600	46	2	↑T2 in GP	Abn	Abn
13	F	5	37	2300	45	2	Normal	Abn	Abn

DDST: Denver Developmental Screening Test; F: female; M: male; TSB: total serum bilirubin; WM: white matter; ↑T1: T1-weighted hyperintense lesion; ↑T2: T2-weighted hyperintense lesion; GP: globus pallidus. Abn: abnormal, N: normal.

effects of high bilirubin concentrations. Some investigators have described clinical and pathologic kernicterus in premature infants that did not have hemolytic disease and whose TSB levels were below 20 mg dL⁻¹. Oh et al. concluded that peak TSB concentrations during the first 2 weeks of life are directly correlated with death, or neurodevelopmental impairment, hearing impairment, and Psychomotor Developmental Index score (11).

Brain MRI studies of infants with kernicterus are inadequate and results are inconsistent. In most of these studies only a few patients have been reported retrospectively. Coskun et al. reported that symmetric involvement of the globus pallidus, seen as hyperintense on T1-weighted MRI, is a characteristic finding of acute kernicterus (7). A bilateral symmetric high signal in the globus pallidus on T2-weighted images is the most common reported finding in ABE (8). Symmetric signal intensity changes in the subthalamic nucleus, in addition to the globus pallidus, in T2-weighted images have also been reported (12). Yokochi reported that high intensity areas in the globus pallidus were demonstrated bilaterally with T2-weighted imaging in 3 children with severe ABE (13). According to Paksoy et al.'s study, signal changes with T2-weighted MRI, not only in the globus pallidus, thalamus, and subthalamic nucleus, but also in the hippocampus, may be seen in patients with kernicterus (14). To the best of our knowledge the present study is the first to investigate if MRI findings predict neurodevelopmental outcome of newborns with ABE. Only 5 of the 13 patients with ABE had pathological MRI findings in the present study. Two of them had white matter hyperintensity on T2-weighted MRI, 2 of them had white matter hyperintensity on T1-weighted MRI, and 1 had globus pallidus hyperintensity on T2-weighted MRI. Only 2

of the 5 patients had normal neurological development at 6 months of age. On the other hand, 4 of the remaining 8 patients had moderate to severe neurological sequelae, although they did not have abnormal MRI findings.

We also investigated the relationship between DDST score and ABE. The DDST is a 105-item developmental screening instrument with 4 subscales of behavior: social, adaptive, language, and motor behavior. These scales are scored as definitively normal, possibly abnormal, and definitively abnormal. It is known that DDST has low sensitivity and high specificity for neurodevelopmental screening (15,16). The sensitivity may be improved by physicians experienced with DDST. In the present study we used the DDST Turkish Modification and it showed some improvement in the patients at 6 months of age, as compared to 3 months (10). The improvement in the DDST parameters can be attributed to 2 factors: increased sensitivity of DDST with age, and clinical improvement in ABE. Some other tests have been used for evaluating neurodevelopmental outcome in kernicterus. The Psychomotor Developmental Index and Mental Developmental Index have been used to identify the association between peak serum bilirubin and neurodevelopmental outcome in extremely low birth weight infants (11); however, Newman et al. did not observe any serious neurodevelopmental sequelae in infants with very high TSB levels (≥ 30 mg dL⁻¹) (17).

In conclusion, the present study shows that MRI did not predict neurodevelopmental outcome in newborns with ABE. DDST, an easy and inexpensive method, may be used for neurodevelopmental evaluation in these patients at 6 months of age, but not at 3 months.

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