



## Cranial Magnetic Resonance Imaging Findings in Patients with Indirect Hyperbilirubinemia

### İndirekt Hiperbilirubinemili Hastalarda Kranial Manyetik Rezonans Görüntüleme Bulguları

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#### Abstract

**Purpose:** To describe the magnetic resonance imaging (MRI) changes in the patients with indirect hyperbilirubinemia.

**Methods:** MRI findings of eighteen neonates with indirect hyperbilirubinemia were reported by us. The differences in imaging, clinical and biochemical data between three groups were evaluated statistically.

**Results:** Peak bilirubin levels were between 20 and 24 mg per deciliter in 5 of the newborns (group 1), 25 and 29 mg per deciliter in 6 of the newborns (group 2) and 30 mg per deciliter or more in 7 newborns (group 3). There was statistically significant difference between the neurological findings and MRI findings of the patients between three groups.

**Conclusion:** We always demonstrated MRI changes in the patients with kernicterus. Firstly, T1 weighted changes were described in patients with hyperbilirubinemia despite normal neurological examinations. Larger studies with clinical follow up are needed for further understanding of toxic effect of bilirubin in brain.

**Key words:** magnetic resonance imaging, kernicterus, neonatal hyperbilirubinemia

#### Özet

**Amaç:** İndirekt hiperbilirubinemili hastalarda manyetik rezonans görüntüleme (MRG) değişikliklerinin sıklığını tanımlamak.

**Yöntem:** Biz indirek hiperbilirubinemili 18 yenidoğanın MRG bulgularını sunduk. Üç grup arasındaki biokimyasal, klinik ve görüntüleme farkları istatistiksel olarak değerlendirdik.

**Bulgular:** Pik bilirubin seviyeleri 5 yenidoğanda (grup 1) 20- 24 mg/dl, 6 yenidoğanda (grup 2) 25- 29 mg/dl ve 7 yenidoğanda (grup 3) 30 mg/dl ve daha yüksekti. Üç grup arasında hastaların MRG bulguları ve nörolojik bulguları arasında istatistiksel olarak önemli fark vardı.

**Sonuç:** Biz kernikteruslu hastalarda MRG değişiklikleri bulduk. Nörolojik muayeneleri normal olmasına rağmen hiperbilirubinemili hastalarda öncelikle T1A görüntülerde değişiklikler saptadık. Beyinde bilirubin toksik etkilerinin anlaşılması için klinik takiple birlikte büyük çalışmalar gerekmektedir.

**Anahtar Kelimeler:** Manyetik Rezonans Görüntüleme, Kernikterus, Neonatal Hiperbilirubinemi

## INTRODUCTION

Kernicterus (bilirubin encephalopathy) is a neurological syndrome resulting from the deposition of unconjugated bilirubin in brain cells. It is rare complication of infantile hyperbilirubinemia, resulting from preferential deposition of bilirubin in the globus pallidus (GP), subthalamic nucleus, hippocampus, putamen, thalamus, and cranial nerve nuclei (especially III, IV, and VI)<sup>1</sup>. Magnetic resonance imaging (MRI) has a large impact on the evaluation and diagnosis of kernicterus. The symmetric, high intensity signal in the bilateral globus pallidus on T1 and T2 weighted images is the most characteristic finding<sup>2,3</sup>. In otherwise, healthy infants, extremely high total serum bilirubin levels, usually more than 30 mg per deciliter, are known to cause kernicterus, but the risks associated with less extreme elevations of total serum bilirubin levels are unclear<sup>4</sup>. There are also limited numbers of reports describing the relationship between the MRI findings, neurological findings, and the bilirubin levels of the patients with indirect hyperbilirubinemia especially in lower bilirubin levels<sup>3,5</sup>. Coskun et al reported that GP on MRI might be normal in some patients with bilirubin encephalopathy without clear cause<sup>1</sup>. In contrast, Harris et al reported that one patient with hyperbilirubinemia had bilateral GP hyperintensity on T1 weighted images in acute period although normal neurological findings<sup>6</sup>. Katar et al reported that 2 patients had increased signal in the globus pallidus on T2 weighted images, although normal clinic findings<sup>7</sup>. The frequency of MRI changes in

18 infants with mild to severe hyperbilirubinemia were documented by us.

## MATERIALS and METHODS

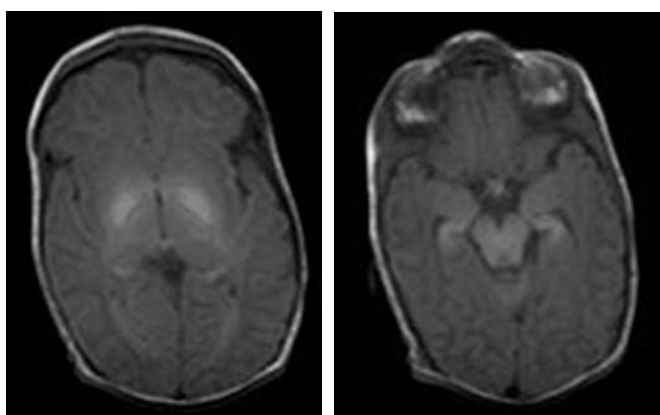
Eighteen neonates (thirteen boys, five girls) with indirect hyperbilirubinemia were included in the study. All patients had jaundice and their serum indirect bilirubin levels were equal or more than 20 mg/dL. The peak indirect serum bilirubin levels on admission ranged between 20 and 49 mg/dL. The patients were divided into three groups. Peak bilirubin levels were between 20 and 24 mg/dL in 5 of the newborns (group 1), between 25 and 29 mg/dL per deciliter in 6 of the newborns (group 2), and 30 mg/dL or more in 7 newborns (group 3) on MRI examination. The patients were excluded if there was evidence of hypoxic ischemic encephalopathy. There was no evidence of fetal stress (fetal heart rate abnormalities, meconium-stained amniotic fluid, acid-base status of the fetus, Apgar scores and pathological placental conditions). The gestational ages were between 27 and 40 weeks. Fourteen of the patients were born at term, while four were born at preterm (1 in group 1, 2 in group 2 and 1 in group 3). The mean birth weight was 3.01 kg (range 9.50 to 4.51 kg). Their ages ranged between 1 to 31 days at admission and 8 days to 45 days at the time of MR examination. All of these neonates have been diagnosed with jaundice. Seven patients had neurological findings such as poor feeding, hypotonia, hypertonia, retrocollis, and high pitched cry. The treatment involved phototherapy in 7 and exchange transfusion in 11 patients. The cranial MRI was performed by utilizing a 1.5-T MR scanner (Siemens Symphony, Erlangen

Germany) with the patients under sedation. Axial and sagittal T1-weighted spin-echo (TR:550 ms; TE:14 ms), T2-weighted turbo spin-echo (TR:2000 ms; TE:100 ms), and axial FLAIR (TR:4700 ms; TE:100 ms; IT: 2000) images were obtained. The images were retrospectively evaluated by a neuroradiologist from whom data regarding the neurological manifestations and levels of indirect bilirubin were restricted. All areas of brain and basal ganglia were taken into consideration for any pathologic signal changes, paying particular attention to the globus pallidus. The differences in imaging, clinical and biochemical data were tested for significance by using Mann Whitney U test for continuous variables or a chi-square test for categorical variables. Probability values of less than .05 were considered significant.

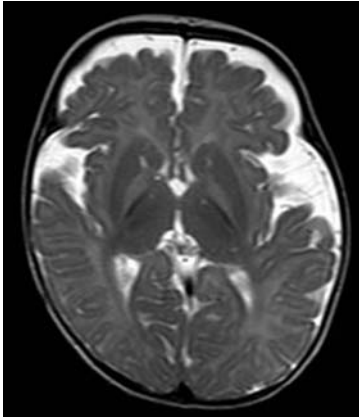
## RESULTS

On cranial examination, T1 hyperintensity of GP was detected in ten patients. Beside T1 hyperintensity of the hippocampus was present in two patients (Figure 1). T2 hyperintensity of GP was noticed in two

patients (Figure 2). Except one all patients in the group 1 had normal GP. Two patients in the group 2 had normal GP on MRI. The MRI findings were positive in all of the patients in group 3. There were totally 5 patients with positive MRI findings (T2 hyperintensity in four and T1 hyperintensity in one patient) despite normal neurological examination. There was not statistically significant difference between descriptive findings (the age at admission or birthweight) of three groups ( $p>0.05$ ). There was statistically significant difference between three groups for the neurological findings of the patients ( $p>0.05$ ). The neurological findings were normal in all of the patients in group 1. Whereas, seven of the patients had abnormal neurological findings. All of the patients with bilirubin levels were equal to or more than 29 mg/dL had MRI changes. When the radiological findings of the patients were evaluated, statistically significant difference was found for T1 hyperintensity and for T1 or T2 changes between three groups ( $p<0.05$ ). Unfortunately the clinical follow up of the patients could not be obtained.



**Figure 1.** 18 days old patient with hyperbilirubinemia and normal neurological examination. T1 weighted magnetic resonance image shows hyperintense globus pallidus (A) and hippocampus (B) .



**Figure 2.** 39 days old patient with hyperbilirubinemia and hypertonia and retrocollis. T2 weighted magnetic resonance image shows hyperintense globus pallidus.

## DISCUSSION

Bilirubin encephalopathy was described in 1904 by Schmorr, who reported the postmortem pathological finding of yellow staining of the basal ganglia in infants to be associated with neonatal jaundice. The causes of kernicterus (hyperbilirubinemia) are sepsis, haemolysis (G6PD deficiency, ABO or Rh incompatibility, ellipto- or spherocytosis), disorders of hepatic bilirubin metabolism (Crigler-Najjar syndromes), protracted enterohepatic circulation of bilirubin (breast milk jaundice) and acquired defects in bilirubin conjugation (Lucey-Driscoll syndrome). Phototherapy and exchange transfusions are two therapeutic options in the neonate, which have significantly reduced the prevalence of bilirubin encephalopathy<sup>2,3</sup>.

The neurological symptoms are somnolence, hypotonia, opisthotonus, rigidity and high-pitched cry. Early in the course of the disease, the symptoms may be subtle, mimicking sepsis, asphyxia, or hypoglycemia. There is progression of symptomatology to fluctuating hypotonia and hypertonia, high

pitched cry, retrocollis, and opisthotonus<sup>8</sup>. Initially seizures are uncommon. After the

neurological complications develop, the prognosis is poor<sup>5</sup>. Long-term survivors of kernicterus can have athetoid cerebral palsy, deafness or hearing loss, impairment of upward gaze, and enamel dysplasia of the primary teeth<sup>9</sup>. Laboratory studies document abnormal or absent brainstem auditory evoked potentials.

To the best of our knowledge, few cases of hyperbilirubinemia with initial MR imaging findings have been reported<sup>1-3,7-9,11-13</sup>. MRI findings during the acute phase of kernicterus has been described, with abnormally increased signal intensity on T1 weighted images in the globus pallidus and subthalamic nuclei. Loss of this T1 marker and conversion to the more permanent change in T2 hyperintensity in these regions is reported to occur during the late neonatal period<sup>6,12</sup>. The posteromedial border of the GP has been shown by MR imaging is the most sensitive area to kernicterus reported in the literature<sup>12</sup>. But none of our patients had this characteristic feature. In our study, the

earliest T1 and T2 weighted changes were detected on MRI is 8th and 39th day respectively. Interestingly, in literature, and in our study, none of the patients had both T1 and T2 changes on MRI examinations. The effect mechanism of bilirubin to T1 and T2-weighted images is not known. The pathogenesis of kernicterus is complex. Bilirubin affects mitochondrial function and uncouples oxidative phosphorylation. The relatively high resting neuronal activity in the globus pallidus and subthalamic nuclei are postulated to make them more vulnerable to oxidative stresses from mitochondrial toxins such as bilirubin, or from genetic mitochondrial disorders<sup>13</sup>.

The clinical and laboratory findings were not always correlated with MRI findings in the patients with indirect hyperbilirubinemia. The few studies about this issue have been documented. Example, Harris et al reported that 5 of the 6 patients with bilirubin levels more than 30 mg/dL had neurological findings and 3 of them had MRI in one month period which is normal. In addition, one patient with normal physical examination had bilateral GP hyperintensity on T1 weighted images and 26.4 mg/dL bilirubin level<sup>6</sup>. Katar et al. reported that there was moderate increase in intensity of globus pallidus on T2-weighted images in 2 patients had normal neurological findings. In addition, they demonstrated that there were normal findings on cranial MRI in 3 patients had kernicterus findings in the neurological examination. In study of Katar et al, all patients of bilirubin levels were higher than 25 mg/dL<sup>7</sup>. Coskun reported that 5 of 13 patients with bilirubin levels higher than 29 mg/dL had abnormal neurological findings and interestingly they had normal GP on MRI

obtained in one month period<sup>1</sup>. In our study, all MRI examinations were obtained within 2 months period. Only seven of the eighteen patients had abnormal neurological findings (38.8%) although twelve of them had hyperintense GP on T1 or T2 weighted images (66.6%). There was 5 patients with positive MRI (4 on T1 weighted images and one on T2 weighted images) without clinical abnormality. We firstly described in the literature that abnormal hyperintensity of GP might be detected also on T1 weighted images beside T2 weighted images despite normal neurological findings. Distinctly from literature, we examined the patients with mild to severe hyperbilirubinemia, so the bilirubin levels are larger in range compared to other studies in the literature. There was no patient with normal MRI but had abnormal neurological findings in our study in contrast to other studies<sup>6,12</sup>. MRI changes were always observed in the patients with neurological abnormalities in our study.

Sugama suggested that preterm infants with kernicterus may have a subtle clinical presentation and can result from relatively low serum levels of bilirubin. Therefore, the evaluation of risk for kernicterus may be difficult in the neonatal period. They reported two preterm patients with normal neurological examination, low levels of bilirubin and who had kernicterus in follow up period. MRI showed abnormally high signal intensity in the bilateral globus pallidus on T2 weighted MR images<sup>3</sup>. There were 4 preterm patients in our study, and only one of them had typical clinical findings with 35 mg/dL bilirubin level for kernicterus.

The gliosis, demyelination, and inhibition of glutamate (Glu) uptake by astrocytes in the

basal ganglia are neurotoxic effects of bilirubin. Oakden et al considered that the MR spectroscopic data of the patients with kernicterus to provide new insights into the pathophysiology of bilirubin neurotoxicity. They showed that ratios of taurine, glutamate and glutamine, and myoinositol relative to creatine were significantly elevated, whereas the ratio of choline to creatine was significantly decreased in infants with kernicterus compared with normal values in same age group<sup>14</sup>. The studies about hepatic encephalopathy have shown increases in Gln and Glu and decreases in Cho and ml<sup>15</sup>. The similarity of basal ganglion involvement and MR spectroscopic findings might indicate a possible link between the hepatic encephalopathy and kernicterus.

### SUMMARY

Recent reports of kernicterus indicate this condition, although rare, is still occurring, yet most cases are preventable. Usually, supportive treatment is perform, and MRI is positive in the most of patients with neurological abnormalities. But, some patients without neurological abnormalities may have positive MRI changes. It was known that in patients with normal neurological findings, cranial MRI may detect T2 hyperintensity. However, in our study, patients with hyperbilirubinemia without abnormal neurological findings had changes firstly on T1 weighted images. We always observed MRI changes in patients with kernicterus that had higher than 29 mg/dL bilirubin levels. We believe that larger studies with clinical follow up are needed for further understanding of toxic effect of bilirubin in

patients with mild to severe hyperbilirubinemia.

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