Cholestatic hepatitis like syndrome and congenital hypothyroidism

Konjenital hipotiroidizm ve kolestatik hepatit benzeri sendrom

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Abstract
The early manifestations of congenital hypothyroidism are non-specific and development of the typical features usually occurs gradually. Cholestatic jaundice in newborn is also a difficult diagnostic problem and often leads to extensive investigations. Early diagnosis is important for proper management. It has been shown in several previous studies that biliary sludge can be identified in normal fetuses and this may persist after delivery. Postnatal gallbladder sludge formation was frequently reported in premature neonates receiving total parenteral nutrition. We described a newborn infant with congenital hypothyroidism, gallbladder sludge formation, cholestatic hepatitis like syndrome and abdominal distension, which improved with treatment of sodium-L-thyroxine and presented this case because of its rarity.

Key Words: **Congenital hypothyroidism.**

Özet
Konjenital hipotiroidinin klinik bulguları yenidoğan döneminde non-spesifik olup tipik bulgularının gelişmesi oldukça yavaştır. Erken tanısı prognoz açısından çok önemlidir. Kolestaz ise yenidoğan döneminde tanısı zor ve zaman alıcı bir hastalıktır. Safra kesesinde çamurlaşma prenatal hayatta görülebilen bir bulgu olup kendiliğinden düzelebilir. Doğumdan sonra safra çamurunun en sık nedeni parenteral beslenmedir. Gelişinde kolestatik hepatit tablosu tespit edilip, konjenital hipotiroidi tanısı alan ve bütün bulguları levotiron tedavisiyle düzelen bir yenidoğan vakası takdim ettik. Konjenital hipotiroidinin vakamızda kolestatik hepatit, karında şişme ve safra çamurlaşması ile başvurması ilginç bulunarak sunuldu.

Anahtar kelimeler: **Doğumsal hipotiroidizm.**

This manuscript can be downloaded from the webpage:
http://tipdergisi.erciyes.edu.tr/download/2007;29(2):168-171.pdf

Submitted : May 2, 2006
Revized : September 14, 2006
Accepted : January 10, 2007

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Introduction

Since the early manifestations of congenital hypothyroidism are non-specific and development of the typical features usually occurs gradually, even in the most medically advanced countries no more than half the affected infants can be diagnosed clinically by the age of 3 months, which is dangerously late for the initiation of treatment (1). Neonatal cholestasis is defined as prolonged elevation of serum levels of conjugated bilirubin beyond the first 14 days of life. The clinical features of any form of cholestasis are similar. In most cases, the cause of cholestasis is obscure (2). It has been shown in several previous studies that biliary sludge can be identified in normal fetuses and this can persist after delivery, no cause had been identified (3, 4). Postnatal gallbladder sludge formation has been reported especially in premature neonates receiving total parenteral nutrition (5). We described a case of congenital hypothyroidism with hepatitis syndrome in a newborn male baby, with gallbladder sludge formation and abdominal distension on admission.

Case Report

A 23 day-old male infant was referred to our neonatal intensive care unit because of prolonged jaundice, abdominal distension and poor feeding. The baby was born by spontaneous vaginal delivery at 40 weeks of gestation. He was the 3rd child of a healthy 23-year-old mother and 28-year-old father. There was no consanguinity between the parents. Family history was insignificant. A routine ultrasound performed at another health care center at 39 weeks of gestation had confirmed normal gallbladder and fetal morphology. The pregnancy had otherwise been unremarkable. His weight was 3200 g, length was 49.8 cm, head circumference was 35.2 cm, and temperature was 35.2^{0}C. No drugs had been administered.

At the time of admission, the baby was sleepy, hypoactive and somnolent. On physical examination, the baby was icteric and he had an abdominal distension. Due to this abdominal distension, ultrasonographical examination was performed on admission, which showed gallbladder sludge formation and air-filled bowel (Pic.1). Laboratory investigations including white blood cell, hemoglobin, hematocrit, serum calcium, phosphorus, BUN, creatinine, electrolytes, blood sugar, lipid profile, CRP, and acid-base values were normal. Conjugated bilirubine was 1.8 mg/dl, and unconjugated bilirubine was 15.1 mg/dl on admission. The patient had been diagnosed as neonatal sepsis. Sepsis work up was performed and the infant was started on 50 mg/kg ampicillin and 7.5 mg/kg amikacin twice a day intravenously for 86 hours. Blood and urine cultures did not yield any organism. There was developed neonatal hepatitis syndrome like picture on the 25th day of life (Conjugated bilirubine 14.3 mg/dl, unconjugated bilirubine 18.1 mg/dl, alkaline phosphatase 750 U/L, GGT 490 U/L, SGOT 202 U/L and SGPT 358 U/L). Special emphasis was then given to clarify the etiology of the neonatal hepatitis and gallbladder sludge in our patient. After the liver was primed with phenobarbitona, radioisotope scan study was performed. Hepatobiliary excretion was delayed by more than 24 h in radioisotope scan study. The antibodies for congenital viral infections were negative. The serum levels of cortisol, growth hormone, LH and FSH were within normal ranges. In thyroid function test (on the 27th day of life); free T3 was 0.06 pg/ml (normal range: 2.2-4.7), free T4 was 3.04 pg/ml (normal range: 8-20), TSH was 161.27 uIU/ml (normal range: 0.2-4.5) and thyroglobulin was 48 ng/ml (normal range: 0-70). Thyroid volume was measured as 0.25 ml.

During the follow up period, the patient with the treatment of sodium-L-thyroxine (15 μg/kg/day) thyroid function tests improved (free T3 2.18 pg/ml, free T4 14.35 pg/ml, TSH 8.2 uIU/ml and thyroglobulin 32.53 ng/ml) within 15 days. The serum levels of conjugated bilirubine, unconjugated bilirubine, alkaline phosphatase, GGT, SGOT and SGPT (0.6 mg/dl, 4 mg/dl, 250 U/L, 70 U/L, 39 U/L, 32 U/L, respectively) and gallbladder ultrasonographical examination improved with the treatment of sodium-L-thyroxine (Pic. 2).

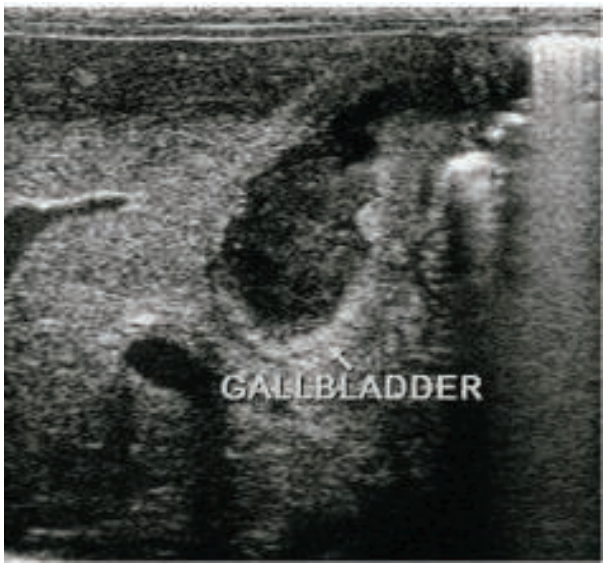
Discussion

Our patient was presented with neonatal sepsis like clinical picture. He was sleepy, hypoactive and somnolent. There were jaundice, abdominal distension and feeding difficulties. Hepatobilier ultrasonography showed sludge and thickened gallbladder wall on admission. Initial diagnosis of the patient at the admission was neonatal sepsis. Clinical, laboratory and radiological investigations suggested the diagnosis of congenital hypothyroidism on the 4thday of admission. With the treatment of L thyroxine, the clinical and laboratory abnormalities of the patient improved. Cancho Candela et al. (3) found echogenic material in 0.45% of pregnancies. Of the 42 fetuses with echogenic foci in the gall bladder, they regarded 31 (74%) as having biliary sludge. Of those, 13% scanned postnatally showed persistence of biliary sludge but follow-up sonography showed spontaneous resolution. All children

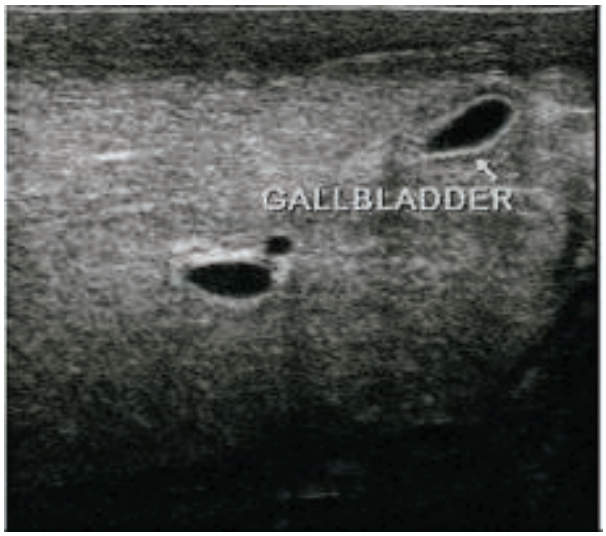
were asymptomatic. Brown et al. (4) described echogenic material in 26 fetal gall bladders. Postnatal examination of 17 infants showed that echogenic foci persisted in 3 for up to 4.5 years. The follow-ups of pregnancy of the mother had been carried out meticiously and it was determined from the regular fetus ultrasound that the gallbladder was normal until the delivery in our case. Gallbladder sludge formation was reported especially in premature neonates receiving total parenteral nutrition. The occurrence of this abnormality was related to three main factors: prematurity with immaturity of the enterohepatic circulation of bile acids, duration of TPN, and lack of enteral nutrition (5). Our patient had not received total parenteral nutrition.

The mechanism of cholestasis in hypothyroidism has not been explained exactly. Laukkarinen at al. (6) suggest that hypothyroidism might result in delayed emptying of the biliary tract, as studied with quantitative ^{99m}Tc HIDA cholescintigraphy. In our patient, hepatobiliary excretion was delayed by more than 24 h in radioisotope scan study. They suggested that in addition to the changes in bile composition and excretion rate, changes in biliary emptying also may be included in the probable causes for the increased prevalence of common bile duct stone in hypothyroidism. Matveenko et al. (7) found that the absorptive-excretory liver function was decreased in moderate hypothyroidism and hypertension of the biliary tract sphincters was revealed in > 50 % of their study group. The other causes of neonatal hepatitis and sludge gallbladder were excluded in our patient. Our patient had all features of neonatal hepatitis syndrome and cholestasis. Laukkarinen at al. (8) showed that T4 has a direct pro-relaxing effect on the human sphincter of Oddi that expresses thyroid hormone receptors beta1 and beta2. This effect is mediated through a transcriptional mechanism that requires new mRNA and protein synthesis and subsequently leads to the activation of K+ channels. Inkinen at al. (9) suggested that a significant association between common bile duct stones and previously diagnosed hypothyroidism. The stronger association between the common bile duct stones and hypothyroidism compared to gallbladder stones and hypothyroidism suggests a mechanism other than merely the cholesterol metabolism mediated mechanism. We believe that all these findings could explain the mechanism of sludge gallbladder and congenital hypothyroidism in our patient.

In conclusion, we described a newborn infant with congenital hypothyroidism associated with cholestatic hepatitis like syndrome because of its rarity.



Picture 1: Showed the gallbladder sludge formation on the admission



Picture 2: Ultrasonoghraphic view of normalized gallbladder on the 42nd day of life

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