# Leptospirosis in Childhood Which Presents with Hypoalbuminemia and Gallbladder Hydrops: Report of Three Cases

## Belirgin Özelliği Hipoalbuminemi ve Safra Kesesi Hidropsu Olan Çocukluk Çağı Leptospirozisi: Üç Olgunun Sunumu

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Geliş Tarihi/*Received:* 04.02.2009
Kabul Tarihi/*Accepted:* 18.11.2009

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**ABSTRACT** Leptospirosis has a wide spectrum that changes from subclinical disease to well defined clinical syndromes. Here, in have been presented three children with leptospirosis having different clinical and laboratory features. Three children who were 14, 9 and 5 years old; respectively admitted to our center with different complaints. First case had high grade fever, jaundice, bilateral moderate pretibial edema, and gallbladder hydrops in upper abdominal ultrasonography. Second case had high grade fever and myalgia. Third case had abdominal pain, burning sensation while urinating and jaundice. Urine samples of all three children were examined under dark field microscopy by which, motile, spiral microorganisms can be distinguished. Serum samples of the cases were analyzed for leptospirosis with patoc-I strain using Microscopic Agglutination Test (MAT). All three cases had hypoalbuminemia, hyperglobulinemia and different levels of liver and renal involvement. As the clinical signs of leptospirosis are not generally typical, it results in delays in diagnosis and treatment. The detection of gallbladder hydrops, hypoalbuminemia, and hyperglobulinemia may be an inducing clue for the diagnosis of leptospirosis.

**Key Words:** Leptospirosis; hypoalbuminemia; acalculous cholecystitis

**ÖZET** Leptospirozis subklinik hastalıktan iyi tanımlanan klinik sendromlara kadar değişen geniş bir spektruma sahiptir. Burada, klinik ve laboratuvar bulguları farklılık gösteren leptospirozisi olan üç çocuk sunulmaktadır. On dört, 9 ve 5 yaşında üç çocuk merkezimize farklı yakınmalarla başvurdu. Birinci olguda yüksek ateş, sarılık, bilateral orta derecede pretibial ödem ve üst abdomen ultrasonografisinde safra kesesinde hidrops, ikinci olguda yüksek ateş ve miyalji, üçüncü olguda karın ağrısı, idrar yaparken yanma ve sarılık vardı. Üç çocuğun da idrar örnekleri hareketli spiral mikroorganizmaları ortaya çıkarabilen karanlık alan mikroskobunda incelendi. Olguların serum örnekleri leptospirozis Patoc-I suşu için Mikro Aglütinasyon Testi (MAT) kullanılarak analiz edildi. Hastaların hepsinde hipoalbuminemi, hiperglobulinemi ve karaciğer ile böbrek fonksiyonlarında değişen şiddette bozulma mevcuttu. Genel olarak leptospirozis'in klinik belirtisi tipik olmadığından tanı ve tedavide gecikmelere neden olabilmektedir. Bu yüzden, safra kesesi hidropsu, hipoalbuminemi ve hiperglobulinemi leptospirozis için kuşku uyandıran belirtiler olabilir.

**Anahtar Kelimeler:** Leptospirozis; hipoalbuminemi; akalkulös-taşsız kolesistit

**Turkiye Klinikleri J Pediatr 2010;19(3):268-74**

Leptospirosis is a worldwide zoonosis caused by spirochaetes, *Leptospira interrogans.*

*L. interrogans* in the urine of infected animals infects its host either by penetration through mucous membrane or through the skin that is broken or macerated through prolonged immersion in water. Epidemiological stu-

dies have shown leptospirosis to be more prevalent during the wet seasons, which allows for an increase in exposure by walking barefooted on puddles. After an incubation period of 2-20 days, it may cause two clinical syndromes-anicteric and icteric leptospirosis.[1]

Among the patients with leptospirosis, 90% have the milder anicteric form of the disease, and 5-10% has severe leptospirosis with jaundice (Weil's disease).[2] Primary pathological findings in leptospirosis are tubular damage in the kidneys and hepatocellular functional impairment. Leptospirosis can result in severe hepatocellular damage and impairment of hepatocellular synthesis functions. In the kidneys, ischemia may cause tissue hypoxia, tubular damage, and renal failure. Eighty-five to 90% of leptospirosis infections are self-limiting.[2]

For definite diagnosis, either isolation of the organism from any specimen or evaluation of specific antibody (seroconvertion or four-fold or greater rise in antibody titer) are essential, on the basis of compatible clinical history. Presumptive diagnosis depends on either a microscopic agglutination titer (MAT) of 1/100 or a positive slide agglutination test in the presence of compatible clinical illness. The MAT test, which uses live antigen, is more specific. It is used for determination of antibody titer and tentative identification of tentative serotype.[2]

Herein, we present clinical and laboratory features of three children with leptospirosis with renal and liver involvement who were diagnosed serologically.

## CASE REPORTS

### CASE 1

A 14-year-old male patient admitted to our hospital in June 2005, because of high grade fever of 10 days' duration, fatigue, abdominal pain, vomiting, jaundice, and dark-colored urine. History of symptoms revealed that one month before the initiation of his complaints, he frequently went fishing in the river, ran in their village barefoot and there had been a history of jaundice in the cattle in his village. His physical examination revealed that his body temperature (axillary) was 39.5 °C, heart rate (HR) 100/min, respiratory rate (RR) 28/min, arterial blood pressure (BP) 110/60 mmHg, body weight (BW) 46 kg (25-50%), height 1.64 m (25-50%). He had severe jaundice, localized palpable mass of 4x6 cm dimensions below the right costal margin, moderate pretibial edema on both lower extremities.

Some of the laboratory findings have been presented in Table 1. Direct abdominal X-ray, revealed a mass which displayed the same opacity with the liver below the right costal margin, suggestive of gallbladder hydrops (Figure 1). Abdominal ultrasonography revealed hydrops of the gallbladder, biliary mud, perihepatic and peritoneal fluid accumulation (Figure 2). In the dark field microscopic examination of the urine, motile spiral microorganisms were observed. Leptospira microscopic agglutination test (MAT) was found (1/400) positive. Diagnosis of icteric leptospirosis was made and treatment of 200,000 U/kg/day crystallin penicillin G was started. Since high fever could not be controlled until the seventh day of crystallin penicillin G therapy, it was changed to tetracycline (20 mg/kg/day). After tetracycline therapy was started, the urinary findings disappeared within two days, jaundice resolved within 4 days. However, PT could normalize at the end of the first month, despite recurrent vitamin K infusions. At the end of 1 month, he was discharged with a full recovery of both physical and laboratory parameters. During the next one-year of follow-up, both his physical and laboratory finding remained stable.

### CASE 2

A 9-year-old male patient was admitted in August 2005, because of high fever of 10 days' duration, neck and leg pain, difficulty in walking, fatigue and loss of appetite. History of symptoms revealed that he had swum in the river for the past two months frequently.

His physical examination revealed that his fever was 39°C, HR 110/min, RR 30/min, BP 100/70 mmHg, BW 26 kg (25-50%), Height 125 cm (10-

**TABLE 1:** Laboratory features of leptospirosis cases.

| | Case | | | |
|---|---|---|---|---|
| **Laboratory parameters** | **1** | **2** | **3** | **Normal** |
| Leukocyte (/µL) | **16.4** | 6.4 | 11.4 | 6000-15000 |
| Hb (g/dl) | **9.9** | **9.8** | 11.1 | 11-16 |
| Hematocrit (%) | **29.7** | **30.7** | 35.4 | 34-40 |
| Platelet (/µL) | 140 | 282 | 269 | 130000-400000 |
| Total bilirubin (mg/dl) | **8.84** | **1.5** | **3.4** | 0.2-1 |
| Direct bilirubin (mg/dl) | **4.81** | **0.3** | **1.7** | 0-0.2 |
| AST (U/L) | **200** | 18 | **301** | 5-45 |
| ALT (U/L) | **216** | 14 | **380** | 5-45 |
| GGT (U/L) | **101** | 9 | **214** | 5-32 |
| ALP (U/L) | **789** | 253 | **1236** | 145-420 |
| CPK (U/L) | 107.3 | 34 | 117 | 5-130 |
| LDH (U/L) | **518** | **368** | **777** | 120-330 |
| Albumin (g/dl) | **2.2** | **2.8** | **3.1** | 4-5.3 |
| Globulin (g/dl) | **4** | **3.4** | **3.7** | 1.1-3.2 |
| Urea (mg/dl) | 36 | **211** | 11 | 10-40 |
| Creatinine (mg/dl) | 0.8 | **5.8** | 0.3 | 0.5-1 |
| Sodium (mEq/L) | 136 | **130** | 139 | 136-146 |
| Potassium (mEq/L) | 3.6 | **3.3** | 3.5 | 3.5-5.5 |
| Calcium (mg/dl) | **6.7** | **8.2** | 9.1 | 8.8-10.8 |
| aPTT (sec) | **43.3** | 29.8 | 31.1 | 25-35 |
| PT (sec) | **18** | 11.4 | 11.4 | 11-14 |
| ESR (mm/hr) | **105** | **78** | **47** | 0-20 |
| Urine microscopy | Several leukocytes and tubular epithelia cells. several very motile microorganisms | Several leukocytes and tubular epithelia cells. several very motile microorganisms | Several leukocytes and several very motile microorganisms within or outside tubular epithelial cells | |

AST: alanine transaminase, ALT: aspartat transaminase, GGT: gamma glutamic transpeptidase, ALP: alkaline phosphatase, CPK: creatine kinase, LDH: lactate dehydrogenase, aPTT: activated partial thrombine time, PT: prothrombine time, ESR: erythrocyte sedimentation rate.
Not: Patolojik olan değerler koyu olarak yazılmıştır.

25%). His nuchal and gastrocnemius muscles were tender upon palpation. In the dark field microscopic examination of fresh urine samples, several spiral microorganisms that were motile in every direction were observed. Renal ultrasonography displayed acute pyelonephritic changes. Leptospira MAT was 1/800 positive. The diagnosis of leptospirosis was made. Crystallie penicillin G 200.000 U/kg/day was administered for 10 days. Fever disappeared within 2 days and myalgia within 5-6 days. Urinary findings normalized within two days; urea and creatinine normalized within four days; hypoalbuminemia, hyperglobulinemia and all other abnormal findings normalized within two weeks. After two weeks, he was discharged with a full recovery of both physical and laboratory parameters. During the next one-year follow-up, both his physical and laboratory finding remained stable.

## CASE 3

A five-year-old girl was admitted in September 2005, with complaints of frequent urination, dark coloration of urine, burning sensation upon urinating and abdominal pain of three days' duration. It was learned that in the last three months she had played in the water running from the fountain in their village. She did not have fever. On in-

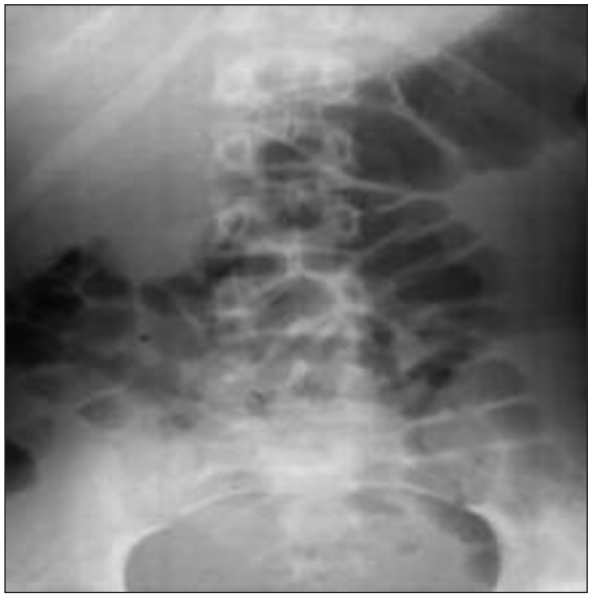

**FIGURE 1:** Radiograph demonstrating a dilated, opague gallbladder protruding from the inferior margin of the liver.

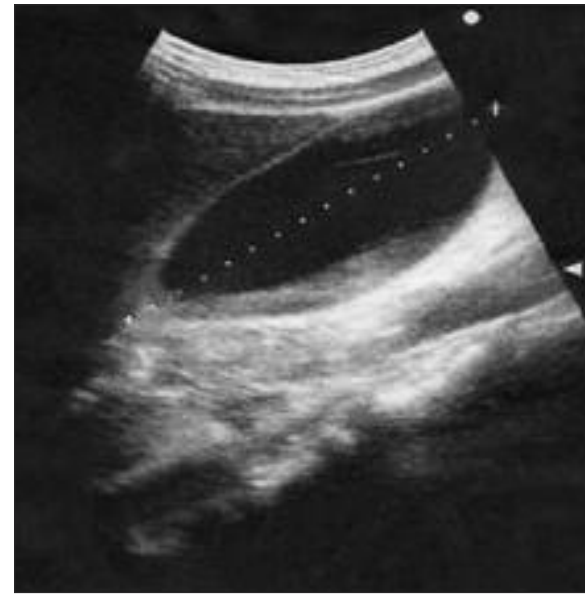

**FIGURE 2:** Abdominal ultrasonography revealed that gallbladder was hydropic with biliary mud measuring 45X98mm.

terview with the local veterinarian of the patient's town we learned that cases of leptospirosis had been observed during summer and winter in that district.

Her physical examination revealed that her fever was 37°C, HB 86/min, RR 32/min, BP 80/60 mmHg, BW 16 kg (25-50%), Height 105 cm (10-25%). Her sclerae were icteric and her liver was 4cm palpable below the right costal margin, on the midclavicular line. Leptospirosis was considered as a possible diagnosis. In the darkfield microscopic examination of the fresh urine sample, there were several hypermotile spiral microorganisms the shape of which changed while moving. Ultrasonographic examination of the kidneys revealed findings of bilateral acute pyelonephritis. Leptospirosis MAT was 1/100 positive. Crystallie penicillin G (200,000 U/kg/day) was administered for 10 days. Urinary findings normalized within 1-2 days, hyperbilirubinemia within 8 days, hypoalbuminemia and hyperglobulinemia within 15 days. After 2 weeks, he was discharged with a full recovery of both physical and laboratory parameters. During the next one–year follow-up, both his physical and laboratory finding remained stable.

## DISCUSSION

Leptospirosis is an acute generalised infectious disease, characterized by extensive vasculitis. Its incidence is highest during summers when heavy rains and floods occur in urban areas.[2] The severity of the disease ranges from an asymptomatic subclinical course to a fatal outcome.[3] Indirect contact with infected animals, via water or soil contaminated with infected urine, is a more common cause of human infection than direct animal contact. Occupational exposure (farmers, veterinarians, abattoir workers) and recreational exposure (campers, swimmers) are common.[2] All of our patients came from villages of different subprovinces of Kars and were admitted to our hospital in or in the end of summer when there are heavy rains in this area. The families were engaged with farming and animal breeding activities. All three cases were in close contact with water where animal breeding outside the barns were carried out.

Anicteric leptospirosis, a more common and milder form of leptospirosis is characterized by abrupt onset with fever, headache, severe muscle aches, and malaise. Nausea, vomiting, and abdominal pain occur in various combinations

in up to 95% of the patients.[2] Our patients had similar complaints in the early period of the disease.

Most frequent clinical manifestations are myalgias, fever, jaundice and gastrointestinal symptomps.[4] In the severe form (icteric leptospirosis or Weil's disease), patients develop febrile illness with hepatic dysfunction, acute renal failure and haemorrhagic diathesis.[5,6]

Jaundice occurring in leptospirosis is not commonly associated with hepatocellular necrosis and impaired liver function. There are moderate elevations in transaminase levels, and moderate elevation of alkaline phosphatase level usually occurs[5,7]. Transient hepatic dysfunction occurs, and it is a rare cause of death. The serum bilirubin levels is usually <20 mg/dL, but can be as high as 60-80 mg/dL[2]. In our patients, the serum bilirubin levels of all cases were high (1,5-8,84 mg/dL). In case 1 and 3, the serum alkaline phosphatase levels were high. The serum LDH levels of all cases were high (368-777 U/L). In other large series, myalgia and increased creatine kinase rates were reported between 20-100%.[8,9] Only case 1 had myalgia. The serum creatine kinase levels of all cases normalized. Depressed activity of plasma prothrombin are noted occasionally. Hypoprothrombinemia responds uniformly to parenteral administration of vitamin K[2]. Only case 1 had persistent prolongation of PT which normalized only after recurrent administrations of vitamin K (5 mg/dose).

It can be concluded that the hepatic manifestations of leptospirosis, including jaundice, are most likely a result of hepatocellular injury. Because hemolysis is not a consistent finding and neither intrahepatic nor extrahepatic biliary stasis was observed morphologically or clinically.[2] Çetin et al[10] have identified hypoalbuminemia (1.1-3.3 g/dl) in all of their 13 leptospirosis cases. Although hypoalbunemia was detected in many of the reported cases, hypoalbunemia was not presented as a striking finding of leptospirosis in neither of these reports.[11-14] All our cases had hypoalbumineamia and hyperglobulinemia while only the first case had gallbladder hydrops, ascites and peripheral edema. Proteinuria that might lead to hypoalbuminemia, diarrhea, growth-developmental abnormality was not observed in any of our cases. After treatment, serum albumin and globulin levels of the patients normalized within 15-25 days. First and third cases had findings of hepatitis.

As in hyperbilirubinemia, hypothrombinemia, hypoalbuminemia and hyperglobulinemia that are the findings of liver failure resolved with antibiotherapy, we have considered Leptospira as the etiological agent. Hypoalbuminemia, hyperglobulinemia and especially edema are not a prominent laboratory or clinical manifestation of the leptospirosis. There are several reasons for causing both hypoalbuminemia and hyperglobulinemia such as kala-azar, autoimmune hepatitis, and systemic lupus erythematosus (SLE). We think that establishment of globulin and albumin levels which reflect synthesis function of liver, is also important in the diagnosis, Therefore, the low level of albumin and the high level of globulin may be clues for leptospirosis.

In 55% of children with leptospirosis, there is cholecystitis without stones and gallbladder hydrops.[2,15] We, previously[16] reported gallbladder hydrops in two out of three cases of childhood leptospirosis. We have considered nonobstructive, toxic dilatation of the gallbladder.

Ninety percent of cases with leptospirosis have an anicteric course; that is why the disease is not not easily diagnosed. In feverish patients who developed both renal impairment and jaundice, leptospirosis should be considered if no pathogen microorganisms could be grown with traditional methods.[17-19] Only the third case had lower urinary system symptoms; however several leukocytes and tubular epithelial cells and hypermotile spiral-shaped microorganisms were observed in the microscopic examination of the urine of all cases. In the third case, several motile microorganisms were present even within the tubular epithelial cells. Pathogen microorganisms did not grow in urine cultures. Urine findings normalized within the first days of treatment.

Renal involvement can be observed in all froms of leptospirosis regardless of the serotype of the causative microorganism or the severity of the disease. Oliguria or anuria may develop early in the course of the disease and may persist. In leptospirosis renal failure is generally reversible. However, the main cause of death is renal failure as well.[2,20] In Thailand, Vachvanchsnong[20] et al. had three cases of childhood leptospirosis all of whom developed tubulointerstitial renal failure. In all of these patients there was acute non-oliguric renal failure together with mild hypocalcemia, mild metabolic acidosis and uremia. On the sixth day of the treatment the patients improved completely without necessitating dialysis. In Brasil, Seguro et al[21] reported 56 cases of acute renal failure caused by leptospirosis. In this population, non-oliguric renal failure was more frequent than oliguric renal failure; nonoliguric renal failure resulted in less mortality and morbidity compared to oliguric renal failure. Furthermore 45% of the patients were hypokalemic while none of them had hyperkalemia. All our patients had urinary microscopic findings reflecting renal involvement. However, in only two cases uremia was accompanied by mild hyponatremia, hypopotassemia and hypocalcemia. Blood pressures of the cases were normal, they could urinate sufficiently; they did not have acidotic respiration or edema. Although our findings were in correlation with the data in the literature, we consider tubular damage as the main cause of renal failure. Because,the main pathological feature of leptospirosis is renal tubular damage and hepatocellular impairment. As a result of ischemia of the kidneys, renal failure due to tissue hypoxia and tubular damage develops.[2] As the reabsorption of sodium from the proximal tubules is impaired, it reaches the distal tubules at a level beyond its reabsorption capacity; thus it is excreted in the urine together with the potassium, as a result of the sodium-potassium exchange taking place in the distal tubules[21]. In leptospirosis, there are several leptospira in the tubulus lumen. In the kidneys leptospira are protected by host defense mechanisms and create a focus for the dissemination of the infection.[2]

Although we had a limited number of cases, we strongly suggest that the present study would lead to several studies in this field and shed light to the disease in terms of diagnosis and possible treatments.

***Acknowledgement***

*I am grateful to Ass.Prof. Lale Olcay for her kind comment.*

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