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*Case Report*

# Treatment of severe leptospirosis with therapeutic plasma exchange in a pediatric patient

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**Leptospirosis is a common zoonotic disease caused by spirochetes of the genus *Leptospira*. Although it is mostly a tropical disease, some case reports have been published from temperate regions of the world. The disease presents with a wide spectrum; from asymptomatic self limited disease to a fatal illness characterized by multi-organ involvement.**

**An 8-year-old girl presented with a 5-day history of fever, myalgia, fatigue, vomiting and diarrhea. She developed anuria, hypotension and became unconscious one day after admission and was referred to our pediatric intensive care unit for further evaluation and treatment. Initial physical examination revealed fever, jaundice, diffuse petecchiae on whole body, hepatomegaly and severe hypotension. Laboratory investigations showed elevated liver enzymes and bilirubin levels, elevated creatinine and creatine kinase levels and trombocytopenia. The diagnosis of Leptospirosis was detected by rapid IgM test and confirmed by microscopic agglutination test later. She was treated with mechanical ventilation, wide spectrum antibiotics, positive inotropic agents and penicillin G plus two days of continuous renal replacement therapy and five sessions of therapeutic plasma exchange performed daily. She recovered completely and was transferred to the pediatric ward on the 14$^{th}$ day of hospitalization.**

**The exact role of therapeutic plasma exchange has not been well documented yet, it seems to have benefical effects on clinical and laboratory findings and survival as we observed in our patient and learned from experiences in adult patients presented as case reports.**

***Key words: leptospirosis, multipl organ failure, therapeutic plasma exchange.***

Leptospirosis is a bacterial zoonotic disease caused by spirochetes of the species *Leptospira interrogans*. The disease is one of the most common, widespread and underdiagnosed infections transmitted from animals to human with a higher incidence in countries with humid subtropical or tropical climates. The natural hosts for this organism are mammals (such as dogs, cats, farm animals, mice and wild rodents) and they excrete infected urine that can remain infectious for years.[1] Direct contact with urine of infected animals or contaminated water and soil through the broken and water-soaked skin, intact mucous membranes or conjunctiva causes human leptospiral infection.[2] The disease presents with a wide spectrum: from asymptomatic or subclinical self limited influenza-like disease in which only a positive serological response is detected- to septic shock and multiorgan dysfunction (known as Weil's Disease) which can present with fever, acute kidney injury, pulmonary hemorrhage, acute respiratory distress sydrome (ARDS), bleeding diathesis, impaired hepatic functions, jaundice, trombocytopenia, circulatory collapse and perhaps death.[3]

In leptospirosis, appropriate antibiotic therapy is still the cornerstone of treatment and

penicillins may shorten the duration of disease if given in the infective phase but supportive measures are also important especially in fulminant disease characterized with septic shock and multi-organ failure[4]. In this paper, we report severe leptospirosis in a pediatric case successfully treated with continuous renal replacement therapy (CRRT) and therapeutic plasma exchange (TPE).

**Case Report**

An 8-year-old girl was admitted to a public hospital with a 5-day history of fever (39°C), myalgia, fatigue, vomiting and diarrhea. She was hospitalized there with a preliminary diagnosis of acute gastroenteritis. She was treated with antipyretics (paracetamol), empiric ceftriaxone and intravenous fluids. During follow-up, she became unconscious, anuric and hypotensive 2 days after admission. On the second day of hospitalization she was referred to our pediatric intensive care unit (PICU) for preliminary diagnosis of acute gastroenteritis and septic shock.

On physical examination at admission, she was unconscious (Glasgow coma scale 6) and intubated with an endotracheal tube. Her temperature was 38.7°C (rectal). Initial blood pressure (BP) was 70/35 mmHg (mean:51 mmHg) and she was tachycardic (heart rate:132 beats per minute). Capillary refill time was prolonged at about 4-5 seconds. Her oxygen saturation was 98% ($FiO_2$: 60%) and there were wide crackles on her pulmonary examination. There were no lymphadenopathy. The examination of the abdomen was normal except hepatomegaly about 4-5 cm. There were diffuse petechiae on her body, she was icteric and she had marked pretibial edema. The results of initial laboratory testing were as follows: Arterial gases were between normal ranks (pH:7.37, $PO_{2:}$ 106 mmHg, $PCO_{2:}$ 35 mmHg, $HCO_{3:}$ 21 mmol/L, base excess: -4 mmol/L and lactate was 2 mmol/L). The complete blood count revealed trombocytopenia, leukocytosis (neutrophils, 84%; lymphocytes, 12%; monocytes, 4%) and a hemoglobin level of 9.8 g/dl (Table I). The coagulation parameters and other laboratory findings were shown in Table 1. Serum electrolytes, albumin, glucose, amylase, ammonia levels and urinary sediment were normal. Chest radiograph showed bilateral diffuse pulmonary infiltrates. The abdominal ultrasonography showed hepatomegaly about 5 cm and other findings were normal. Sepsis work-up including blood, urine, endotracheal aspirate and stool cultures were negative. Anti-hepatitis A (HAV) immunglobulin M, anti-hepatitis C (HCV), anti-HBc and surface antigen hepatitis B (HBV) were negative. Investigations including screening for Epstein-Barr virus (EBV), cytomegalovirus (CMV), human immundeficiency virus (HIV), Crimean-Congo hemorrhagic fever (CCHF), Parvovirus B19, rubella, toxoplasma, herpes simplex virus, mycoplasma, chlamydia, rickettsia, salmonella and brucella tests were all negative. Anti-nuclear antibody, anti-ds DNA were negative and serum complement levels (C3, C4) and immunoglobulin levels were within normal limits. Because of the initial presentation and a history of living in a small town and contact with animals, leptospirosis was suspected to be the final diagnosis. Spirochetes were viewed under dark field microscopy directly and serologies for leptospira IgM rapid test was positive with ELISA on the first day. The microscopic agglutination test (MAT) was performed for confirmation of our diagnosis and showed low antibody positivity (1/50) against Leptospira. Control serological testing (MAT) two weeks later was planned.

Vancomycin, ciprofloxacin, amikacin and penicillin G was started immediately. Despite receiving adequate intravenous fluids she was hypotensive, dopamin, dobutamin and noradrenaline infusions were started for circulatory support. Double lumen 9-Fr transient hemodialysis catheter (Duo-flow, Medcomp®, Harleysville, PA) was inserted with anatomic landmark approach to right femoral vein. Continuous veno-venous hemodiafiltration (Prismaflex®, M 60 filter, Gambro Lundia AB, Sweden) was started for anuria and fluid overload at the 6$^{th}$ hours after admission. TPE was performed with a centrifugation technique (Spectra Optia; CaridianBCT, Lakewood, CO) on the first day. Total plasma volume (TPV) was calculated manually with this formula: TPV=total blood volume X (1-hematocrit). We removed 1.700 ml of dark golden plasma (1.1 times estimated plasma volume) and replaced 1550 ml of fresh frozen plasma on the first day. The plasmapheresis procedure was continued daily for 4 following days, with 5 equal sessions totally. The average removed plasma volume

was 1530 ml per session (minimum: 1300 ml, maximum: 1640 ml). The average time of the sessions was 132 min (minimum: 112 min, maximum 153 min). We used citrate to prevent clot formation in the extracorporeal circuit and gave 1 ml/kg calcium gluconate infusion intravenously during each session to prevent hypocalcemia. We used fresh frozen plasma as a replacement fluid in the first session because of abnormal coagulation parameters in her laboratory studies. On the other four procedures we used fresh frozen plasma and 5% human albumin in 1/1 ratio. No life-threatening complications were observed during procedures. CRRT was continued for 2 days and was stopped because of the normalization of creatinine levels and spontaneous diuresis on the second day. There was no elevation of creatinine levels or any electrolyte imbalance after stopping CRRT.

After the first session of TPE, the dose of the inotropes were tapered and all inotropes were totally withdrawed after the second session. Trombocytopenia, direct hyperbiluribinemia, pulmonary infiltrates on chest X-ray and mental state improved (Figure 1 and 2) and she was extubated on the 8th day of hospitalization. The antibody titer on the 10th day of hospitalization was 1/200 in MAT (4-times elevation despite 5 sessions of TPE) confirming our diagnosis. She was transferred to the pediatric ward with no sequela on the 14th day of hospitalization to the PICU.

Written informed consent was obtained from the parents for publication of this case report.

## Discussion

Leptospirosis is a common zoonotic disease caused by spirochetes of the genus Leptospira and it is a great health hazard especially in tropical regions. Incidence of the disease in the tropics is approximately 10 times higher than the other parts of the world.[5] It is not a common disease in our country and is reported sporadically as case reports or series in certain regions of Turkey.[6]

After an incubation period of 2 to 26 days (average 10 days), the disease presents with fever, general malaise, myalgia and headache in 75% to 100% of the patients. This initial phase is called infective or septicemic phase and lasts for 4 to 7 days. The clinical course of the disease after these initial symptoms is variable. Most of the cases are mild, subclinical and self limited while some patients (5-10%) develop jaundice, pulmonary hemorrhage, ARDS, renal failure, myocarditis, uveitis and rhabdomyolysis

**Table I.** Laboratory Parameters at Admission and During Hospitalization.

| | 1st day | 2nd day | 3rd day | 5th day | 7th day | 10th day |
|---|---|---|---|---|---|---|
| Hemoglobin (g/dl) | 9.8 | 8.7 | 9.1 | 7.7 | 9.9 | 11.2 |
| White blood cell (/mm$^3$) | 28.000 | 20.090 | 15.560 | 7.400 | 13.170 | 11.200 |
| Thrombocytes (/mm$^3$) | 42.000 | 65.000 | 65.000 | 79.000 | 165.000 | 523.000 |
| Prothrombin time (sec.) | 14.3 | 11.6 | 11 | 12 | 11.3 | 11.7 |
| INR | 1.2 | 0.8 | 0.96 | 1.06 | 1.03 | 1.03 |
| APTT (sec.) | 56 | 32 | 26 | 25 | 21 | 21 |
| Fibrinogen (mg/dl) | 135 | 210 | 128 | 154 | 192 | 232 |
| AST (IU/L) | 248 | 163 | 105 | 72 | 63 | 31 |
| ALT (IU/L) | 165 | 101 | 78 | 62 | 64 | 34 |
| Total bilirubin (mg/dl) | 4.5 | 4.6 | 3 | 1 | - | 0.9 |
| Direct bilirubin(mg/dl) | 3 | 3.2 | 1.6 | 0.3 | - | 0.2 |
| BUN (mg/dl) | 44 | 29 | 22 | 29 | 16 | 16 |
| Creatinine (mg/dl) | 1.15 | 0.75 | 0.45 | 0.44 | 0.33 | 0.3 |
| CK (U/L) | 6309 | 4242 | 1687 | 807 | 142 | 68 |
| Procalcitonin (ng/ml) | 82 | 40 | 10 | 0.5 | - | 0.1 |

INR: international normalized ratio, APTT: activated partial thromboplastin time, AST: aspartate aminotransferase, ALT: alanine aminotransferase, BUN: blood urea nitrogen, CK: creatine kinase

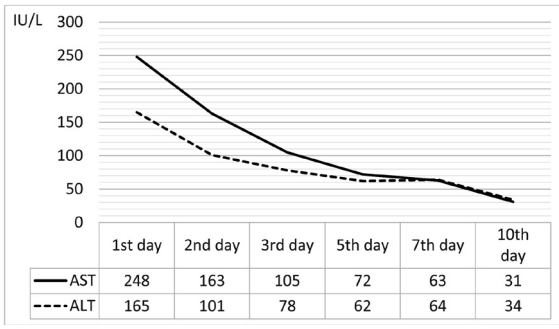


**Fig. 1.** Serial levels of AST and ALT during hospitalization.

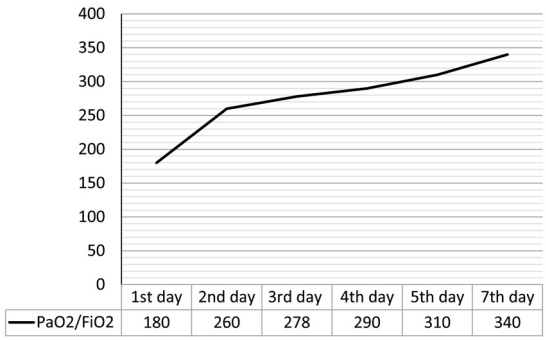


**Fig. 2**. $PaO_2/FiO_2$ changes during treatment.

known as 'Weil's Disease'. This second phase is the immune phase in which serological tests for anti-Leptospira IgM becomes positive in blood tests. The fatality of the disease ranges from 4% to 52% according to the affected organs and systems.[7,8] Our patient developed septic shock and multi-organ failure 7 days after the initial symptoms of Leptospira infection and this is coinciding with the immune phase of the disease.

Treatment of severe leptospirosis consists of two major components and first step is the choice of appropriate antibiotics. Ceftriaxone or penicillin G are the main treatment options for severe disease whereas ampicillin, amoxicillin or doxycycline are recommended for mild disease.[9] Penicillins may shorten the duration and severity of the disesase if given in the early phase of the disease.[4] In our patient, we gave wide spectrum antibiotics initially, and added penicillin G to the therapy after the positive rapid Leptospira serology test on the first day of hospitalization. The other component is the supportive measures and are as important as appropriate antibiotic therapy. Severe cases with multi-organ involvement should be followed-up in an intensive care unit. Cases with severe pulmonary hemorrhage or ARDS should be mechanically ventilated. Positive inotropic agents should be added to the therapy in patients with circulatory collapse that is unresponsive to intravenous fluids.

CRRT would be an ideal option for patients who developed acute renal failure during the disease. The incidence of acute renal failure is between 10% to 60% depending upon the severity of the disease.[10] The reason of acute renal failure in leptospirosis is tubulointerstitial nephritis associated with direct invasion of the microorganism into kidneys. Other contributing factors are hyperbilirubinemia, endotoxins, hypotension, hypovolemia and rhabdomyolysis. It usually manifests as non-oliguric acute kidney injury[11]. Atypically we observed an oliguric renal failure despite adequate intravenous fluids in our patient and started to perform CRRT in the first day of treatment, lasting for two days. Her urine output improved after renal replacement therapy.

Although leptospirosis is still not included in the seventh edition of the American Society for Apheresisis (ASFA) guidelines for TPE which was published in 2016, therapeutic plasma exchange has been reported as an adjunctive therapy for patients with severe leptospirosis in recent years; especially in adults.[12] The exact mechanisms of how it works in leptospirosis are not clear yet but we know that it removes circulating endotoxins, bilirubin and inflammatory mediators and prevents immune complex mediated tissue injury which would contribute to a decrease in toxic insult to hepatic, renal, pulmonary and cardiac cells. Taylor et al.[12] reported an adult patient of 67 years old with severe leptospirosis successfully treated with two sessions of plasma exchange and they highlighted a dramatic reduction of serum bilirubin levels and improvement in mental state and respiratory functions after the second session. Tse et al.[13] described a dramatic improvement in an adult patient with a single plasma exchange only. Trivedi et al.[14] reported that plasma exchange with immunosuppression improved survival in patients of pulmonary alveolar haemorrhage due to leptospirosis in a study of 114 adult patients. TPE and CRRT improved systemic and renal hemodynamics in severe cases with renal failure and multi-organ involvement in another study.[15] Yeşilbaş et al.[16] reported a 15-year-old pediatric patient

with fulminant leptospirosis complicated with macrophage activation syndrome and sclerosing cholangitis successfully treated with CRRT and TPE.

As we searched current literature, our patient is the second pediatric patient in the literature that TPE was performed in severe leptospirosis.

In conclusion, our patient highlights the fact that leptospirosis should be considered as a differential diagnosis in a children with septic shock and multi-organ failure, especially if there is positive history of contact with animals or infected water and in whom jaundice, acute renal failure, rhabdomyolysis and pulmonary involvement seen in the early phase of the disease. Although we cannot determine the exact effect of TPE on our patient's survival, we believe that plasma exchange should be considered as an adjunctive therapy in pediatric cases with fulminant leptospirosis.

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