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CASE REPORT

The unusual clinical presentation of leptospirosis is masked by Gilbert's syndrome

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Abstract

Leptospirosis is a zoonotic disease endemic to tropical regions, with flu-like symptoms that make early diagnosis difficult. This study describes the case of a 23-year-old man with a history of Gilbert's syndrome and mixed anxiety and depressive disorder who presented with headache radiating to the cervical region, jaundice, generalized abdominal pain, nausea, and vertigo. Initially, he was diagnosed with an exacerbation of Gilbert's syndrome; however, after 24 hours, he returned with persistent symptoms. The patient's history revealed that he had been in contact with his sick dog, which died a few days before the first consultation. Laboratory tests suggested acute febrile syndrome, and serological tests confirmed leptospirosis. Treatment with doxycycline was initiated, and the patient gradually improved, with persistent jaundice and hepatomegaly. Jaundice in leptospirosis could guide diagnosis, but Gilbert's syndrome, which causes intermittent jaundice, can mask this sign. Nevertheless, the patient's prognosis was favorable, given the absence of complications and good clinical outcome.

Keywords: Zoonoses; Gilbert Disease; Jaundice; Doxycycline; Canine diseases

Presentación clínica inusual de leptospirosis enmascarada por el síndrome de Gilbert

Resumen

La leptospirosis es una enfermedad zoonótica endémica de regiones tropicales, con síntomas similares a los de la gripe, lo que dificulta su diagnóstico precoz. El presente estudio describe el caso de un hombre de 23 años con antecedentes de síndrome de Gilbert y trastorno mixto de ansiedad y depresión, que presentó cefalea irradiada a la región cervical, ictericia, dolor abdominal generalizado, náuseas y vértigo. Inicialmente, se le diagnosticó exacerbación del síndrome de Gilbert; sin embargo, después de 24 horas, reapareció con síntomas persistentes. La anamnesis del paciente reveló que estuvo en contacto con su perro enfermo, el cual falleció pocos días antes de la primera consulta. Las pruebas de laboratorio sugirieron síndrome febril agudo y la serología confirmó leptospirosis. Se inició tratamiento con doxiciclina y el paciente mejoró gradualmente, con ictericia persistente y hepatomegalia. La ictericia en la leptospirosis podría guiar el diagnóstico, sin embargo, el síndrome de Gilbert que cursa con ictericia intermitente puede enmascarar este signo. No obstante, el pronóstico del paciente fue favorable, dada la ausencia de complicaciones y su buena evolución clínica.

Palabras clave: Zoonosis; Enfermedad de Gilbert; Ictericia; Doxiciclina; Enfermedades caninas

Introduction

Gilbert's syndrome is a common, benign liver condition characterized by mild, intermittent unconjugated hyperbilirubinemia (elevated levels of bilirubin in the blood). It is an inherited disorder caused by decreased activity of the enzyme UDP-glucuronosyltransferase (UGT1A1), which is responsible for conjugating bilirubin (a byproduct of red blood cell breakdown) into a water-soluble form for excretion. Approximately 10% of the population is affected, with a higher prevalence in men (ratio of 3:1)[1,2]. While the syndrome can present disadvantages, such as increased toxicity with certain medications and the effects of xenobiotics, it is also believed to have advantages, including immunomodulation, greater tolerance to oxidative stress, and protection against heart disease, obesity, metabolic syndrome, diabetes, and cancer[1,3].

The liver's role in bilirubin metabolism is particularly relevant when considering diseases that cause liver dysfunction. One such disease is leptospirosis, a zoonosis caused by spirochetes of the pathogenic complex *Leptospira interrogans sensu lato*. This is a significant re-emerging disease worldwide[4], with animals as its primary hosts. Different serovars show a predilection for various animal species, including canines,

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bovines, porcine, and rodents. In Colombia, leptospirosis was first diagnosed in 1969; however, it was not until 2007 that the disease was consistently reported by the National Public Health Surveillance System[5,6]. The most prevalent serogroups in the Department of Meta are Canicola and Ballum, which are associated with dogs and rats, respectively[5]. This highlights the importance of liver health in response to infectious diseases, particularly those that can cause hepatic involvement and subsequent hyperbilirubinemia.

The patient in this case was from a tropical region where leptospirosis is a leading cause of undifferentiated acute febrile syndromes. However, because the area is also endemic for arboviruses, leptospirosis is often overlooked by clinicians, leading to underreporting. The diagnosis was further complicated by the patient's reported history of Gilbert's syndrome and recent initiation of medication for anxiety and depressive disorder.

Case report

A 23-year-old male patient residing in an urban area of Villavicencio, Meta, Colombia, with a history of Gilbert's syndrome, was diagnosed approximately two years prior due to the presence of intermittent jaundice, exacerbated by factors such as insomnia, stress, and dietary disturbances. Complementary studies, including complete blood count, liver profile, and bilirubin levels, were performed. The complete blood count showed normal hemoglobin levels, ruling out hemolysis, and bilirubin levels were elevated at the expense of indirect bilirubin. Abdominal ultrasonography was performed and did not reveal any hepatobiliary abnormalities.

The patient consulted the emergency department in September 2024, with a 3-day clinical picture characterized by a holocranial headache of intensity 8/10 according to the analogous pain scale that radiated to the cervical region, concomitant with mild generalized abdominal pain, retroocular pain, nausea, and vertigo. He reported taking venlafaxine 75 mg every 24 h and zopiclone 7.5 mg every 24 h six days before the consultation due to anxiety and depressive disorder diagnosed three years prior. Physical examination revealed icteric sclerae with no other findings, and the patient was diagnosed with an exacerbation of Gilbert's syndrome and sent home with recommendations and warning signs. However, due to the persistence of headache, chills, asthenia, and adynamia, the patient consulted the emergency room again 24 h later, where a complete blood count, liver function profile, renal function, and coagulation tests were performed. The complete blood count did not show leukocytosis, anemia, or thrombocytopenia; renal function was normal; transaminase levels were slightly elevated (ALT); mild hyperbilirubinemia was found; and the coagulation time was prolonged (PTT) (Table 1). Based on the laboratory results, in-hospital management was indicated to rule out infectious diseases such as leptospirosis, hepatitis A, and hepatitis B. However, the patient refused in-hospital management and requested voluntary discharge.

Seven days after the initial consultation, the patient returned to the emergency department with a positive IgM laboratory report for *Leptospira* spp. of 83 UI/mL (positive > 20) (ELISA, Serion, Diagnostics). The results for hepatitis A and B anti-core IgM were negative by chemiluminescent ELISA (0.10 and 0.23 S/CO, respectively), and Hepatitis B Anti-HBs by chemiluminescent CMIA showed protection against the hepatitis B virus (29.3 mUI/mL). The patient had persistent headache, asthenia, jaundice, and odynophagia, and decided to self-medicate with diclofenac, dexamethasone, methocarbamol, ibuprofen, and amoxicillin. The patient was asked about the possible route of infection by *Leptospira* spp., and he reported that six days before the presentation of his symptoms, his dog had become ill and died. The dog had sudden respiratory failure without response to stimuli and convulsive episodes with tonic-clonic movements, sphincter relaxation, and sialorrhea.

Post-mortem canine tests showed elevated aminotransferase and creatine phosphokinase levels, and the blood count showed leukocytosis without neutrophilia, anemia, thrombocytopenia, or hyperglycemia. The patient reported contact with animal fluid and urine.

Physical examination revealed icteric sclerae and a congested pharynx without plaques or exudates. Neurological deficits or signs of respiratory failure were ruled out, and due to the diagnosis of uncomplicated leptospirosis, it was decided to discharge the patient with oral doxycycline 100 mg every 12 hours and acetaminophen. On the fifth day after treatment (15 days after the onset of the clinical picture), the patient visited the outpatient clinic with persistent malaise and headache. Control tests showed persistent hyperbilirubinemia, normalized aminotransferase levels, and preserved renal function (Table 1). Physical examination revealed icteric sclerae and terminal nuchal rigidity, with no other signs of meningeal irritation, bilateral conjunctival hemorrhage, or painful hepatomegaly on abdominal palpation. Given these warning signs, hospitalization was ordered, but the patient refused. We then decided to extend the antibiotic treatment and added acetaminophen and codeine due to the severe headache. Three days after codeine treatment, the headache disappeared, and general improvement was noted in the patient.

Discussion of the case

Leptospirosis generally presents in two phases: the septicemic phase, which has an abrupt onset of headache, myalgia, and cough; splenomegaly and hepatomegaly are not common in this phase; and the immune phase, which involves a decrease in fever, the appearance of antibodies, elimination of the bacteria through urine, and can last between 4 and 30 days. In advanced stages, leptospirosis can result in meningitis and severe pulmonary involvement[6].

In this case, the coexistence of leptospirosis and Gilbert's syndrome represented a significant diagnostic challenge. Mild hyperbilirubinemia at the expense of the indirect fraction, a typical finding of Gilbert's syndrome, led to the initial presentation being interpreted as an exacerbation of this benign condition. This diagnostic bias delayed the suspicion of an infectious process, particularly leptospirosis, whose clinical presentation can be nonspecific and confused with other liver diseases.

Few cases have been described in whom the presence of Gilbert's syndrome hampered the early identification of acute liver disease of infectious origin. In these publications, the diagnostic delay was related to the initial interpretation of jaundice as an expected finding of the underlying condition without considering other possible etiologies[7]. This pattern is repeated in diseases such as leptospirosis, where jaundice has been documented to be marked, with a predominance of the direct fraction and only slightly elevated transaminases, which can lead to confusion with other causes of non-obstructive jaundice. Recent studies in endemic areas have shown that leptospirosis is an underestimated cause of jaundice in adults, with positive serology results in a significant percentage of cases initially attributed to yellow fever or other viral liver diseases[8].

The differential diagnosis of jaundice in adults is broad and should include hepatic causes (viral hepatitis, alcoholic liver disease, and autoimmune hepatitis), hemolytic causes (autoimmune hemolytic anemia, Glucose-6-phosphate dehydrogenase deficiency), obstructive causes (cholelithiasis, cholangiocarcinoma, periampullary neoplasms), and non-viral infectious causes such as leptospirosis, typhoid fever, yellow fever, and other zoonoses prevalent in tropical areas. In regions where multiple endemic agents coexist, such as arboviruses, malaria, and *Leptospira* spp., it is essential to integrate the epidemiological history (exposure to contaminated animals or water), evolution of symptoms (fever, headache, myalgia, asthenia), and atypical laboratory parameters for Gilbert's syndrome, such as elevated aminotransferases or the presence of direct hyperbilirubinemia[1,2].

In our case, the identification of a history of contact with the urine of a sick dog clarified the source of infection. Therefore, it is important to remember that finding jaundice in patients with epidemiological risk factors requires ruling out infectious etiologies before attributing it exclusively to a pre-existing condition, such as Gilbert's syndrome[7].

In this case, Gilbert's syndrome diverted attention from the infectious nature of leptospirosis. Early in the diagnosis, it was thought that venlafaxine and zopiclone, which share hepatic metabolism, could have exacerbated jaundice; therefore, the symptoms were due to Gilbert's syndrome combined with the patient's anxious depressive disorder. This is because it is common for patients with Gilbert's syndrome to have exacerbations when taking medications with hepatic metabolism[1,2]. For this reason, it is crucial to understand that Gilbert's syndrome is asymptomatic, has a benign course, and will never present with other signs such as headache, chills, and, much less, with alterations in aminotransferases or conjugated (direct) bilirubin, as was seen in the case described.

The prognosis in this case was favorable, with no renal, neurological, or hemorrhagic complications, progressive resolution of hyperbilirubinemia, and normalization of the liver enzymes. This outcome is consistent with the literature, which states that uncomplicated forms of leptospirosis, when treated promptly, have good clinical outcomes[9]. In summary, this case reinforces the need to maintain a broad diagnostic vision in adult jaundice syndrome, especially in endemic areas, and to avoid anchoring the diagnosis to benign conditions when the clinical and epidemiological contexts suggest another etiology.

Ethical considerations

Protection of people and animals. No experiments have been conducted in humans or animals.

Protection of vulnerable populations. There were no photographs that allowed for patient identification.

Confidentiality. The authors declare that no data that can identify patients appear in this article. Right to privacy and informed consent. Minute 022-2024 of the Research Ethics Committee of the IIBT of the University of Cordoba.

Privacy. In this article, no names, initials, or hospital medical record numbers were used in either the text or the photograph to identify the patient, thus ensuring their privacy.

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