Dubin Johnson Syndrome Presented with Persistence Conjugated Hyperbilirubinemia Unmasked by Brucella Hepatitis: A Case Report

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Introduction

Multiple causes could alter liver functions including infections, biliary disorders, viral or non-viral hepatitis, autoimmunity, and drugs. Brucellosis, zoonotic infection, presents with unspecific varied signs and symptoms affecting multiple organs (1). This infection is widely prevalent in both animals and humans (2). The liver is commonly involved in both acute and chronic cases of Brucellosis. When infected, patients may experience a slight increase in transaminase levels and mild swelling of both the liver and spleen. Occasionally, acute hepatitis can occur, but it's usually not the only symptom of infection (3). Conjugated hyperbilirubinemia along with normal liver transaminase, serum alkaline phosphatase (ALP), and jaundice highly suggest Dubin-Johnson syndrome (DJS). Patients less likely present with mild abdominal pain, pruritus, nausea, or vomiting. DJS is a rare, chronic mainly autosomal recessive disease caused by mutations in the gene encoding for proteins involved in hepatobiliary transport of non-bile salt organic anions, leading to conjugated hyperbilirubinemia (4). Mutations in the *multidrug resistance-associated protein-2 (MRP-2)* gene are responsible for this disorder (4). The diagnosis of this benign condition is important to avoid unnecessary anxiety or intervention (5). Herein, for the first time, we report a case of a 35-year-old man presenting with jaundice for the first time in his life caused by brucella hepatitis, that lead to the diagnosis of concomitant DJS.

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Case Presentation

A 35-year-old man presented with a month of fluctuating fever accompanied with progressive icterus. He was referred to our hospital due to the primary complaints of myalgia, arthralgia, epigastric pain, itching, and weakness, which had worsened over the last three days. He also experienced anorexia, a slight epigastric pain but had no nausea, vomiting, or productive cough. He also complained of a recent red colored urine, dysuria, and urine frequency. No history of acholic stool was declared, or similar previous complaints. He had a past medical history of autosomal dominant polycystic kidney disease (ADPKD), which was also present in his father, sister, and brother. He had no recent travel history, no employment in paddy fields,

no engagement in high-risk sexual behavior, no use of any kind of medication, no drug abuse, no raw dairy ingestion, and no alcohol consumption or smoking. He had recently started taking opium as a painkiller. On examination, he was febrile with temperature of 39°C, tachycardia (109 beats/min), and normal respiratory rates (17/minute). His blood pressure was 125/75 mmHg. Physical examination showed was quite evident icteric sclera in addition to skin jaundice on his abdomen, a midline scar was detectable due to a laparotomy procedure performed seven years ago for an appendectomy. He had slight epigastric tenderness and Hackett's grade 3 splenomegaly with the spleen expanding to the umbilicus. A mild unspecific hepatomegaly was also present. However, no other signs of chronic liver failure or portal hypertension such as ascites, spider angioma, or gynecomastia. Other systemic examinations such as skin, and neurologic were unremarkable. Initial laboratory tests showed no abnormalities in blood cell counts with retic count of 0.7. Biochemical tests showed a total serum bilirubin of 10 mg/dL, a direct serum bilirubin of 8 mg/dL, AST97 U/L, ALT157 U/L, ALP 495 U/L, and GGT 27 U/L. He had Serum creatinine (Cr) of 1.53 and urea of 47, in addition to many RBCs in urine analysis were reported. Amylase and lipase were both in normal range. The other hematologic parameters were as follows: PT 13, PTT 26, ESR, 59 mm/h, CRP 2+. Viral hepatitis markers were all negative (Anti-hepatitis C virus antibody (Anti-HCV), Anti-hepatitis A virus antibody (Anti-HAV (total)), Anti-HAV (IgM/ IgG), hepatitis B surface antigen (HBsAg), and anti-Hepatitis B core antibody (anti-HBc) (total/IgM/IgG)). The patient's initial laboratory findings are reported in Table 1. In upper abdominal ultrasonography, minimal increase in liver size (160mm), and huge splenomegaly with accessory spleen (132 mm), dilated CBD (7.5mm), dilated portal vein (17mm), ADPKD, renal stones, and hemorrhagic cysts measuring 55mm in right and 36mm in left kidneys were reported. Abdominopelvic computed tomography (CT) scan without contrast confirmed the findings of ultrasonography in addition to absence of dilatation in intra and extra hepatic ducts, ruloing out malignancies and hepatobiliary stenosis. High Resonance CT (HRCT) revealed unspecific longitudinal consolidation collapse at the base of the lungs. According to clinical, laboratory and sonographic findings of dilated CBD, magnetic resonance cholangiopancreatography (MRCP) was performed and showed normal findings. We evaluated further causes of infectious hepatitis. Regarding high geographical prevalence of leptospirosis IgG and IgM, in addition to HIV antibody, tuberculin test, and VDRL were all checked and negative. Then, we conducted the wright, Coombs-wright, and 2ME test, which initially showed a titer of 1/640, 1/640, and 1/160, respectively on the second day of admission. Simultaneously, blood culture grew *Brucella melitensis* . According to the patient's positive Coombs-Wright test, high levels of liver enzymes, and the history of sudden exacerbating systemic symptoms, we made a diagnosis of Brucella hepatitis. Subsequently, he was started on streptomycin 1 mg/ IM daily for the first 14 days, followed by the preferred first-line drugs, a doxycycline-aminoglycoside combination for six weeks. After a week of follow-up, general condition was improved, fever subsided, and symptoms were relieved. After a month, significant improvement in laboratory findings were also present, all signs and symptoms were gone, however, conjugated hyperbilirubinemia remained untreated (Table 2). Thus, secondary work-ups were performed to examine concomitant autoimmune hepatitis, Wilson's disease, hemochromatosis, alhpah1-anti trypsin deficiency, rheumatologic diseases, and multiple myeloma. Ceruloplasmin, α-1 Anti Trypsin, Anti LKM Ab, Anti EMA (IgG, IgM), ASMA, AMA, ANA, P-ANCA, HLA-B51and blood protein electrophoresis were all normal. Additionally, we asked about possible hepatotoxic agents. The patient's history of no drug intake, herbals or OTCs, but routine and very low dose consumption of painkillers was completely reliable, ruling out the drug-induced liver injury. Finally, with the possible diagnosis of DJS, he underwent a liver biopsy. The lobular liver structure was normal during Hematoxylin and Eosin (H&E) staining, however, vivid dark brown pigments in the hepatocyte cytoplasm was found, confirming the diagnosis of DJS in concomitant with brucella hepatitis (Figure 1). The Periodic Acid-Schiff-diastase (PAS-D) method was negative for alpha-1-antitrypsin globules. The patient was insured and underwent follow-up, and after one year, his condition returned to normal.

Discussion

Currently, we reported a case of DJS diagnosed after a course of brucella hepatitis, confirmed by liver biopsy. The fact that comorbidity can aggravate DJ syndrome is known; however, this is the first study reporting DJ syndrome unmasked with Brucella hepatitis. Previously, there have been cases of acute hepatitis caused by brucella. Denk et al. reported a 19-year-old man with fever, arthralgia, icterus, and impaired liver transaminases with mild conjugated hyperbilirubinemia (6). In contrast, another study demonstrated two patients of brucella hepatitis with normal bilirubin levels, but elevated liver transaminase and LDH 7 times higher than normal (7). Concurrent to fluctuating fever and new-onset jaundice for a month, our patient showed impaired AST, and ALT concentrations with mild rise of LDH to 529 U/L, indicating cell destruction of intracellular brucella. A 79-year-old woman has also shown liver failure due to brucellosis infection with impaired bilirubin more than 20 times normal (8). In this case while he had no other signs of liver failure, he presented with direct hyperbilirubinemia of 8mg/dL and total bilirubin of 10mg/dL. In a study on liver involvements of patients suffering brucellosis, mean total and direct bilirubin in diffuse and granulomatous hepatitis were 2.18±2.33 and 3.78±2.05, respectively (9). Thus, high levels of bilirubin in brucella hepatitis could be a sign of liver failure, however, if liver function remains normal, concomitant underlying liver disease should be evaluated. Moreover, regarding previous reports, after standardized treatment of brucellosis, all the patients showed significant decrease in liver enzyme levels and bilirubin, however, although reduced, jaundice and direct hyperbilirubinemia remained. This also highlights the importance of further assessments. In DJS, liver function tests remain in normal range, and the total serum bilirubin levels increase, generally ranging from 2 to 5 mg/dL. However, in 5% of cases, this increase exceeded 10 mg/dL (10). Other liver function tests yield normal results. Although rare, there are previous reports of persistent conjugated hyperbilirubinemia resulted in the diagnosis of the disease (11, 12). DJS is the impairment of transporting direct bilirubin into the bile duct system, leading to its accumulation in hepatocytes and rise in blood levels (5). Grossly black liver, normal architecture, in the presence of accumulation of coarse granular dark pigments located in the centrilobular hepatocytes are particular pathological characteristics of DJS (13, 14). Similarly, Liver biopsy of our patient showed vivid dark brown pigments in the hepatocyte cytoplasm via PAS-D method. A liver biopsy provides essential information about the extent and severity of liver damage in patients with DJS. This information is critical in determining the appropriate course of treatment and monitoring the progression of the disease. If there is evidence of significant liver damage, the patient may need to undergo a liver transplant. In the presence of minimal damage, the patient may only need to be monitored regularly to ensure that the disease does not progress. A liver biopsy is useful for distinguishing DJS from other liver disorders that have similar symptoms and biochemical abnormalities, such as primary biliary cirrhosis, and primary sclerosing cholangitis can also cause conjugated hyperbilirubinemia (15, 16). In ultrasonographic and CT scan assessments, our patient had massive splenomegaly and hepatomegaly. Liver enlargement has been previously seen among both DJS and patients suffering from brucellosis, however, splenomegaly has been reported upon 30-60% of brucellosis and DJS could not cause splenomegaly (17-19). In a study of 251 patients with brucellosis, Pourbagher et al. identified 21 (8.4%) patients with splenomegaly, 15 (6%) patients with hepatomegaly, 4 (1.6%) patients with splenic abscess, 2 (0.8%) patients with splenic cyst, 2 (0.8%) patients with acute appendicitis, 1 patient (0.4%) with acute acalculous cholecystitis (20). There are also further reports of brucella hepatitis presented with huge splenomegaly, even spleen infarction, and its rupture (21-23). Importantly, massive splenomegaly has limited etiologies such as major beta-thalassemia, acute leukemias, lymphomas, cirrhosis with portal hypertension, and myeloproliferative neoplasms (24). Regarding that massive splenomegaly found in our patient revealed after full-treatment of brucellosis, further analysis of the ethnologies deems necessary to elucidate whether this novel report could be due to DJS and brucellosis concomitancy. It is important to mention certain limitations that were encountered. Firstly, the rarity of both Brucella hepatitis and DJS presents challenges in diagnosing and managing such cases, especially when they occur concomitantly. Limited clinical experience and awareness of these conditions among healthcare professionals may contribute to delays in diagnosis or misinterpretation of symptoms. Additionally, the lack of specific diagnostic markers for DJS can make its identification challenging, often necessitating a comprehensive evaluation and ruling out of other liver pathologies. Based on his past medical

history, laboratory tests, and clinical evaluation, a diagnosis of Dubin-Johnson syndrome was suspected. Of course, urine high coproporphyrin I fraction could lead to a straight diagnosis of DJS, nevertheless, unfortunately we do not have the kit in our hospital. We referred the patient to the central hospital of gastroenterology, but he hesitated and in other sessions of follow-up we found out he did not follow the instructions and hesitated to travel to another city for further evaluations. We had to perform liver biopsy to not only approve our diagnosis of DJS, but also make sure there were no sign of viral hepatitis with negative viral markers, further masked infections, alhpah1-anti trypsin deficiency or hepatic granulomatosis. H&E staining only showed vivid dark brown pigments in the hepatocyte cytoplasm, and PAS-D was negative for alpha-1-antitrypsin globules, confirming the diagnosis of DJS.

Conclusion

Currently, we reported the first DJS diagnosed by persistent direct hyperbilirubinemia after brucella hepatitis in a young man. Clinicians should be aware of unusual rise in liver function tests and carefully monitor the response to therapy, to avoid neglecting benign conditions such as DJS and long-term consequences. To date, concomitant DJS with other liver diseases has not been adequately addressed. Further studies should evaluate possible novel and exaggerated clinical findings, as well as the unexpected long-term consequences.

Declarations

Ethical Approval

The written informed consent was obtained from the patient. The local ethics committee at Golestan University of Medical Sciences approved this study (IR.GOUMS.REC.1401.603).

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Consent for publication

The written informed consent was obtained from the patient.

Availability of data and materials

All data used in this work could be available by contacting the corresponding author.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author Contribution

Fatemeh Hasani: conceptualization, methodology, resources, data curation, writing – original draft, project administration & editing;**Zahra Norouzi:** methodology, investigation, Supervision, project administration & editing; **Kimia Jazi:** data curation, writing – original draft, project administration & editing; **Sina Khamaki:** data curation, writing – original draft, project administration & editing; **Sakhi Ghezel:** methodology, investigation; project administration & editing; **Masoud Sotoudeh:** methodology, investigation, Supervision, project administration & editing; **Alireza Norouzi:** methodology, investigation, Supervision, project administration & editing. All authors contributed in writing original draft of the article.

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Tables

Table 1. Initial Laboratory Findings

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	Test, Unit	Result	Reference Range
Biochemistry	AST, U/L	97	Up to 35
	ALT, U/L	157	Up to 45
	ALP, U/L	495	64-306
	Total Bilirubin	10	0.1 to 1.2
	Direct Bilirubin	8	0 to 0.3
	GGT	27	0 to 30
	Haptoglobin	NL	–
	LDH	529	140 to 280
	Iron	18	10 to 30
	Ferritin	201	12 to 300
	TIBC	265	240 to 450
	Amylase	58	40 to 140
	Lipase	52	0 to 160
	Urea	47	13-43
	Cr	1.53	0.6-1.1
	CPK	22	10 to 120
	Na	135	135-145
	K	5.2	3.5-5.5
Urine Analysis	WBC	2-3	–
	RBC	many	–
	Protein	negative	–
	Bilirubin	negative	–
Hematology	WBC, µL	8500	4000-11000
	Hb, g/dL	12.8	12-16
	Platelet, µL	241000	150000-450000
	PT	13	11 to 13.5
	PTT	26	25 to 35
Serology and others	ESR 1h	59	positive: >30
	CRP	2+	–
	HLA-B51	negative	–
	HIV-Ab	negative	–
	HCV-Ab	negative	–
	HBS-Ag	negative	–
	HBC Ab (IgM/IgG)	negative	–
	HAVAB (total/IgM/IgG)	negative	–

	Test, Unit	Result	Reference Range
	ACE, mg/ liter	29	Less than 40
	ANA	negative	–
	P-ANCA	negative	–
	TSH, mIU/L	1.28	0.5-5

Table 2. Follow-up laboratory results from the beginning and after initiating treatment for brucellosis

	(1)	(2)	(3)	(4)	(5)	Reference Range
Coombs Wright	1/640	1/320	1/160	1/80	–	1/20 to 1/80
2ME	1/640	–	1/80	1/40	–	>1/80
AST, U/L	97	46	40	36	32	Up to 35
ALT, U/L	157	70	20	30	27	Up to 45
ALP, U/L	495	465	330	310	260	64-306
Total Bilirubin	10	8.6	4	2.5	3.8	0.1 to 1.2
Direct Bilirubin	8	6.7	3.5	2.2	3.4	0 to 0.3
ESR	59	–	–	8	–	Up to 15

Figures

Figure 1. Histopathological view of liver needle biopsy shows vivacious dark brown pigments.