

**Brucellosis as trigger for autoimmune hepatitis
In susceptible individual**

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Summary

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Background: Autoimmune hepatitis (AIH) is a rare chronic liver disease of unknown etiology, characterized by hypergammaglobulinemia, characteristic autoantibodies, and a favorable response to immunosuppressive treatment.

Strong circumstantial evidences denoted that there is quite long list of environmental factors such as (food additiives and drugs), viruses and toxins which play an important role in precipitating this disease.

Brucellosis is endemic in Iraq. It may involve any organ in the body. Liver is frequently involved. Doxycycline used for treatment occasionally may lead to hepatotoxicity.

Objective: the aim of the study is To show the relationship between brucellosis , AIH, and hepatotoxicity of doxycycline .

Methods: the study was performed on 2 Iraqi patients with brucellosis, attending the teaching hospital for gastroenterology and liver disease in the period between November 2003 and July 2004. Brucella were studied by Rose Bengal test and confirmed by indirect immuno florescence assay (IIF).

Results: anti-SLA/LP Abs was detected in 2 patients with brucellosis.

Conclusion: brucellosis or doxycycline is a trigger of AIH

Introduction:

Brucellosis can present with various manifestations and may involve any organ in the body. Hepatic pathology comprises noncalcified granulomas, suppurative abscesses, and mononuclear cell infiltration. Liver and spleen enlarge in 15-20% of cases. Elevated liver enzymes and bilirubin levels accompany these pathologies(1).

Doxycycline, used for brucellosis, can cause toxic hepatitis. Doxycycline may lead to microvesicular fatty infiltration as the other members of the tetracycline family. There is only one report about toxic hepatitis caused by doxycycline in human despite various studies done on rats by Böcker *et al.*, showing microvesicular fatty infiltration with 50-100 mg/kg doxycycline(2-5). Hepatocytes are filled with fat droplets that do not displace the nucleus. They occur as a result of beta oxidation of fatty acids. Fatty infiltration is either diffuse or zonal. It is partially correlated with dosage (6). Streptomycin, another drug used for brucellosis, has no known hepatotoxicity.

Autoimmune hepatitis (AIH) is a self-perpetuating hepatocellular inflammation of mysterious aetiology, characterized by the presence of interface hepatitis on histologic examination, hypergammaglobulinaemia, and circulating autoantibodies, which in most cases, respond to immunosuppressive treatment (7,8).

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Several studies indicate that some viruses (HAV, HBV, HCV, CMV, and EBV), some drugs e.g. tienilic acid, dihydralazine and halothane, and toxins were shown to induce hepatitis with autoimmune involvement (9,10).

Patients and Methods:-

Two womans, who was diagnosed with brucellosis by serological and clinical means, received a treatment regimen of doxycycline and streptomycin. They was attending The Teaching Hospital for Gastroenterology and liver disease in a period between November 2003 and July 2004 because of partially improved fatigue and elevated liver enzymes.

Laboratory investigation:

Brucella was detected using Rose Bengal test and confirmed by indirect immuno florescence assay (IIF), significant titer was 1/16.

Anti-SLA/Lp Abs was detected using the Euroline method, which has been supplied by Euro-immune Company, Germany. The kit contains test strips coated with parallel lines of antigens, which have been purified by affinity chromatography.

Result

Two patients with brucellosis were found to be positive for anti-SLA/Lp, those patients fulfilling standard diagnostic criteria for AIH The laboratory finding for the 2 patients were present in table-1

Table 1: Clinical finding for patients with AIH

Lab. finding	Patient No. 1	Patient No. 2
SGOT	65.0	77.0
SGPT	45.0	55.0
Alkaline phosphates	158.0	142.0
TSB	7.7 mg/dl	8.0 mg/dl
ANA,SMA, and anti-LKM 1	Negative	Negative
Viral markers	Negative	Negative
Anti-SLA/LP	Positive	Positive
Histologic features	Interface hepatitis	Interface hepatitis
Rose Bengal test	Positive, titer 1/320	Positive, titer 1/640
IFAT for brucellosis	Positive, titer 1/32	Positive, titer 1/64

Discussion:

Several abroad studies declared that, autoantibodies that characterize autoimmune hepatitis may occur in conjunction with antibodies to hepatitis A, B, and C viruses (11, 12, 13). In this study, for the first time in Iraq, we report 2 cases of AIH followed brucellosis.

In these 2 cases liver involvement due to brucellosis recurrence and toxic hepatitis was suspected at admission.

In addition, microvesicular fatty infiltration, suggesting toxic hepatitis due to tetracycline and doxycycline, was not evident, hence, histopathology did not support toxic hepatitis.

Therefore, we focused on AIH and evaluated immunologic markers of AIH. Interestingly, anti-SLA/LP Abs positivity supported AIH, female gender, negative viral markers, and absence of other causes of chronic liver diseases.

The two cases were diagnosed according to the AIH scoring system probably triggered by doxycycline. However, Clinical and biochemical response to steroid therapy is achieved.

In spite of the limited facilities available, yet it was possible to deeply search for the role of brucellosis in the pathogenesis of AIH, whereas only few reported works have been carried out abroad (14, 15).

It's generally accepted that, Liver involvement in brucellosis is not restricted to granulomatous hepatitis; nonspecific cell infiltration (mononuclear cell and plasmocyte) is evident in most cases. This finding suggests that hepatic involvement of brucellosis may contribute to hepatic injury in our cases.

Whether brucellosis or doxycycline is a trigger of AIH is an important question waiting for an answer.

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