Research Article

Rheumatological manifestations of chronic viral hepatitis

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Date Submitted:24.5.2012

Date Accepted:4.10.2012

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Abstract

Aims: To evaluate and assess the rate of rheumatological manifestations in patients with chronic viral hepatitis.

Patients and Methods: Sixty four patients with chronic viral hepatitis were included in this cross-sectional study. The diagnosis of viral hepatitis is established by clinical & laboratory study.

Full history was taken from all patients with special concentration on rheumatological manifestations and complete clinical examination was done for all of them, blood test including liver function tests, viral serology, viral load, and renal function.

Results: All together, sixty four patients were recruited and studied, fifty (32males and 18 females) of them (78.1%) had shown rheumatological manifestations. Thirty one of patients were reported with HCV infection & 19 patients with HBV infection. The rate of chronic fatigue was reported in 24 patients (48%). Myalgia was presents in 21patients (42%) which was more in patients with HCV. Arthralgia was present in 19 patients (38%). Sicca syndrome was presented in 12 patients (24%). Schirmer's test was positive in 2 patients (4%). Skin rash occur in 6 patients (11.1%). It's nonspecific purpuric rash, Arthritis was reported in 3 patients (6%), all of them with HCV infection. Also there were 16 patients (32%) of all patients on treatment with interferon-alpha or antivirus measure or both.

Conclusions: Chronic viral hepatitis infection patients shows various rheumatological manifestations in more than 75% of cases so it is suggested to investigate patients with unexplained rheumatological manifestations who are at risk for viral hepatitis for these viral infections.

Keywords: Viral Hepatitis, Chronic liver disease, Rheumatological manifestation

INTRODUCTION

Chronic viral hepatitis is caused by hepatitis B virus (HBV) and hepatitis C virus (HCV) in which HBV is a DNA virus while HCV is RNA virus. Extrahepatic findings are common in patients with HBV infection, arthralgia and skin rashes occur in 25% of cases.[1]

HBV infection may cause an immune–complex mediated arthritis during the pre-icteric prodromal period, usually sudden and often severe, joints involvement is usually symmetric with a simultaneous involvement of several joints at onset, but arthritis may be migratory or additive. The joints of the hands and knees are most often affected but wrists, ankles, elbows, shoulders and other large joints may be involved as well.[2] Fusiform swellings may

be seen in the small joints of the hands, morning stiffness is common, arthritis and urticaria may precede jaundice by days to weeks and may persist for several weeks after jaundice, however, arthritis and rash usually subside soon after onset of clinical jaundice,[3] while arthritis is usually limited to the pre-icteric prodrome. Those patients who develop chronic active hepatitis or chronic HBV viraemia may have recurrent arthralgia or arthritis. The pathogenesis of HBV arthritis is thought to be mediated by immune-complex deposition in the synovium. Joint fluid examination is not diagnostic; management of arthritis is supportive with NSAID.[4]

Before the isolation of HCV the possibility that HBV might play a predominant role in causing essential mixed cryoglo-bulinaemia was supported by some authors who reported the existence of HBs Ag and/or HBs Ab in a substantial number of patients with mixed cryoglobulinaemia.[5, 6] Subsequent studies fail to confirm these finding[7, 8] and showed that the prevalence of HBV related markers in a large series of cryoglobulinaemic patients was not significantly different from the prevalence observed in blood donors[9] and has been shown to be associated more frequently with chronic HCV infection.[10]

Polyarteritis nodosa with systemic vasculitis can occur with either acute or chronic, but frequently with chronic HBV viraemia. This syndrome typically present with abdominal pain resulting from arteritis of the medium – sized arteries with ischaemia of the intestine or gall bladder. Other manifestations of HBV – associated vasculitis include neuropathy (mononeuritis), cutaneous vasculitis, arthritis and Raynauds phenomenon.[4]

HBV infection can cause also cutaneous vasculitis which is typically seen on the legs and buttocks. Skin biopsy reveals the presence of immune-complex and complement in blood vessel walls. Other features of chronic viral hepatitis are post hepatitis syndrome which is characterized by prolonged malaise, elevated serum amino-transferases levels.[2] Sicca syndrome (dryness of month and eye) in chronic viral hepatitis dry mouth is more common than dry eyes. Polyneuropathy (usually related to polyneuritis) and Guillain – Barre syndrome, a severe serum-sickness like syndrome with immune-complex deposition occurs more rarely and can result in angioneuritic edema.[10]

Acute HCV infection is usually followed by chronic hepatitis in up to 80% of infected patients. Sometime infections are anicteric and asymptomatic and prior to cirrhosis liver enzymes are usually minimally elevated to normal, while some cases may present because of more symptomatic illness in which significant enzyme elevation, occur, however, fulminant HCV hepatitis is rare.[11]

HCV has been recognized increasingly as a cause of significant extrahepatic disease which will develop in approximately 1-2% of HCV infected patients. Reported extrahepatic manifestations include essential mixed cryoglobulinemia, leukocytoclastic vasculitis, focal lymphocytic sialadenitis, rheumatoid arthritis like disease and others.[12]

Fatigue is presents in 53% of patients with HCV. Fatigue is severe, impairing activities, occur more with female gender, age over 50 year, cirrhosis, depression and purpura, also it was associated with arthralgia, myalgia, paresthesia, sicca syndrome and pruritus. It is not associated with viral load or genotype, alcohol consumption, abnormal thyroid function and type and level of cryolgobulinaemia. So fatigue is the most frequent extrahepatic manifestations in patient with HCV infection. The prevalence of fibromyalgia as defined by the association of fatigue with arthralgia or myalgia is 19%.[13]

Cutaneous manifestations is non specific and did not suggest vasculitis.[14]

Arthropathy is one of the common extrahepatic manifestations of HCV infection. It is displayed by up to 20% of infected patients. The arthritis associated with HCV infection involves multiple small joints, usually symmetrically with morning stiffness and positive rheumatoid factor. This is very similar to rheumatoid arthritis. In fact those patients often meet the diagnostic criteria for rheumatoid arthritis. Thus patients with rheumatoid arthritis like joint disease and HCV infection should be carefully diagnosed. In contrast to classical rheumatoid arthritis, HCV associated arthropathy is nondeforming or non-bone erosive and is free from subcutaneous nodules. Furthermore only half of the patients show elevated ESR. These features would be useful for differentiation of two categories of disease. Although treatment of HCV-associated arthropathy has not been established, antivirus treatment with interferon-α would be effective. This would lead to substantial clinical improvement of the arthropathy even without a complete biochemical or virological response.[15, 16] Additionally low dose corticosteroids, NSAID and disease modifying drugs such as sulfasalazine can be

used. Hepatotoxic drugs such as methotrexate or immunosuppressant would not be recommended at least as a primary choice.[17]

HCV infection is strongly implicated in the pathogenesis of essential mixed cryoglobulinaemia (MC) presumably by immune-complex deposition. Anti HCV antibody are found in serum of 50-90% of patients with essential MC. Furthermore, MC is found in approximately half of patients infected with HCV. The existence of circulating cryoglobulin is not always associated with symptomatology. The term cryoglobulinaemic syndrome is used when patient with cryoglobulinaemia have clinical manifestations which develop in only 25-30% of HCV infected patients. The clinical symptoms are particularly the triad of purpura, arthralgia and myalgia or symptoms ranging from fatigue, arthraliga or arthritis to purpura, Raynauds phenomenon, vasculitis, peripheral neuropathy and glomerular nephritis.[18, 19]

The main clinical hallmark of cryoglobulinaemic syndrome is palpable purpura usually confined to the lower extremities.[18] Furthermore, 50-80% of patients complain of arthralgia and the joints most frequently involved are proximal interphalangeal joints, metacarpophalangeal joints, knees and ankles. MC leads to systemic vasculitis because of inflammation of the vessel walls induced by deposition of IgM – IgG complex and subsequent complement activation or cause an ischaemic phenomenon due to a direct obstruction of vessels.[20] Peripheral neuropathy ranges from 7-60% and usually involves sensory nerve, with pareshtesias, pain or loss of sensitivity, renal involvement as proteinuria which progress to renal failure without treatment.[4]

Most of the so-called essential cryoglobulinaemia are associated with HCV infection.

Classification of crysoglobulinaemia on immunochemical properties.

Type I are composed of single monoclonal immunoglobulin while types II and III are composed of immune-complexes formed by monoclonal (in type II) or polyclonal (in type III) IgM with rheumatoid factor and the corresponding antigen (usually polyclonal IgG). For this reason these last two types are referred to as mixed cryoglobulinaemia which is considered as indolent B-cells lympho-proliferation disorder with a potential switching over to frank malignancy. HCV is a lymphotropic virus and a persistent stimulation of the immune system by the virus seems to be responsible for the appearance of the cryoglobuline in HCV infected individual.[21]

The first report of cryoglobulinaemia was in patient with Sjogren's syndrome, the prevalence of cryoglobulinaemia in primary Sjogren's syndrome range from 6-61%. Cryoglobulins are a sensitive index for systemic extraglandular involvement in Sjogren's syndrome.[22, 23] Furthermore, non organ specific auto-antibodies are frequently expressed in patients with HCV infection. Rheumatoid factor positive sera were found in 52% of patients, antinuclear antibodies with titer less than 1:40 found in 20%, antismooth muscle antibodies with titer less than 1:40 found in 20%, antidouble stranded DNA antibodies were negative, C_3 and C_4 components of complements are low.[24, 25]

Aim of study

This study was conducted to evaluate and assess the rate of rheumatological manifestations in patients with chronic viral hepatitis infection, and to identify possible relation between hepatic and extrahepatic rheumatologic features to plan for diagnosis and treatment of those patients.

PATIENTS AND METHODS

A cross-sectional study of sixty four patients with chronic viral hepatitis was studied. Fifty of them were reported to have had rheumatological manifestations. They were randomly recruited from the Gastroenterological Center and Baghdad Teaching Hospital. They all gave signed consent for inclusion in this study. In all cases the diagnosis of chronic viral hepatitis was established by the following criteria.

1 - Liver function test (S. Alanine aminotransferse and S. Aspartate aminotransferase S. alkaline phosphatase prothrombin time and others).

2- Positive serological markers of viral hepatitis infection such as HBsAg, HBsAb, HBcAb and HCV antibody by enzyme immunoassay kit.

3- Viral load by Branched Chaii RNA study.

4- Liver biopsy.

5- The absence of any other causes of chronic liver diseases.

6- Patients with uraemia are excluded.

7- Patients on interferon and antiviral drugs are studied and labeled as on treatment.

Various rheumatological manifestations were assessed and investigated.

Schirmer's test which defines abnormal tear production as 5mm or less of wetting of a standard rectangular strip of filler paper in 5 minutes.

RESULTS

Sixty four patients with chronic viral hepatitis were recruited. Fifty of them (78.1%) had rheumatological manifestations, whom they were studied. The sex distribution characteristics of the patients with chronic viral hepatitis are shown in table (1) and fig (1).

Table 1. and Figure 1. Distribution of studied sample according to gender and viral hepatitis.

Gender	Patients No.		
	HBV	HCV	Total
Male	14	18	32 (64%)
Female	5	13	18 (36%)

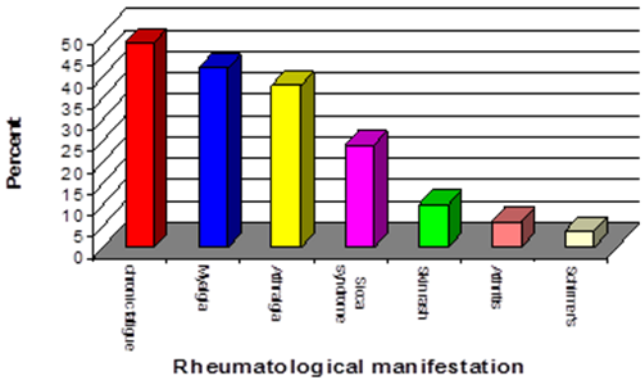
The rheumatological manifestations are shown in table (2) and fig (2). The most common rheumatological symptoms are chronic fatigue which was present in 24 patients (48%). It was (54.1%) in patients with HBV infection and (45.9%) in patients with HCV infection it is more common in female gender 66% and it is associated with myalgia and arthralgia, fatigue is represented by easy fatigability even by minimal exertion as walking.

Myalgia occurs in 21 patients (42%) it is more in patients with HCV infection (62%) while its (38%) in patients with HBV infection. Myalgia is not severe and involves mainly the girdle muscles and it is not tender myalgia.

Arthralgia was reported in 19 patients (38%). It is (52.6%) in patients with HBV infection and (47.3%) in patients with HCV infection. Arthralgia involves the large joints especially of the lower limbs (knees) and it's not associated with morning stiffness.

Table 2. and Figure 2. shows the rheumatological manifestations of viral hepatitis.

	Total No.	HBV No. and (%)	HCV No. and (%)
Chronic fatigue	24	13(54.1)	11(45.9)
Myalgia	21	8(38)	13(62)
Arthralgia	19	10(52.6)	9(47.4)
Sicca syndrome	12	3(25)	9(75)
Skin rash	6	2(33.3)	4(66.7)
Arthritis	3	0(0)	3(100)
Schirmers test	2	1(50)	1(50)



Sicca syndrome is present in 12 patients (24%). Nine patients (75%) occur with HCV infection while, it occurs in 3 patients (25%) with HBV infections. Sicca syndrome presents clinically by dry eyes and dry mouth in these 12 patients with chronic viral hepatitis (75%) complain of dry mouth only.

Shirmer's test was positive in only 2 patients (4%) half of them in patients with HBV infection and half of them in patients with HCV infection.

Skin rash presents in 6 patients (12%) it is more in those with HCV infection (4 patients (66.7%)) and in 2 patients (33.3%) with HBV infection, skin rash is macular , presents as redness, not itchy fade on pressure and it is not suggestive of vasculitis.

Arthritis present in 3 patients (6%) all of them with HCV infection, arthritis is involving knees only in all patients, it is with mild effusion, not associated with morning stiffness and there is no deformities of joints and no erosion on X-ray and all of the patients with arthritis are male patients.

Sixteen patients (32%) the received treatment which was combination pegylated IF-α and Ribavrine which is the

standard treatment for HCV infection while IF-α and other antivirus treatment for HBV infection.

DISCUSSION

It has been reported that viral hepatitis was implicated in various rheumatological manifestations.[10, 13, 14] Although rheumatic manifestation can be the presenting complaint. Viral hepatitis seemed to trigger autoimmune responses that might be manifested as extrahepatic manifestations.[26]

In this study, the patients showed various rheumatological symptoms, but there was no specific rheumatological disease that fulfilled ACR diagnostic criteria. The absence of specific rheumatological disease may be explained by several factors. First, the number in this study may have been too small to detect the disorders. Second, the duration of hepatitis infection may be of importance for the development of rheumatic features and patients with longer periods of infection may be more likely to develop symptoms [27] but unfortunately it is difficult to establish onset of hepatitis infection, thus the disease duration generally cannot be defined.

In this study chronic fatigue was 48% and is close to the study of T. Poynard et al.[14] Arthralgia and skin rash were present in 38% and 11% and it differ from the study of Hollinger F.B. et al.[3] which shows 25% for both of this symptoms. These differences may be due partially for inclusion of patients with acute and chronic viral hepatitis in Hollinger study compared to patients with chronic viral hepatitis in this study.

Arthritis which involve large joints of lower limbs especially knees which is also reported in other studies and it is 6% in this study while it is up to 20% in Zuckerman E. et al.[15] because this study discuss acute and chronic viral hepatitis infection.

Sicca syndrome was reported in 12 patients (24%) mainly manifested as dry month and its comparable to Ramos-Casals M. et al. study.[23]

Conclusion

Rheumatic manifestations are common in patients with viral hepatitis but these symptoms and signs do not fulfill criteria for diagnosis of any rheumatic or connective tissue disease.

Recommendations

1. From this study it's recommended that chronic viral hepatitis infection could be included as one of the causes of unexplained rheumatological manifestations so it should be kept in mind especially in those at risk for viral hepatitis, and the treatment of rheumatological symptoms is different in patients with liver diseases.
2. Larger study is indicated to explain better the association of viral hepatitis and rheumatological manifestation, in the possible association between viral infection, autoimmunity and inflammation might yield valuable information on the pathological mechanisms of arthritic disorders.

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