The Presence of the Tender Points in Female Patients with Hepatitis C Virus Infection: Is it Related with the Clinical Findings of Fibromyalgia?: A Preliminary Report

HEPATİT C VİRÜS ENFEKSİYONU OLAN KADIN HASTALARDA, HASSAS NOKTALARIN VARLIĞI: FİBROMİYALJİNİN KLİNİK BULGULARI İLE İLİŞKİLİ MİDİR?: ÖN ÇALIŞMA

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Abstract

Objective: Fibromyalgia (FM) may be related with hepatitis C virus (HCV) infection. Tender points are also the hallmark of the FM and may be precipitated by infection. We planned a study to determine if HCV infection is associated with the development of tender points, which are the diagnostic hallmark of FM.

Material and Methods: A total of 40 female subjects diagnosed as having HCV infection were assessed by physical examinations (palpation of 18 tender points) and laboratory tests. In addition, visual analogue scale (VAS) for pain assessment was performed for all subjects. Patients were compared with age and sex matched FM patients [diagnosed by American College of Rheumatology (ACR) criteria] and healthy controls.

Results: There was a statistically significant difference between patients with HCV infection and FM patients regarding tender points ($p< 0.01$). Patients with HCV infection had lower counts of tender points than FM patients had. Tender points were also lower in controls. In addition, VAS score was significantly different in all groups ($p< 0.01$). FM patients had the highest VAS score.

Conclusions: Patients with HCV infection did not meet FM criteria in terms of tender points. Tender points, which are diagnostic for FM, are not a common finding in HCV infection. As a result, we may suggest that HCV infection may not be related with FM and its etiopathogenesis.

Key Words: Fibromyalgia, hepatitis C

Özet

Amaç: Fibromiyalji (FM), hepatit C virüsü (HCV) enfeksiyonu ile ilişkili olabilir. Hassas noktalar FM'nin belirleyici bulgusu olup, enfeksiyon ile tetiklenebilir. FM'nin tanısal belirleyicisi olan hassas nokta gelişiminin HCV enfeksiyonu ile ilişkili olup olmadığını belirlemek için, çalışmayı planladık.

Gereç ve Yöntemler: HCV enfeksiyon tanısı almış, 40 kadın hasta, fizik muayene (18 hassas nokta palpasyonu ile) ve laboratuvar testleri ile değerlendirildi. İlave olarak, görsel analog skalası, tüm hastalarda ağrıyı değerlendirmek için uygulandı. Hastalar, aynı yaş ve cinsiyette olan FM'li hastalar (Amerikan Romatoloji Birliği kriterlerine göre) ve sağlıklı kontroller ile karşılaştırıldı.

Bulgular: HCV enfeksiyonu olan hastalar ve FM'li hastalar arasında, hassas nokta sayısı açısından istatistiksel olarak anlamlı farklılık vardı ($p< 0.01$). HCV enfeksiyonu olan hastalarda, hassas nokta sayısı FM'li hastalara göre daha düşüktü. Kontrol grubunda, hassas nokta sayısı en düşük sayıdaydı. İlave olarak, VAS skoru, tüm gruplarda, anlamlı olarak farklıydı ($p< 0.01$). FM'li hastalarda, VAS skoru, diğer gruplara göre, en yüksek seviyedeydi.

Sonuç: Hassas nokta sayısı göz önüne alındığında, HCV enfeksiyonu olan hastalar, FM tanı kriterlerini taşımamaktaydı. FM için teşhis kriteri olan hassas noktalar, HCV enfeksiyonunda, sık rastlanan bulgu değildir. Sonuç olarak, HCV enfeksiyonunun FM ve onun etiyopatogenezi ile ilişkili olmadığı düşünülebilir.

Anahtar Kelimeler: Fibromiyalji, kronik hepatit C virüs enfeksiyonu

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FM is a common disorder of diffuse aching and pain or stiffness of muscles and joints.[1] It is characterized by multiple tender points (TPs) at specific musculoskeletal sites with widespread pain.[1] It affects mainly women.

Fatigue, morning stiffness, and sleep disturbances are the symptoms of FM.[1] It accounts for 15% of rheumatology clinic visits, up to 5% of primary care appointments and has a prevalence of 2% in the general population.[1]

Although the pathophysiological mechanism is still unknown, reports suggest that it may be multifactorial.[2] Some rheumatological diseases, physical trauma, and psychological disorders may trigger FM.[2]

The recently accepted criteria for the diagnosis of FM are the 1990 ACR criteria and they include the presence of widespread pain related with TPs at specific anatomical sites.[3]

Recently, FM was associated with a number of chronic infections such as Lyme disease, parvovirus infection, human immunodeficiency virus (HIV) infection, and coxsackie virus infection.[4-6] A few studies reported the coexistence of HCV infection with FM.[7] Musculoskeletal manifestations including arthralgia, arthritis, myalgia, vasculitis and essential mixed cryoglobulinemia were recognized as the manifestations of HCV infection.[7]

The aim of this study was to investigate the presence of clinical findings of FM such as TPs and pain severity (VAS) in female patients with HCV infection by comparing them with female FM patients and healthy controls.

Material and Methods

Forty consecutive anti-HCV positive patients were enrolled in the study. All patients were newly diagnosed and none received interferon therapy at enrollment. All patients and control subjects were female. Chronic HCV infection was diagnosed histopathologically according to established criteria[8] was well as by the presence of anti-HCV antibodies and HCV-RNA in sera and/or by elevated serum aspartat aminotransferase (AST) and alanin aminotransferase (ALT) activities observed over a period longer than six months. Liver tissues obtained from chronic hepatitis patients were scored for hepatic activity index (0 to 18) and fibrotic index (0 to 4) using classification of chronic viral hepatitis described by Knodell et al.[8]

The liver samples from CVHC patients were subsequently divided into three groups as follows: Minimal liver disease (MLD), Knodell score 0 to 3; moderate liver disease (MoLD), Knodell score 4-12; and severe liver disease (SLD), Knodell score over 12.

Third generation ELISA kits (Abbot AXSYM System Texas, USA) were used to determine anti-HCV. Qualitative HCV RNA in serum was tested according to the Amplicor HCV protocol (Roche Diagnostic Systems, F. Hoffmann-La Roche Ltd, Basel, Switzerland).

Two control groups were used: 40 healthy controls and 40 consecutive FM patients (age and sex matched). The FM patients were newly diagnosed. Patients with systemic diseases, inflammatory or rheumatic diseases were excluded. Healthy controls and FM patients were randomly recruited without any evidence of HCV infection or any liver enzyme abnormalities.

The FM patients were diagnosed according to the criteria of ACR: Widespread pain in combination with tenderness at 11 or more of the 18 specific TP sites.[3]

Forty age and sex matched healthy subjects comprised the control group.

All participants gave written consent after being informed about the study in detail.

The patients used the VAS to evaluate their severity of pain. The items were scored on a scale of 0-10 points with 10 denoting the worst possible condition.

In all subjects, a count of 18 TPs at 9 symmetrical sites was performed by thumb palpation. The amount of manual pressures applied over a TP was 4 kg/cm^2.

Definite tenderness at any of the TPs was considered to be present if some involuntary verbal or facial expression of pain occurred or withdrawal was observed.

Statistical analysis;

SPSS 9.05 was used for statistical analysis. Data were expressed as mean ± 1SD. One-way analysis of variance (ANOVA) was used to com-

pare the groups. p value< 0.05 was considered significant. Pearson correlation test was used for some correlations.

Results

There was no statistically significant difference between patients with HCV infection, FM and controls regarding age. (44.3 ± 3.6, 43.4 ± 2.5, 44.2 ± 2.7 respectively, p= 0.487). There was no statistically significant difference in body mass index (BMI) between patients and controls (26.6 ± 3.6, 26.3 ± 2.6, 27.3 ± 4.7 respectively). (Table 1)

The mean AST and ALT levels were 66.2 ± 70.2 and 51.8 ± 53.4 in HCV patients.

The mean duration of symptoms (pain, myalgia, fatigue) were 4.2 ± 4.0 years for FM and 6.1 ± 6.4 years for HCV patients and the difference was insignificant (p= 0.387) (Table 1).

The mean number of TPs was 14.5 ± 0 for FM patients, 4.9 ± 4.9 for HCV patients and 3.3 ± 4.7 for healthy controls and the difference was significant (p= 0.01) (Table 1).

The mean VAS score was 6.05 ± 2.2 cm for FM patients, 4.0 ± 2.1 cm for HCV patients and 4.5 ± 2.3 cm for healthy controls and the difference was significant (p= 0.00). (Table 1).

Discussion

This study demonstrated that HCV patients did not meet FM criteria. FM patients had more TPs than patients with HCV infection and the mean VAS score was higher in FM patients than in HCV positives.

Table 1. Characteristics of patients with HCV, FM and controls.

	HCV group (n= 40)	FM group (n= 40)	Controls (n= 40)
Age (year)	44.3 ± 3.6	43.4 ± 2.5	44.2 ± 2.7
BMI (Kg/m^2)	26.6 ± 3.6	26.3 ± 2.6	27.3 ± 4.7
Duration of symptoms (year)	6.1 ± 6.4	4.2 ± 4.0	–
Tender points (Kg)	4.9 ± 4.9	14.5 ± 0	3.3 ± 4.7
VAS score (cm)	4.0 ± 2.1	6.05 ± 2.2	4.5 ± 2.3

Various rheumatic disorders were associated with HCV infection.[7] Reports suggest that circulating cytokines may produce many of the extra hepatic manifestations of chronic HCV infection including myalgia, in the absence of cryoglobulins, immune complexes or complement consumption.[9,10] Wallace et al demonstrated elevated serum levels of IL-1R and IL-8 and elevated concentrations of IL-6 in the supernatants of in vitro activated blood mononuclear cells derived from patients with FM. Thus, contribution of cytokine production may play a central role in HCV infection-mediated myalgia.[11,12]

Moder and Lindor reported musculoskeletal complaints in 69% of 42 HCV patients, most of which were myalgias and arthralgias.[10] Garcia et al reported that more than 50% of 56 patients with chronic hepatitis C had rheumatic manifestations including myalgias (16%) and FM (10%).[13] Buskila et al diagnosed FM in 14 (16%) out of 90 patients with HCV, whereas none in the healthy control group had FM.[14]

Although tender points are the hallmark of FM, there are scant data in the literature concerning the relationship between TPs and HCV infection.[15]

In the present study, all patients had mild pain evaluated by VAS score and TPs. In addition, no patients had history of arthralgia, sicca syndrome, and cryoglobulinemia in this study. However, no patients with HCV met the FM criteria of the ACR.

Previous studies suggest TPs to be the most powerful discriminator between patients with FM and healthy subjects.[16,17] Indeed, some authors suggest that it may be more useful to study TPs and their distribution rather than FM.[16] In epidemiologic studies, TPs are markers of and correlate directly with fatigue, pain and depression.[16] Studies in both general and clinical populations consistently observed that tender point counts and frequency of FM increased with age and female sex.[1] In our study, the study population was female with older patients with HCV infection at premenopausal period, which may interfere with FM. The

prevalence of FM is high in adult women. Genetic factors, peripheral mechanisms, central mechanisms, nueroendocrine or immunologic abnormalities, physical trauma, and psychological distress may play a role in the etiology of FM.[1]

In our study, despite low counts of TPs in HCV patients, generalized pain at admission was similar to the pain in FM patients.

Rivera et al determined the prevalence of HCV infection in 112 patients with FM.[18] Furthermore, they looked for evidence of FM in 58 patients diagnosed with chronic hepatitis C due to HCV.[18] Thirty-one patients (53%) had diffuse musculoskeletal pain while six (10%) fulfilled FM diagnostic criteria. They also divided HCV patients into two groups according to the count of tender points (group 1: Less than seven TPs and group 2: Seven or more TPs). They found no significant differences between groups regarding immunological alterations.[18] Similarly, in the present study, all patients with HCV had no evidence of immunologic findings (RF, ANA).

Although authors suggested that FM like symptoms were more common among chronic HCV patients, the main limitation of these studies was patient selection in endemic regions where coincidental disease was more likely to be observed.[19]

HCV infection can mimic FM and reports had a relatively small number of patients and inadequate number of controls or lacked a control group.[19]

Narvaez et al also reported that it seemed unlikely that HCV infection played a pathogenic role in FM. They claimed that HCV infection might coexist with FM simply by chance alone. Thus, to show convincingly that FM is linked with HCV, studies that include control populations matched for age, sex, race and other demographic variables are required.

In conclusion, we could not find any FM criteria in HCV patients; however the presence of TPs despite low counts, together with diffuse pain should be kept in mind for investigating the underlying reason such as hepatitis C by excluding other systemic, viral and bacterial disease. However, the relationship between HCV and FM should be investigated in further studies with large series.

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