Relationship Between Epstein Barr Virus Infection and Primary Fibromyalgia

EBSTEIN BARR VIRÜS ENFEKSİYONU İLE PRİMER FİBROMYALJİ ARASINDAKİ İLİŞKİ

Ali BİÇER*, Candan ÖZTÜRK**, Günşah ŞAHİN*, Hayal GÜLER*, Canan ERDOĞAN*

* University of Mersin, School of Medicine, Department of Physical Medicine and Rehabilitation,
** University of Mersin, School of Medicine, Department of Microbiology, Mersin, TURKEY

Summary

Objective: The aim of this study was to investigate the serologic evidence of epstein-barr virus infection in patients diagnosed as having primary fibromyalgia.

Material and Methods: A total of 163 subjects; 91 patients diagnosed as primary fibromyalgia according to the 1990 American College of Rheumatology criteria and 72 controls were studied serologically (ELİSA). Visual analog scale (VAS) was used to assess pain.

Results: The mean age of patients was 38.2±7.5 years and the mean age of controls was 37.7±5.5 years. The mean VAS score for the patients and the controls was 6.05±2.2 cm and 4.5±2.3 cm respectively ($p<0.05$). Of the patients; 12 had anti-epstein-barr virus IgM positivity. None of the subjects in the control group had anti-epstein-barr virus IgM positivity ($p>0.05$).

Conclusion: Although the relationship between fibromyalgia and epstein-barr virus is still controversial , the presence of epstein-barr virus infection should be kept in mind in the etiopathogenesis of primary fibromyalgia.

Key Words: Epstein-barr virus, Fatigue, Fibromyalgia

T Klin J PM & R 2002, 2:112-115

Özet

Amaç: Bu çalışmanın amacı, primer fibromiyalji tanısı olan hastalarda epstein-barr virus enfksiyonunun serolojik olarak varlığını araştırmaktı.

Materyal ve Metod: 1990 American College of Rheumatology kriterlerine göre primer fibromiyalji tanısı alan 91 hasta ve 72 kontrol olmak üzere toplam 163 olguda serolojik olarak (ELİZA) çalışılmıştır. Ağrının değerlendirilmesinde görsel analog skala kullanılmıştır.

Bulgular: Hastaların yaş ortalaması 38.2±7.5, kontrollerin yaş ortalaması ise 37.7±5.5 idi. Hasta ve kontrollerin görsel analog skala ortalaması sırasıyla 6.05±2.2 cm ve 4.5±2.3 cm idi ($p<0.05$). Hastaların 12'sinde anti-epstein-barr virus IgM pozitifliği vardı. Kontrol grubundaki hiçbir hastada anti-epstein-barr virus pozitifliği yoktu ($p>0.05$).

Sonuç: Primer fibromiyalji ile epstein-barr virus arasındaki ilişki halen tartışmalı olmasına rağmen primer fibromiyalji sendromunun etyopatogenezinde epstein-barr virüs enfeksiyonu akla gelmelidir.

Anahtar Kelimeler: Epstein-barr virus, Primer Fibromiyalji, Yorgunluk

T Klin FTR 2002, 2:112-115

Fibromyalgia (FM) is one of the most common rheumatologic disorder characterized by chronic widespread pain stiffness, fatigue and non-restorative sleep, accompanied by multiple tender points on physical examination. The underlying pathogenesis and the cause of this syndrome is unknown and the symptom complex of diffuse body pain, sleep disturbance and fatigue may lead to misdiagnosis (1). The development of generally accepted diagnostic criteria according to the American College of Rheumatology (ACR) based on clinical findings has made the diagnosis easier (2).

Much recent interest has focused on the sleep physiology, infection disorders, neurohormonal, psychological, immunological factors as FM syndrome has been described in association with many conditions (3). Various strengths of association have been reported with viral infections including coxsackievirus, parvovirus, humon immunodeficiency virus (HIV) and Epstein-Barr virus (EBV) in patients with FM (4-7).

Epstein-Barr virus is ubiquitous in humans with most individuals being infected by early adulthood, usually asymptomatic but sometimes it results in infectious mononucleosis (8). The clini-

cal presentation of primary FM is similar in some respects to EBV infection and share certain common features especially fatigue, myalgias and arthralgias which may mimic fibromyalgia (7).

For this reason, we aimed to investigate the possible relationship between primary fibromyalgia and the presence of serological evidence of EBV infection.

Materials and Methods

Ninety-one female consecutive patients diagnosed as having primary FM and 72 age and sex matched patients diagnosed as non-specific (non-articular) pain syndromes except FM who served as control group were enrolled in the study. The patients were recruited from the Physical Medicine and Rehabilitation out-patient clinic during the period from January 2000 to February 20001.

The control group was also recruited from patients with non specific pain syndromes (chronic lumbar strain, mechanic low back pain and non specific back pain) who consulted to the outpatient clinic. There was no any important clinical finding in their physical examination except pain.

Primary FM syndrome was diagnosed according to the 1990 ACR criteria. Patients with secondary FM, any systemic diseases, history of trauma, or under any medical treatment were excluded.

Tender points were evaluated by manual palpation (18 tender and four control points). Palpation was performed with the thumb or fore finger applying pressure approximately equal to a force of four kg.

Visual analog scale (VAS) was used to assess the pain. Pain at the last 24 hours was evaluated by VAS score. VAS consist of a 10 cm horizontal line with the two endpoints labeled no pain, and worst pain. The patient is required to place a mark on the 10 cm line at a point which corresponds to the level pain intensity she feels. The distance in centimeters from the low end of the VAS to the patient's mark is used as a numerical index of the severity of pain. The last pain at 24 hours was assessed by VAS score.

Laboratory and virologic evaluation: Routine biochemical tests, complete blood cell count, erythrocyte sedimentation rate (ESR), muscle enzyme levels, thyroid function tests, serum rheumatoid factor (RF), anti-nuclear antibody (ANA) and blood, urine and throat cultures were performed for all subjects. From each patient, a single serum specimen was obtained. Titers of IgM and IgG antibodies to the viral capsid antigen (VCA) of EBV (VCA-IgM and VCA-IgG, Zeus, U.S.A., product series:919201M) were determined by enzyme-linked immunosorbent assay (ELİSA).

All data were analyzed using SPSS for windows (9.01) computer software package. A level of $p<0.05$ considered statistically significant for all tests. The relationship between groups were calculated by independence t-test and chi-square test. All values are expressed as means ± SD unless otherwise noted.

Results

The mean ages and standard deviations of the patient group and the control group were 38.2±7.5 years and 37.7±5.5 years recpectively. The mean VAS score was 6.05±2.2 cm for patients and 4.5±2.3 cm for controls (Table 1).

In laboratory evaluation, routine biochemical tests, complete blood cell count, ESR, RF,ANA, muscle enzyme levels, thyroid function tests, were in normal limits in both groups. Blood, urine and throat cultures revealed no growth in both groups. Results of roentgenograms of the cervical and lumbar spine were unremarkable. On X-ray , there was no any evidence of cervical rib, increased lordosis of cervical and lumbar spine or any osteophytes at cervical and lumbar spine in both groups.

Table 1. Characteristics of the patients and controls

	Patients N=91	Controls N=72	P value
Age	38.2±7.5	37.7±5.5	0.90
Visual Analog Scale(cm)±SD	6.05±2.2	4.5±2.3	0.65
Anti EBV-VCA IgM	12	0	∗0.001
Anti EBV-VCA IgG	13	4	0.07

Pulmonary radiograph was also normal in both groups.

Among the sera of patients studied, 79 had no anti EBV-VCA-IgM positivity (86.8%) while 12 (13.2%) had anti EBV-VCA-IgM positivity. None of the subjects in the control group had anti EBV-VCA-IgM positivity. The difference between two groups was statistically significant ($p=0.001$, $p<0.05$) (Table 1).

In the patient group, 78 had no anti EBV-VCA-IgG positivity (85.7%) and 13 had anti EBV-VCA-IgG positivity (14.3%) (Table 1). In the control group, 68 had no anti EBV-VCA-IgG positivity (94.4%) while only four had (5.6%). The difference between two groups was not statistically significant ($p=0.077$, $p>0.05$).

Discussion

Fibromyalgia syndrome is a chronic, painful musculoskeletal disorder of unknown etiology; prevalence studies have shown that 2% of the population have this painful condition. The overwhelming majority are women (9). In the present study, the mean age of patients was in accordance with in the ACR 1990 criteria study (49%) and all our patients were female.

Various factors including physical, environmental emotional stress have been reported to aggravate the symptoms of FM syndrome. Potentially important are the reports by many FM patients that their symptoms began suddenly, during or after a "flu-like" episode and in a retrospective study 55% of 50 patients with PFM attributed their symptoms to a "flu-like" illness (5). Nash et al reported a case of coxackie virus infection mimicking FM (4). Lawrence et al have presented three cases which were seropositive for acute human parvovirus B19 infection in patients with PFM suggesting a close temporal relationship between these disorders (5). PFM syndrome in patients with human immunodeficiency virus has also been reported (6). However , there is no clear evidence that infection agents are directly responsible for the symptoms of PFM.

Chronic form of EBV infection syndrome has gained increasing recognition among the physicians (3). Many features of this syndrome are similar to primary FM. Myalgias, fatigue, arthralgias, recurrent headaches and chronic sleep disorder have been reported with either fibromyalgia and chronic fatigue syndrome or chronic EBV infection (10). Thus, on clinical grounds alone, there appears to be a considerable overlap between the two syndromes and this raises the question of whether the same etiologic agent might be involved. However, Buchwald et al. have found no significantly high levels of EBV titers when compared with those found in control subjects. They also stated that there was no evidence that reactivation of latent EBV infection was associated with PFM, despite hints of a possible viral etiology (7). Fye et al have also found no increased titers of anti-VCA for EBV in patients with fibrositis (11). In the present study, different from controls, we found increased titers of anti-VCA IgM antibodies in patients with PFM.

Diagnosis of recent infection by EBV may be confirmed by detecting the presence of anti-VCA IgM antibodies. Elevated levels of virus specific IgM antibodies may persist for months with IgG antibodies developing several weeks after infection (8). In the present study, recent EBV infection was documented by the presence of anti-VCA IgM antibodies in the blood of 12 subjects (12/163, 7.4%) together with anti-VCA IgG antibodies of 17 subjects (17/163, 10.4%). We found a greater prevalence of positive titers of anti-VCA antibodies indicating a recent infection was found in patients than controls.

Several infectious agents were investigated in the etiology of primary FM. Due to lack of clear evidence of a certain infectious agent and the fact that EBV infection and FM share somehow certain clinical features led us to carry out this prospective study. Data obtained from the present study shows that relationship of viral agents and FM may be occur or coexist. The possibility of EBV infection in the etiology of FM should not be entirely excluded despite a f ew number of reports on this subject. We suggest that the syndrome may be activated by an infectious agents in susceptible population and more careful investigation should be performed after excluding other diseases.

REFERENCES

1. Fitzcharles MA. The overdiagnosis of fibromyalgia syndrome. Am J Med 1997; 103:44-50.
2. Wolfe F, Smyte HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg D et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Arthritis Rheum 1990;33: 160-72.
3. Simms RW. Fibromyalgia Syndrome: Current concepts in pathopysiology, clinical features, and management. Am J Med 1996; 9 (4):315.328.
4. Nash P, Chard M, Hazleman B. Chronic coxsackie B infection mimicking primary fibromyalgia. J Rheumatol 1989; 16: 1506-08.
5. Lawrence J, Leventhal LJ, Naides SJ, Freundlich B. Fibromyalgia and parvovirus infection. Arthritis Rheum 1991;34:1319-24.
6. Simms RW, Zerbini CA, Ferrante N, Anthony J, Felson DT, Craven DE. Fibromyalgia syndrome in patients infected with human immunodeficiency virus 1992;92:368-74.
7. Buchwald D, Goldenberg DL, Sullivan JL, Komaroff AL. The chronic active epstein-barr virus infection syndrome and primary fibromyalgia. Arthritis Rheum 1987;30 (10):1132-36.
8. Kimura HK, Hoshino Y, Kanegane H, Tsuge I, Okamura T, Kawa K. Clinical and virologic characteristics of chronic active epstein-barr virus infection. Blood 2001;98:280-6.
9. Wolfe F, Ross K, Anderson J, Russell IJ, Herbert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38:19-28.
10. Buchwald D, Ashley RL, Pearlman T, Kith P, Komaroff A. Viral serologies in patients with chronic fatigue and chronic fatigue syndrome. J Med Virology 1996 (50):25-30.
11. Fye KH, Whiting-O'Keefe QE, Lennette E, Jessop C. Absence of abnormal epstein-barr virus serologic findings in patients with fibrositis. Arthritis Rheum 1988; 31(11):1455-56.

Geliş Tarihi: 27.03.2002

Yazışma Adresi: Dr.Ali BİÇER
Mersin Üniversitesi Tıp Fakültesi
Fiziksel Tıp ve Rehabilitasyon AD
Zeytinlibahçe Caddesi, 33079, MERSİN
alibicer@mersin.edu.tr