Behçet disease: clinical spectrum and association with hepatitis B and C viruses

S. Farajzadeh,[1] M.R. Shakibi,[2] S. Darvish Moghaddam[3] and Z. Rahnama[1]

داء بهجت: الطيف السريري، وارتباطه بفيروسَيْ التهاب الكبد «بي» و «سي»

سعيدة فرج زاده، محمد رضا شكيبي، صديف درويش مقدم، زهرا رهنما

الخلاصة: تم في إطار هذه الدراسة بحث حالة 48 مريضاً بداء بهجت (التهاب أوعية العين والفم) لتحديد الطيف السريري للمرض. كما تمت مقارنةُ إيجابية المصل لدى المرضى المصابين بعدوى فيروسَيْ التهاب الكبد بي B وسي C مع مجموعة مرجعية من الأصحَّاء، لتحديد وجود ترابُط من عدمه. وتمثَّلَتْ الموجودات البدنية الرئيسية في ما يلي: وجود الداء القلاعي aphthosis الفموي بنسبة 93.8٪، والداء القلاعي التناسلي بنسبة 77.1٪، ومظاهر عينية بنسبة 64.6٪. ولم يوجد أي مريض إيجابي المصل لأضداد فيروس التهاب الكبد سي، ولكن لوحظ وجود 3 مرضى إيجابيي المصل (أي بنسبة 3.1٪) بين المجموعة الشاهدة. ولوحظ وجود مريض واحد (أي بنسبة 2.1٪) إيجابي للمستضد السطحي لفيروس التهاب الكبد بي، ووجود مريضين في المجموعة الشاهدة (أي بنسبة 2.1٪) إيجابيَّيْن للأضداد اللُّبيَّة لفيروس التهاب الكبد بي. ولم تكن الفروق ذات أهمية إحصائية. ومن ثم لا يوجد ما يدعو إلى التوصية بإجراء التحرِّي الفيروسي للالتهاب الكبدي بي و سي بين المصابين بداء بهجت في الوقت الحاضر.

ABSTRACT We studied 48 patients with Behçet disease to determine the clinical spectrum of the disease. We also compared the seropositivity of patients for hepatitis B (HBV) and C (HCV) infection with a healthy control group to determine whether there is an association. The major physical findings were oral aphthosis 93.8%, genital aphthosis 77.1% and ocular manifestations 64.6%. No patients were HCV antibody seropositive, but 3 of the control group (3.1%) tested seropositive. One patient (2.1%) and 2 in the control group (2.1%) tested positive for both HBV surface antigen and HBV core antibody. The differences were not statistically significant. There is, therefore, no case for recommending viral screening for HBV and HCV in Behçet disease patients at present.

Maladie de Behçet : spectre clinique et association avec les virus des hépatites B et C

RÉSUMÉ Nous avons étudié 48 patients atteints de la maladie de Behçet pour déterminer le spectre clinique de la maladie. Nous avons également comparé la séropositivité des patients pour l'infection par le virus de l'hépatite B (VHB) et C (VHC) par rapport à un groupe témoin de sujets sains afin de déterminer s'il y avait une association. L'aphtose buccale (93,8 %), l'aphtose génitale (77,1 %) et les manifestations oculaires (64,6 %) constituaient les principales constatations physiques. Aucun patient n'était séropositif aux anticorps anti-VHC, mais trois personnes dans le groupe témoin (3,1 %) présentaient une séropositivité. Un patient (2,1 %) et deux personnes dans le groupe témoin (2,1 %) ont été trouvés positifs pour l'antigène de surface du VHB et les anticorps anti-HBc. Les différences n'étaient pas statistiquement significatives. Il n'y a donc pas lieu à l'heure actuelle de recommander le dépistage du VHB et du VHC chez les patients atteints de la maladie de Behçet.

[1]Department of Dermatology; [2]Department of Rheumatology; [3]Department of Gastroenterology, Kerman Medical University, Kerman, Islamic Republic of Iran (Correspondence to S. Farajzadeh: safaderm@yahoo.com).

Received: 10/12/03; accepted: 22/03/04

Introduction

Behçet disease, a multisystem vasculitis, is seen most frequently in Far Eastern and Middle Eastern countries. Prevalence is estimated to be 1.67/10 000 population in the Islamic Republic of Iran [*1*]. Incidence is relatively higher from eastern Asia to the Mediterranean, roughly 1–10 in 10 000 people whereas it is only 1–2 in 1 000 000 people in the United Kingdom and North America [*2*]. The etiopathogenesis of this chronic disease is unknown; it is suspected, however, that some type of infection such as human herpes virus 1 or *Streptococcus* sp. initiates an autoimmune reaction in genetically predisposed individuals [*3*]. Recently, the association between Behçet disease and hepatitis C virus (HCV) [*4–6*] and hepatitis B virus (HBV) [*6,7*] infection has been studied.

Infection with HCV is widespread and it is estimated that chronic infection affects 170 million people worldwide. [*8*]. Numerous extra-hepatic disorders have been recognized in association with HCV infection, among which dermatological diseases are central [*9–11*]. While there is at least 1 report which favours an association between Behçet disease and HCV [*12*], other studies dispute it [*4–6*].

Additionally, HBV remains an important causative agent of chronic liver disease worldwide, and it is estimated that over 35% of Iranians have been exposed to the virus [*13*]. Few studies have, however, been done concerning an association between HBV and Behçet disease [*6–7*]. The high prevalence of HBV infection in the Islamic Republic of Iran might be a possible causative factor in the disease in this part of the world [*13*].

In order to determine the clinical specturum of Behçet disease and whether there is an association between Behçet disease and major agents of viral hepatitis, we carried out a case–control study in Kerman, a southern province in the Islamic Republic of Iran.

Methods

The participants in this case–control study included all patients with Behçet disease who were referred to the rheumatology and dermatology clinics of Kerman Medical University from May 2001 to May 2002. Diagnosis of Behçet disease was based on the 1990 international classification criteria [*14*]. The control group was selected from healthy blood donors attending the Kerman branch of the Iranian blood donation organization after history taking and clinical examination. Informed consent was given by all participants in both the case and the control groups. There were no refusals to take part in the study.

A total of 48 patients with the disease (24 women and 24 men) and 96 healthy volunteer blood donors (43 women and 53 men) participated in the study. The 2 groups were matched for age and sex. People with a history of transfusion of blood and blood products, haemophilia, thalassaemia and HBV vaccination as well as haemodialysis patients and intravenous drug users were excluded from both groups. There were no exclusions from the test group but 3 people were excluded from the control group, 2 with a past history of blood transfusion and 1 who had previous HBV vaccination.

History taking and physical examination (cutaneous examination by a dermatologist and systemic examination by a rheumatologist) were done to detect the cutaneous and other organ involvement. Liver disease was evaluated by the determination of serum levels of alanine aminotransferase, aspar-

tate aminotransferase, alkaline phosphatase and total and fractionated bilirubin.

Serum was tested for HCV antibodies using an enzyme-linked immunosorbent assay (bioMerieux Kits, Marcey L'Etoile, France) and positive cases were confirmed by second-generation recombinant immunoblot assay in both groups. Markers for HBV were evaluated via HBV surface antigen (HBs Ag) and total anti-HBV core antibody (HBc Ab), also detected by the enzyme-linked immunosorbent assay method.

The data were recorded and analysed using *SPSS*, version 10. The Fisher exact test was used for statistical comparison of the 2 groups.

Results

Mean age for the 48 people in the patient group was 30.3 years (standard deviation 11.0) and for the 96 in the control group was 31.4 years (standard deviation 8.7).

The major physical findings in the patients were oral aphthosis (93.8%), genital aphthosis (77.1%), ocular manifestations (64.6%) and skin changes (62.5%). The most frequent ophthalmic involvement was anterior uveitis (39.6%). Other ocular manifestations included posterior uveitis (35.4%) and retinal vasculitis (22.9%). Skin manifestations were varied, the most common being pseudofolliculitis (62.5%). Less-common types included erythema nodosum (39.6%), papules (22.9%), superficial phlebitis (2.1%) and skin aphthosis (12.5%). Of the minor manifestations, the most frequent finding was joint involvement in the form of peripheral arthritis (66.7%). Other minor manifestations included central nervous system (20.8%) and renal (4.2%) involvement. Pulmonary, gastrointestinal and cardiac involvements were not found. Except for 1 person in the patient group who had elevated alanine aminotransferase and aspartate aminotransferase, the function tests were normal for both groups.

Table 1 **Seropositivity for hepatitis C virus (HCV) among patients with Behçet disease and a control group**

Outcome	Patients (*n* = 48)		Controls (*n* = 96)		Total
	No.	%	No.	%	
HCV Ab +	0	–	3	3.1	3
HCV Ab –	48	100	93	96.9	141

The difference between the 2 groups was not significant.
Fisher exact test, P ***= 0.55.***

No anti-HCV antibody was detected in the patient group, but 3 people in the control group were positive for antibodies (Table 1). One patient and 2 people in the control group tested positive for both HBsAg and anti-HBcAb. The results were not statistically significant (Table 2).

Discussion

There have been many reports on the clinical picture of Behçet disease from different

Table 2 **Seropositivity for hepatitis B virus among patients with Behçet disease and a control group**

Outcome	Patients (*n* = 48)		Controls (*n* = 96)		Total
	No.	%	No.	%	
HBs Ag +	1	2.1	2	2.1	3
HBs Ag –	47	97.9	94	97.9	141

The difference between the 2 groups was not significant.
HBs Ag = hepatitis B surface antigen.
Fisher exact test, P ***= 1.0.***

parts of the world [*1,15–17*]. In a large survey by Davatchi et al. on 3443 Iranian patients, the findings were similar to those in our study except for lower incidence of genital aphthosis (–12.9%) and a higher incidence of skin involvement (+11.1%) [*1*]. The differences may be related to sample size, since theirs was a nationwide study, and diagnosis in their study being based on the clinical picture. Comparison between other studies and our survey reveals some differences in the frequency of the physical findings. In Saudi Arabia a higher incidence for genital aphthosis (+9.9%), and a lower incidence of joint manifestations (–29.7%) was found [*15*], and in England a higher incidence of genital aphthosis (+13.9%) and a lower incidence of ocular (–39.6%) and articular (–19.8%) manifestations was found [*16*]. In a study done in Turkey, the incidence of ophthalmic (–17.2%) and joint (–19.8%) manifestations was lower, while the incidence of skin involvement was higher (+15.3%) [*17*]. In another study which was done in Iraq, the incidence of ophthalmic (–16.6%) and joint (–18.7%) manifestations was lower, while the incidence of cutaneous manifestations was higher (+12.5%) [*18*]. These differences may be explained by racial and geographical divergence, method of patient selection and the diagnostic criteria used by different authors.

Because of the unpredictable course of Behçet disease and the difficulty in management, some researchers have tried to discover the etiopathogenesis and consequently a possible therapy for this prolonged systemic disease. In this regard, some studies have been done on the possible association with HBV and HCV [*4–7*]. In our study, we found 3 of the control group positive for HCV antibodies but none of the patient group. We also found 2 people positive for HBV markers in the control group and 1 in the patient group. The differences between the 2 groups were not statistically significant. Indeed, in our study the rate of seropositivity in people with Behçet disease and those in the control group was comparable with the rate for chronic carriers in the Islamic Republic of Iran, 1.7% to 5.0% [*13*].

The results of 3 studies done in Turkey on association with HCV are similar [*4–6*]. Hamuryudan, Sonsuz and Yurdakul studied 13 patients with severe Behçet disease; all were negative for HCV antibodies [*4*]. The study carried out by Ilter et al. on 35 patients with Behçet disease and 35 patients with various cutaneous disorders also showed no positive correlation [*5*]. In another study, Asku et al. compared the frequency of hepatitis A, B, C and E virus serology in 124 patients and a control group of healthy and diseased individuals. No difference was found in the frequency of hepatitis A, C and E seropositivity. For unexplained reasons, however, the frequency of HBV seropositivity was significantly lower among those with Behçet disease [*6*]. One case was reported by Munke, Stockman and Ramadori who presented a Behçet disease patient with associated HCV infection in Germany [*12*]. In a Turkish study, the incidence of HBs Ag, anti-HBc Ab and anti-hepatitis A virus immunoglobulin (IgG, IgM) was no higher in patients with Behçet disease than in the control group [*7*].

In conclusion, the results of our study were in agreement with those of other reports, and no significant difference was found between people with Behçet disease and healthy controls for HCV and HBV infection. Therefore, we do not recommend serologic screening for HCV and HBV in Behçet disease patients until more data are collected. On the other hand, because there may be some unknown epidemiologic and

immunologic factors which could affect the association of the disease with HCV and HBV, we recommend doing more research in different parts of the world, i.e. other than Turkey and the Islamic Republic of Iran.

References

1. Davatchi F et al. Behçet disease. Analysis of 3443 cases. ***APLAR journal of rheumatology***, 1997, 1(1):2–5.
2. Suzuki Kurokawa M, Suzuki N. Behcet's disease. ***Clinical and experimental medicine,*** 2004, 4(1):10–20.
3. Alpsoy E et al. Interferon alfa-2a in the treatment of Behçet's disease: a randomized placebo-controlled and double-blind study. ***Archives of dermatology***, 2002, 138(4):467–71.
4. Hamuryudan V, Sonsuz A, Yurdakul S. More on hepatitis C virus and Behçet's syndrome. ***New England journal of medicine***, 1995, 333(5):322–3.
5. Ilter N et al. Behçet's disease and HCV infection. ***International journal of dermatology***, 2000, 39(5):396–7.
6. Aksu K et al. Prevalences of hepatitis A, B, C and E viruses in Behçet's disease. ***Rheumatology***, 1999, 38(12):1279–81.
7. Gurler A et al. Behçet's hastali-ginda hepatit markerlarinin rolu. In: Tuzun Y, Kotogyan A, Serdaroglu S, eds. ***Ulusal dermatoloji kongeresi serbest bildiriler kitabi***. Istanbul, Teknografik Matbaacilik, AS, 1988:37–42 [in Turkish].
8. Dhumeaux D, Marcellin P, Lerebours E. Treatment of hepatitis C. The 2002 French consensus. ***Gut***, 2003, 52(12): 1784–7.
9. Hadziyannis SJ. Skin diseases associated with hepatitis C virus infection. ***Journal of the European Academy of Dermatology and Venereology***, 1998, 10(1): 12–21.
10. Krengel S et al. Hepatitis C virus-associated dermatosis: a review. ***Hautarzt***, 1999, 50(9):629–36.
11. Gordon SC. Extrahepatic manifestations of hepatitis C. ***Digestive diseases***, 1996. 14(3):157–68.
12. Munke H, Stockmann F, Ramadori G. Possible association between Behçet's syndrome and chronic hepatitis C virus infection. ***New England journal of medicine***, 1995, 332(6):400–1.
13. Merat S et al. Hepatitis B in Iran. ***Archives of Iranian medicine***, 2000, 3(4):192–201.
14. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. ***Lancet***, 1990, 335: 1078–80.
15. Al-Dalaan AN et al. Behçet's disease in Saudi Arabia. ***Journal of rheumatology***, 1994, 21(4):658–61.
16. Chamberlain MA. Behçet's syndrome in 32 patients in Yorkshire. ***Annals of the rheumatic diseases***, 1997, 36(6):491–9.
17. Yurdakul S et al. The prevalence of Behçet's syndrome in a rural area in northern Turkey. ***Journal of rheumatology***, 1988, 15(5):820–2.
18. Al-Rawi ZS et al. Behçet's disease in Iraqi patients. ***Annals of the rheumatic diseases***, 1986, 987–90.