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ABSTRACT

Objective: **To investigate the role of homocysteine metabolism due to *Helicobacter pylori* infection on the development of deep vein thrombosis (DVT) in patients with Behcet's disease (BD).**
Design: **Prospective clinical study.**
Setting: **Teaching hospital.**
Subject: **Fifty-five patients with BD divided into groups, with DVT and without DVT, 19 healthy individuals and 18 patients with coronary artery disease (CAD) were enrolled into the study.**
Interventions: **Plasma homocysteine and Hp seropositivity were determined.**
Results: **There was significant Hp positivity in all groups ($p > 0.05$). Homocysteine levels were not significantly different for each group except patients with CAD ($p > 0.05$).**
Conclusion: **There was no difference for frequency of Hp infection in all groups. We conclude that Hp does not influence DVT seen in BD via homocysteine metabolism, but the methinnin-loading test would be appropriate for enlighting patients whose fasting plasma homocysteine levels are found to be normal.**

INTRODUCTION

The recognition of *Helicobacter Pylori* (Hp) infection as a causative agent of gastritis, peptic ulcer disease is one of the major discoveries in medicine in last two decades (1). Hp has also been associated with a variety of extragastric disease (2,3). Sternby reported the relationship between the vascular pathology and the peptic ulcer disease in 1976 (4). Since Hp was discovered, the relationship between Hp and vascular diseases has become the point of interest. It has been discussed whether Hp is an aetiologic factor or a factor that worsens the course or trigger the diseases of unknown aetiology such as BD (5,6). In the vascular form of the BD, the venous involvement is seen more commonly than the arterial one (7-11).

Mild hyperhomocysteinaemia is an established risk factor for vascular disease including DVT (12-15). Although the exact mechanism is not fully understood, endothelial damage due to leucocytoclastic vasculitis leading to defective prostacyclin generation or defective fibrinolysis has been implied in the pathogenesis of thrombosis in BD (16). Possible role of hyperhomocysteinaemia on the development of DVT in BD has not been clarified yet (17-19). As suggested in a previous study, coagulation abnormality did not contribute to thrombotic complications and hyperhomocysteinaemia may play a role in the hypercoagulability of BD patients (17). Even though there was no other study supporting this suggestion, Sung and Sanderson (20) have proposed that Hp infection predisposes to hyperhomocysteinaemia through nutritional deficiencies of folate, vitamine B6 and B12.

In this study, incidence of Hp infection and the possible association between development of DVT in BD and the Hp infection was investigated to reveal the cause or a potential triggering effect of Hp infection on the development the venous thrombosis in patients with the BD.

MATERIALS AND METHODS

Fifty five patients with BD (25 men, 30 women; mean age 37, 95± 1.25; range 18-61 year old), were enrolled into the study. The diagnosis was based on the decision of an experienced clinician according to the criteria of the International Behçet's Study Group (21). The patients were divided into two groups including with (19 patients) and without (36 cases) DVT. Nineteen healthy volunteers and 18 patients with CAD were also enrolled as a control group.

A senior clinician and radiologist diagnosed the DVT by the colored Doppler ultrasound (Toshiba Eccocee, Japan) in addition to the clinical and the laboratory evaluations. Diagnostic criteria for colour-coded duplex sonography was: visualisation of an intraluminal thrombus in a deep vein; lack of or incomplete compressibility; absence of flow spontaneously and following distal manipulation.

Five millilitres of venous blood was drawn in the morning under standardised conditions. Within 30 minutes, the blood was centrifuged and immediately divided into aliquots. Specific anti-Hp Ig G were measured by "*Helicobacter Pylori* Double Spot Test" (Medisera Diagnostics, Annacis Biolab Ltd., Canada) according to manufacturer's instructions. Sensitivity and specifity for this method were 96% and 95% respectively(22). Plasma homocysteine levels were measured by fluorescence polarisation immunoassay technology (FPIA) (Abbot GmBH Diagnostika Max- Planck-Ring2 D-65205 Wiesbaden Delkenheim, Germany). Normal range of the kit was 5-15μmole/l.

Data are presented as the mean ± SD. Statistical analysis was performed by an IBM computer with the use of Statistical Package of Social Science ver. 9.0 (SPSS ver. 9.0). Differences of frequencies of Hp were tested with the X^2 test or Fisher's exact test. Kruskal- Wallis method was used to determine the differences between the groups. The comparison between the measured homocysteine levels was made by using one- way variance analysis (ANOVA). $p<0.05$ was considered statistically significant.

RESULTS

Helicobacter pylori (Hp) was positive in 15 of the 19 patients (%78.9) with DVT. The mean total homocysteine levels were 11.67±0.88 μmole/L in patients with BD. There was not significant differences for homocysteine levels between patients with and without Hp infection ($p>0.05$) (Table 1). Hp was positive in 27 (75.0%) of the 36 patients with BD and without DVT. It was negative in nine (25.0%) of them. The mean homocysteine levels were 10.97±0.58 μmole/l in this group. Homocysteine levels between patients with and without Hp, who had no DVT, was not also significantly different ($p>0.05$) (Table 1). Hp was positive in 13 (68.4%) of the healthy control group. Hp was 77.8% positive in 18 patients with CAD. There was also no significant differences for homocysteine levels between Hp positive and negative in either healthy controls or patients with CAD ($p>0.05$) (Table 1). There were no significant differences for Hp seroprevalence among all groups ($p>0.05$). On the other hand, mean homocysteine levels in patients with CAD was significantly higher than the others ($p<0.05$).

DISCUSSION

In this study, we have determined that there was no significant difference for Hp seropositivity among groups including BD. Mendall *et al*. (23) have reported the possible association between Hp infection and coronary heart disease. In a meta analysis, Danesh and Peto (24) reported that there was no relationship between the Hp seropositivity and the vascular diseases. Avci *et al*. (25) suggested that Hp seroprevalence between patients with BD and controls did not show significant difference, but the number and the size of oral and genital ulcers decreased and the clinical manifestations regressed with the eradication of Hp. These findings suggest that Hp infection may be one of the triggering factors which induce immunological phenomena in the pathogenesis of BD. On the other hand, in that study, there was no data about DVT. In the present study, we did not determine any significant differences for Hp seroprevalence between DVT positive and negative patients with BD. However, it is difficult to say that Hp does not play a role in the aetiology of DVT in patients with BD because high Hp seroprevalence in Turkey may mask the possible relation.

Several mechanisms have been proposed for how Hp might increase CAD risk (26). Sung and Sanderson (20) hypothesised to prove that Hp gastritis could cause vitamin B deficiency, leading to hyperhomocysetinaemia and thus increased risk of CAD. Wilcken and Wilcken (27) suggested that homocysteine metabolism may contribute to the pathogenesis of some cardiovascular diseases of young adults. There were various reports about association of arterial disease and hyperhomocysteinaemia, but the relation between homocysteine level and development of venous thromboembolism is still in debate (28-31). Although the relationship between hyperhomocysteinaemia and venous thrombosis has been shown by epidemiological data (12,26), the pathophysiology has not been clarified yet. In a prospective study by Ridker *et al*.(32), homocysteine levels were found to be high before the thrombotic event and it was suggested that hyperhomocysteinaemia must be considered as a causal

Table 1

Demographic and clinical characteristics of total groups

	BD with DVT	BD without DVT	Healthy Controls	Controls With CHD
No (n)	19	36	19	18
Female/Male	10/9	20/16	7/12	8/10
Age mean (year)	39.11	37.33	34.16	56.83
H. pylori positivity (%)	15(78.9)	27(75)	13(68.4)	14(77.8)
Mean plasma homocysteine levels(μmol/L)	11.67	10.97	11.43	16.43

(BD = Behçet's disease, DVT = Deep venous thrombosis, CAD = Coronary artery disease, CG = Control group)

factor in venous thrombosis. The results of a previous study suggested homocysteine levels were not elevated in BD when compared with the healthy controls (33). In our study, homocysteine levels were not significantly different among groups except control patients with CAD. On the other hand, homocysteine levels in patients with BD with and without DVT and in healthy control group can not suggest that the homocysteine metabolism is intact, because we measured only fasting plasma homocysteine levels but methionin loading test was not performed.

Finally, although there is no effect of Hp on DVT seen in BD through homocysteine metabolism in our study, it can not suggest that the homocysteine metabolism is intact. The methionin loading test would be appropriate to this subject at least for patients whose fasting plasma homocysteine levels are in normal range. Further studies are needed to clarify the clinical implication of this situation.

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