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THROMBOPHLEBITIS

A Cardinal Symptom of Behçet's Syndrome

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Abstract. Sixteen (44.4 %) of 36 cases of Behçet's syndrome revealed involvement of veins. 13 presented superficial thrombophlebitis, mainly of lower extremities, 3 superficial migrating thrombophlebitis and 3 had involvement of superior or inferior vena caval veins. In 11 patients the fibrinolytic activity was investigated. 5 patients revealed marked elevation of fibrinogen level and 3 had a significant prolongation of euglobulin-lysis time. It is suggested that venous involvement is a cardinal symptom in Behçet's syndrome and that fibrinolytic enhancement therapy may play a part in its control.

The triad of recurrent aphthous stomatitis, uveitis and genital ulceration constitutes the fundamental features of the syndrome described by Behçet (8). Recent publications, however, have stressed the relative frequency of a variety of other symptomatology (2, 11). In 1966, an analysis of our first 11 cases of the disease revealed that after genito-oral ulceration, the venous involvement was most common and occurred more frequently than the ophthalmological manifestations (12). Subsequent cases have further confirmed this observation (13, 14).

The purpose of our present paper is to review the incidence of venous involvement as revealed in 36 cases with Behcet's syndrome observed in our department, to describe briefly their clinical features and to discuss the possible etiological factors.

METHOD

All patients were hospitalized and have since then remained under our observation. The diagnosis of these cases was based upon the presence of at least 2 of the cardinal and 1 of the other symptoms recognized as part of the disease picture. The recurrent nature of symptoms and the hyperreactivity of the skin "pathergy" (17) have also been taken into consideration in establishing the diagnosis. In 11 patients, 5 with and 6 without venous lesions, the fibrinolytic activity was measured by euglobulin-lysis time (3) and in addition fibrinogen and fibrinogen split products were estimated by the tanned red cell inhibition technique of Merskey (18).

RESULTS

There were 30 male and 6 female patients in the range 17 to 54 years. The average age of onset of their disease was 23.4 years. Twenty-three of the 36 have been under our observation from 7 to 20 years. The follow-up period of the remaining 13 does not exceed the 5-year period. Twenty-one patients were born in Israel, 4 in Iraq, 4 in Morocco, 3 in Bulgaria and 1 in each of the following countries: Turkey, Egypt, Congo-Brazaville and Poland.

The various manifestations of their disease in the order of their frequency are shown in Table I.

All patients with involvement of veins were males. Thirteen of the 16 suffered from recurrent superficial thrombophlebitis of the lower extremities, 3 showed migrating thrombophlebitis of the upper and lower extremities. In 1 of the latter the venous lesion preceded the mucocutaneous symptoms by 6 months. In addition to superficial thrombophlebitis 3 patients revealed involvement of the caval veins. The first developed occlusion of the lower third of the inferior caval and of the right iliac veins. In the second there was thrombosis of the superior vena cava and of the right subclavian veins. The third presented at first an occlusion of the lower third of the inferior vena cava and 10 years later he also developed thrombosis of the superior vena caval, the right subclavian and of the right axillary veins.

The results of fibrinolytic activity as revealed in 11 patients thus investigated are given in Table II. The fibrinogen was appreciably elevated in 5 patients, 3 of whom had venous involvement. Two patients with a history of venous lesions, however, had normal fibrinogen levels. The euglobulin lysis time was significantly prolonged in 3 patients, 2 with venous disease. In another 2 cases of venous involvement, the lysis time was at the upper limit of normal. In only 1 patient was the level of fibrinogen degradation products elevated.

Table I. *Manifestations in the Order of their Frequency*

Symptom	No. of cases	%
Aphthous stomatitis	36	100
Ulceration of genitals	34	94.4
Involvement of veins	16	44.4
Ocular symptoms	12	33.3
Erythema nodosum-like lesion	11	30.5
Postular lesions & furunculosis	11	30.5
Joint pathology	10	26
Central nervous system	3	8.3
Orchitis	3	8.3
Gastro-intestinal	3	8.3
Epididymitis, lymphadenopathy, headache and mental disturbances in 2 cases each (5.5 %)		

DISCUSSION

The average reported incidence of venous involvement in cases with Behçet's syndrome is 25% (4, 8, 10, 21). In our series, however, this incidence is higher and more frequent than the ophthalmological manifestations, 44.4% as compared with 33.3%. As early as 1965, Pallis (22) commented that thrombophlebitis is perhaps a more frequent third component of the syndrome than ocular symptoms. In 1966, Mounsey (19) proposed a muco-cutaneous thrombophlebitic form in the spectrum of the disease in order to emphasize the importance of the latter component.

The pathogenesis of this occlusive venous process is still somewhat obscure. Stasis does not appear to be a relevant contributory factor and no abnormality of the hemostatic mechanism has been demonstrated (16). Accordingly there is little to support the concept of hypercoagulable state. It remains likely that changes in the venous endothelium predispose to the local thrombus formation. In support of this concept is the finding of inflammatory changes in the veins as well as in the arteries, as demonstrated histologically (9, 10, 15, 20, 21). Indeed, veins and arteries of all sizes have been reported to have been involved in the disease.

Hyperfibrinogenemia was a not-uncommon finding in our series. However, elevated fibrinogen is a frequent finding in any inflammatory disease. It is therefore not thought to be a contributory factor in the thrombotic diathesis. Of considerable interest is the finding of impaired fibrinolytic activity in 3 out of 11 patients studied, 2 of whom presented with thrombosis. A further 6 patients had an euglobulin-lysis time at the upper limit of normal.

The underlying pathology of Behcet's syndrome is vasculitis. A decreased blood fibrinolytic activity has been reported in patients with cutaneous vasculitis (6, 7). Although venous endothelium is a major source of plasminogen activator production, it is unlikely that the reduced fibrinolytic activity is the result of venous occlusion—on the contrary—recurrent venous occlusion may be enhanced or perhaps induced by decreased fibrinolysis (5).

We may therefore conclude that affliction of veins may be considered as a cardinal symptom in Behcet's syndrome and that fibrinolytic enhancement therapy may play a part in the control of vascular manifestations of this disease.

Table II. *Results of Fibrinolytic Activity*

No.	Age	Venous complications	Fibrinogen (mg/100 ml)[a]	Euglobulin lysis time (hours)[b]	F.D.P. (μg/ml)
1	43	—	258	3 hours	2.12
2	36	—	475	3.30 min	1.06
3	25	—	348	1 hour 50 min	< 10
4	28	Calf vein thrombosis	321	2 hours 10 min	2.12
5	21	—	333	3 hours	—
6	17	—	311	3 hours 10 min	
7	48	—	1 252	7 hours 50 min	2.12
8	22	Saphenous vein thrombosis	377	3 hours 55 min	< 1.06
9	52	Recurrent thrombophlebitis Calf vein thrombosis	977	5 hours 5 min	33.92
10	44	Superior vena cava thrombosis	692	6 hours 10 min	4.24
11	53	Inferior vena cava thrombosis	1 280	4 hours	2.12

[a] Normal range 200–400.
[b] Normal range 3–4 hours.

REFERENCES

1. Behçet, H.: Über rezidivierende aphthoese, durch ein Virus verursachte Geschwüre am Mund, am Auge, und an den Genitalien. Derm Wschr *105:* 1152, 1937.
2. Berlin, C.: Behçet's disease as a multiple symptom complex: report of ten cases. Arch Derm *82:* 73, 1960.
3. Buckell, M.: The effect of citrate on euglobulin methods of estimating fibrinolytic activity. J Clin Invest *2:* 403, 1958.
4. Carr, G. R.: Cellulitis and thrombophlebitis in Behçet's syndrome. Lancet *II:* 358, 1957.
5. Chajek, T. & Fainaru, M.: Behçet's disease with decreased fibrinolysis and superior vena caval occlusion. Br Med J *I:* 782, 1973.
6. Cunliffe, W. J.: An association between cutaneous vasculitis and decreased blood-fibrinolytic activity. Lancet *I:* 1226, 1968.
7. Cunliffe, W. J. & Menon, I. S.: Treatment of Behcet's syndrome with phenformin and ethyloestrenol. Lancet *I:* 1239, 1969.
8. Dowling, G. B.: Behçet's Disease. Proc Roy Soc Med *54:* 101, 1961.
9. Enoch, B. A.: Gangrene in Behçet's syndrome. Br Med J *3:* 54, 1969.
10. France, R., Buchanan, R. M., Wilson, M. W. & Sheldon, M. B.: Relapsing iritis with recurrent ulcers of mouth and genitalia (Behçet's syndrome): review of literature with report of additional case. Medicine (Baltimore) *30:* 335, 1951.
11. Haim, S.: Behçet's syndrome as a generalized systemic disease. Harefuah, *78:* 63, 1970.
12. Haim, S. & Sherf, K.: Behçet's disease: presentation of 11 cases and evaluation of treatment. Isreael J Med Sci *2:* 69, 1966.
13. Haim, S.: Contribution of ocular symptoms in the diagnosis of Behçet's disease: study of 23 cases. Arch Derm *98:* 478, 1968.
14. Haim, S., Barzilai, D. & Hazani, E.: Involvement of veins in Behçet's syndrome. Br J Derm *84:* 238, 1971.
15. Hills, E. A.: Behçet's syndrome with aortic aneurysms. Br Med J *4:* 152, 1967.
16. Kansu, E. Ozer, F. L., Akalin, F., Gules, Y., Sileli, T., Tanman, F., Kaplaman, E. & Muftuogla, E.: Behçet's syndrome with obstruction of the venae cavae. Quart J Med *41:* 151, 1972.
17. Katzenellenbogen, I.: Survey of 22 Cases of Behçet's Disease: The Significance of Specific Skin Hyperreactivity. Read before the XIII Congressus Internationalis Dermatologique (München, 1967), p. 321. Springer-Verlag, Berlin, Heidelberg and New York, 1968.
18. Merskey, C., Kleiner, G. J. & Johnson A. J.: Quantitative estimation of split products of fibrinogen in human serum; relation to diagnosis and treatment. Blood *28:* 1, 1966.
19. Mounsey, JPD: cited ref. 16.
20. Mowat, A. G. & Hothersall, F. E.: Gangrene in Behçet's syndrome. Br Med J *2:* 636, 1969.
21. Nazzaro, P.: Cutaneous Manifestations of Behçet's Disease: Clinical and Histological Findings. Proc. Intern Symposium on Behcet's Disease, p. 15. S. Karger, Rome and Basel, 1966.
22. Pallis, G. A.: In the discussion, clinico-pathological conference: orogenital ulceration with phlebothrombosis (Behçet's syndrome) complicated by osteomyelitis of lumber spine and ruptured aorta. Demonstrated at the Postgraduate Medical School of London. Br Med J *1:* 357, 1965.

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