
Mortality in Behçet's syndrome

H. Yazici, F. Esen

Division of Rheumatology, Cerrahpaşa
Medical Faculty, University of Istanbul,
Istanbul, Turkey.

Hasan Yazici, MD

Fehim Esen, Medical student

Please address correspondence to:

Hasan Yazici MD, Safa sok. 17/7, Kadikoy,
Istanbul, 34710, Turkey.

E-mail: hyazici@attglobal.net

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ABSTRACT

Behçet's syndrome significantly increases mortality especially when seen in the young male, while it is less severe among females and the aged. In many patients, the condition abates with the passage of time. The main cause of mortality is large vessel disease, especially bleeding pulmonary artery aneurysms (PAA), almost exclusively seen among men. Central nervous system disease comes second. Interestingly, not much increased atherosclerosis is seen in Behçet's syndrome when compared to other inflammatory diseases. In controlled studies, there has been no increase in history of increased angina or myocardial infarction. Similarly, atherosclerotic plaque formation is not increased by ultrasound. On the other hand, intermittent claudication can be seen. However, this is not due to arterial involvement but due to venous disease of the lower extremities. Recently there has been a substantial decrease in mortality due to PAA thanks to prompt disease recognition and treatment.

Introduction

It must have been 25 years ago that one of us (HY) had just given his oral presentation at the then Heberden Society (now the British Society for Rheumatology) annual meeting and was proudly standing by his poster describing the age and sex associations within the course of Behçet's syndrome (1). The data included the fate of 62 patients at 5 years. There were no deaths and the obvious conclusion was that BS did not affect mortality. Prof. P.H. Wood, the eminent chief of the Manchester epidemiology unit did not agree. He stood only briefly by the poster and simply said. "Good work, but I do not believe it." Noting an ashen face he continued: "You see, any disease, when followed long enough in enough patients increases mortality." He proved to be right. A subsequent study at 10 years

among 152 patients (2) indeed showed increased mortality, just as Prof. Wood had predicted. A 20-year prospective study from our unit indicated a total of 42 deaths among 387 patients followed for 20 years: 3 in women and 39 in men (3). Although men do have higher mortality rates in general, this observation also reflects the more severe disease among men with this condition. Men have more eye, major vascular, and central nervous system disease than women with Behçet's syndrome. The visual prognosis is distinctly more guarded among males, while the condition with the highest mortality, pulmonary artery aneurysm, is seen almost exclusively among men (4).

Major causes of mortality in Behçet's syndrome

In the 20-year outcome survey we observed that the main cause of mortality in the patients was major vessel involvement (17 of the reported 42 deaths) followed by central nervous system involvement (5 of the reported 42 deaths) (3). The major causes of mortality are tabulated in Table I.

Figure 1 shows the stratification of the standard mortality ratios (estimated from the national actuarial data) from a) male Behçet's syndrome patients when first seen at the clinic, and b) after 7, 14 and 20 years of follow-up. It is clear that at each time-period during

Table I. Causes of mortality in a 20-year outcome survey of a cohort of 387 BS patients (ref. 3).

| Probable cause of death | Number of patients (%) |
|------------------------------------|------------------------|
| Major vessel disease | 17 (41) |
| Central nervous system involvement | 5 (12) |
| Heart disease | 5 (12) |
| Renal disease | 4 (10) |
| Neoplasms | 4 (10) |
| Others | 4 (10) |
| Unknown | 3 (7) |

Competing interests: none declared.

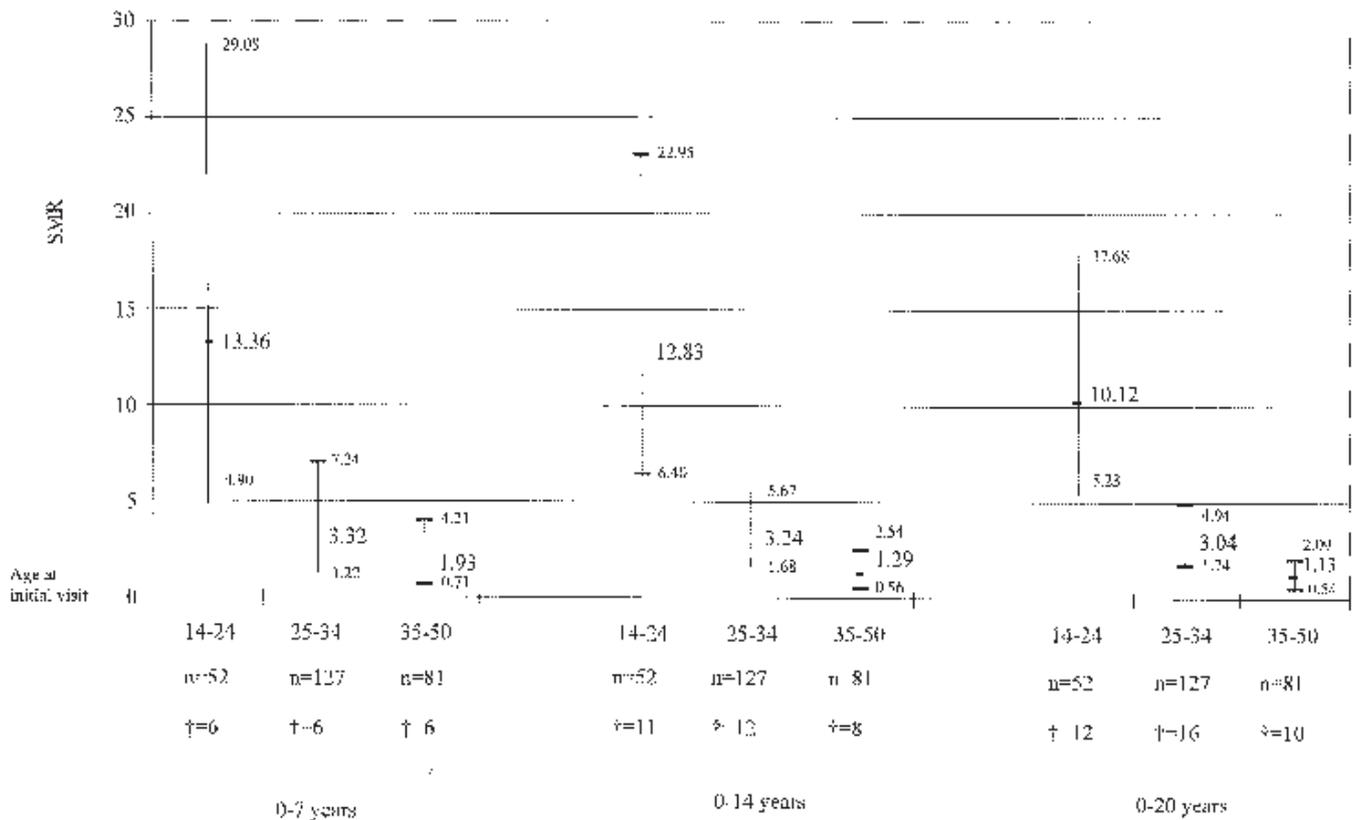


Fig. 1. Standardized mortality ratios (SMRs with 95 % confidence interval) of a cohort of 260* male patients with Behçet's syndrome. †Number of patients who had died. * 2 patients were excluded because they were over the age of 50 at their initial visits (see text). (Figure reproduced from reference no. 3 by permission from the publisher.)

the course of follow up, those patients who first registered at the outpatient clinic at younger ages had a less favorable course. In other words, the earlier the syndrome is acquired, the shorter the expected lifespan.

Another interesting aspect of this mortality survey was that the standardized mortality ratio (SMR) tended to go down with the passage of time, unlike what we see in other chronic diseases like rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), where increasing rates of mortality with the passage of time has been reported (5, 6). Apart from factors related to the primary illness, accelerated atherosclerosis resulting from inflammation is thought to play a part in this (7). The observation that mortality actually decreased with the passage of time in Behçet's syndrome prompted us to conduct a series of clinical studies to analyze this matter. It must also be pointed here that in many patients, especially those with skin-mucosa lesions, the disease activity wanes over

time and many patients do not fulfill any classification criteria at the end of 20 years (3).

Atherosclerosis and coronary artery disease in Behçet's syndrome

We first surveyed the presence of coronary calcification in Behçet's syndrome by electron beam computed tomography "under worse case conditions" in an open, uncontrolled study (8). Only 3 out of 24 patients, all of whom had prolonged periods with widespread and longstanding vascular disease, had atherosclerotic plaques. Many were also smokers and had used corticosteroids for prolonged periods. We reasoned that Behçet's syndrome patients probably did not have much increased atherosclerosis in contrast to a similar group with longstanding SLE or RA who would be expected to have considerably more atherosclerosis (9-11).

We then formally surveyed carotid and femoral atherosclerosis by Doppler ultrasound in 239 Behçet's syndrome patients (167 with severe disease and

72 with only mucocutaneous and/or joint disease), 100 patients with RA, 74 patients with ankylosing spondylitis (AS) and 156 healthy controls (12). The frequency of plaques and the mean intima thickness (IMT) in the carotid and femoral arteries were similar between patients with Behçet's syndrome, AS, and healthy controls and also between Behçet's syndrome patients with mild and severe disease. Only male patients with RA were found to have significantly increased frequency of carotid artery plaques after adjustment for risk factors.

A further search for clinical evidence of coronary and peripheral artery disease was conducted in a controlled study (13). It turned out that Behçet's syndrome patients did not have a history of increased myocardial infarction or angina pectoris when compared to age- and sex-matched healthy control subjects. Behçet's syndrome patients did have more intermittent claudication, but their symptoms resulted from peripheral venous disease, *i.e.*, *venous*

rather than *arterial* claudication. This is described, we believe, for the first time in this condition.

The observations that coronary artery disease and cerebrovascular events are not usual features of Behçet's syndrome support these clinical studies (14, 15), and we can propose several explanations for the apparent absence of increased atherosclerosis in Behçet's syndrome. These may include:

- a) the disease burden is more on the venous side (14, 15);
- b) there is a tendency for the disease to abate with the passage of time (3);
- c) a combination of the two, which we believe is most likely.

Pulmonary artery aneurysms and mortality

The highest mortality rates in Behçet's syndrome are seen in patients with pulmonary artery aneurysms. In our initial review, only 50% of 24 patients with pulmonary artery aneurysms survived 1 year (16). A decade later this survival went up to 62% at 5 years (17). There was basically no difference in the demographic (all male) and the clinical features or in the type of treatment they received. Both groups were treated with corticosteroids and cyclophosphamide in similar doses. A significant difference between the 2 groups, however, involved the times that passed to diagnosis, and therefore the starting times of treatment, between the 2 groups. This was 6.4 ± 7.5 months for the earlier versus 2.6 ± 2.8 months for the later group ($p=0.03$). In earlier years the onset of hemoptysis in a Behçet's syndrome patient would not immediately prompt a search for pulmonary artery aneurysms and its treatment, whereas it does today. The diagnosis is complicated by the fact that 80% of patients with pulmonary artery aneurysms have

peripheral thrombophlebitis, and an inexperienced clinician might interpret this clinical picture erroneously as pulmonary emboli.

Final remarks

Within the last few years we have been able to recognize and treat Behçet's syndrome better. Not only do we have newer drugs (18), but we also know how to use the old ones more effectively (19). On the other hand, we still do not know whether improved therapies can be translated into decreased mortality, especially among young males. We suspect a cohort analysis of the type we reported (3) might not be adequate to document a recent increase in longevity presumably brought about better diagnosis and management. We envisage that the "period analysis" method (20), thus far mainly used in oncology for a similar purpose, might be helpful here to clarify whether we are indeed improving life expectancy in our patients.

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