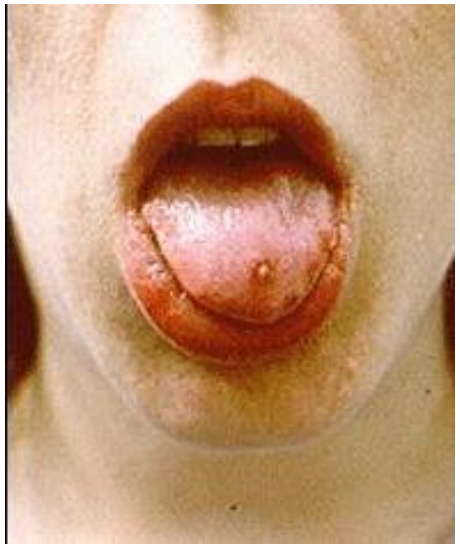
HULUSI BEHÇET

Behçet's Disease

- Multi-system inflammatory vasculitis
- Involves vessels of different types and sizes
- Dominated clinically by recurrent ocular symptoms, oral and genital ulcers and skin lesions



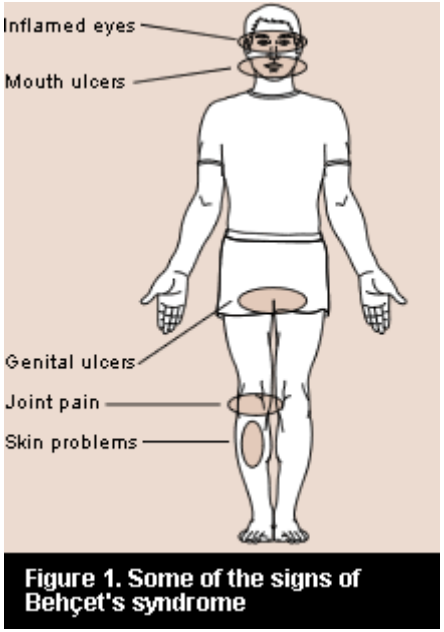
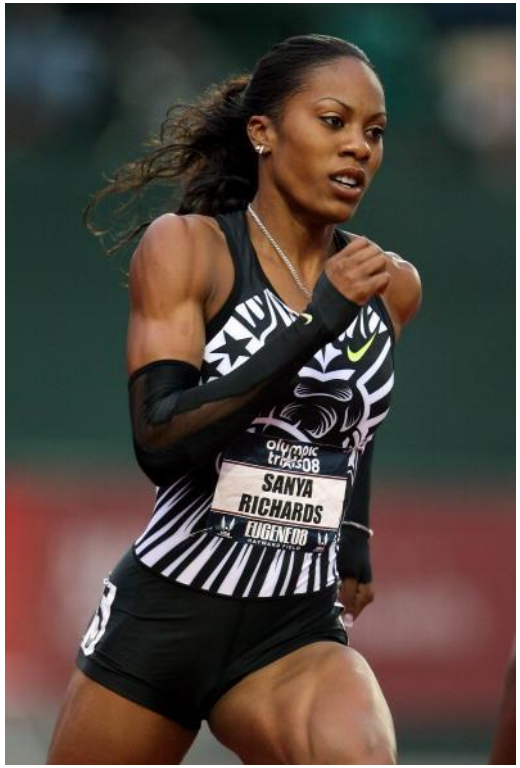


Figure 1. Some of the signs of Behçet's syndrome

Incidence and Prevalence

- **Most common along the ancient Silk Route**
  - **Turkey : 420 /100,000**
  - **Israel: 120/100,000**
  - **Japan: 15/100,000**
  - **North America: 1/300,000**
- **Mean age at onset 25-30 years**
- **M=F**
  - **Disease more severe in males**
  - **In Israel, more common in females - 39.4:60.6 in Jews, 55.9:44.1 in Arabs (Krause et al., 1999,2001)**



Criteria for Diagnosis

Table 1. International Study Group Criteria for Behçet's Disease (1990)[a]

Recurrent oral ulceration	Minor aphthous, major aphthous or herpetiform ulceration observed by physician or patient, which recurred at least 3 times in one 12-month period.
Plus 2 of:	
Recurrent genital ulceration	Aphthous ulceration or scarring, observed by physician or patient.
Eye lesions	Anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination; or retinal vasculitis observed by ophthalmologist.
Skin lesions	Erythema nodosum observed by physician or patient, pseudofolliculitis or papulo-pustular lesions; or acneiform nodules observed by physician in post-adolescent patients not on corticosteroid treatment.
Positive pathergy test	Read by physician at 24-48 hrs, performed with oblique insertion of a 20-gauge or smaller needle under sterile conditions.

[a] All clinical findings are applicable to the diagram of Behçet's disease only in the absence of other clinical explanation.

Pathogenesis

Pathogenesis

1. Infectious/environmental agents
2. Triggering an Autoimmune or an Autoinflammatory reaction
3. In a genetically predisposed individual

1. Infectious agents

- Oral microbial flora has long been implicated
  - Disease usually starts from the oral mucosa (oral apthae first manifestation in 70%)
  - Oral manifestations increased after dental manipulations
- Immune hyperreactivity to streptococcia
- Other Possibly related agents– HSV1, E.coli

2. Autoimmune

- **Unusual Autoimmune disease**
  - No female preponderance
  - No association with other autoimmune diseases or typical HLA antigens (DR3, DR4)
  - No significant high-titre autoantibodies or antigen-specific T-cells present
    - Some have circulating Ab in late stages: α-enolase of endothelia, ASCA
  - Effective treatment by TNF-α-antagonists
    - Anti inflammatory agents
    - contraindicated in AI diseases such as SLE and MS.

Autoinflammatory

- **Unusual Autoinflammatory disease**
  - Autoinflammatory diseases are characterized by absence of pathogens, autoantibodies or antigen specific T cells.
  - primary dysfunction of the **innate immune system**, without evidence of adaptive immune system dysregulation.
- In BD an adaptive response is also sustained
  - high T-cell immune responses to 60/65 kDa heat shock protein.
  - hyperreactivity to streptococcia

Autoimmunity vs autoinflammation in Behcet's disease: do we oversimplify a complex disorder?

H. Direskeneli, Rheumatology 2006;45:1461–1465

- It seems too simplistic to describe Behcet's disease as either autoimmune or autoinflammatory
- An infectious agent > triggers innate-derived inflammation> an adaptive response sustained through 'bacterial persistance' or autoantigen activated antigen-presenting cells.

3. Genetics

- Genetic basis suggested by:
  - Geographic distribution
  - Association HLA haplotypes
  - Some familial aggregation (10% have effected family member)
- Inheritance does not follow Mendelian patterns.

Genetics of Behçet disease inside and outside the MHC

Meguro et al, Ann Rheum Dis 2010;69

- Dual, independent, contribution of two HLA alleles to the pathogenesis

1. **HLA-B51** – Strongest risk factor
   - Transgenic HLA-B51 mice show excessive neutrophilic function, associated with high degree of neutrophilic infiltration in disease lesions
2. **HLA-A26** – Significantly associated with BD in Japanese, Taiwanese and Greek population

Genetics

- **MIC-A** (MHC class I chain-related gene A)
  - Functional gene located between the HLA-B and TNF genes .
  - Mainly expressed in epithelial cells, fibroblasts, endothelial cells, monocytes.
  - Close linkage with HLA-B51 makes independent contribution to the disease hard to define, but it may be useful as a marker


Behcets Disease
BLOWS!