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Behçet's syndrome: clinical presentation and prevalence in Switzerland

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Summary

OBJECTIVE: Behçet's syndrome is a rare systemic autoimmune/autoinflammatory disease affecting mucocutaneous tissues, the skin and the eyes, as well as the joints, the central nervous system, the gastrointestinal tract and blood vessels. Because of the lack of clinical data in Switzerland, the aims of this cohort study were to calculate the disease prevalence and to analyse the disease manifestations and the immune-suppressive medication.

METHODS: Data were extracted from 52 patient charts. Thereafter, all patients were interviewed with a questionnaire and 46 had an additional physical examination and laboratory analyses. For calculation of prevalence, data of the national statistical bureau were used.

RESULTS: A disease prevalence of 4.03/100,000 inhabitants was calculated. The mean delay between first disease manifestation and diagnosis was 8 years. It was 2 years longer for Swiss than for non-Swiss individuals (p = 0.45). The time intervals between diagnosis and occurrence of different organ manifestations ranged from +8 to −11 years. There was no difference in organ involvement between different ethnicities. Colchicine was prescribed for 52% of patients only, whereas tumour necrosis factor (TNF) inhibitors and glucocorticoids were most frequently prescribed (80 and 64%, respectively). In almost half of the patients, TNF blockers could be stopped and replaced by conventional immunosuppressive drugs.

CONCLUSION: The data from this cohort of Behçet's syndrome patients, the largest in Switzerland, documents a prevalence higher than anticipated. The diagnostic delay underlines an urgent need to improve awareness of the disease and allow timely treatment.

Keywords: *Behçet's disease, Behçet's syndrome, prevalence, diagnosis, management, TNF blockers*

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Introduction

Behçet's syndrome is a chronic relapsing systemic autoimmune/autoinflammatory disease with a genetic background and inflammatory features. It was described by the Turkish dermatologist Hulusi Behçet in 1937 [1]. He suggested that the symptom triad of recurrent oral aphthae, genital ulcers and eye inflammation is a distinctive disease. Soon it was recognised that Behçet's syndrome also affects the skin, joints, central nervous system, gastrointestinal tract and blood vessels. The most recent version of the Chapel Hill Classification for vasculitides includes Behçet's syndrome [2]. In contrast to other vasculitides, Behçet's syndrome affects all types and sizes of blood vessels.

In 1990, the International Study Group (ISG) published the first broadly accepted criteria for diagnosing Behçet's syndrome [3]. These were revised in 2006 and in 2010, which resulted in the current "international criteria for Behçet's disease" which require a score of ≥4 points, based on the following: oral aphthae, genital aphthae and eye involvement (each counting two points); skin, vascular, neurological manifestations and a positive Pathergy test (each counting one point) [4].

It is recognised that human leucocyte antigen B51 (HLA-B51) and other genetic markers are associated with Behçet's syndrome [5]. In 1997, the concept of a T-helper cell 1 (Th1) driven disease was introduced [6], and in 2011 the role of Th17 lymphocytes was discussed [7]. In addition to these autoimmune features, many disease characteristics argue for a dysregulated inflammation. This is fuelled by an important role of proinflammatory cytokines [8] and by the beneficial therapeutic effect of tumour necrosis factor (TNF) blocking agents [9].

The prevalence of the disease shows a strong geographic variation. It is highest in the countries between the Mediterranean Sea and East Asia, the so-called silk road (up to 420/100,000) [10], but low in non-Mediterranean and non-Asian countries. A recent meta-analysis showed a prevalence of 3.3/100,000 for European countries [11].

Organ involvement and prognosis vary widely. The most prevalent mucocutaneous lesions are painful, but have a good prognosis and often heal without scarring. In contrast, eye involvement remains one of the leading causes of blindness in south-eastern countries. Vascular involvement, such as pulmonary aneurysm, is a life-threatening manifestation in young males and central nervous system involvement is a characteristic vascular or encephalitic complication in young females [12, 13].

As a result of the low prevalence of Behçet's syndrome, few randomised controlled trials of immunosuppressive drugs have been performed. The current knowledge has

been condensed in the first consensus paper of The European League Against Rheumatism (EULAR) published in 2008 [14]. An update is awaiting publication.

In Switzerland there are no published data regarding prevalence of Behçet's syndrome, its manifestations or its management. Our cohort study addressed these issues.

Methods

Patients

The catchment area of the University Hospital is the canton of Bern and areas of neighbouring cantons adding up to 1.5–2 millions of inhabitants. In an attempt to reach all Behçet patients of our catchment area, we contacted the rheumatologists of the Swiss Society of Rheumatology and the heads of ophthalmology, dermatology, angiology, gastroenterology, neurology and gynaecology of the University Hospital of Bern.

Clinical and serological data were extracted from the patient charts of the outpatient clinic, the day clinic and the rheumatology ward of the University Hospital of Bern, Switzerland. In addition, patients were asked to answer a questionnaire, 5 refused to show up for a further clinical examination. The database was established 8 years ago and is run by the Clinical Trial Unit (CTU) of the University of Bern, Switzerland.

Behçet's syndrome was categorised as "diagnosed" if the patient fulfilled the international criteria for Behçet's syndrome [4]. "Suspicion" of Behçet's syndrome was defined by clinical manifestations characteristic of Behçet's syndrome but do not fulfil the criteria. Before inclusion into the study diagnosis were assessed and confirmed by the supervisors S. Adler or P. Villiger.

Prevalence

For calculation of prevalence, an anonymised list of the patients fulfilling the criteria (including the patients who refused to have their data analysed) was used. Based on the postal code, municipality was identified [15]. The population density of each municipality/canton was extracted from tables of the Bundesamt für Statistik (the Swiss Federal Office of Statistics) [16, 17]. Boundaries of each municipality/canton were retrieved from the Bundesamt für Landestopografie swisstopo [18]. The spatial distribution of patients was visualised on maps: (i) whole of Switzerland, (ii) Bern only, (iii) with population, and (iv) with population density. Additionally, we calculated the prevalence of non-Swiss patients originating from high-prevalence countries.

Regarding extrapolation of the findings of the Canton of Bern to Switzerland, the following facts need to be taken into account. The Canton of Bern lays in the geographic centre of the country, it covers areas of the Jura, the Midland and the Alps, it represents cities and rural areas, and the number of inhabitants represents one seventh of the whole population of Switzerland. On the other hand, the percentage of non-Swiss inhabitants is 40% lower in the Canton of Bern than in the country as a whole.

Statistical Analysis

Data were exported from RedCAP. Data clearance and statistical analysis were performed by Lukas Bütikofer, statistician of the CTU of the University of Bern Switzerland. Continuous and categorical variables are presented as median (lower quartile, upper quartile) or number and percentage of patients. The number of patients for a specific variable refers to the number of non-missing observations. The difference between groups is indicated as a probabilistic index (PrI) for continuous and as a risk difference (RD) for categorical variables. The former refers to the probability that the variable of interest is larger in one group than in the other (50% indicates no difference between the groups).

Ethical approval and patient informed consent

The study was approved by the ethical commission of Bern, Switzerland. The study was performed in accordance with the Declaration of Helsinki. All patients gave written informed consent.

Results

Patient characteristics

Patient characteristics are summarised in table 1. Of 52 patients, 46 (88%) fulfilled current criteria for Behçet's syndrome, whereas 6 (12%) were diagnosed with Behçet's syndrome but did not fulfil criteria. The median age on the day of analysis was 47.8 years (33.7, 56.9). Of the 52 patients, 28 (54%) were male and 31 (61%) were of Swiss origin. The median duration of the disease was 19 years (14.1, 27.7), the median age at symptom onset was 21.4 years (12.7, 35.6). The mean diagnosis delay (time between first symptom and diagnosis) was 8 years; (2.17, 17.00). The diagnostic delay was shorter in non-Swiss patients (median 7 years. 2.00, 17.00) than in patients with Swiss ethnicity (median 9 years; 2.17, 19,00; Prl 43.6%, 95% confidence interval [CI] 26.1–61.1; p = 0.45).

Prevalence in Switzerland

Sixty patients fulfilled the criteria for Behçet's syndrome, 41 in the Canton of Bern and 19 in neighbouring cantons. Based on the geographical distribution of the patients, we calculated a prevalence of 4.03/100,000 inhabitants for the Canton of Bern. Figure 1 displays the number of patients per canton (a) and per community in the Canton of Bern (b).

As displayed in table 2, the inhabitants of Bern represent one seventh of the population of Switzerland. The percentage of foreigners is 37% lower in the Canton of Bern than in the whole country (15.5 and 24.6%, respectively), but

Table 1: Baseline characteristics of the patients.

Variable	n (%) or mean	Number of subjects analysed
Mean age, years	47.8	52
Male sex, n (%)	28 (54)	52
Diagnose confirmed, n (%)	46 (88)	52
Ethnic origin Swiss, n (%)	31 (61)	51
Years since symptom onset	19	49
Age at symptom onset	21.4	49
Years since diagnosis	7.91	52
Age at diagnosis	36.1	52
Years from symptom onset to diagnosis	8	49

the percentage of foreigners of high-risk countries is nearly identical (48.7 and 50.9%, respectively). The prevalence of Behçet's syndrome in non-Swiss individuals originating from high-prevalence countries is 19.54/100,000.

Organ involvement and clinical characteristics

Organ involvement and clinical characteristics are presented in table 3. The most frequent clinical manifestations were oral aphthae (including minor, major and herpetifom aphthae) (n = 48), skin involvement (including pseudo folliculitis, erythema nodosum, acneiform lesions, papulopustular lesions and positive Pathergy test) (n = 41), joint involvement (including arthralgia and arthritis) (n = 40) and genital aphthae (n = 35).

Vascular disorders (including deep vein thrombosis, thrombophlebitis, arterial thrombosis, acute arterial occlusion and aneurysm) were reported by 27 patients. Twentfive persons suffered from eye inflammation (uveitis, retinitis, episkleritis, skleritis and conjunctivitis, glaucoma and cataract). Neurological manifestations such as headache, peripheral neuropathy, thrombosis of the sinus vein, aseptic meningitis, optic neuritis, stroke and transient ischaemic attack, epileptic seizure and other symptoms were reported in 22 cases. Sixteen patients suffered from gastrointestinal symptoms such as abdominal pain, diarrhoea, melaena / blood in stool, perforation/surgery.

Figure 1a: Cantons of Switzerland and their populations per km^2 (grey), with the number of patients with Behçet's syndrome per canton.

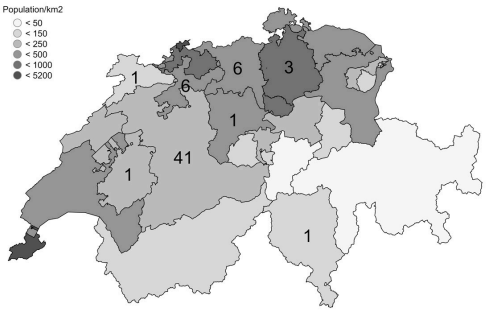
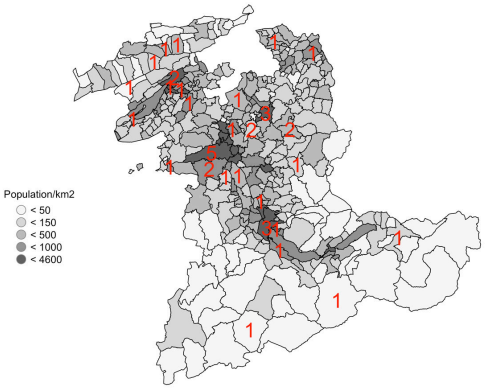


Figure 1b: Communities of the Canton of Bern and their populations per km^2 (grey), with the number of patients with Behçet's syndrome per community in red.



Time interval between disease manifestation and diagnosis

The interval between occurrence of a given organ manifestation and diagnosis of Behçet's syndrome varied between −8 and +11 years (fig. 2). Whereas oral aphthae preceded diagnosis of Behçet's syndrome for up to 8 years, vessel or central nervous affection occurred up to 11 years after diagnosis of Behçet's syndrome.

Laboratory findings

The levels of inflammatory parameters help to quantify disease activity; immunoglobulin levels increase in chron-

Table 3: Organ involvement (total n = 52).

Clinical signs	n	%
Oral aphthae	48	92
Genital aphthae	35	67
Eye	25	48
Skin	41	79
Joint	40	77
Gastrointestinal tract	16	31
Central nervous system	22	42
Blood vessels	27	52
Pathergy phenomenon	26	65*

* tested in 40 patients

Table 2: Prevalence of Behçet's syndrome.

		Canton Bern	Switzerland
Number of residents	Total	1,017,483	8,327,126
	Swiss	860,017	6,278,459
	Foreign	157,466	2,048,667
	High-risk countries*	76,758	1.042,783
Foreign national / residents (%)		15.5	24.6
High-risk countries / foreign nationals (%)		48.7	50.9
Patients with Behçet's syndrome	All	41	–
	High-risk countries*	15	–
Prevalence (/100,000 inhabitants)	All	4.03	–
	High-risk countries*	19.54	–

* Countries along the silk road: Afghanistan, **Albania,** Andorra, Armenia, Azerbaijan, Bahrain, Bangladesh, Bhutan, Bosnia and Herzegovina, Cambodia, China, Croatia, Cyprus, Egypt, **France**, Georgia, Greece, Hungary, India, Indonesia, Iran, **Iraq**, Israel, **Italy**, Japan, Jordan, Kazakhstan, Korea (North), **Kosovo**, Kuwait, Kyrgyzstan, Laos, Lebanon, **Libya**, Macedonia, Malta, Moldova, Monaco, Montenegro, Myanmar, Oman, Pakistan, Palestine, Philippines, Qatar, Romania, San Marino, Saudi -Arabia, Serbia, Singapore, **Spain**, **Sri Lanka**, Syria, Taiwan (Chinese Taipei), Tajikistan, **Tunisia**, **Turkey**, Turkmenistan, United Arab Emirates, Uzbekistan, Vatican City, Vietnam, Yemen. High-risk countries of origin for patients in the cohort are in bold type. Data source: Ständige und nichtständige Wohnbevölkerung nach institutionellen Gliederungen, Geburtsort und Staatsangehörigkeit; 31 December 2015; BFS Reference code: px-x-0102010000_104; Availlable at: https://www.pxweb.bfs.admin.ch/pxweb/de/

ically active disease. The erythrocyte sedimentation rate (ESR) and of C-reactive protein levels (CRP) were normal: median values 8 mm/h (4.00, 12.00) and 3 mg/l (1.00, 4.00), respectively; also the median of the total immunoglobulin G (IgG) concentration in serum was normal at 10.4 g/l (8.6, 11.9). HLA B51 was positive in 18 of 40 analysed cases.

Medication

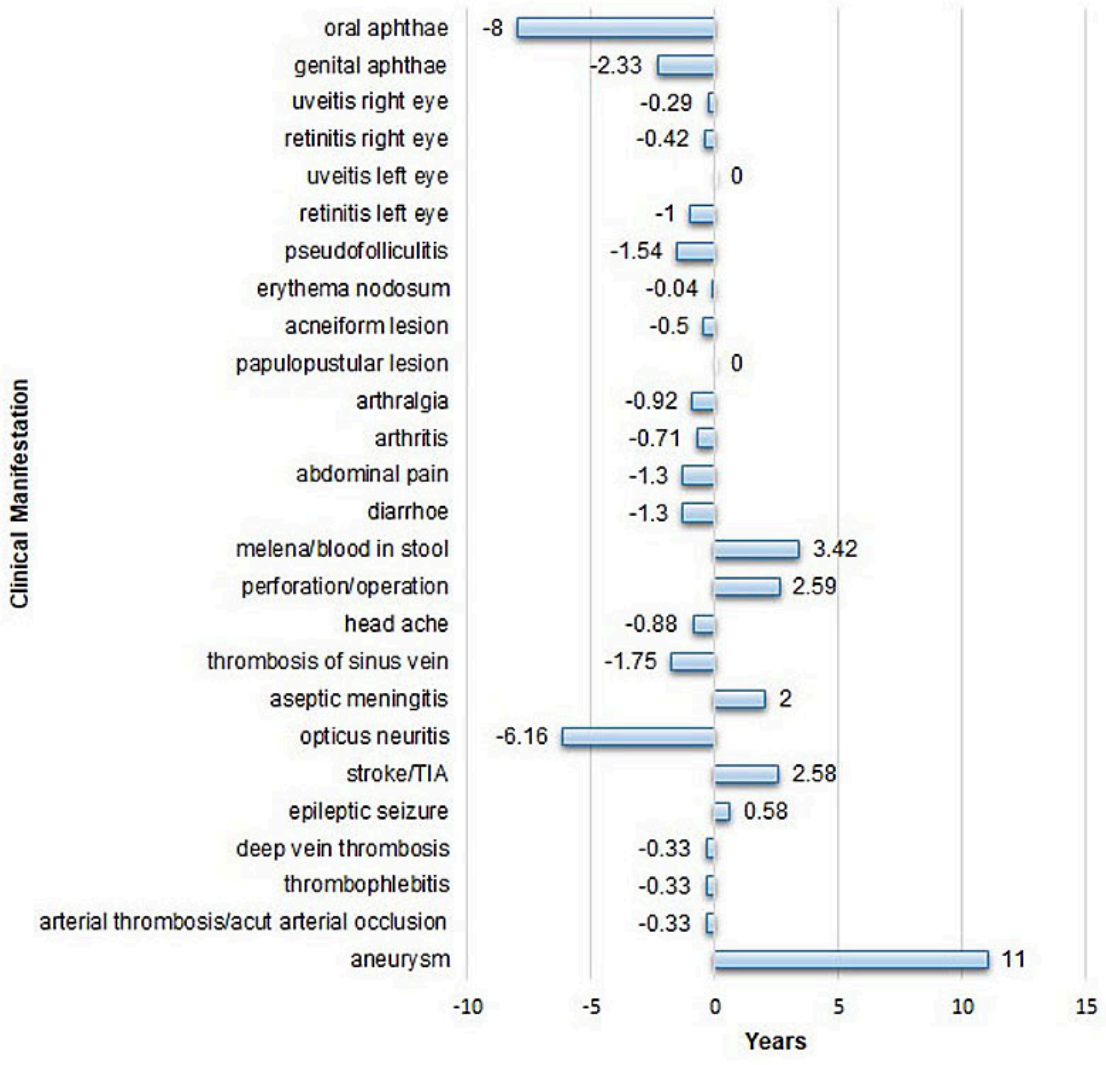
Fifty of the 52 patients had received medication during their disease course (table 4). Systemic glucocorticoids were the most commonly used drugs (80%), followed by TNF inhibitors (64%) and topical glucocorticoids (60%), azathioprine (60%), colchicine (52%) and nonsteroidal antirheumatic drugs (NSARs; 50%). Methotrexate was used by 20 patients (40%), ciclosporin by 12 patients (24%). Dapsone, thalidomide, cyclophosphamide, chlorambucil and sulfasalazine were prescribed for a few patients only. Anticoagulant medications were prescribed for almost half of the cases (48%).

Of the five currently available TNF-inhibitors, infliximab was prescribed for 21 patients, adalimumab for 10, etanercept for 5, golimumab for 3 and certolizumab for 1. TNF inhibitors were switched over time in seven cases (with two switches in one case), and could be stopped in 10 patients. TNF inhibitors were switched because of recurrent thrombophlebitis, heart insufficiency, insufficient efficacy

Table 4: Medication (total n = 50).

Medication	n	%
Topical glucocorticoids	30	60
Systemic glucocorticoids	40	80
Colchicine	26	52
Thalidomide	2	4
Dapsone	1	2
Azathioprine	30	60
Ciclosporin	12	24
Cyclophosphamide	2	4
Methotrexate	20	40
TNF inhibitors	32	64
Chlorambucil	1	2
Sulfasalazine	1	2

Figure 2: Time (in years) between diagnosis (0) and occurrence of disease manifestation. Negative values represent the delay of diagnosis after occurrence of disease manifestation; positive values indicate the occurrence of manifestation after diagnosis. Values represent the median time between diagnosis and the respective disease manifestation.



and in one case because of an allergic reaction to infliximab. The TNF inhibitors were stopped because of lasting remission, pregnancy and insufficient effect, and once because of a complement-induced reaction to infliximab.

Discussion

This is the first study analysing in detail the disease characteristics and the disease management of Behçet syndrome in Switzerland, as well as assessing its prevalence.

Based on the collected data of the Canton of Bern, the prevalence of Behçet's syndrome in Switzerland is 4.03/100,000 inhabitants. This corresponds to the recently published data for Europe [11] and equals the figure published for southern Sweden [19]. Several arguments have to be taken into account when interpreting these figures: As other disciplines involved in diagnosing and treating Behçet's syndrome were asked to share information about patients, it appears unlikely that many cases were missed. As all patients were reassessed at study inclusion, there should not be misdiagnoses. However, based on the long diagnostic delay there will exist not yet diagnosed cases. In summary, the true prevalence will be slightly higher than the calculated 4.03/100,000 inhabitants.

When extrapolating from the Canton of Bern to the whole country, one has to consider that the Canton of Bern lies in the middle of the country and it is large, representing approximately one seventh of the whole population. Remarkably, however, the percentage of non-Swiss inhabitants originating from high-prevalence countries is substantially lower in the Canton of Bern than in the whole country. This indicates that the prevalence of Behçet's syndrome in Switzerland is higher than calculated. Further support for this interpretation is the fact that the calculated prevalence of Behçet's syndrome in individuals from high-prevalence countries is 19.54/100,000.

The patient characteristics of this Swiss cohort resemble the characteristics of the cohorts of Western Europe and the United States. Cohorts in high-prevalence countries such as Turkey and Iran, however, are reported to have lower percentages of vascular and neurological involvement [12, 13]. Interestingly, disease pattern and disease severity are different in Turkish patients living in Turkey compared with Turkish patients living in Germany [20]. Indeed, the difference between German and Turkish patients living in Germany is small, pointing to the importance of environmental factors regarding disease phenotype.

A major issue of our findings is the diagnostic delay of 8 years. Remarkably, the difference in delay between immigrants and Swiss did not reach significance. This contrasts to Germany, where immigrant patients are diagnosed significantly earlier than German patients [20]. This difference was explained by the fact that physicians are aware of Behçet's syndrome in patients from the countries of the Silk Road. It appears likely that the difference in Switzerland did not reach significance because of the lower patient numbers. The delay in diagnosis of disease manifestations that eventually lead to severe damage or even to sudden death is of particular concern. This is all the more unacceptable as, as a result of recent progress regarding pathogenesis and treatment, there is an increase in therapeutic options to control the disease and to prevent severe damage [14, 21, 22].

We observed an interesting difference in diagnostic delay as a function of disease manifestation. Patients with mild mucocutaneous disease may be misdiagnosed until more severe organ involvement occurs. On the other hand, severe vascular disease often follows milder disease manifestations, exemplified by a patient who had 11 years of known disease until arterial aneurysms developed. Thus, earlier recognition of Behçet's syndrome would help to avoid potentially fatal disease complications. This is corroborated by our recent case series of patients with severe vascular Behçet [22]. It illustrates how ignorance of Behçet's syndrome may lead to life-threatening complications. In conclusion, it supports the notion that patients at highest risk of severe organ involvement – young male patients with an established diagnosis – should be informed about the signs of major organ involvement and should be followed up on a regular basis by physicians experienced with this form of vasculitis.

Several findings are of interest regarding treatment. Colchicine, which is largely used in south-eastern and Asian countries [23], was prescribed for half of the patients only. This may be explained by the off-label status of this drug in Switzerland, and also by the fear of patients, physicians and pharmacists of potential (but rare) side effects. Interferon α, a drug mainly proposed for treatment of ocular manifestations [24, 25], is used rarely in Switzerland and in none of the patients of our cohort. On the other hand, TNF blocking agents are prescribed liberally. There was concern that TNF inhibition, in contrast to interferon therapy, would need to be continued for years, leading to substantial costs and risks. It is remarkable that TNF inhibition was stopped in almost 30% of our cases, in several because of lasting remission. A further example is a patient with potentially fatal pulmonary aneurysms [26]. After achieving complete remission, infliximab was stopped and azathioprine was introduced to successfully maintain remission. Another surprise regarding medication is the frequent prescription of methotrexate, which is not listed in the EULAR recommendations at all [14]. As referring physicians are informed at inclusion of patients into the registry about our conclusions and get therapeutic recommendations, and also because many patients are now managed in our out-patient clinic, treatment decisions largely reflect the management by our own senior physicians. Thus, for TNF inhibitors and methotrexate, rheumatologists appear to extrapolate from positive experience in the treatment of autoimmune arthritides.

In summary, the data show a prevalence of Behçet's syndrome of 4.03/100,000 inhabitants in Switzerland. They document an alarming diagnostic delay, which suggests a need for measures to increase awareness of this disease. Furthermore, they report disease management that only partially follows current EULAR guidelines. Taken together, the data suggest that establishing a national registry for Behçet's syndrome might help to improve diagnosis and management and to address unmet needs of patients.

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Potential competing interests
The authors declare no conflict of interest relevant to this article.

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