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ORIGINAL ARTICLE

Differential clinical presentation of Adamantiades–Behçet's disease in non-endemic and endemic areas: retrospective data from a Middle-European cohort study

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Abstract

Objectives: To assess demographical and clinical data in a Middle-European cohort of patients with Adamantiades–Behçet's disease (ABD), together with the use of medication in adherence to international guidelines.

Methods: In a retrospective cohort study, in- and outpatients of an Austrian secondary and tertiary university hospital center were analyzed independent from the medical discipline involved. After ethics approval, screening for ABD-patients in the clinical information system resulted in 1821 documents from 1997 to 2016. Patients fulfilling the International Criteria for Behçet's Disease were included, and ABD symptoms and signs together with medical interventions for immunosuppression, anticoagulation and pain management were identified by individual chart reviews and evaluated for conformity with international recommendations.

Results: A total of 76 ABD patients were identified with 39.1% Austrian and 37.0% Turkish origin. Genital aphthae and skin manifestations were more frequent, neurological, gastrointestinal and vascular manifestations less frequent in ABD patients of Turkish origin living in Austria compared to those living in Turkey (each $P < 0.05$). The male-to-female ratio averaged 0.86 (0.39 in patients with Austrian and 1.43 with Turkish backgrounds), and was 3.3 in patients with venous manifestations. Out of 174 medical interventions, 55.2% fully matched the European League Against Rheumatism recommendations of 2008, and 93.7% were considered at least as equal to the recommendations. Indications for tumor necrosis factor inhibition were in line with the 2007 Sfikakis recommendations.

Conclusions: In this Middle-European ABD cohort clinical presentations between patients of Austrian and Turkish origin do not strongly vary, whereas Turkish patients from the non-endemic Innsbruck cohort present differently compared to patients living in Turkey. The role of such cohort analyses will increase, from the epidemiological as well as the management perspective.

Key words: Behçet's disease, clinical aspects, drug treatment, epidemiology, guideline, vasculitides.

INTRODUCTION

Adamantiades–Behçet's disease (ABD) is an immune-mediated systemic vasculitic disease with autoinflammatory features,[1] possibly involving small, medium

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and large arteries and veins[2] and as such is classified as variable vessel vasculitis according to the revised Chapel Hill Consensus Conference Nomenclature of Vasculitides.[3] Middle-Europe is a non-endemic region for ABD, which may therefore present differently with research needed into a potentially less severe form of ABD.[4] So far clinical data are available for Germany,[5] northern and southern Italy,[6,7] but not for patients living in Austria, between the northern European and the Mediterranean region.

Because of multi-organ involvement, limited evidence from prospective clinical trials and therefore lack of authority-approved drug indications, treatment decisions may be difficult. At present, two international guidelines are available for general ABD management by the European League Against Rheumatism (EULAR)[8] and for the use of tumor necrosis factor (TNF)-blocking agents by an international task force.[9] Unfortunately, drug approvals by authorities for ABD and/or ABD organ involvements are rare, with only a few immunosuppressive drugs listed by the European Medicines Agency and the Food and Drug Administration.[10,11]

The objective of this study was to assess demographical and clinical data together with the use of medication in ABD patients in an interdisciplinary Middle-European secondary and tertiary care setting. Further, we assessed the conformity of treatment approaches with international guidelines in this retrospective cohort.

METHODS

Type of study

This is a retrospective cohort study.

Setting

The study involved in- and outpatients of an Austrian secondary and tertiary university hospital center, independent from the medical discipline involved.

Ethics considerations

This study complies with the Declaration of Helsinki. The study was approved by the local ethics committee of the Medical University of Innsbruck (AN2014-0322, 343/4.11 and 344/4.2).

Identification of ABD patients

Patients were identified using the clinical information system of the local hospital, which has been available since 1997 and was screened for 'Behçet' and a similar word with a frequent spelling mistake, 'Bechet'. As an interdisciplinary study, the search included all clinical, laboratory and imaging reports, independent from the discipline involved and the treating physicians. All 1821 documents from the hospital data search were then screened for patients with ABD diagnosis according to the International Criteria for Behçet's Disease (ICBD).[12] Additional ABD patients were recruited during ongoing clinical routine work and added to the summary data sheet.

Assessment of clinical manifestations and signs

Each chart was reviewed in detail for clinical, laboratory and imaging results. In case of doubtful diagnosis, diagnoses were verified according to reported findings, and patients were excluded for further analysis if not fulfilling ABD diagnosis according to the ICBD criteria.[12] Findings were then detailed for female and male patients as well as patients from Austrian and Turkish origin. The latter details were compared to the ICBD dataset,[12] a German[5] and a Turkish[13] ABD cohort.

Assessment of therapeutic approaches and conformity with guidelines

Medical interventions were also identified by individual chart reviews, according to their indication of immunosuppression, anticoagulation or pain management. In a second step, all interventions were evaluated for conformity with the TNF-α inhibiting therapeutic recommendations from 2007[9] and the EULAR recommendations for ABD management from 2008.[8]

Statistics

Descriptive analyses were performed using mean percentages. Fisher's exact test was used to test for significance between groups. SPSS (IBM SPSS Statistics for Windows, Version 20.0., IBM Corp., Armonk, NY, USA) was used for statistical analyses.

RESULTS

Between 1997 and 2016, a total of 76 patients were identified as diagnosed with ABD according to the ICBD criteria[12] with at least one consultation in the university hospital of Innsbruck.

Patients' characteristics and clinical manifestations

Adamantiades–Behçet's disease manifestations and signs are detailed in Table 1. Out of 76 ABD patients, 53.9% were women with an average male-to-female ratio of 0.86, compared to 3.3 in the subgroup of

patients with venous manifestations. The average age was 38.1 (16–64) years, and patients had a mean body mass index of 25.0 (15.6–43.3).

Concerning the ethnic background, 39.1% of the ABD patients were known to be of Austrian origin, followed by 37.0% of Turkish, each 6.5% of Italian and Balkanese, and each 2.2% of German, Armenian, Portuguese, Thai and Tunesian origin. Details for both the Austrian and the Turkish ABD subgroup are given in Table 1 together with comparisons to the ICBD dataset, data from a German[5] and a Turkish cohort.[13] With 5.6 (0–18), 10.0 (0–26) and 6.9 (± 6.2) years, the average disease durations were comparable between the Austrian and the Turkish subgroup of the Innsbruck cohort and the cohort living in Turkey.[13] The male-to-female ratio was 0.39 for the Austrian subgroup and 1.43 for the Turkish subgroup of patients from the Innsbruck cohort. There was no clear difference between the Innsbruck ABD patients of Austrian versus those of Turkish origin, and the Innsbruck ABD patients of Austrian origin versus those from the German cohort, even for those manifestations which differ between German and Turkish patients of the German cohort.[5]

When comparing the Innsbruck ABD patients of Turkish origin with those of a Turkish cohort,[14] genital aphthae and skin manifestations were less frequently observed in Innsbruck, whereas neurological, vascular and gastrointestinal manifestations were less frequently observed in the Turkish cohort (Table 1). When comparing the total Innsbruck cohort with the ICBD dataset, the Innsbruck cohort had especially reported less oral/genital aphthae and skin manifestations, but more musculoskeletal, vascular manifestations, gastrointestinal and lung manifestations. Innsbruck patients' data also reported more often a positive family history than the ICBD dataset. Other frequencies were comparable between the groups.

Patients' medications

A total of 174 medical interventions were identified for immunosuppression, anticoagulation and pain relief. Out of these, 55.2% fully matched the EULAR

Table 1 Origin-specific distribution of ABD symptoms and signs in Innsbruck compared to other cohorts

Signs/symptoms	ICBD dataset (p1)	German cohort (p2)	Turkish cohort (p3)	Innsbruck cohort		
				Total	Austrian origin (p4)	Turkish origin
Oral aphthae	98%*	99%	100%	93%	94%	94%
Genital aphthae	74%*	65%#	80%*	62%	56%	53%
Skin manifestations	70%**	73%#	93%**	47%	56%#	24%
Ocular manifestations	55%#	43%†	35%	46%	56%	47%
Musculoskeletal manifestations	51%*	52%	74%	65%	67%	59%
Neurological manifestations	17%	20%	4%*	21%	22%	24%
Vascular manifestations	19%*	21%	12%*	30%	22%	29%
Urological manifestations	7%	15%†	0%$^{n.d.}$	7%	6%	12%
Gastrointestinal manifestations	6%**	17%†	0%**	21%	11%#	41%
Cardiological manifestations	2%	3%	0%$^{n.d.}$	3%	0%	6%
Lung manifestations	2%**	6%†,#	0%$^{n.d.}$	11%	11%	18%
Renal manifestations	0%$^{n.d.}$	2%†	0%$^{n.d.}$	1%	0%	6%
Positive pathergy test	47%	31%	n.d.	40%	33%	67%
Family history positive for ABD	11%*	4%†	n.d.	26%	14%	38%
HLA-B51 positivity	51%	43%†	n.d.	56%	47%#	11%

Data are given for the Innsbruck cohort (with subgroups of defined Austrian and Turkish background, $n = 18$ and $n = 17$, respectively) compared to international patients recruited for the International Criteria for Behçet's Disease (ICBD) dataset,[14] from the German cohort ($n = 7125$) and a Turkish cohort ($n = 107$[13]). *P*-values are calculated using Fisher's exact test of significance (#$P < 0.1$; *$P < 0.05$; **$P < 0.01$) for comparison between the ICBD dataset with data of the total Innsbruck cohort (p1), between the Austrian patients of the Innsbruck cohort and those of the German cohort (p2), and between the Turkish patients of the Innsbruck cohort and those of the Turkish cohort (p3). †Data from patients with German origin (representing 39% of the German cohort, including those with significant differences to the total German cohort). ABD, Adamantiades–Behçet's disease; HLA, human leukocyte antigen; n.d., not described.

recommendations exactly, and 93.7% were considered at least as equal to the recommendations. There was 52.6% of the treatments performed before publication of general guidelines in 2007 and 2008. Conformity of treatments to EULAR guidelines are detailed in Table 2. The use of anticoagulation in most patients with vascular involvement was not considered as non-conformity to EULAR guidelines, as anticoagulation was not definitely denied by the EULAR taskforce at this time.[8] Non-conformity was described if arterial aneurysms were not treated with cyclophosphamide as recommended.

Tumor necrosis factor inhibition was applied only in men. Infliximab and etanercept were used in three patients, adalimumab in four and golimumab in one patient, with two patients receiving two different TNF inhibitors. All TNF inhibitors were considered as equivalent alternatives, and TNF inhibition was applied according to the recommendations in eight out of nine men. In one patient, chart review did not allow confirmation of the indication in agreement with the recommendation. Indications for TNF inhibition were pretreated uveitis/iritis with or without retinitis (3×), epididymitis and orchitis (2×), multiple ocular vein thromboses, bilateral neuritis nervi optici, gastrointestinal manifestations with severe joint involvement, oral/genital aphthae with folliculitis and cephalea. Success of TNF blockade was not documented, as patients were not routinely followed in this center.

DISCUSSION

This is the first description of a Middle-European ABD cohort, involving both patients of Austrian origin and immigrants in a non-endemic area as recently proposed by Leccese *et al.*[4] Most interestingly, the Innsbruck patients of Turkish origin clearly presented differently from those of a Turkish cohort living in Turkey, with more genital aphthae and skin manifestations, but fewer neurological, gastrointestinal and vascular manifestations than in Turkey. This result suggests a different environmental influence on the pathophysiological processes of ABD in Middle-Europe despite the same genetic background. Accordingly, clinical data from Innsbruck ABD patients of Austrian and Turkish origin were comparable and also those of Innsbruck ABD patients of Austrian origin and those from an independent German cohort. This observation contradicts the findings from the Paris metropolitan area with a higher prevalence of ABD among North African and Asian immigrants than in the original European population, comparable with prevalences reported in the countries of the immigrants' ancestry.[15] In conclusion, the French study with North African and Asian immigrants suggested a primarily hereditary basis of ABD, whereas our data with Turkish immigrants support more the concept of a possible role for still undefined environmental factors in ABD. Thus our data are in line with another Turkish study, which described that human leukocyte antigen (HLA)-B51 explained only 19% of the genetic susceptibility to ABD.[16] We can only speculate whether the difference may be explained by the different countries of the immigrants' origin. In our cohort, we were unable to examine the age-at-immigration effect on ABD risk, which was excluded in the French study.

Apart from the clinical presentation, patients were more likely to be women in the Austrian than in the Turkish subgroup of Innsbruck ABD patients as was described earlier for American sites compared to Turkey,[13] possibly reflecting a sociopsychologic background for populations with reluctance of women to undergo medical examination, for example of genital aphthae.[17] Indeed, men are more frequently affected with ABD in the Middle East and the Mediterranean area and women more in Western Europe, Japan and Korea with male-to-female ratios between 0.36 in Western Europe and 4.9 in Arabic populations.[18,19] The different clinical presentations between the Innsbruck patients and the ICBD dataset can be explained by the fact that the ICBD dataset includes not only patients from European and Turkish origin, but also from other countries of the silk road, Northern Africa and the Far East.[12]

It could be speculated whether treatment of a rare disease like ABD in a non-endemic area reaches the quality level achieved by specialists in an endemic area. Indeed, the interdisciplinary approach in Innsbruck led to the management of ABD patients which in 93.7% turned out as equivalent to the 2008 EULAR guidelines, even for those 52.6% of the cohort's patients treated before 2008. As strong evidence for ABD treatment is rare (with paucity of approved indications for drugs), and treatment strongly depends on the organs involved and the severity of organ involvement,[20] this analysis accepted therapeutic interventions as equally effective in case of similar mode of action (as for newer TNF-blocking agents) or if established in single disciplines for organ diseases, for example with mycophenolate mofetil in ABD uveitis as applied by ophthalmologists for non-infectious uveitis.[21] Thus we report much higher rates of conformity to the existing 2008 guidelines compared to a recent analysis from Northern

Table 2 Adherence of patients' management to EULAR 2008 recommendations in the non-endemic Middle-European area

Recommendations with short versions	Evidence	*n*	Conformity†	Comments
1. Uveitis posterior: AZ A+CS	Ib	0	—	
2. Severe eye involvement: CyA/IFX + AZA + CS	Ib/IIb	2	100%	MMF used instead of AZA
3. Vascular involvement: DVT – immunosuppression, arterial aneurysms – CyPh + CS	III	11 1	81.8% 0%	
4. Vascular involvement: lack of evidence for anticoagulation	IV	15	Not included	Lacks further conclusions
5. Gastrointestinal involvement: immunosuppression before surgery	III	14	92.9%	
6. Joint involvement: colchicine considered effective in most patients	Ib	24	91.7%	More effective IS accepted
7. Neurological involvement: parenchymal disease – CS, IFN, AZA, CyPh, MTX, αTNF; SVT – CS	III	3	100%	
8. Neurological involvement: cave CyA, except for urgent eye involvement	III	16	100%	
9. Skin and mucosal lesions: topic treatment (± CS) before colchicine, AZA, IFN, αTNF	Ib	70 15 17 1	OA: 95.7% Acne: 93.3% EN: 94.1% IS last: 100%	Depends on type of lesion

†Evidence is described according to EULAR.[8] Conformity with guidelines, organ-specific treatment or better alternatives accepted. AZA, azathioprine; CS, corticosteroid; CyA, cyclosporin A; CyPh, cyclophosphamide; DVT, deep vein thrombosis; EN, erythema nodosum; EULAR, European League Against Rheumatism; IFN, interferon; IFX, infliximab; IS, immunosuppressives; MMF, mycophenolate mofetil; *n*, number of evaluable patients; OA, oral aphthae; SVT, sinus vein thrombosis; TNF, TNF-blockers.

America and the Netherlands, which described treatment adherence ranging from 21% versus 31% in posterior uveitis, 50% versus 25% in arterial disease and 38% versus 55% in erythema nodosum, before and after publication of the guidelines, respectively.[14] In routine clinical treatment, missing drug approvals for treatment of ABD or ABD organ involvement, may be compensated by the support of international guidelines. For the future, updates of guidelines might be more important, especially for rare diseases with few drugs approved by regulatory authorities.

In Innsbruck, the medical interventions which turned out as not conforming to the EULAR guidelines, were related especially to the vessels, as in this center anticoagulation was often considered sufficient for treatment of recurrent deep vein thromboses without immunosuppression in ABD patients, which nowadays is not in line with evidence and guidelines for ABD.[22] Indeed, anticoagulation is still used according to in-house guidelines in Innsbruck, but patients' numbers and outcome data are insufficient for valid conclusions when comparing with previous retrospective studies from the UK, France and China commonly using warfarin[23–25] or from Turkey where warfarin has not been commonly used.[22] Also, the use of nonsteroidal anti-inflammatory rheumatic drugs alone in ABD patients with destructive joint disease, recurrent oral aphthae or skin lesions without additional immunosuppression is insufficient and does not conform to EULAR guidelines.

The major limitations of this study are the few ABD patients compared to the large cohorts from the areas endemic for ABD, and the missing data because of the retrospective trial design (as HLA-B51 was available only in nine Turkish patients). Especially before the year 2000, patients' clinical data were not fully available. Results of pathergy tests were often only reported but not detailed as performed. The interdisciplinary approach of this study allowed us at least to search for documents also in the early phase of electronic documentation. Another flaw of this study is that it lacks data on disease activity, disease severity and quality of life.

For the future, a prospective design is planned and already approved by the local ethics committee. This will allow not only the precise evaluation of disease activity, severity and quality of life, but also the better estimation of Middle-European ABD prevalence if patients from other non-Middle-European areas can be excluded. At present, the estimated prevalence of 5.1–10.1 per 100 000 inhabitants nearly doubles the expected prevalence in an area of 750 000 (Tyroleans alone) to 1 500 000 inhabitants (North and East Tyrol,

South Tyrol/Alto Adige and Vorarlberg taken together). Given an estimated 50% rate of patients referred from other Austrian and foreign areas, the estimated prevalence data of 2.6–5.1 per 100 000 inhabitants has to be considered as reliable in view of other Western European prevalence data of 0.55–7.5 per 100 000 inhabitants.[19]

CONCLUSION

This interdisciplinary non-endemic Middle-European ABD cohort is unique in this area, and shows comparable clinical presentations for patients of non-endemic and endemic origin for ABD living under the same environmental conditions, but different presentations when comparing Turkish patients living in the non-endemic Middle-European area and Turkey as an endemic area. ABD guidelines and current literature facilitate clinical decision-making in rare diseases like ABD, as drug indications for rare diseases like ABD are often not approved by regulatory authorities.

DISCLOSURE

The following authors received honoraria for attending symposia, speaking at symposia, educational programs or positions on advisory boards from pharmaceutical companies (in total less than 5000 € per author from pharmaceutical companies): W.H., G.R., W.S., B.T., T.D.Z. and M.S. Otherwise, all authors state they have no conflicts of interest.

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AUTHORS CONTRIBUTIONS

Conceptualization, methodology, project management: T.M., V.C., S.M.; investigation, data curation, formal analysis, validation: all authors; visualization, writing – original draft preparation: T.M., M.S.; writing – review and editing: all authors.

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