ORIGINAL ARTICLE

Adamantiades – Behcet Disease (ABD) in Northern Greece Patients: Experience from a single center

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Abstract

Objective - Methods: Adamantiades-Behcet disease (ABD) is a multi-systemic vasculitis of unknown origin, with a characteristic geographic distribution, that affects vessels of all kinds and sizes and is characterized by recurrent mucosal, skin and ocular lesions. In the present study, a series of 36 patients from Northern Greece is analyzed retrospectively in regard to the epidemiological, clinical and immunological parameters.

Results: All patients had recurrent oral ulcerations (36/36, 100%), while 23/36 (63.9%) experienced genital ulcerations and 22/36 (61.1%) developed ocular disease. Skin manifestations were observed in 23/36 patients (63.9%) and pathergy test was found positive in 14/36 patients (38.9%). Other manifestations included central nervous system involvement, recurrent genitourinary inflammations, arthralgias and superficial thrombophlebitis. Laboratory findings were not specific, partly reflecting the severity of inflammation. Ocular disease was more often observed in HLA-B51 (+) patients (20/31, 64.5%) than in HLA-B51 (-) patients. Standard of care (SOC) treatment consisted of cyclosporine A, azathioprine, methylprednisolone and aspirin, whereas refractory disease was treated with intravenous pulses of methylprednisolone and cyclophosphamide. Occasionally, anti-TNF agents (infliximab) were applied to treat refractory ocular disease.

Conclusion: The findings of the present study come in agreement with those reported for other Mediterranean series. HLA-B51 seems to predispose to more severe disease, while early therapeutic intervention is beneficial for these patients. *Hippokratia 2007; 11 (4): 210-215*

Key words: Adamantiades-Behcet disease, clinical manifestations, pathergy, HLA-B51

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There were other forms of fever… Many developed aphthae, ulcerations…
Many ulcerations about the genital parts…
Watery ophthalmies of a chronic character with pains…
Hippocrates, 5th century BC, 3rd Book of Endemic Diseases

Adamantiades-Behcet disease (ABD) is considered to be a clinical entity of an immunopathological basis although of unknown etiology. It is defined as a multisystemic vasculitis, with a characteristic geographic distribution, that affects vessels of all kinds and sizes and characterized by recurrent mucosal, skin and ocular manifestations[1].

The first description of the disease was reported by Hippocrates, 5th century BC, in his third book of endemic diseases[2]. In 1930, Adamantiades presented a case of "recurrent iritis with hypopyon" in the *Annales d' Oculistique,* while in 1936 the Turkish dermatologist Hulusi Behcet described two cases in *Dermatologische Wochenschrift*[3,4].

The disease can, practically, affect every tissue and organ of the body, simultaneously or sequentially. Prognosis is designated by the target organs involved. Multiple factors seem to participate in ABD etiology and pathogenesis, such as genetic predisposition, various infectious agents and an autoimmune response, based on molecular mimicry, which is directed against self antigens[1]. Aim of the present study is the epidemiological, clinical and immunological analysis of 36 patients with ABD from Northern Greece.

Patients and Methods

Thirty six patients from Northern Greece (21 male and 15 female, ratio 1.4:1) were included in the present study. The medical records of the patients were studied retrospectively, from March 1995 until March 2006, while information was collected according to a pre-established questionnaire with special interest in the epidemiological, clinical and immunological parameters and the patients' response to applied therapy. Orogenital and skin manifestations were evaluated by inspection, while ocular manifestations were evaluated by ophthalmologists. Pathergy test was evaluated 24-48 hours after transaction.

Laboratory investigation included routine tests, while immunologic investigation included the individual autoantibody profile with special concern for anticardiolipin

antibodies (ACA) and anti-neutrophil cytoplasmic antibodies (ANCA), that were detected with an enzyme-linked immunosorbent assay (ELISA), (R&D systems, Minneapolis, USA). Concerning antinuclear antibodies (ANA), patients were screened by an indirect immunofluoresence assay (IFA) in a Hep-2 substrate, followed by an ELISA, when necessary. Complement components C_3 and C_4 and also CRP were defined by nephelometry (Behring, Germany). HLA-B51 typing was performed using the polymerase chain reaction-sequencing-based typing (PCR-SBT) method.

Results

Epidemiology

Mean age at diagnosis was 42.6±14.4 years, while mean duration of disease was 11.6 years and mean follow up period was 65.6 months, as shown in Table 1. All patients fulfilled the diagnostic criteria of the International Study Group for Behcet's Disease, established in 1990 (sensitivity 91%, specificity 96%)[5,6].

Table 1. *Epidemiologic characteristics of the patients (SD: standard deviation, HLA: Human Leukocyte Antigen)*

Number of patients	36
Nationality	Greek (Northern Greece)
Male/Female	21/15 (ratio 1.4:1)
Mean age (±SD)	42.6±14.4 years
Mean disease duration (±SD)	11.6±7.2 years
Mean follow-up duration (±SD)	65.6±22.7 months
HLA-B51 positivity	20/31 (64.5%)

Clinical manifestations

In the present study, all patients (36/36, 100%) suffered from aphthous ulcerations of the oral mucosa, that recurred at least three times during a 12-month period. Thirty five patients presented with minor (diameter <10mm) ulcerations (35/36, 97.2%), while six patients simultaneously expressed major (diameter>10mm) ulcerations (6/36, 16.7%) and one only herpetiform ulcerations (1/36, 2.8%).

Recurrent genital ulcerations were observed in 23/36 patients (63.9%), while one female patient developed scars in the genitalia during follow up. Sixteen patients were male (16/23, 69.6%) and ulcerations developed mainly on the scrotum, the base of the penis and the perianal area. Seven patients were female (7/23, 30.4%) and ulcerations developed mainly on the major labia and the vagina. Six male patients suffered from recurrent aseptic genitourinary inflammations, four from orcheo-epididymitis and two from prostatitis (6/36, 16.7%).

Skin manifestations were observed in 23/36 patients (63.9%). Erythema nodosum was seen in 13/23 patients (56.5%), acneform lesions in 10/23 patients (43.5%) and pseudofolliculitis in 6/23 patients (26.1%). Pathergy test was performed according to the International Study Group for Behcet's Disease recommendations and was found positive in 14/36 patients (38.9%).

Ocular manifestations of the disease were initially observed in 22/36 patients (61.1%). These represented mainly anterior or posterior uveitis (iridocyclitis or retino-choroiditis) in 15/22 patients (68.2%), retinal vasculitis in 9/22 patients (40.9%), inflammation of the vitreous body (vitritis) in 7/22 patients (31.8%), edema of the fovea centralis in 4/22 patients (18.2%), optic nerve atrophy in 4/22 patients (18.2%) and retinal hemorrhage in 2/22 patients (9.1%). It should be mentioned that partial loss of visual acuity was observed in 12/22 patients (54.5%), while in four male patients ABD was sight-threatening (visual acuity <2/10).

Central nervous system (CNS) involvement was observed in five patients (5/36, 13.9%), two with memory disorders, one with seizures (grand-mal type), one with left pyramidal syndrome with hemiparesis, hypesthesia and seizures and one with memory disorders and cognitive impairment. Only in the latter two patients, there were pathological findings in MRI study of the brain, such as lesions located in the basal ganglia, diencephalon and hippocampi, that were characterized by glial proliferation. In one of the two patients, there were findings in the magnetic resonance venography (MRV) too, indicating thrombosis of the dural sinus. This patient was diagnosed to suffer from combined parenchymal and vascular involvement, while the other patient suffered from parenchymal disease only.

One patient presented with pulmonary complications of the disease (1/36, 2.8%), such as pulmonary vasculitis with pseudo-aneurysms and interstitial lung disease, that led to restrictive pulmonary disease.

Furthermore, 5/36 patients (13.9%) presented with superficial thrombophlebitis of the lower limbs; one patient suffered from thrombosis of the abdominal aorta. Arthralgias were present in 11/36 patients (30.6%), while four patients suffered from tendonitis and tendosynovitis of the shoulder and Achilles' tendon.

Main clinical manifestations of the patients are designated in Table 2.

Disease Severity

Patients were evaluated for disease severity during follow up according to the criteria proposed by Behcet Disease Research Committee of Japan in 2003 (table 3)[7]. Twelve patients were at stage I (no ocular lesions), 7 patients were at stage II (plus iridocyclitis), 6 patients were at stage III (retino-choroiditis), 10 patients were at stage IV, which represents special disease types (neuro-Behcet, vasculo-Behcet) or patients with possible visual loss, while one patient was at stage V, which represents progressive neuro-Behcet disease.

Table 2. *Systemic clinical manifestations of the patients (CNS: central nervous system)*

Superficial thrombophlebitis	5/36 (13.9%)
Skin manifestations	23/36 (63.9%)
Sight-threatening disease	4/22 (18.2%)
Pathergy	14/36 (38.9%)
Partial Visual Acuity Loss	12/22 (54.5%)
Oral ulcerations	36/36 (100%)
Ocular manifestations	22 (61.1%)
Musculoskeletal manifestations	11/36 (30.6%)
Genital ulcerations	23/36 (63.9%)
CNS manifestations	5/36 (13.9%)

Laboratory investigation

Thirty-three patients (33/36, 91.7%) presented with an elevated erythrocyte sedimentation rate (ESR), while 26/36 (72.2%) had elevated serum levels of C-reactive protein (CRP) at presentation. Serum levels of IgA, IgM and IgG were mostly normal, while there were no alterations in serum levels of complement components of C_3 and C_4. Antinuclear antibodies (ANA) were detected in 15/36 patients (41.7%), mostly speckled pattern and in low titers, while anti-neutrophil cytoplasmic antibodies (ANCA) were detected in 4/36 (11.1%) in low titers (all of them were MPO-ANCA) and anticardiolipin antibodies (ACA) were detected in high titers in one patient (1/36, 2.8%).

HLA typing

HLA typing was performed in 31 patients and HLA*B51 allele was found in 20 patients (20/31, 64.5%), (Table 3). According to HLA-B51 presence or not, patients were subdivided in two groups. Group A consisted of 20 B51 (+) patients and group B of 11 B51 (−) patients. The two groups were compared for the frequency and severity of the clinical manifestations using the χ^2 test. A statistically significant increase in the frequency of positive pathergy test and ocular manifestations ($p<0.05$) was observed in group A patients. Concerning disease severity, B51 (+) patients expressed mainly posterior uveitis and/or retinal vasculitis and suffered from more relapses than B51 (-) patients. Sight-threatening disease was observed in three B51 (+) patients and in one B51 (−) patient. CNS involvement was observed in two B51 (+) patients, both suffering from severe recurrent eye disease. Antinuclear antibodies were detected more frequently in B51 (+) patients ($p<0.05$). Comparisons between B51 (+) and B51 (-) patients are given in Table 4.

Therapy

Therapeutic approach was based on disease severity and vital organ involvement. Patients that did not express aggressive recurrent vital organ involvement received basic treatment, that consisted of methylprednisolone (4-64 mg/day) in 24 patients, cyclosporine A (100-300 mg/day) in 30 patients, azathioprine (50-150 mg/day) in 23 patients and aspirin (100-325 mg/day) in 29 patients. Additionally, intravenous pulse treatment with methylprednisolone (1000 mg-7000 mg) and cyclophosphamide (500 mg/month for 6 months) was administered in eight patients, who experienced severe eye and CNS disease manifestations (Table 3). Anti-TNFa treatment (infliximab) was administered to four patients, three with refractory ocular involvement and one with combined ocular and CNS involvement (data not shown).

Discussion

Adamantiades-Behcet disease represents a multi-systemic disorder that usually affects young adults in third and fourth decade of life[8,9]. The sex ratio seems to be approximately 1:1 in large reported series[8]. In the present study, mean age at the time of diagnosis was 42.6±14.4 years, while male to female ratio was 1.4:1. Kaklamani et al reported a ratio of 1.9:1 (male predominance) in other Greek patients[9].

Oral aphthae may be minor, major or herpetiform and represent the cornerstone for ABD diagnosis, as described in ISG criteria[5]. However, several authors have reported cases of ABD without aphthous stomatitis (minimal reported frequency was 92%)[10-13]. In studies from European countries, reported frequency ranges from 98% to 100%[10-12]. Patients included in this series were diagnosed according to the ISG criteria and, hence, all suffered from recurrent aphthous ulcerations.

The prevalence of genital aphthae was 64% in our patients, while in previous series a percentage that is ranging between 62 and 97% was reported[8,12]. In a previous study in Greek patients the reported frequency was 78%[9]. Interestingly, six male patients (16.7%) had recurrent "aseptic" epididymitis and prostatitis (serial negative cultures), a finding that comes in agreement with another Greek study (13%)[9]. Although not included in the ISG criteria, epididymitis is reported as an additional symptom in the 2003 revised Japanese criteria[7].

Skin manifestations of ABD, localized mainly in the lower limbs, are estimated to vary widely (range 39% to 93%) in large series.[8, 12] In this study, it was found to be within this range (63.9%). Pathergy test represents a non-specific skin delayed type hypersensitivity.[9] Its positivity depends on several factors, such as disease activity etc. Reported frequency of positivity varies between 30% and 61%, compared to 39% in this study and 30% in another Greek study[9,12].

Concerning ocular manifestations, a variety of lesions have been described[9]. Most frequent type of involvement is panuveitis, while retinal vasculitis and vitritis are the most common funduscopic findings and macular edema is the most frequent complication[14]. Findings of this study are quite similar to those reported in the European literature[10,11]. It should be mentioned that eye involvement in ABD can be sight-threatening. Before the introduction

Table 3. *HLA-B51 positivity, disease severity according to Japanese criteria and basic therapeutic approach are displayed. (M=male, F=female, ND=no data, NT=no systemic treatment, CyA=cyclosporine A, AZA=azathioprine, CS=corticosteroids, ASA=aspirin, CyP*=cyclophosphamide iv, CS*=corticosteroids iv, IVIGs= iv immunoglobulins)*

N	Sex/Age	Severity	HLA-B51	Treatment
1	M/31	V	(+)	CyA, AZA, CS, ASA / CyP*, CS*, IVIGs
2	M/29	III	(-)	CyA, AZA, CS, ASA / CyP*, CS*
3	M/45	IV	(+)	CyA, AZA, CS, ASA / CyP*, CS*
4	M18	IV	(+)	CyA, AZA, CS, ASA / CyP*, CS*
5	F/65	III	(+)	CyA, AZA, ASA
6	M/24	III	(+)	CyA, AZA, CS, ASA
7	M/29	I	(-)	NT
8	F/40	IV	(+)	CyA, AZA, CS, ASA / CyP*, CS*
9	M/64	I	ND	AZA, CS, ASA
10	M/32	I	(-)	NT
11	F/50	I	(-)	CyA,CS, ASA
12	M/24	II	(-)	CyA,CS, ASA
13	F/47	I	ND	AZA, CS
14	F/42	III	(+)	CyA, AZA, CS, ASA
15	F/46	II	(+)	CyA, AZA, ASA
16	F/42	IV	(-)	CyA, AZA, ASA
17	M/55	IV	(+)	CyA, AZA, CS, ASA
18	F/45	I	(+)	NT
19	M/33	I	(-)	CyA, CS
20	F/54	III	(+)	CyA, AZA, ASA
21	F/19	II	ND	CYA, CS, ASA
22	M/65	IV	(+)	CyA,CS, ASA
23	M/61	II	(+)	CyA, AZA, ASA
24	M/45	IV	(+)	CyA, AZA, CS, ASA / IVIGs
25	F/26	II	(-)	CyA,CS, ASA
26	F/51	II	(-)	CyA, AZA, ASA
27	M/34	IV	(+)	CyA, AZA, CS, ASA / CyP*, CS*, IVIGs
28	M/34	IV	ND	CYA, CS, ASA
29	M/20	I	(+)	NT
30	M/61	I	ND	CyA, AZA, ASA
31	F/35	I	(-)	CyA,CS, ASA
32	F/52	IV	(-)	CyA, AZA, CS, ASA / CS*
33	M/70	II	(+)	CyA, AZA, CS
34	M/44	III	(+)	CyA, AZA, CS, ASA / CS*
35	M/58	I	(+)	CyA,CS, ASA
36	F/43	I	(+)	CyA, AZA, ASA

Table 4. *Comparison between HLA-B51 (+) and HLA-B51 (-) patients in disease expression (NS= non significant)*

	HLA-B51 (+)	HLA-B51 (-)	*P*
Oral ulcers	20/20 (100%)	11/11 (100%)	NS
Genital ulcers	14/20 (70%)	7/11 (63.6%)	NS
Skin manifestations	13/20 (65%)	8/11 (72.7%)	NS
Ocular manifestations	16/20 (80%)	4/11 (36.4%)	*p<0.05*
Posterior uveitis and/or retinal vasculitis	13/16 (81.3%)	2/4 (50%)	NS
Positive pathergy test	11/20 (55%)	2/11 (18.2%)	*p<0.05*
CNS involvement	2/20 (10%)	0/11 (0%)	NS

of cyclosporine A, vision was lost in an average of 3.36 years after the onset of ocular symptoms[15]. Early and aggressive immunosuppressive treatment with new agents has been shown to reduce the rate of visual loss[16,17].

Central nervous system involvement in ABD ranges from 3% to 10% and is associated with a poor prognosis[18]. There are two distinct patterns of CNS involvement in ABD; parenchymal disease and vascular disease, where vasculitis may affect major vessels, arteries and/or veins[18]. In our study, CNS involvement was 13.9%, compared to 20% reported by Kaklam-

ani et al[9]. We have recently described one patient who experienced combined recurrent relapsing CNS involvement[19]. Cognitive impairment without overt neurological involvement in ABD patients is being investigated, but memory disorders seem to be the most frequent manifestation[20]. It is discussed that there are lesions not visible by brain MRI in neuro-Behcet patients[20]. New methods like CNS-SPECT could give answers in the evaluation of such patients.

Superficial thrombophlebitis is a common feature of ABD, as well as other thrombotic phenomena[8,12]. It is not clear whether they are related to the presence of antiphospholipid antibodies (secondary antiphospholipid syndrome) or they can be attributed to the generalized vascular inflammation of the disease[21]. In the present study, 14% of our patients developed superficial thrombophlebitis, while only one had elevated titers of anticardiolipin antibodies, without thrombotic manifestations.

In general, reported frequency of certain clinical manifestations of ABD varies widely in different parts of the world[12]. This discrepancy may have several explanations, such as differences in referral patterns, disease duration, ethnic and genetic background and, finally, in patient selection. Therefore, comparisons between different ethnic studies should be made cautiously.

Laboratory investigation has little to offer in the diagnostic process of ABD patients since findings are either not specific or irrelevant to clinical manifestations. However, inflammation markers such as ESR, CRP and, lately, neopterin and interleukin-8 could be used in order to assess clinical activity in such patients[22,23].

The role of HLA-B51 in the pathogenesis of ABD has been extensively studied during the last years[24]. In a previous report concerning Greek patients, HLA-B51 positivity was 80.6% compared to 64.5% in our patients and 61% in a multi-center study from Italy[10,25]. In the present study, HLA-B51 was shown to predispose to more severe disease with features like posterior uveitis (main cause of visual loss) and CNS involvement. Increased severity of eye involvement (posterior uveitis) in B51 (+) patients has been described in Greek patients again[25,26]. However, it is not yet known either if B51 is correlated to certain patterns of disease expression (like concurrent ocular and CNS involvement), or if it is related to a poor response to therapy. In the present study, 12 patients expressed relapsing disease; nine of them were B51 (+), whereas 3 were B51 (-). Additionally, three or more relapses were observed only in B51 (+) patients. It should be mentioned that most relapses occurred during tapering of basic treatment, while in a few cases an infection triggered the pathogenetic process.

In general, therapeutic approach was based on disease severity and vital organ involvement, according to the Japanese revised criteria[7]. Oral and genital aphthae could often be managed with topical steroids[16,27]. Systemic corticosteroids in combination with cyclosporine A and azathioprine were used for their synergistic effect in vital organ involvement, mainly the eyes[27,28]. Aspirin in low doses was added to the majority of these patients for its anti-platelet effect and vascular protection in the long term. More aggressive treatment (iv cyclophosphamide plus iv methylprednisolone and/or iv immunoglobulins) is often required to control the pathogenetic process[29]. Anti-TNF agents (infliximab) seemed to be beneficial in refractory ocular disease (personal data not shown)[17,30].

In conclusion, the frequency of clinical manifestations, HLA-B51 presence and disease severity in this study do not differentiate significantly, compared to other studies in European populations. However, therapeutic impact on disease evolution and outcome is still inconclusive, because of the lack of large randomized placebo-controlled trials.

ABD, a chronic, relapsing disease with a negative influence on patients' quality of life, demands the collaboration of well-trained and experienced specialists; treatment must be tailored to the organ involvement and degree of severity for all patients individually. Early therapeutic intervention is believed to be beneficial in patients with vital organ involvement. HLA-B51 clearly seems to predispose to more severe disease and its presence should be considered for aggressive treatment from the onset of the disease, in parallel with a more intensive follow up.

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