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KEYWORDS:

THE SPECTRUM OF CLINICAL PROFILE, COMPARISION BETWEEN DIFFERENT CRITERIA AND OUTCOME IN HLA B51 POSITIVE SOUTH INDIAN BEHCETS PATIENTS - A RETROSPECTIVE TERTIARY CENTER STUDY

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Abstract:

The diagnostic utility of HLA B51 (Human Leukocyte Antigen) in association with Behçet's disease(BD) has been identified. However, the clinical manifestations of HLA B51 positive patients who have not satisfied the criteria for Behcet's have been rarely reported. Our objective was to study the clinical profile of HLA B51 positive patients and to include them under the spectrum of International criteria for Behcet's disease (ICBD) and the modified Japanese criteria, and also to study the outcome in these patients. This is a retrospective prospective observational study conducted over 3 years (2018-2021) in HLA B51 positive patients. The clinical presentations, treatment given and follow up response to treatment were observed. In the study cohort of 28 HLA-B51 positive patients, mean age was 41.7 years. 17 (60.7%) had oral ulcers, 5 (17.8%) genital ulcers, 7 (25%) skin lesions, 11 (39.2%) had Pathergy positivity, 19 (67.8%) ocular, 7 (25%) neurological, 3 (10.7%) Gastro-intestinal (GI) and 3(10.7%) had vascular manifestations.12 (42.8%) satisfied ICBD criteria and 2 (7%) satisfied Japanese criteria for BD. 15 (53.5%) were given immunosuppressant therapy with [Azathioprine (AZA) in 10(35.7%), Mycophenolate mofetil (MMF) in 4(14.2%) and cyclophosphamide (CYC) in 1(3.5%)]. Biologics were given in 7 (25%) with [Adalimumab(ADA) in 6(21.4%) and Rituximab (RTX) in 1(3.5%)]. Our study showed female predominance, with more ocular manifestations , oral aphthous ulcers and less gastrointestinal involvement. Azathioprine (AZA) showed better response compared to Mycophenolate mofetil (MMF).

Background:

Behcet's disease (BD) is a multisystem disorder, first described by the Turkish dermatologist Hulusi Behcet with a triad of oral aphthous ulcers, genital ulcers and uveitis1. It can manifest as skin lesions, arthralgias, central nervous system (CNS) , cardio vascular system (CVS) and gastro intestinal (GI) tract involvement. It has a geographical distribution along the ancient silk route, where HLA B51 positivity was found to be high. Diagnosis of BD is made by clinical manifestations (as a syndrome) as there is no disease specific symptom or definitive diagnostic test available. Ohno et al2 first identified statistically significant incidence of HLA B51 positivity in BD in Japanese population.

Meta-analysis done by M de Menthon et al3 described the genetic effect of HLA B51 allele on the risk of developing BD. Many authors attempted to identify a possible relationship of clinical features in Behcet's disease with HLA B51 positivity. There is paucity of data in HLA B51 positive patients with suspicious features of BD, who have not fulfilled the criteria for BD. In our study, we assessed HLA B51 positive South Indian patients who presented with clinical features of BD, and attempted to include them under the spectrum of ICBD4 and Japanese criteria for Behcet's disease5.

Methodology:

This was a retrospective observational study, done at a tertiary care centre in South India. Patients who visited our Rheumatology clinic from March 2018 to March 2021 were taken up for our study. We included HLA B51 positive patients with age more than 18 years, who presented with clinical manifestations of BD and excluded patients with symptoms of BD, who were HLA B51 negative.

From the medical records, data regarding demographic details, clinical manifestations and laboratory findings using a standard proforma was obtained. The clinical manifestations during disease course, treatment given and response to treatment during follow up were observed in both in and out patients. Patients were classified as possible, probable, highly likely and definitive Behcet's based on ICBD 2012 criteria4. They were classified as incomplete and complete Behcet's based on Japanese Behcet's criteria5. HLA B51 allele typing was done in patients by allele specific PCR (Polymerase Chain Reaction).

Continuous and categorical variables were reported as mean with standard deviation and percentage or proportion respectively.

Results: 28 patients were included in our study, who were followed up for a mean duration of 2.3 years. The mean age at presentation was 41.7 ± 2.5 years. 64.3% were females and 35.7% were males.

Ocular involvement was most common and noted in 67.8% of our cohort (Table 1). Uveitis constituted 46.4% of these patients.

Oral ulcers were seen in 60.7% (Table 1). Pathergy positivity was seen in 39.2% of patients. Skin lesions and neurological involvement (recurrent stroke, CNS vasculitis, seizures) were seen in 25%. Musculoskeletal manifestations (polyarthritis, spondyloarthritis, polyarthralgia) were seen in 24.7%. Gastrointestinal features such as aphthous ulcers were seen in 10.7%.(Table 1)

As per ICBD criteria4, 42.8% were diagnosed as Behcet's (point score ≥4) and 32% were diagnosed as possible Behcet's(Table 2). As per Japanese criteria5, 7% were diagnosed as Behcet's and 42.8% were

diagnosed as incomplete Behcet's (Table 3).

Table 1: Demographic and clinical data in HLA B51 positive Behcets patients.

Clinical features	N(%)
Median age	41.7 yrs
Sex	Female -18 (64.3%) Male-10 (35.7%)
Oral ulcers	17 (60.7%)
Genital ulcers	5 (17.8%)
Skin lesions	7 (25%)
Erythema nodosum	4 (14%)
Skin ulcers	3 (10.7%)
Pathergy	11 (39.2%)
Ocular lesions	19 (67.8%)
Neurological	7(25%)
Vascular thrombosis	4(14%)
Arterial	2(7%)
Venous	2(7%)
GI ulcers	3(10.7%)
Skeletal manifestations	
Polyarthralgias	3(10.7%)
Polyarthritis	2(7%)
SpA	2(7%)

Table 2: Patients classified under spectrum of ICBD criteria

ICBD SCORE	N = 28	Spectrum
ICBD ≥6	5	Almost certainly BD
ICBD =5	1	BD highly likely
ICBD =4	6	Probable BD
ICBD =3	9	Possible, but unlikely BD
ICBD =2	6	BD very unlikely
ICBD ≤1	1	Almost certainly not BD

Table 3: Patients classified under Japanese criteria

Spectrum	Criteria	N = 28
Complete Behcets	4 major criteria	2
Incomplete Behcets	3 major	5
	2 major + 2 minor	2
	1 ocular (major) + 1 major or 1 ocular (major) + 2 minor	5

Table 4: Associated clinical conditions in patients with Behcet's.

ASSOCIATED CONDITIONS:	N / (%)
TB	
Latent TB -	7 (25%)
Active TB	2 (7%)
Other autoimmune disease:	9 (32%)
APLA	3 (10.7%)
RA	2 (7%)
Psoriasis	2 (7%)
SpA	1 (3%)
SjS	1 (3%)

Fig 1: Treatment and response for all clinical manifestations

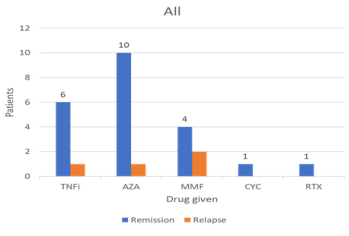
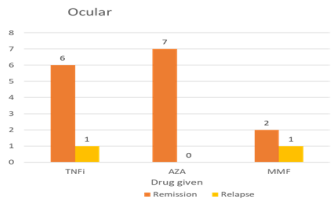


Fig 2: Treatment and response for ocular manifestations:



Discussion:

There are sparse studies on Behcet's disease from South Indian population. In this study, we have studied HLA B51 positive patients who presented with clinical features suggestive of BD. By using diagnostic criteria for BD, 7% and 42.8% of patients were diagnosed as Behcet's and 42.8% and 32% of patients were classified as incomplete Behcet's and possible Behcet's, as per Japanese Behcet's criteria 20105 and ICBD4 (International Criteria for Behcet's Disease) respectively. Higher number of patients satisfied ICBD4 criteria compared to Japanese criteria5.

Ocular manifestations were more common in our study in contrast to Japanese population (Yuki Mizuki et al)6 , Korean population (Hee Jung Ryu et al)7 and Turkish population (Demir seren)8 where oral ulcers were common.

Isolated uveitis without any other manifestation was seen in 21.4% of patients. Our study showed anterior uveitis is more common whereas data from Yokihoro et al14 showed panuveitis was the most common ocular feature. A meta-analysis done by Malini C et al9 mentioned HLA B51 positivity as an independent risk factor for ocular manifestations. Tursan et al10 also showed that ocular manifestations can present as an isolated entity in HLA B51 positive patients.

Table 5: comparison of clinical data from various studies.

CLINICAL MANIFESTATIONS	OUR STUDY (N=28)	JAPANESE (Yuki Mizuki et al.,) (N=12) %	KOREAN (Hee Jung Ryu et al.,) (N=40) %	TURKISH (Demir Seren) (N=20) %
Age at presentation (years)	41.7	38	43.4	37.2
Sex (M/F)	36% / 64%	47.6% / 52.4%	40% / 60%	Males > females
Oral ulcers	60.7%	**97.9%**	**100%**	**85%**
Genital ulcers	17.8%	62.4%	82.5%	80%
Ocular	**67.8%**	47.3%	22.5%	40%
Skin	10.7%	85.5%	90%	35%
Pathergy	39.2%	23.4%	20%	35%
Arthritis	14%	49.3%	47.5%	70%
GI	10.7%	22.9%	2.5%	5%
Neurological	25%	26%	2.5%	25%
Vascular	14%	10.6%	2.5%	10%

Oral ulcers were the second common manifestation in our population though it was most common in other studies6,7,8. Pathergy positivity was seen more commonly in our study as compared to Japanese6, Korean7 and Turkish8 population. Skin involvement , genital ulcers and arthritis were less in our study group compared to others6,7,8. Vascular and neurological manifestations were similar to Japanese6 and Turkish8 studies.

The criteria for other autoimmune diseases were satisfied in 32% of patients in our study. Luis salayandia et al11 cohort showed, 31% of autoimmune diseases in HLA B51 positive patients. Rheumatoid arthritis (RA), Spondyloarthritis (SpA) and Sjögren's syndrome (SjS) were seen in 7%, 3% and 3% in our study, whereas 7.3%, 9.1% and 7.3% in their cohort11. Our study also showed Anti phospholipid antibody syndrome (APLA) positivity in 10.7% and psoriasis in 7%. Louis etal11 group also observed, systemic lupus erythematosus (SLE) in 10.9%, scleroderma/CREST (Calcinosis, Raynauds, oesophageal dysmotility, sclerodactyly, telangectasias) in 7.3%, dermatomyositis (DM) in 1.8% and Polymyalgia rheumatica (PMR) criteria in 3.6% of patients.

In Vijaya Lakshmi et al12 cohort of Tuberculosis patients, HLA B51

positivity was seen in 77%, but data about clinical features of BD not available.

In our cohort of HLAB51 positive Behcet's, 25% had latent TB infection and 7% had active TB. Hence the significance of isolated B51 positivity in TB patients needs further exploration.

There is no treat to target therapy for BD. EULAR 2018 recommendations for BD13 were evidence based. Even in these guidelines, no strong recommendation was made for individual manifestations of BD because of limited amount of evidence.

Colchicine was recommended as first line management for mucocutaneous BD13. Colchicine was given to 67% of patients with mucocutaneous and gastrointestinal manifestations and majority of them showed good response in our study.

Systemic glucocorticoids, Azathioprine (AZA), Cyclosporine A (Cyc A), anti TNF (Tumour necrosis factor) antibodies were recommended for ocular involvement.13. In 13 patients with uveitis, 4 were given ADA (minimum 6 doses) , 6 were given AZA (minimum duration of 18 months) and 2 were given MMF (minimum duration of 18 months). All had remission except 1 patient with MMF who showed relapse. For scleritis (2) 1 was given AZA and 1 ADA. For retinal vasculitis, 2 were given ADA and 1 was given AZA. Pateints with ADA showed relapse after increasing the spacing between injections (6 injections 2 weekly, followed by 4 doses 3 weekly and 3 doses 4 weekly).

Rituximab was given for 1 patient who presented with acute stroke [MCA (middle cerebral artery) territory] with multiple peripheral venous thromboses and APLA positivity. Cyclophosphamide was given for 1 patient with CNS vasculitis with bilateral optic neuropathy. Both these patients showed a good response on follow up.

Among the 2 patients who had psoriasis along with HLA B51 positivity, both had mucocutaneous involvement,1 had anterior uveitis treated with azathioprine showed good response. Both were treated with topical steroids and emollients for psoriasis. Out of the 2 HLA B51 positive patients who also had RA, 1 was given ADA for uveitis and improvement in both uveitis and arthritis was observed. The other one who had genital, oral and GI ulcers was given colchicine and was treated with DMARDs. 1 who had SpA with bilateral sacroiliitis also had uveitis, B/L retinal vasculitis and scleritis was treated with ADA. Both ocular and SpA features showed good response. 1 who had SjS with sicca showed good response to Hydroxycholoroquine. 3 patients showed APLA positivity, out of which 1 presented as probable CAPS (catastrophic APLA) with myocardial infarction, arterial stroke and deep vein thrombosis of lower limb treated with Rituximab and anticoagulation showed good response. This patient also had recurrent oral and genital ulcer improved with colchicine. Other 2 APLA positive patients had presented with recurrent cerebral venpous thrombosis with aneurysms and was treated with MMF. His oral ulcers improved with colchicine. The third patient who was APLA positive had acute superior saggital sinus thorombosis, oral ulcers, oral and ocular sicca with SjS. She responded to colchicine and hydroxychloroquine. All 3 patients with DVT were given anticoagulation.

Conclusion: Among the clinical manifestations which were positive for Behcet's disease in HLA B51 positive patients in our study, ocular manifestations were common. Isolated uveitis was seen in these patients without other autoimmune features. More patients satisfied ICBD criteria compared to modified Japansese criteria for Behcet's disease. Azathioprine showed good response for isolated ocular manifestations.Adalimumab showed good response to severe ocular manifestations.

Other co-existing autoimmune diseases were seen in HLA B51 positive patients. Screening for Tuberculosis in HLA B51 positive patients should be considered.

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