كليـــــــة الـطـب
والصيدلة - مراكش
FACULTÉ DE MÉDECINE
ET DE PHARMACIE - MARRAKECH
MARRAKECH
جامعة القاضي عياض
UNIVERSITÉ CADI AYYAD

Year 2025 Thesis N°193

Impact of biological inflammatory markers on ocular activity in Behçet's disease

THESIS

PRESENTED AND PUBLICLY DEFENDED ON 04/07/2025

BY

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Born on January 04th 2000 in Jerada

TO OBTAIN THE DEGREE OF DOCTOR OF MEDICINE

KEYWORDS

Behçet disease –Ocular Behçet – Inflammatory biomarkers .

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بسم الله الرّحمن الرّحيم

“Glory be to You (Allah). We have no knowledge except
what You have taught us. You are truly
the All-Knowing, All-Wise”
(2-32)

Oath of Hippocrates

At the time of being admitted as a member of the medical profession:

I solemnly pledge to dedicate my life to the service of humanity

The health and well-being of my patient will be my first consideration

I will respect the autonomy and dignity of my patient

I will maintain the utmost respect for human life

I will not permit considerations of age, disease or disability, creed, ethnic origin, gender, nationality, political affiliation, race, sexual orientation, social standing or any other factor to intervene between my duty and my patient

I will respect the secrets that are confided in me, even after the patient has died

I will practise my profession with conscience and dignity and in accordance with good medical practice

I will foster the honour and noble traditions of the medical profession

I will give to my teachers, colleagues, and students the respect and gratitude that is their due

I will share my medical knowledge for the benefit of the patient and the advancement of healthcare

I will attend to my own health, well-being, and abilities in order to provide care of the highest standard

I will not use my medical knowledge to violate human rights and civil liberties even under threat

I make these promises solemnly, freely, and upon my honour.

Geneva Declaration, 1948

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322	MANSOURIMaria	MC	Génétique
323	ERRIFAIYHayate	MC	Anesthésie-réanimation
324	BOUKOUBNaila	MC	Anesthésie-réanimation
325	OUACHAOUJamal	MC	Anesthésie-réanimation
326	ELFARGANIRania	MC	Maladiesinfectieuses
327	IJIM Mohamed	MC	Pneumo-phtisiologie
328	AKANOURAdil	MC	Psychiatrie
329	ELHANAFIFatimaEzzohra	MC	Pédiatrie
330	MERBOUHManal	MC	Anesthésie-réanimation
331	BOUROUMANEMohamedRida	MC	Anatomie
332	IJDDASara	MC	Endocrinologieetmaladies métaboliques
333	GHARBIKhalid	MC	Gastro-entérologie
334	ATBIBYassine	MC	Pharmacieclinique
335	ELGUAZZARAhmed(Militaire)	MC	Chirurgiegénérale
336	HENDYIliass	MC	Cardiologie
337	MOURAFIQOmar	MC	Traumato-orthopédie
338	ZAIZIAbderrahim	MC	Traumato-orthopédie
339	HATTABMohamedSalahKoussay	MC	Stomatologieetchirurgiemaxillofaciale
340	DEBBAGHFayrouz	MC	Microbiologie-virologie
341	OUASSILSara	MC	Radiologie
342	KOUYEDAicha	MC	Pédopsychiatrie
343	DRIOUICHAicha	MC	Anesthésie-réanimation
344	TOURAIFMariem	MC	Chirurgiepédiatrique
345	BENNAOUIYassine	MC	Stomatologieetchirurgiemaxillofaciale

346	SABIREs-said	MC	Chimiebioorganiqueclinique
347	IBBAMouhsin	MC	Chirurgiethoracique
348	LAATITIOUISana	MC	Radiothérapie
349	SAADOUNEMohamed	MC	Radiothérapie
350	TLEMCANIYounes	MC	Ophtalmologie
351	SOLEHAbdelwahed	MC	Traumato-orthopédie
352	OUALHADJHamza	MC	Immunologie
353	BERGHALOUTMohamed	MC	Psychiatrie
354	ELBARAKA Soumaya	MC	Chimieanalytique-bromatologie
355	KARROUMISaadia	MC	Psychiatrie
356	ZOUITENOthmane	MC	Oncologie médicale
357	EL-OUAKHOUMIAmal	MC	Médecineinterne
358	AJMANIFatima	MC	Médecinelégale
359	MENJELImane	MC	Pédiatrie
360	BOUCHKARAWafae	MC	Gynécologie-obstétrique
361	ASSEMOualid	MC	Pédiatrie
362	ELHANAFIAsma	MC	Médecinephysiqueetréadaptation fonctionnelle
363	ABDELKHALKIMohamedHicham	MC	Gynécologie-obstétrique
364	ELKASSEHMostapha	MC	Traumato-orthopédie
365	ELOUAZZANIMeryem	MC	Anatomiepathologique
366	HABBABMohamed	MC	Traumato-orthopédie
367	KHAMLIJAimadAhmed	MC	Anesthésie-réanimation
368	ELKHADRAOUIHalima	MC	Histologie-embryologie-cyto-génétique
369	ELKHETTABFatimazahra	MC	Anesthésie-réanimation
370	SIDAYNEMohammed	MC	Anesthésie-réanimation
371	ZAKARIAYasmina	MC	Neurologie
372	BOUKAIDIYassine	MC	ChirurgieCardio-vasculaire

LISTE ARRETEE LE 03/02/2025

DEDICATIONS

With profound gratitude and deepest appreciation,
I dedicate this thesis to..

To ALLAH

The Almighty and Merciful, Who gave me the strength and the patience to accomplish this modest work, Who inspired and guided me on the right path, I owe Him what I have become. Praises for His clemency and mercy.

To my precious Mother, Fatima TAKOUAT

In your embrace, I found my first home — a place where fear dissolved and love spoke in silence. You have been the quiet force behind every smile, every step forward, every moment I dared to dream. You gave without asking, loved without condition, and stood by me with a heart full of patience and grace. I am who I am because of the light you poured into me, day after day. You sacrificed your time, your dreams, your own comfort, all so that I could grow, thrive, and find my own path. Your sacrifices often went unnoticed, but they have shaped every part of my life and allowed me to become who I am today. I carry your strength and your love with me always.

I cherish deeply our special bond and the conversations we share—they are moments of warmth, understanding, and joy that I treasure beyond words.

I am forever honored and grateful to be your child

To my dear Father Ali BOUYAKNIFEN

You have always been my foundation, the steady presence I could lean on, the quiet strength that carried me through. With you, I learned how to stand firm with humility, how to face challenges with calm, and how to love without needing to say much

You didn't always speak with many words, but your actions taught me more than any lesson could. Through your example, I understood the meaning of hard work, perseverance, and staying true to who you are.

For all you are and all you've given , I cannot be but eternally grateful .

To my dear Brother, Zakaria BOUYAKNIFEN

From childhood memories to grown-up conversations, you've been more than just family. With you, I've shared laughter that still echoes in my heart and challenges that made us stronger together.I admire the person you are strong, loyal, and true. Your support means more to me than I can say,I'm grateful for every moment, every joke, every serious talk, and every silent understanding between us. Thank you for being my brother and for being one of the best parts of my life.

To my dear Sister, Chaimaa BOUYAKNIFEN

Our relationship has been filled with laughter, shared memories, and sometimes disagreements but through it all, the love we share has always been strongerI admire the person you've become: strong, compassionate, and true to yourself. Watching you grow and face life with courage fills me with pride.
No matter what the future holds, know that my love and support for you will never fade.

To my heart's companion, MOHAMED TALEB

My partner in love, life, and purpose. More than a husband, you've been a friend, and a second father to me . A steady presence full of strength, wisdom, and love. Through every high and low, you stand by my side with patience and unwavering support.I am endlessly grateful for your gentle heart, your understanding, and the way you believe in me even when I doubt myself. With you, I have found a partner who not only shares my dreams but also helps me become the best version of myselfYou're my compass, gently leading me through life's uncertainties and helping me find my way with calm and confidence.

To my lifelong friend DR EZZAIDI OUIAM

For more than nine years, you've been a constant in my life , a loyal, steady, and irreplaceable presence. Our friendship has grown with us, weathered storms, and celebrated countless joys. Through all the changes life has brought, one thing has remained the same: your place in my heart.Thank you for being more than a friend , for being family in every sense that matters. I'm endlessly grateful for you, and I hope you always feel how deeply valued and loved you are.Wherever life takes us, know that I'll always be here, just as you've always been for me.

To my dear friend DR HSAINI IBTISSAME

Having you in my life has been one of my greatest blessings, Over the years, we've shared so many special moments , filled with laughter, honesty, and comfort. I deeply appreciate the time we spend together, the long conversations, and even the smallest chats that always seem to bring me peace or clarity. With you, everything feels lighter. You listen with your heart, speak with kindness, and always know how to make me feel understood.Thank you for being exactly who you are.

To my dear friend DR HAJJY HAFSSA

Having you in my life has brought so much warmth and joy. I'll always cherish the moments we've spent together under your roof — conversations that lasted for hours, smiles that came so naturally, and the comforting feeling of being welcomed without hesitation. Your generosity, both in spirit and in action, is something rare and beautiful.Thank you for being such a giving soul, for sharing your space, your time, and your heart so freely. I'm truly grateful for the bond we share, and I look forward to many more moments by your side.

To my dear binome DR BOUZID OUMAIMA

We've been through it all together — every internship, every challenge, and every exam. Sharing all those experiences with you made the journey not only easier but truly unforgettable. Sharing those shifts with you made even the toughest days feel lighter and full of support. You were not only my binome during those demanding hours but also a source of encouragement and laughter.

Beyond work, I've always admired the delicious meals you prepare , a true reflection of your generous and caring nature. Thank you for being by my side through it all and for bringing so much warmth into my life. I'm truly grateful for our friendship and all the unforgettable moments we share.

To my amazing group 4 (DR BRADIA HAKIM ,DR ASSIA CHAALI , DR BOURI TAOUFIK , DR SOUKAINA CHAJA , DR ACHRAF BOUTMIR , DR CHAIB AINO ZAKARIA)

Learning alongside each of you has been an unforgettable experience. Together, we faced challenges, celebrated successes, and supported one another through every step of this journey. Our teamwork, dedication, and shared passion made even the toughest days brighter and every achievement sweeter. I'm grateful for the laughter, the learning, and the memories we created as a team.

Thank you all for your encouragement, friendship, and the incredible bond we built. I'm proud to have shared this chapter of my life with such a remarkable group of people.

ACKNOWLEDGMENTS

To our Master and Thesis supervisor,
Professor LAMIAA ESSAADOUNI
I sincerely thank you for the kindness and spontaneity with which you graciously agreed to supervise this work.
It was a true pleasure to work under your guidance. You have been both an advisor and a mentor, always welcoming me with sympathy, a smile, and genuine kindness.
Your thoughtfulness, practical expertise, and human and professional qualities inspire my deepest admiration and respect. I hope I have been worthy of the trust you placed in me, and I ask you, dear Professor, to accept here the expression of my sincere appreciation and profound gratitude.

To our Master and thesis president,
Professor MOHAMMAD ZYANI
We extend our deep honor and gratitude for your willingness to chair this thesis defense. Your expertise, extensive knowledge, and compassionate demeanor have made a lasting impact on everyone, from students to patients.
Through this work, we express our heartfelt gratitude and deepest respect to you.

To Professor and jury member,
Professor FOUAD ASRI
Your presence on the jury of this thesis was a great honor for me. I sincerely thank you for your availability, humility, and kindness, which are remarkable qualities alongside your scientific rigor. I dedicate this work to you as a token of my deep appreciation and respectful sentiments.

To Professor and jury member,
Professor MOUNA ZAHLANE

I convey my heartfelt gratitude to you, dear Professor for graciously accepting to be a judge in our thesis defense. Your kindness and benevolence have been evident throughout your compassion and generosity towards patients, coupled with your mentorship and expertise towards students, I am sincerely grateful for your invaluable participation and guidance.

To Professor and jury member,
Professor HASSAN QASIF

It was with great pleasure that I reached out to you to ask you to be a member of the jury for this thesis, which crowns seven years of hard work and medical studies.
I have always admired your simplicity and approachable nature, and I am truly grateful for the knowledge I have gained thanks to your outstanding human and professional qualities.

ABBREVIATIONS

list of abbreviations

BD	:	Behçet's Disease
CRP	:	C-Reactive Protein
CAR	:	CRP to Albumin Ratio
NAR	:	Neutrophil to Albumin Ratio
NLR	:	Neutrophil to Lymphocyte Ratio
PLR	:	Platelet to Lymphocyte Ratio
LMR	:	Lymphocyte to Monocyte Ratio
MPV	:	Mean Platelet Volume
OCT	:	Optical Coherence Tomography
FA	:	Fluorescein Angiography
IOP	:	Intraocular Pressure
VEP	:	Visual Evoked Potentials
CME	:	Cystoid Macular Edema
MEM	:	Macular Epiretinal Membrane
BOS24	:	Behçet's Ocular Attack Score 24
ISG	:	International Study Group
SUN	:	Standardization of Uveitis Nomenclature
HTN	:	Hypertension
CHU	:	Centre Hospitalier Universitaire
DVA	:	Decreased Visual Acuity
RPE	:	Retinal Pigment Epithelium
NK	:	Natural Killer
DC	:	Dendritic Cells
HLA	:	Human Leukocyte Antigen
TNF-α	:	Tumor Necrosis Factor Alpha
IL	:	Interleukin
MRI	:	Magnetic Resonance Imaging

TABLE OF CONTENTS

INTRODUCTION

Behçet Disease or Behçet syndrome ,Described for the first time by Hulusi Behçet in 1937, is a relapsing and remitting variable vessel vasculitis,characterized by recurrent mucocutaneous ulcers that can involve almost every organ system in the body.

Indeed, the presence of recurrent oral or genital ulcers with other auto-inflammatory symptomsshould raise suspicion for this elusive disease.

It is unique among the vasculitides in that it can affect vessels of small, medium, and large size, and tends to involve venous rather than arterial circulation.

Its effects on the pulmonary venous circulation are particularly notable for their role in disease mortality.

Classically seen in Mediterranean, Middle Eastern, and eastern Asian countries, and relatively rare in the United States, prevalence has been increasing, prompting an increased need for internists to be aware of Behcet's clinical presentation and treatment. [1]

Ocular involvement is a frequent and serious manifestation that determines the functional prognosis; it is part of the diagnostic criteria for Behçet's disease (BD).

The new diagnostic criteria for BD, established in 2013, assign significant weight to ocular involvement, attributing it a score of 2 points [2]

The objective of this study is to highlight the biological markers of inflammation and their impact on the activity of ocular Behçet's disease through a retrospective, analytical, and descriptive study involving a series of 92 cases with ophthalmological involvement secondary to Behçet's disease. This study also compares the levels of inflammatory biological markers during the active and inactive phases of ocular involvement.

These patients were followed in the Internal Medicine Department at the university hospital Errazi and followed in consultation over a 14-year period, from January 2010 to December 2023.

PATIENTS AND METHODS

I. Type of study :

This is a retrospective, descriptive study with an analytical component, conducted in the Department of Internal Medicine at Errazi University Hospital over a 14-year period, from January 2010 to December 2023. It included 92 patients diagnosed with ocular Behçet's disease.

II. Patients :

The target population included patients hospitalized or evaluated for ocular involvement related to Behçet's disease.

1. Inclusion criteria :

All patients diagnosed with Behçet's disease based on the 2013 revised International Criteria and presenting with ocular involvement during the period from January 2010 to December 2023 were included in this study.

2. Exclusion criteria :

- Incomplete medical records.
- Records outside the study period.
- Patients with other conditions.
- Patients managed in other departments.

III. Data collection:

Clinical and laboratory data were collected from the medical records of patients followed in the Internal Medicine Department at Mohammed VI University Hospital in Marrakech. Laboratory tests included complete blood count (CBC), C-reactive protein (CRP), CRP/albumin ratio (CAR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and mean platelet volume (MPV), measured during the active phase and after resolution.

The activity of ocular involvement was assessed using the Behçet's Disease Ocular Attack Score 24 (BOS24). This scoring system evaluates six key inflammatory parameters: anterior chamber cells, vitreous haze, peripheral retinal lesions, posterior pole lesions, foveal involvement, and optic disc involvement, each graded according to severity, with a maximum total score of 24 points. The interpretation of the BOS24 score is as follows:

Score = 0 → Inactive disease (no signs of inflammation)

Score ≥ 1 → Active ocular inflammation

Score ≥ 6 → Associated with a higher risk of poor visual outcome

Results obtained during the active and inactive phases were analyzed and compared.

- P-values were calculated to assess the statistical significance of differences observed between the active and inactive phases. The interpretation was as follows:
- $p < 0.001$: highly significant
- $p < 0.05$: significant
- $p \geq 0.05$: not significant

IV. Ethical aspect:

Data collection was conducted in accordance with general ethical principles regarding the respect of confidentiality and the protection of patients' personal data.

RESULTS

I. Epidemiological data:

1. Gender distribution:

In our series, we observed a male predominance, with 64 men (70%) and 28 women (30%), corresponding to a male-to-female ratio of 2.3.

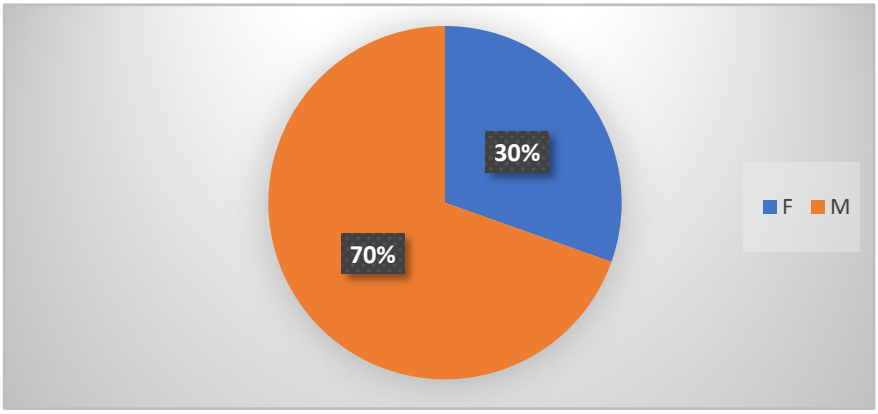

Figure 1: Gender distribution

2. Distribution by age:

In our study, the mean age of patients was 41 years, with ages ranging from 18 to 68 years. The 30-49 age group represented the majority of cases (64.13%), while only 14.13% of patients were between 18 and 29 years old.

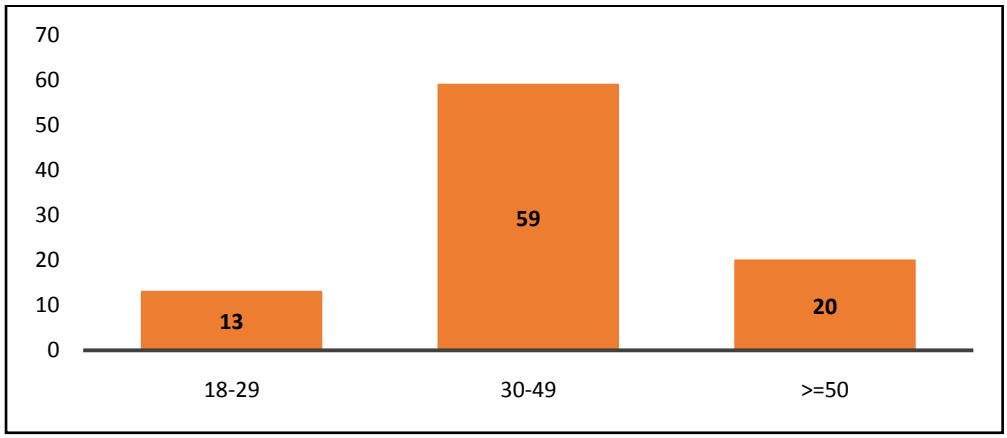

Figure 2: Age distribution

3. Geographic distribution:

All patients enrolled in our study were Moroccan. A majority of them (76%) were from urban areas, whereas only 24% originated from rural regions, highlighting an urban predominance among the study population.

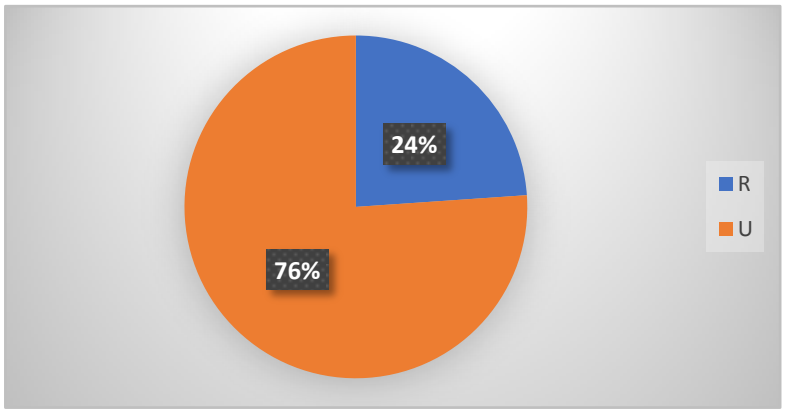

Figure 3: Geographic distribution

II. Clinical data:

1. Personal medical history:

Forty percent of patients in our cohort (n = 37) had a history of prior medical conditions at the time of admission, whereas 60% (n = 55) reported no significant medical history.

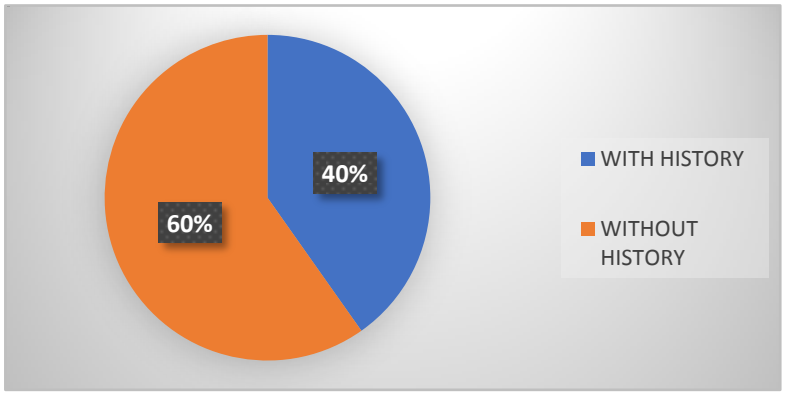

Figure 4: Presence of prior medical history at the time of diagnosis

The specific medical histories documented are summarized in Table I.

Table I:Summary of patients' personal medical histories

Medical History	Occurrence	Frequency
Glaucoma	2	5.41%
Hypertension (HTN)	4	10.81%
Diabetes	7	18.92%
Smoking	12	32.43%
Alcohol consumption	4	10.81%
Cataract surgery	2	5.41%
Monophthalmia	7	18.92%
Thyroid dysfunction	2	5.41%
Dyslipidemia	1	2.70%

2. Family History Cases:

A family history of Behçet's disease was identified in 5 patients, accounting for 5% of all cases.included:two brothers,one brother and two sisters,a father and his son,a brother and a sister,and a mother and her son.

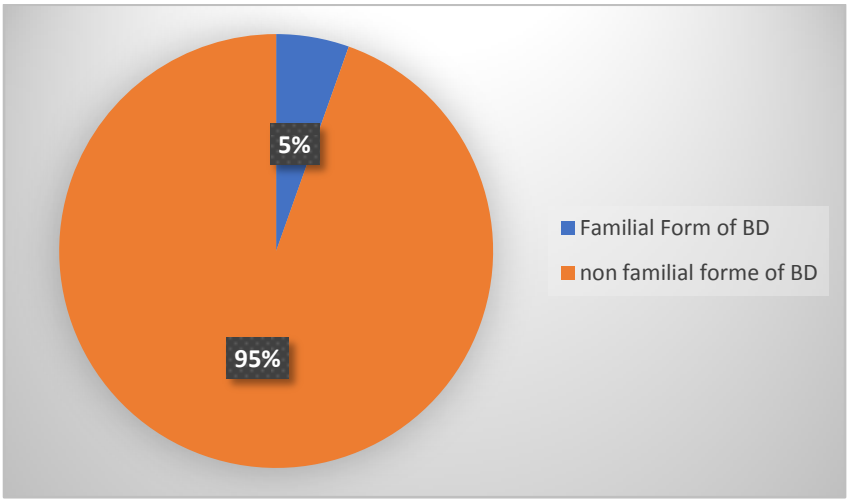

Figure 5:Family history

3. Ocular symptoms:

Decreased Visual Acuity (DVA) was the most common presenting symptom, observed in 94.57% of cases. Ocular redness and periocular pain were seen in 58.70% and 33.70% of patients, respectively. Visual fogginess was reported in 28.26% of cases, while headaches and floaters were less frequent, noted in 8.7% and 3.26% of patients.

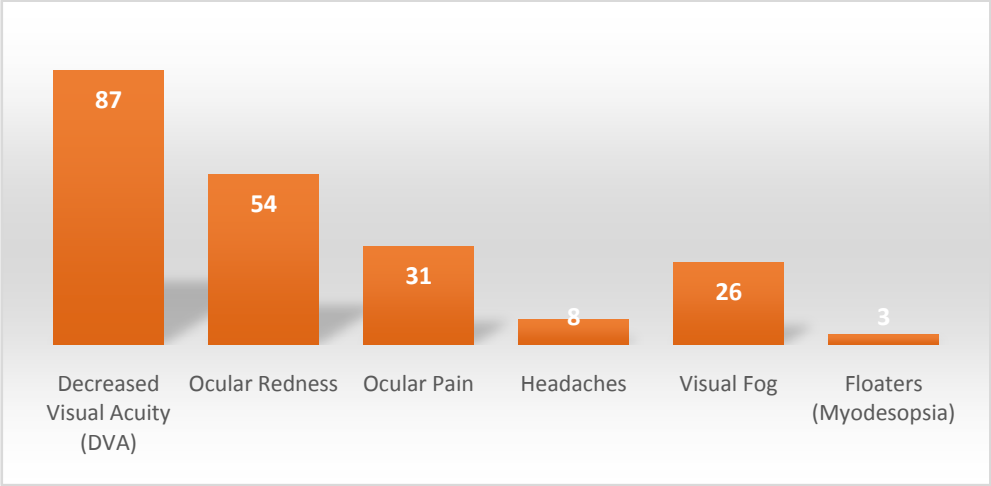

Figure 6:Chiefcomplaint: ocular symptoms

4. Temporal Relationship Between Onset of Ocular Symptoms and Behçet's Disease Diagnosis:

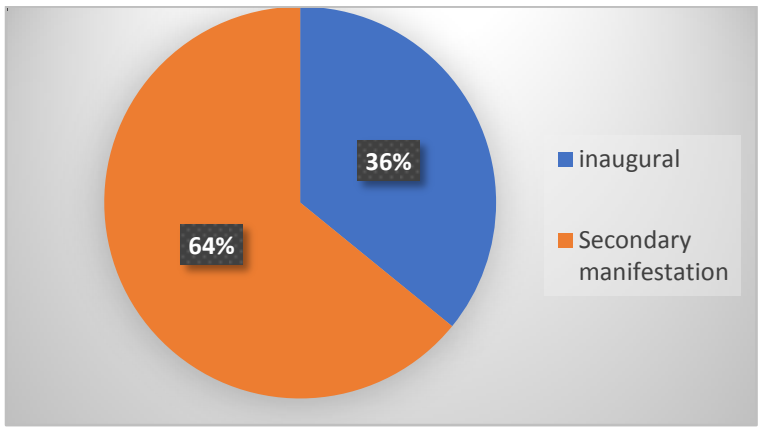

Figure 7: Temporal Relationship Between Onset of Ocular Symptoms and Behçet's Disease Diagnosis:

Ophthalmic manifestations were delayed in 59 patients (64%), with 58% of them developing ocular symptoms within less than 4 years after the diagnosis of Behçet's disease. In contrast, only 36% of patients presented with initial ophthalmic involvement.

Table II: Time interval between the onset of ocular signs and the diagnosis of behçet's disease

Time interval (years)	Occurrence	%	Cumulative %
1	13	22%	22%
2	12	20%	42%
3	2	3%	46%
4	7	12%	58%
5	5	8%	66%
6	1	2%	68%
7	3	5%	73%
8	2	3%	76%
10	5	8%	85%
12	1	2%	86%
14	2	3%	90%
15	2	3%	93%
19	1	2%	95%
20	2	3%	98%
29	1	2%	100%

5. Unilateral versus Bilateral Ocular Involvement in Behçet's Disease

Our sample included 92 patients, with a total of 184 eyes analyzed, of which 163 were affected. Ocular involvement was bilateral in 71 patients (142 eyes), representing 77% of the study population, and unilateral in 21 patients, accounting for 23% of cases.

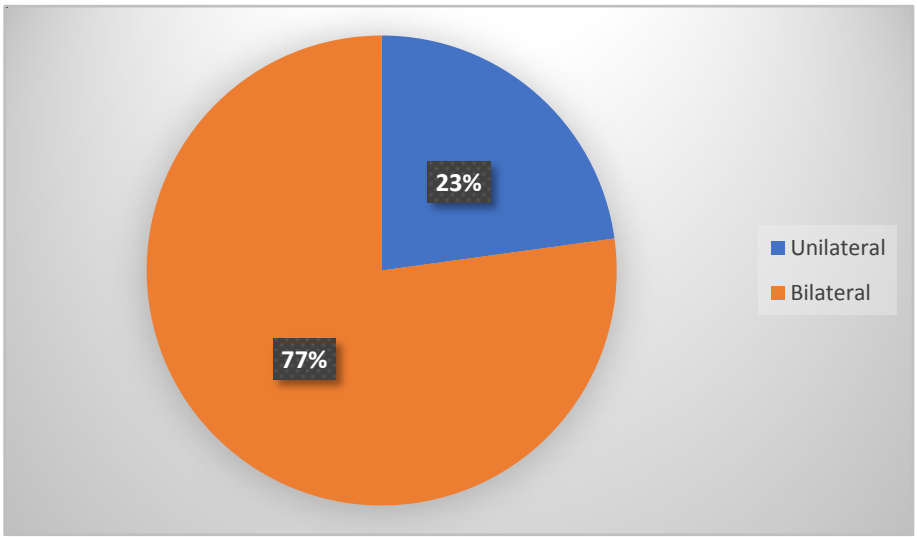

Figure: 8 Distribution of Unilateral and Bilateral Ocular Involvement

6. Clinical Features of Ocular Involvement:

In our series, the clinical manifestations of ocular Behçet's disease, based on ophthalmological examination, were primarily characterized by uveitis in 59 patients (64%). Retinal vasculitis was observed in 43 patients (47%), while maculopathy was present in 9 patients (10%). Papillitis was noted in 6 patients (7%), and optic neuropathy was found in 5 patients (5%) of cases.

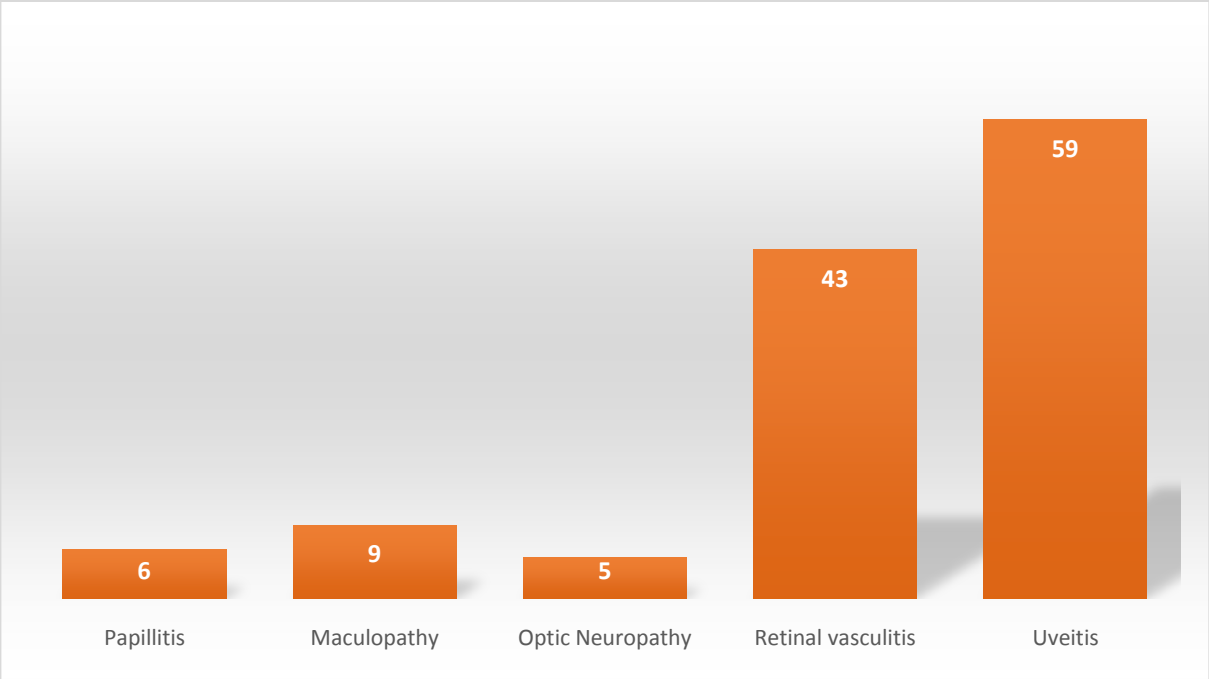

Figure 9: Clinical features of ocular involvement

⇒ **Localization of uveitis:**

Uveitis cases in our cohort were classified according to the criteria of the International Uveitis Study Group (IUSG) [3], (APPENDIX II)

According to this classification, posterior uveitis was the most frequent form, observed in 66% of the cases. Anterior uveitisand panuveitiswere each identified in 10 patients, accounting for 17% of cases respectively. Intermediate uveitis was the least frequent, detected in 10% of patients.

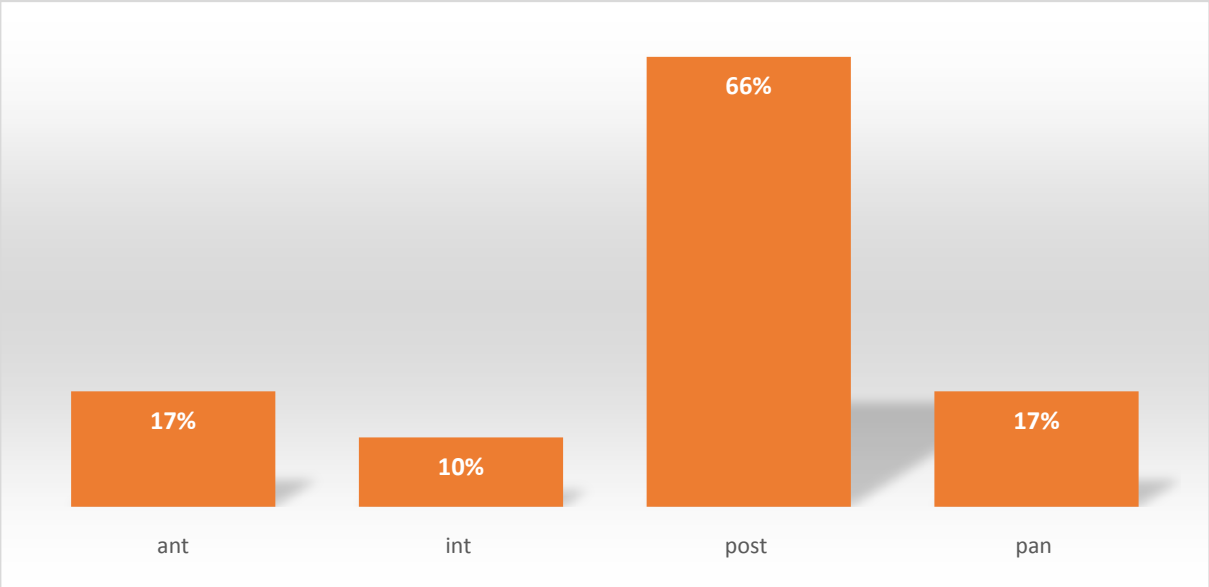

Figure 10:Localization of uveitis

7. Visual Acuity Before Treatment:

The visual acuity assessment of 163 eyes revealed that 36 eyes (22.1%) were limited to counting fingers, 16 eyes (9.8%) could only perceive hand movements, 13 eyes (8%) had positive light perception, and 6 eyes (3.7%) had no light perception. Regarding visual acuity measurable on the Snellen scale, 26 eyes (15.9%) had acuity between 20/20 and 20/30, 24 eyes (14.7%) between 20/40 and 20/80, and 52 eyes (31.9%) between 20/100 and 20/400.

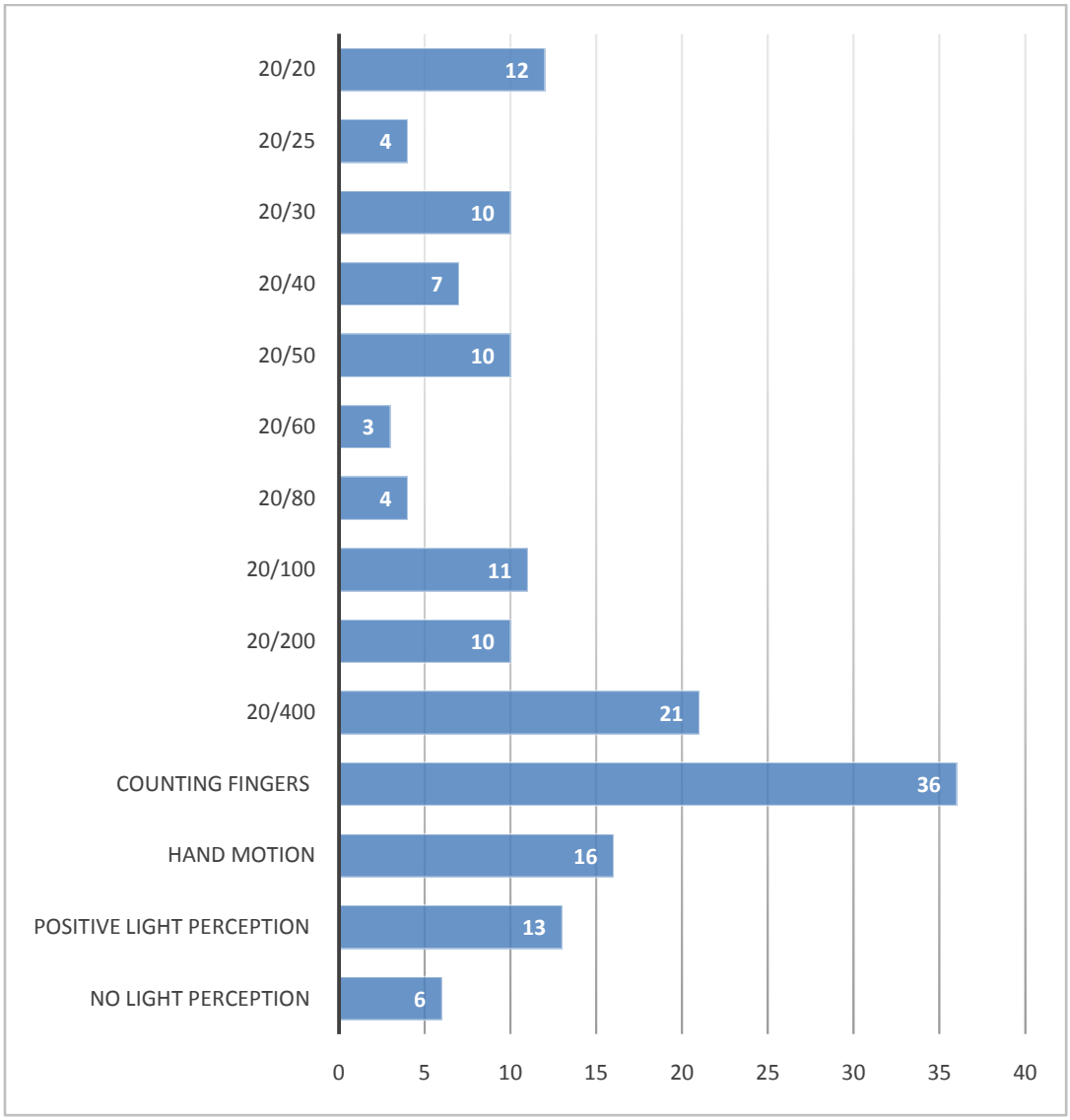

Figure 11: Visual acuity before treatment

III. Paraclinical Evaluation of Ocular Manifestations:

1. Fluorescein Angiography (FA):

Fluorescein angiographic findings were classified using the grading system proposed by Keorochana et al. (2021) [4],(APPENDIX III) based on three criteria: Anatomical location of vascular leakage, Extent of leakage and Severity of leakage

In our study, fluorescein angiography was performed in 46 patients (50% of the total study population) and revealed the following findings:

Table III : Fluorescein Angiographic Findings

Classification Criterion	Finding	Percentage of Eyes (%)
Anatomical Location of Leakage	Posterior pole involvement	54.3%
	Peripheral retinal leakage	43.4%
	Combined posterior + peripheral involvement	26.0%
Extent of Leakage	Diffuse posterior pole leakage	52.1%
	Diffuse peripheral vasculitis	42.5%
Severity of Leakage (late-phase)	Severe posterior pole leakage	23.9%
Ischemic Angiographic Signs	Macular ischemia	4.3%
	Arteriovenous vascular remodeling (AVR)	2.1%

2. Optical Coherence Tomography (OCT):

OCT was performed in 26 patients, representing (28 % of the cases). The following abnormalities were identified:

Table IV :Optical Coherence Tomography

Macular Finding	Number of Cases
Serous retinal detachment	4
Macular edema	18
Macular atrophy	2
Macular hole	4

3. B-Scan Ocular Ultrasonography :

Ocular ultrasound in B-mode was performed in 54 patients, representing (59% of the cases) The following abnormalities were identified:

- 51 cases of hyalitis
- 4 cases of retinal detachment
- 6 cases of Posterior vitreous detachment

IV. Extra-ocular Manifestations of Behçet's Disease:

Behçet's disease was diagnosed clinically according to the International Study Group (ISG) criteria [5]. All of our patients fulfilled these criteria.

The extra-ocular manifestations observed in our patients are presented in the following table:

Table V: Extra-ocular manifestations

Extra-ocular manifestations	Frequency	%
Mucocutaneous involvement	92	100%
Oral ulcer	92	100%
Genital ulcer	63	47%
Erythema nodosum	16	17%
Pseudofolliculitis	26	28%
Articular involvement	32	35%
Neurological involvement:	7	8%
Brainstem lesions	1	1%
Tetrapyramidal and pseudobulbar syndromes	1	1%
Vascular involvement:	11	12%
Deep vein thrombosis of the lower limbs	3	3%
Thrombosis of the right supra-hepatic vein	1	1%
Cerebral venous thrombosis	1	1%
Gastrointestinal involvement	1	1%
ENT involvement:	2	2%
Bilateral hearing loss	1	1%

V. Treatment :

The choice of treatment depends on the type and severity of ocular involvement. Colchicine is mainly used for mucocutaneous and articular manifestations.

1. Local Treatment:

Corticosteroid eye drops were prescribed to 14% of patients (13 cases) to reduce anterior segment inflammation. Additionally, periocular corticosteroid injections were administered to 1 patient (1%) to control severe posterior segment inflammation. Laser treatment was given to 21% of patients.

2. Systemic Treatment:

2.1. Corticosteroids:

All our patients received systemic therapy: all of them were treated with oral prednisone, and 75 patients received intravenous bolus therapy beforehand.

2.2. Immunosuppressants:

In our serie, 86 patients were treated with immunosuppressiveagents,five medications were used:

- Cyclophosphamide
- Azathioprine
- Tacrolimus
- Methotrexate
- Mycophenolatemofetil

Table VI: Use of immunosuppressive agents inour serie

Immunosuppressant	Number of patients	Percentage
Cyclophosphamide	65	71%
Azathioprine	48	52%
Tacrolimus	3	3%
Methotrexate	1	1%
Mycophenolate mofetil	1	1%

2.3. Biologics

Fifteen percent of our patients (14 individuals) received biologic therapy, involving three different agents:

- ADALIMUMAB
- INFLIXIMAB
- TOCILIZUMAB

Table VII: Use of biologics in our serie

BIOLOGICS	Number of patients	Percentage
ADALIMUMAB	6	7%
INFLIXIMAB	3	3%
TOCILIZUMAB	5	5%

VI. Evolutionafter treatment:

Following treatment, 52 patients (57%) showed improvement in their ophthalmologic involvement, indicating a favorable clinical course. Twenty-eight patients (30%) remained stable, with no significant change in ocular symptoms. Thirteen patients (14%) experienced a worsening of their ophthalmologic condition. Additionally, 27 patients (29%) progressed to blindness, primarily due to delayed diagnosis..

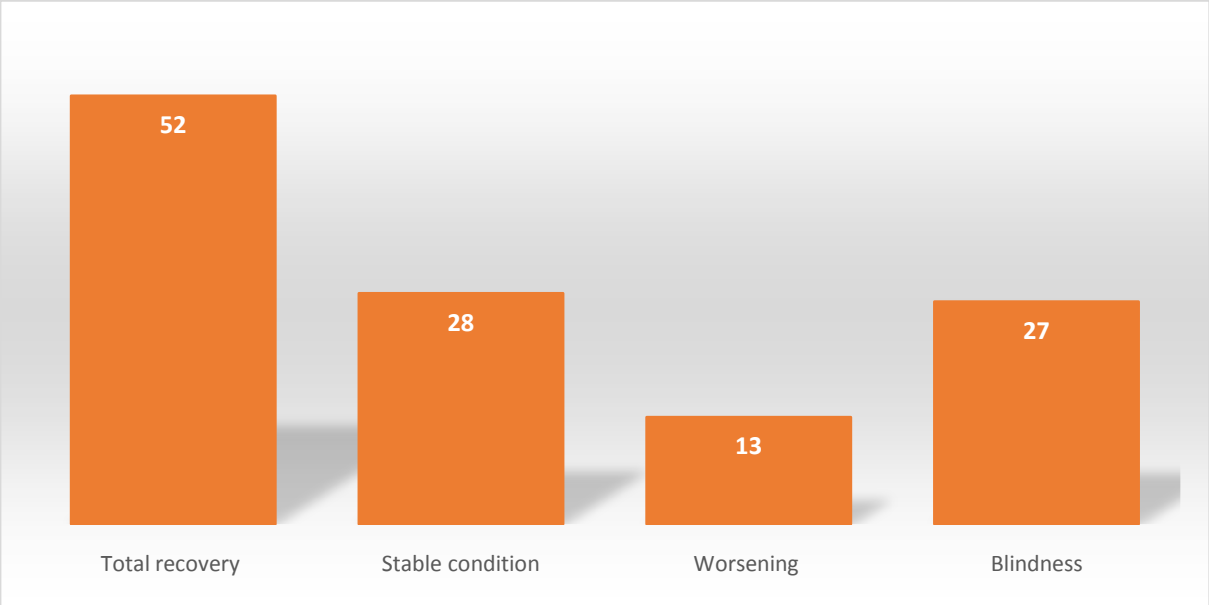

Figure 12:Outcome after treatement

1. Visual acuity after treatment :

A continuous monitoring of visual acuity is conducted by ophthalmologists during consultations, showing an average visual acuity ranging from [no light perception to 20/20]

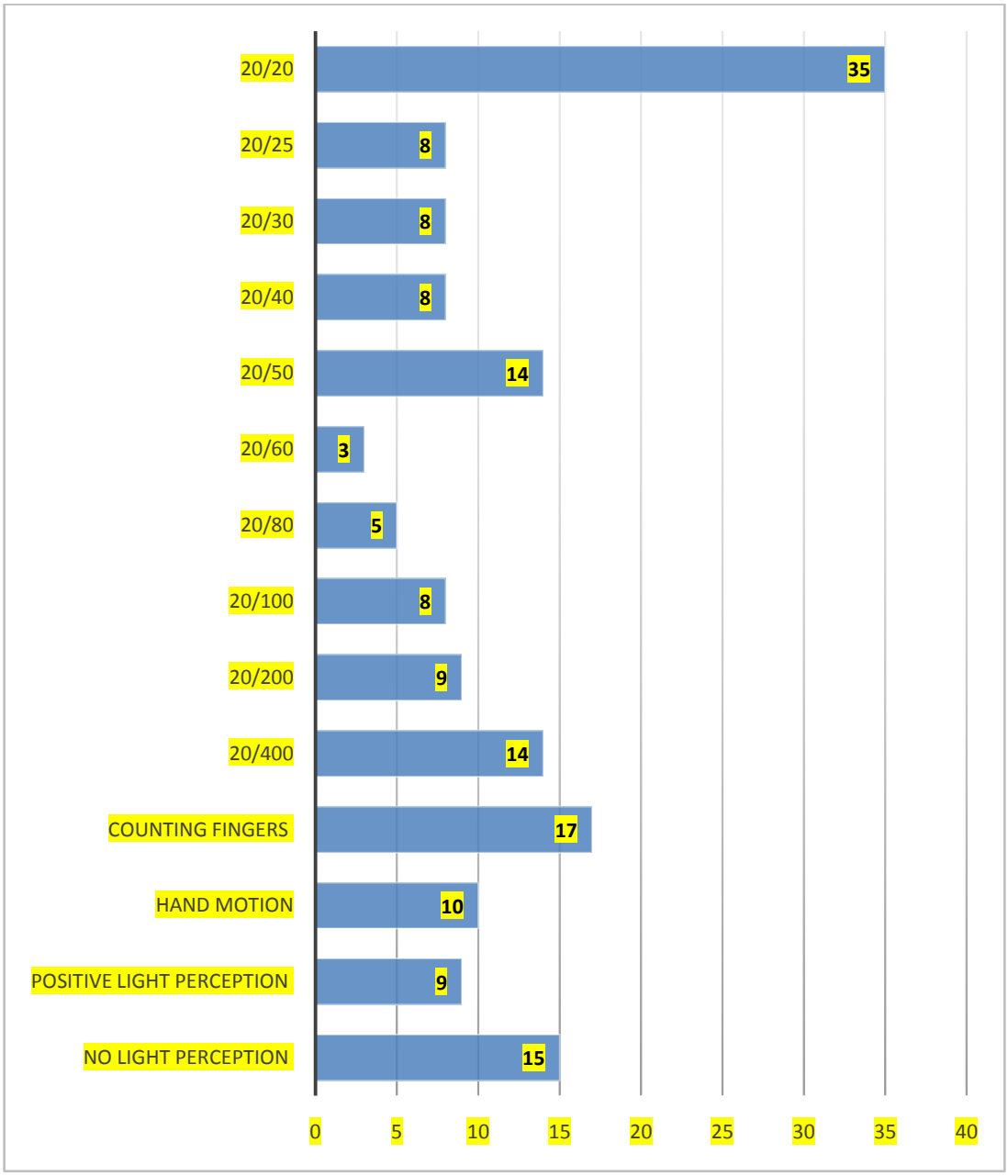

Figure 13: Visual acuity after treatement

2. Ophthalmologic complications after treatment :

The main complications developed by our patients included

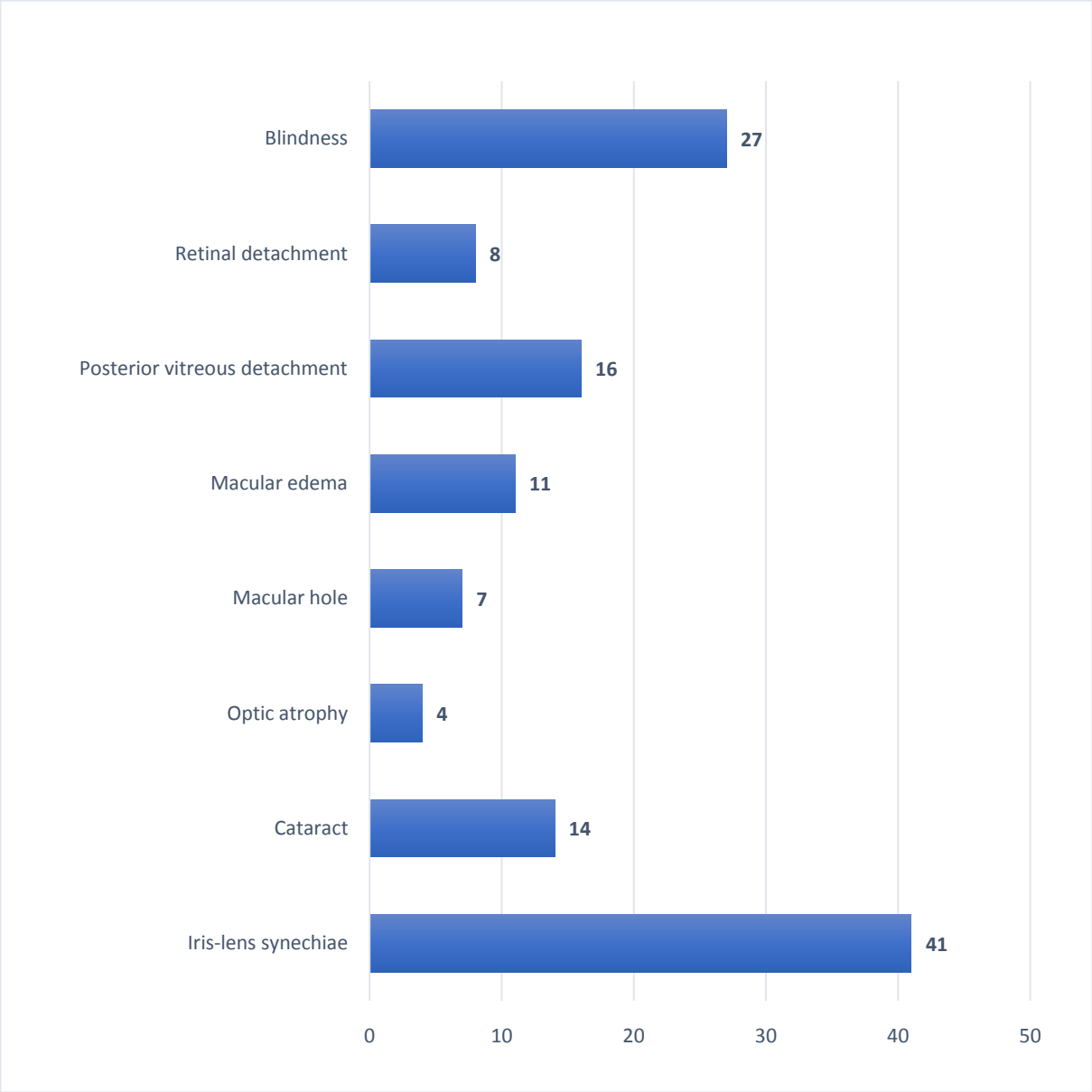

Figure 14: Ophthalmologic complications

VII. Analytical Assessment of Inflammatory Biomarkers in active and inactive pahases:

In our serie,Complete blood count (CBC) testing was performed in 60 patients, C-reactive protein (CRP) levels were assessed in 56 patients, and serum albumin levels were measured in 16 patients, all during both the active and inactive phases of ocular Behçet's disease.

Based on these reports, we calculated the following ratio (Table VI):

- CRP to albumin ratio (CAR),
- neutrophil to albumin ratio (NAR)
- platelets to lymphocytes ratio (PLR),
- lymphocytes to monocytes ratio (LMR),
- neutrophil to lymphocyte ratio (NLR)
- mean platelet volume (MPV),

Statistical analysis revealed significant differences between the active and inactive phases of the disease. MPV and NAR exhibited highly significant changes, with p-values below 0.001. Similarly, LMR and CRP levels showed notable differences, with p-values of 0.023 and 0.007, respectively. The CAR also displayed a statistically significant variation (p=0.014). On the other hand, PLR and NLR did not show any significant changes, with p-values of 0.910 and 0.222, respectively.

Table VIII: P-Value analysis of inflammatory biomarker inour serie

Parameter	Active (mean ± SD)	Inactive (mean ± SD)	P-value	Significance
MPV	10.8 ± 0.6	9.3 ± 0.5	< 0.001	Highly significant
NAR	5.6 ± 1.2	3.4 ± 1.0	< 0.001	Highly significant
LMR	2.3 ± 0.5	2.9 ± 0.4	0.023	Significant
CRP	21.0 ± 6.0	5.8 ± 2.5	0.007	Significant
CAR	1.22 ± 0.35	0.82 ± 0.28	0.014	Significant
PLR	142 ± 46	138 ± 43	0.910	Not significant
NLR	3.6 ± 1.3	3.2 ± 1.2	0.222	Not significant

DISCUSSION

I. Defintion:

Behçet disease is a chronic, relapsing systemic disorder characterized by variable clinical manifestations including oral and genital aphthae, cutaneous lesions, ocular, gastrointestinal, neurological involvement, and arthritis.[6]

The etiopathogenesis of the disease remains unknown, although genetic predisposition, environmental factors and immunological abnormalities have been implicated. [7]

It is unique among the vasculitides in that it can affect vessels of small, medium, and large size, and tends to involve venous rather than arterial circulation.

its effects on the pulmonary venous circulation are particularly notable for their role in disease mortality.[1]

Ocular involvement is a frequent and serious manifestation that determines the functional prognosis; it is part of the diagnostic criteria for Behçet's disease (BD).

The new diagnostic criteria for BD, established in 2013, assign significant weight to ocular involvement, attributing it a score of 2 points [2]

II. History :

First description of BD, also known as the Old Silk Route disease, has been attributed to Hippocrates in the 5th century BC, in the ‘‘Third book of endemic diseases’’. There are also descriptions of patients with constellation of symptoms and signs that are similar to BD since the 18th century all the way to the 20th century, namely by Neumann, Christlieb, Reis, Blu¨the, Gilbert, Adamantiades, Shigeta, Pils, among others.

In 1937, Behçet, a Turkish dermatologist, identified the 3 major signs (recurrent oral aphtae, genital ulcerations, recurrent hypopyon uveitis) and grouped them on a clinical entity, publishing a report in a German journal in 1937 and one in 1938 in a French journal.

Later in 1939 and 1940 he called it the ‘‘triple symptom complex’.

After these descriptions, many reports were followed from different places. Jensen, a Danish doctor, was the first to use the eponym ‘‘Behçet’’ in 2 publications in 1941 (‘‘Sur les ulcerations aphteuses de la muqueuse de la bouche et de la peau ge´nitale combines avec les symptoms oculaires (¼Syndroˆme Behçet)’’ and ‘‘Ulcerous haemorragic colitis associated with Behçet’s syndrome’’). Afterwards, several other authors used the eponyms ‘‘Behçet’s syndrome’’ and ‘‘Behçet’s disease’’.

In 1947, in the International Medical Congress of Geneva, in Switzerland, the disease was named ‘‘Morbus Behçet’’, after Zurich Medical Faculty Professor Mischner’s proposal [11,12]. The disease is sometimes referred as Adamantiades-Behçet’s disease, however, Behçet’s disease should be preferred as suggested by International Associations and Societies of ‘‘Behçet’’. [13]

III. Anatomical and physiological overview of the eye [14]:

The eye is the primary organ of the visual system, capturing images and converting them into electrical signals transmitted via the optic nerve. These signals are then 'interpreted' by the brain in the visual cortex, which processes the information and enables us to perceive and interpret our surroundings

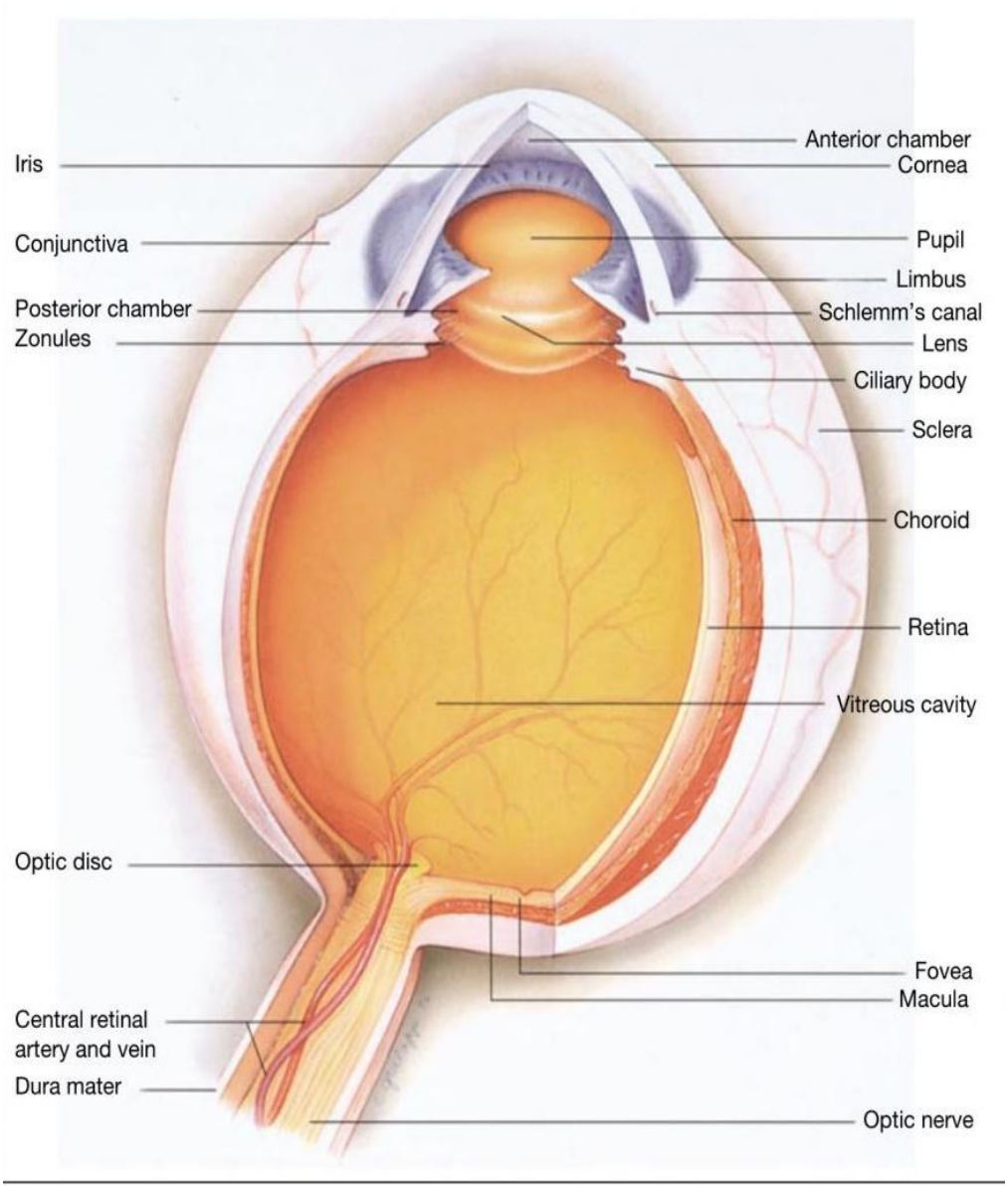

Figure 15: Structure of human eye[14]:

The eye can be broadly divided into two segments; the anterior segment and the posterior segment. The anterior segment consists of cornea, conjunctiva, aqueous humor, iris, ciliary body and crystalline lens. These occupy approximately one-third of the front of the eye. The remaining portion, posterior segment, comprises sclera, choroid, Bruch's membrane, retinal pigment epithelium (RPE), neural retina and vitreous humor.

1. Anterior segment :

1.1. Cornea:

The cornea is thin, transparent, smooth, avascular, highly innervated and the most sensitive tissue in the body. It is convex, aspherical in shape, and directly exposed to the external environment. The cornea is continuous with the white part of the eye, called the sclera, and the semi-transparent tissue, called the conjunctiva. The border of the cornea, where it continues with the sclera, is called the limbus.

1.2. Conjunctiva:

The conjunctiva is a thin, highly vascularized, semi-transparent, mucous- secreting tissue that forms the inner lining of the upper and lower eyelids. It is reflected onto the eye as a thin transparent tissue on sclera and extends up to the corneal limbus. This tissue is highly innervated with efferent, afferent and sensory nerves and is also supplied with lymphoid tissue. The total surface area of conjunctiva is approximately 17 times larger relative to cornea. Due to its elastic nature, conjunctiva facilitates motion of the eyeball and eyelids. A mucous layer of tears in conjunction with a small portion of aqueous humor protect the inner ocular tissues from the external environment. Depending on location, thickness and vascularization, this tissue can be further divided into three types as palpebral, forniceal and bulbar conjunctiva.

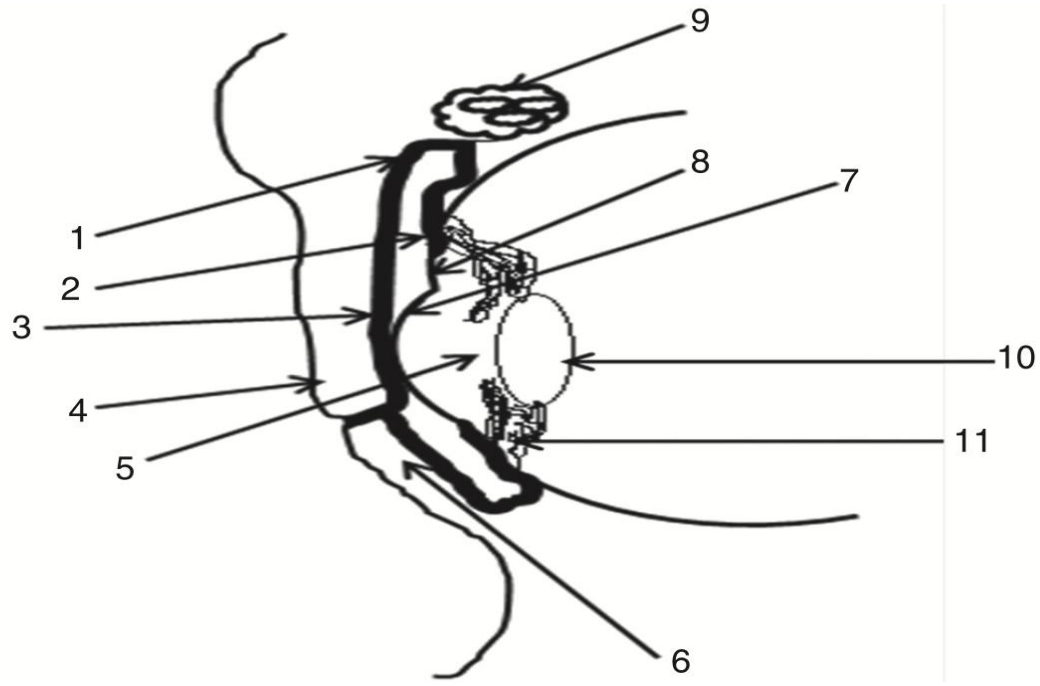

Figure 16: Diagrammatic representation of anterior chamber of human eye with closed eye lids showing three distinct conjunctivas (bold layers) [14]:

(1) Forniceal conjunctiva, (2) bulbar conjunctiva, (3) palpebral conjunctiva, (4) upper eye lid, (5) aqueous humor, (6) lower eye lid, (7) cornea, (8) sclera and (9) lacrimal gland, (10) crystalline lens and (11) iris ciliary body

1.3. Aqueous humor:

Aqueous humor is an optically clear, slightly alkaline ocular fluid that is continuously formed (~□2.5 □L/min in humans) from plasma by epithelial cells of ciliary body. Three different processes – diffusion, ultrafiltration and active secretion – contribute to the chemical composition and formation of aqueous humor. It is estimated that the entire aqueous humor is replaced in approximately 100 min. This fluid contains relatively less protein, albumin and G-globulins, than plasma. Additionally, glucose, lactic acid, ascorbic acid and immunoglobulin G are also present. Aqueous humor supplies nutrients and some oxygen to the ocular avascular tissue, namely cornea and lens. It removes waste products, macrophages, blood and other debris from the posterior of the cornea and anterior of the lens.

Also, it plays an important role in maintaining the shape and internal ailments of the eyeball along with production of intraocular pressure. Aqueous humor produced and secreted into the posterior eye segment passes through the pupil into the anterior chamber. It is drained into the venous blood circulation via the trabecular meshwork and the canal of Schlemm. Approximately 5-10% of aqueous humor is drained following the uveo-scleral pathway

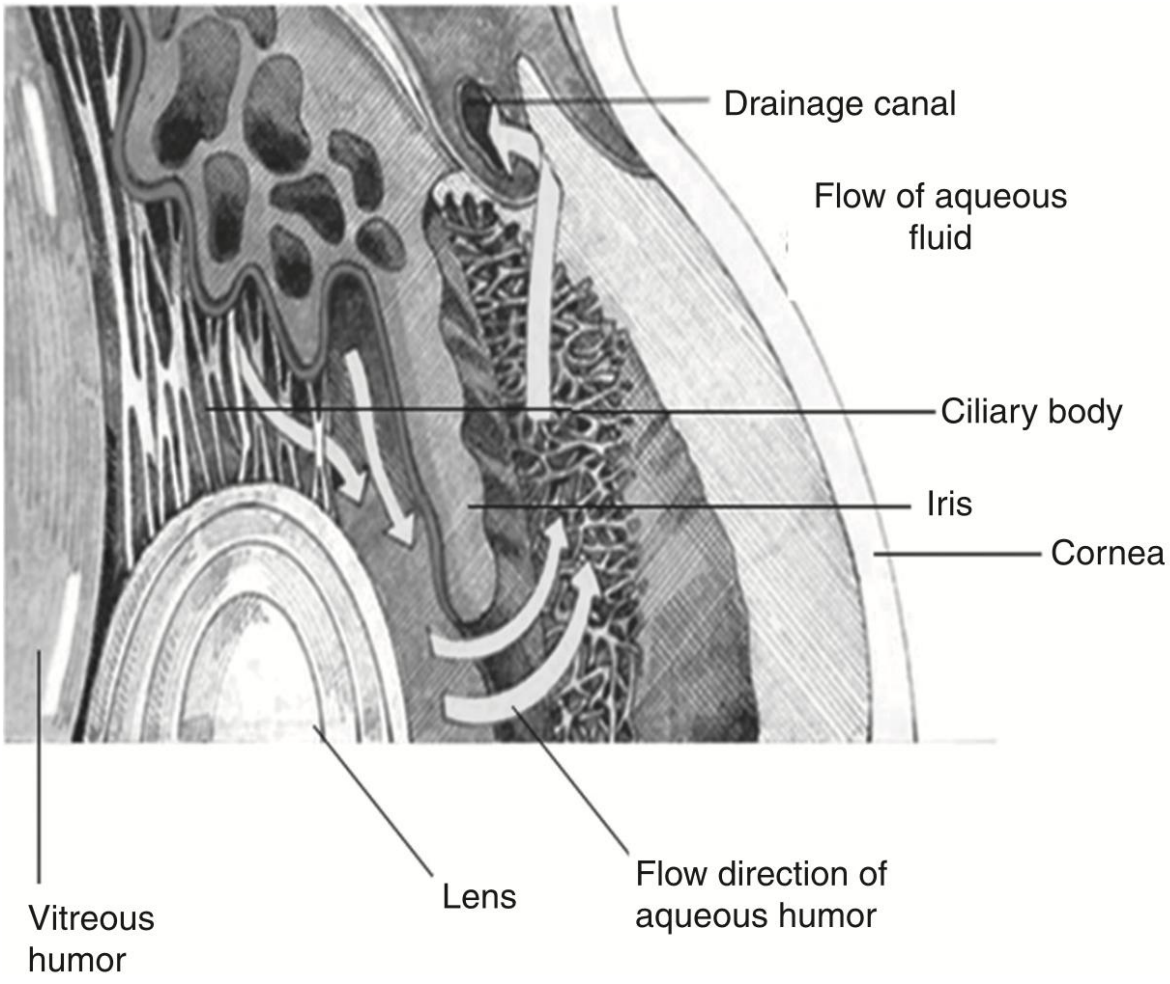

Figure 17: Flow direction of aqueous humor from iris to canal of Schlemm or towards cornea[14]:

1.4. Iris–ciliary body:

Iris and ciliary body are two different tissues with different anatomical locations and physiological functions. For easy understanding and close anatomical localization, their anatomy and physiology are described together.

The iris is located at the posterior region of cornea and appears as a root of the ciliary body. Histologically, the iris is composed of three different layers – endothelium, stroma and epithelium. The iris makes a small circular opening or aperture in front of the lens, called the pupil, which helps to regulate the amount of light passing through to the retina. Each ciliary body contains a ciliary process, which in turn possesses a fibrovascular core that appears to be continuous with the stroma of the ciliary body. The blood flows from the anterior to posterior choroidal veins. All the blood from the ciliary body of the eye is drained out via the vortex vein. The ciliary body is anatomically located anterior to the iris and is involved in regulating three major functions in the eye: it secretes aqueous humor, which passes in front of the lens and drains out of the eye via tubules called the trabecular meshwork and canal of Schlemm near to the junction of cornea and iris; this tissue also contains smooth muscles that act via zonular fibers on the crystalline lens to adjust focus on objects; and it can help in draining aqueous humor from the eye into the adjacent trabecular meshwork by extending smooth muscle fibers and tendons.

1.5. Lens:

The lens (Figure 17) is transparent, avascular, non-innervated and biconvex. It is positioned behind the pupil and iris with the support of the ciliary body's zonular fibers. The anterior lens is covered with aqueous humor and the posterior with vitreous humor. The lens membrane (also known as the capsule) regulates passive exchange of metabolic substrates and waste through simple diffusion regulated by their size and charge. The lens consists of four distinct parts: capsule, epithelium, cortex (fiber cell mass) and nucleus. Also, it controls light entry into the eye and its refraction.

The capsule is an uninterrupted strong, transparent, elastic basement membrane encapsulating the entire lens and providing structural support to the lens within the eye. The thickness of the capsule varies between species and within the same group. For example, the capsule thickness in mouse, rat, rabbit and bovids measures about 10 µm, 13 µm, 14 µm and 48 µm, respectively. Human anterior capsule thickness ranges from 25 to 30 µm relative to posterior, which is 2 µm.

The membrane of the capsule compartmentalizes the lens from direct contact with the surrounding ocular tissues and aqueous fluids. Also, it acts as a reservoir for growth factors by sequestering them within it and provides a protective barrier against microbial attack. The release of growth factors from a capsule promotes development and differentiation of lens cells. The mechanism by which the lens acquires its shape and surface curvature is unclear. A tall columnar epithelial monolayer is present below the anterior lens capsule. The epithelium is absent in the posterior part of the lens, which is in contact with vitreous humor.

The cortex is present below the capsule and next to the lens epithelium. It contains 68.6% water. The lens cortex is composed of recently formed fibers, which make up the bulk of the lens. The fibers are tightly packed, and newly formed fibers contain cell organelles with nucleus. With age, the fibers are displaced towards the center of the lens (Figure 17). During this maturity period, fibers lose their organelles and nucleus, resulting in lens transparency. Arrangement of these fibers in the adult lens resembles a four-pointed star arrangement. Intertwining between neighboring fiber cells may cause interlocking in the deeper lens fibers. As one moves deeper into the lens cortex, near to the nucleus, cells appear in hexagonal shapes with ridges. The interlocking mechanism may help to stabilize the packing arrangement during the process of accommodation and possibly prevent fiber cells slipping against each other.

The lens nucleus is highly protected by its location. It contains 63.4% water and is formed by deposition of old fiber cells that translocate to the center from the periphery. As the result of accumulation of old cells in this region, it becomes very thick and denser.

2. Posterior segment :

2.1. Sclera:

The sclera, commonly called the 'white of the eye', is a tough, avascular, sieve-like elastic tissue present below the conjunctiva and continuous with the cornea. The optic nerve exits posteriorly through this densely interwoven fibrous tissue network called lamina cribrosa. The episclera (topmost layer of sclera) supplies required nutrients to the sclera. The sclera makes up almost 80% of the eye's tunic and the remainder is made by cornea anteriorly. The thickness of sclera depends on its anatomical location. Anterior sclera, near limbus, is thick and as one moves towards the equator, the thickness decreases. Moving to the posterior of the eye, near and around the optic nerve, it doubles in thickness. The sclera is composed of a disorderly network of collagen fibers derived from the dura mater of the central nervous system. This type of arrangement causes scattering of all visible light wavelengths and appears brilliant white in color. At the junction of sclera and cornea this irregular arrangement abruptly changes to a regular and systematic arrangement. Such a change brings opaque white sclera to the transparent cornea. The same collagen fibers are present in the cornea but are arranged in a regular pattern that provides transparency to the tissue. Being hydrated, scleral fibers remain opaque while corneal fibers do not retain water and become transparent. The corneal endothelium helps to maintain its transparency by draining out of water. Sclera, being the outer coat of the eyeball, is subjected to frequent changes of external environment as well as of intraocular pressure. Diameter of the scleral fibers in the equatorial region ranges from 25 to 230 nm and the aqueous pore diameter of the sclera ranges from 20 to 80 nm.

2.2. Choroid:

The choroid is present between peripheral sclera and inner retinal pigmented epithelium. It is a highly vascularized and innervated tissue containing melanocytes along with mucus-like extracellular fluid. The choroid consists of three distinct parts: from outer to inner – suprachoroid, vascular layer and Bruch's membrane.

The suprachoroid is made of six to ten layers, approximately 30 μm in thickness, which form the interface between outer sclera and inner choroid. The suprachoroid continues anteriorly with supraciliary space and extends posteriorly up to the optic nerve. This region is highly innervated with nerve fibers and ganglion but no vasculature. Thin lamellar fibers, in apposition to each other, interconnect the choroid and sclera. This arrangement causes development of a small space between these tissues called the suprachoroidal or perichoroidal space. This space is generally absent as one moves posteriorly towards the macula.

The vascular layer underneath the suprachoroid consists of three distinct vessel layers with gradually decreasing capillary and luminal diameters. These vessels are surrounded by pigmented melanocytes and non-pigmented fibrocytes and occupy the largest choroid volume. The vessels, fibrocytes and melanocytes are embedded in small amounts of choroidal stroma. The density of melanocytes increases from center to periphery. Choroidal vessels are named according to luminal diameter and location as: Haller's layer with outer larger size vessels; intermediately located Sattler's layer with medium-sized vessels; and deeply located choriocapillaries with vessels of small diameter. The blood circulation in choroid is relatively high compared with other ocular tissues and brain . Increased choroidal blood circulation allows nutrient supply and diffusion of high-gradient oxygen into the inner neural retina. Retinal metabolic wastes are removed along with changing intraocular temperature generated by visual process. Also, this accelerated blood flow appears to play a role in regulating intraocular pressure.

Bruch's membrane is the last and innermost layer of choroid that lies above the RPE. It is also called the lamina vitrea. This is a thin, pentalamellar, elastic, acellular membrane-like structure which is produced in collaboration of choriocapillaries and RPE. Bruch's membrane extends from the posterior segment of the eye, i.e. the optic nerve, to the ora serrata of the iris, where its thickness gradually decreases from the back of the eye to the periphery. This membrane separates RPE and choriocapillaries. The retinal cellular organization contains seven different types of cells, including RPE cells. They are photoreceptor cells (rods and cones), horizontal cells, amacrine cells, interplexiform cells, bipolar cells, ganglion and glial cells

2.3. Retinal pigment epithelium (RPE):

Each eye of an individual contains approximately 3.5 million RPE cells, which adhere together to form tight junctions (zonulae occludentes). The retinal pigment epithelium is composed of non-dividing cells, which form a monolayer lining above the neural retina. Though these cells are non-dividing, under pathological conditions they may proliferate. It provides protection to inner ocular tissues and secretes large numbers of growth factors (vascular endothelial growth factor, ciliary neurotropic factor and platelet-derived growth factor). This monolayer maintains ocular immunity and protects from oxidative damage with secretion of immunomodulatory cytokines. The RPE cells produce several enzymes, such as superoxide dismutase, catalase, glutathione and melanin pigment. RPE plays a vital role in providing support and survival of choriocapillaries and functioning of photoreceptors. Therefore, its presence is essential for maintaining visual function. Its functions involve the disposition of photoreceptors to outer segments, retinoid metabolism, maintaining the visual cycle and regulation of the subretinal chemical milieu.

2.4. Neural retina:

Topographically, the retina is organized into macula, optic disc, fovea and peripheral retina. The macula or area centralis is about 1.5 mm in thickness and located approximately 3 mm away from the optic disc. Macula derives its name from the yellow carotenoid pigment, xanthophyll, as the macula lutea. The center of the macula represents an important region of visual acuity and is named the fovea. The fovea has the highest density of narrow and elongated cone receptors to maximize light detection. The center of the fovea is avascular up to 500 μm and the blood supply to this region comes from choriocapillaries. Retinal temporal blood vessels surround/enclose the fovea. The outer layer of the fovea is thick and contains nuclei of photoreceptor cells. The remaining peripheral retina, anatomically one layer of ganglionic cells, is present outside the temporal retinal arteries. Most outer retina gets its blood supply from the choroidal circulation, whereas general retinal circulation fulfills inner retinal blood supply. The inner lining of the eyeball is composed of light-sensitive neural cells, called the neural retina, which transmit sensory information to the brain and interact with the external environment. These sensory nerves originate from the central nervous system. Neural retina is made up of approximately 7.7 million rods and 5 million cones.

The photoreceptor cells consist of rods and cones. These cells mainly function to capture and convert the photons into a nerve signal. Retinal rod cells are responsible for differentiating colors in bright light whereas cone cells take care in distinguishing black and white color in dim light. The highest number of cones are found in the fovea, whereas the rods are distributed through the retina except for the central fovea. The cones and rods are interconnected with inter-neurons called bipolar cells. Visual information is transmitted to ganglion cells through the bipolar cells, which act as a bridge . Ganglionic cells transmit information as electric signals to the central nervous system , i.e. brain. During this process Müller's cells help in regulating th e local microenvironment for proper visual functioning.

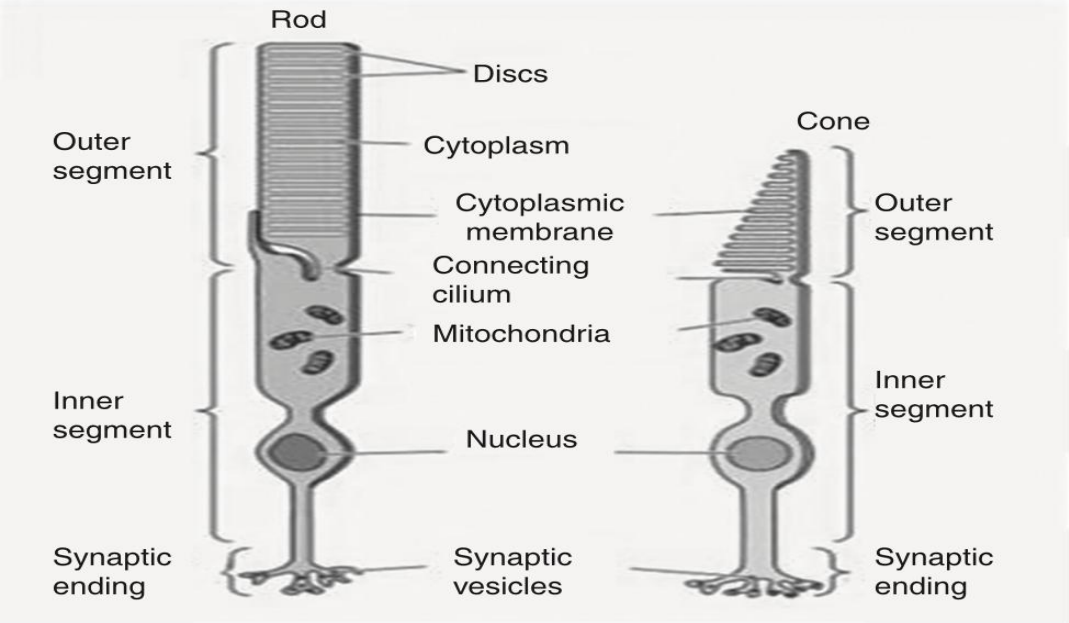

Figure 18: Diagrammatic representation of rod and cone cells of neural retina[14]:

2.5. Vitreous humor:

The posterior segment of the eye is mostly avascular and transparent, thick, gel-like fluid covers the space between lens and retina. It is called vitreous humor or vitreous body. It aids in maintaining the structure of the globe. This fluid is composed of 99.9% water and 0.01% collagen fibrils, hyaluronic acid and ions. The vitreous body and neural retina are separated from each other by an inner limiting membrane. The vitreous is firmly attached to anterior retinal layers at the ora serrata, which is present at the posterior segment of the iris-ciliary body. It is loosely attached at optic nerve and posterior macula. In this way the anterior and posterior chamber fluids are separated. These connections around the optic nerve and macula help to hold the vitreous body against the retina.

The thickness of the fluid decreases with growing age. As this happens, anterior aqueous humor may permeate into the posterior vitreous, resulting in a tugging effect at the attachment point of retina and vitreous fluid. Additionally, this may cause the release of cells into the fluid, which appear as floaters, and if a significant tugging effect is developed it may pull away or detach the retina.

3. Vascularization and Innervation:

3.1 Arterial Vascularization:

a. Main axis: the ophthalmic artery

It is a branch of the internal carotid artery. It arises from the anteromedial aspect of the internal carotid artery just after it exits the cavernous sinus. It consists of three segments:

- Intracranial
- Intracanalicular
- Intraorbital

It terminates by piercing the orbital septum at the superomedial angle of the orbit, approximately 10 mm above the medial canthal tendon. It gives rise to several branches:

- An angular artery
- Frontal branches
- Collateral branches (very numerous, between 10 and 19)
- Arteries supplying the optic apparatus
- Arteries supplying the ocular adnexa

b. Central retinal artery:

c. Posterior ciliary arteries:

3.2 Venous Vascularization:

Venous drainage is ensured by three main veins: the superior ophthalmic vein, the inferior ophthalmic vein, and the middle ophthalmic vein. These veins drain into the cavernous sinus. Additionally, peri-orbital drainage is provided by the angular vein.

- Superior ophthalmic vein
- Middle ophthalmic vein
- Inferior ophthalmic vein
- Angular vein

3.3 Innervation:

Innervation is provided by:

- The optic nerve (cranial nerve II)
- The oculomotor nerve (cranial nerve III)
- The trochlear nerve (cranial nerve IV)
- The abducens nerve (cranial nerve VI)
- Autonomic nerves

IV. Epidemiology:

1. Geographical Distribution:

The geographical distribution of Behçet's disease is distinctive, as it is primarily observed along the Silk Road, stretching from East Asia to countries of the Mediterranean basin. [16] However, this distribution tends to change due to two major factors: the migration of populations from low-prevalence areas to those with higher prevalence, and the improved understanding of the disease, which has facilitated easier diagnosis. [15]

In Morocco, various case series have shown a predominance of patients originating from coastal regions—ranging from 60% to 64%, with 93% of those cases coming from the northern region. [17]

In fact, the underrecognition of Behçet's disease, limited medical access in rural populations, and the lack of systematic data collection at the national level are all factors that hinder the establishment of reliable epidemiological data regarding the prevalence of Behçet's disease across different regions of Morocco.

Figure 19: Geographic map showing the route of the Silk Road between Asia and the Mediterranean. [15]

2. Prevalence:

A prevalence of 20 to 420 cases per 100,000 inhabitants has been reported in Turkey. In contrast, Behçet's disease is less frequent in Europe and the United States, with rates of 3.8 per 100,000 in Italy, 1.5 to 15.9 in Southern Europe, and 0.3 to 4.9 in Northern Europe. Data from North and South America, the Caribbean, and individuals of sub-Saharan African origin suggest that the geographical distribution of Behçet's disease is broader than the classical "Silk Road" region [16].

Behçet's disease typically develops in adulthood and is rare in childhood. In the eastern Mediterranean basin, the disease more commonly affects men, in contrast to findings in parts of Asia where it shows a female predominance [18]. The prevalence of ocular involvement varies across studies, ranging from 40% to 70% [19,20]. Behçet's disease is the leading cause of uveitis in Turkey, accounting for 30% of cases. Its frequency as a cause of uveitis in other parts of the world is reported as follows: 20% in Japan, 18% in Taiwan, 15% in Israel, 12% in Tunisia, 6.5% in Saudi Arabia, 4% in Australia, 3% in China, 0.5-7% in Europe, and 0.1-4% in the United States [21,22].

3. Incidence:

The incidence of Behçet's disease remains one of the least well-defined aspects of the condition. This is largely due to the difficulty in identifying the precise onset of the disease. The diagnostic delay is often prolonged, which can lead to inaccuracies in incidence measurement. The few studies that have addressed the annual incidence of Behçet's disease have reported varying results, ranging from 0.2 [23,24], to 0.46 [25], and up to 0.9 per 100,000 inhabitants [26].

V. Pathophysiology:

Although the etiology of Behçet's disease (BD) remains uncertain, it is believed to be multifactorial, involving several interacting factors that affect a genetically predisposed individual. [27]

Advances in genetics and immunology have led to a better understanding of the immunopathogenesis of BD.

The HLA-B51 allele [28], HLA-B26 [29], and variants of the IL-10 and IL-23/IL-12RB2 loci [30] are among the most strongly associated genetic factors linked to BD.

A Factor V Leiden mutation has been suspected as a contributing factor to the high incidence of venous thrombotic events in Behçet's disease. [31]

Triggering factors include bacterial infections such as Streptococcus, Helicobacter pylori, and Mycoplasma, as well as viral infections such as HSV-1, EBV, hepatitis viruses, and CMV [32], in addition to abnormal autoantigens (such as HSPs, S antigen, and IRBP) [33].

These triggering elements activate both the innate and adaptive immune systems, leading to the production of various cytokines and chemokines aimed at neutralizing antigens and autoantigens.

In the innate immune system, natural killer (NK) cells, γδ T cells, and neutrophils [34] play key roles in the pathogenesis of BD, potentially through a KIR (NKB1) interaction with molecular sequences within HLA-B51, which may impair their function.

NK cells not only exert cytotoxic effects on infected and tumor cells, but also regulate the activity of other immune cells, including dendritic cells (DCs) and T cells, through the secretion of cytokines. [35]

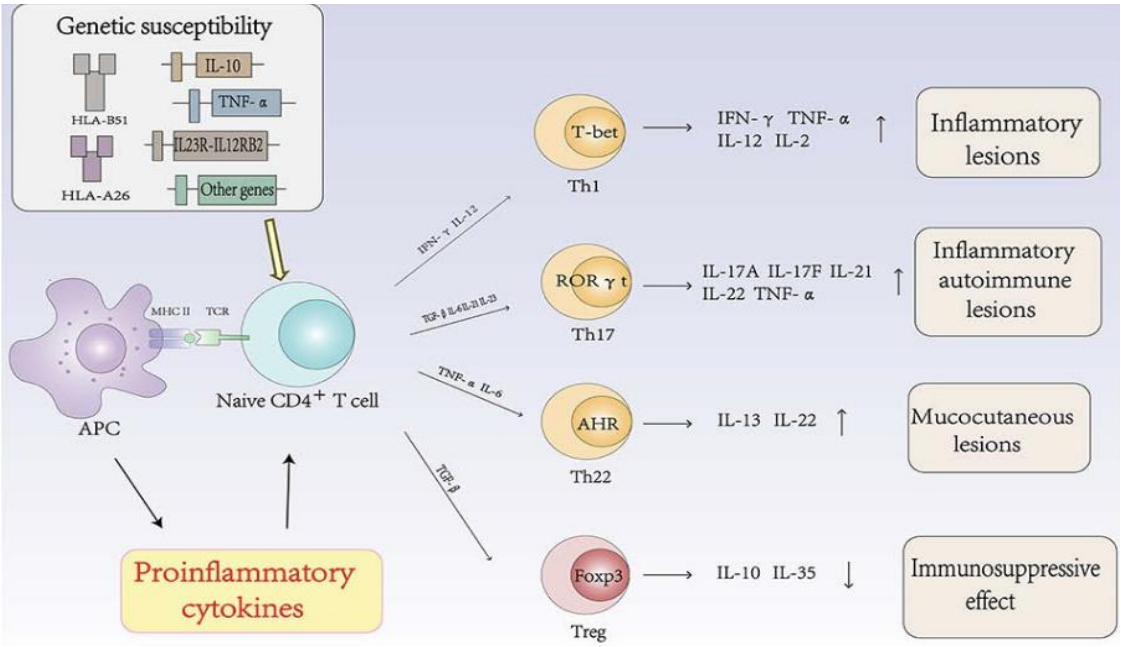

Figure 20: The Role of T Lymphocytes and Cytokines in the Pathogenesis of Behçet's Disease: [35]

This illustrates the involvement of cytokines produced by T cells in the pathogenesis of the lesions observed in Behçet's disease

Behçet's disease (BD) is characterized by venous thrombosis, aneurysms, and vascular occlusions. Histopathological analysis has shown that both arteries and veins are infiltrated by neutrophils and lymphocytes, leading to vascular endothelial dysfunction. Endothelial dysfunction and neutrophilic vascular inflammation are key contributors to thrombosis in patients with BD. CD4+ T cells, including Th1, Th2, Th17, Th22, and Treg cells, along with their associated cytokines in the adaptive immune system, play a crucial role in the pathogenesis of BD. Cytokines are undoubtedly vital in both the initiation and perpetuation of the disease. [35]

VI. Diagnostic criteria for behçet's disease:

The diagnosis of Behçet's disease is based on clinical criteria. There are no biological markers for establishing the diagnosis. For this reason, various classification systems have been developed over the past nine decades. [36]

Table IX : List of different classifications established for behçet's disease [37]

Year of Classifications	Name of the Classification or Author of the Classifications
1946	H. O. Curth
1969	J. Hewitt et al
1969	R. M. Mason and C. G. Barnes
1971	Revision of J. Hewitt's 1969 classification by J. Hewitt et al.
1972	Japanese criteria
1974	A. Hubault and M. Hamza
1974	J. D. O'Duffy
1980	S. P. Chen and X-Q. Zhang
1986	N. Dilsen et al.
1988	Revision of the 1972 Japanese classification by Y. Mizushima
1990	Criteria of the International Study Group
1993	Iranian criteria
1993	Classification Tree created by F. Davatchi, F. Shahram, M. Akbarian et al.
2000	Revision of the 1986 classification by N. Dilsen
2003	Korean criteria created b

All these classifications share the importance of oral ulcerations, but these alone are not sufficient to differentiate Behçet's disease from many other pathologies. In 1990, a group of scientists formed the ISG (International Study Group) and defined Behçet's disease by the presence of a set of diagnostic criteria.

These criteria require the presence of recurrent oral aphthosis (at least three episodes over a period of 1 year) associated with at least two other criteria among the following: recurrent genital aphthosis, uveitis or retinal vasculitis, erythema nodosum, pseudofolliculitis, acneiform papulopustular lesions (outside the pubertal period and without corticosteroid therapy), and hypersensitivity to needle pricks (pathergy test). [38]

Table X: Diagnostic criteria for behçet's disease suggested by the international study group on behçet's disease in 1990

Criteria	Comments
Recurrent oral ulceration	Minor, major, or herpetiform aphthae observed by a physician or the patient, occurring at least 3 times/year
Recurrent genital ulceration	Ulceration or scar observed by the patient or physician
Ocular lesions	Anterior or posterior uveitis or retinal vasculitis observed by an ophthalmologist
Skin lesions	Erythema nodosum, pseudofolliculitis, papulopustular or acneiform nodules observed by a physician, occurring post-puberty in patients not receiving corticosteroids
Positive pathergy test	Performed with a 20G needle and read by a physician between 24 and 48 hours

The diagnosis is established if three or more criteria are positive. These criteria were revised in 2013, and new criteria were established to define a scoring system with improved sensitivity and good specificity for diagnosis.

Ocular, oral, and genital aphthoses are each assigned 2 points, while skin, vascular, and central nervous system involvement are each assigned 1 point. The pathergy test is optional and counts for 1 point only. A total score of 4 or more supports the diagnosis of Behçet's disease.

Table XI: New international criteria for behçet's disease [39]

Clinical Signs	Points
Ocular involvement	2
Genital aphthosis	2
Oral aphthosis	2
Typical skin lesion	1
Neurological manifestation	1
Vascular manifestation	1
Positive pathergy test	1

A score of≥ 4 supports the diagnosis

VII. Ocular manifestations of behçet's disease:

The eye is one of the primary targets of Behçet's disease due to both the frequency of ocular involvement, as shown by epidemiological data, and its severity—given its significant impact on visual prognosis (a major cause of blindness: 25% of cases in Turkey and Japan) [40]; [41]. These factors make ocular involvement a major diagnostic criterion for this condition, and recently, it has even been considered sufficient on its own to diagnose ocular Behçet's disease.

As a result, ophthalmologic manifestations must be studied in a detailed and comprehensive manner in order to establish an effective and early treatment strategy, and to prevent potential complications.

Ocular manifestations are predominantly characterized by uveitis and vascular complications, such as ischemia and periretinal thrombophlebitis, which themselves may lead toischemic optic neuropathy

1. Histopathology:

The primary ocular histopathological lesion, as in other organs, is a non-granulomatous necrotizing occlusive perivasculitis. It is characterized by chronic infiltration of T lymphocytesandneutrophilic polymorphonuclear cells, the latter exhibiting several abnormalities: increased chemotaxis, enhanced production of superoxides and inflammatory chemical mediators, and overexpression of adhesion molecules.

Levels of TNF-α, interleukin-1β, andinterleukin-8 are abnormally elevated. These cytokines contribute to polyclonal activation of B lymphocytes, leading to the formation ofimmune complexes. [42]

In the acute phase, the infiltration is mainly leukocytoclastic, associated with fibrinoid necrosis, whereas in the remission phase, the infiltrate becomes predominantly lymphoid. [42].

2. Ophthalmologic Clinical Examination:

2.1. Visual Acuity:

It must be assessed at both distance and near, with and without correction. Uveitis often leads to decreased visual acuity (DVA), except in intermediate uveitis, where visual acuity may be preserved.

2.2. Intraocular Pressure (IOP):

Intraocular pressure should be evaluated in all cases of uveitis. It is usually decreased, due to reduced aqueous humor production by the ciliary body, secondary to inflammation. However, ocular hypertension may occur if the trabecular meshwork is inflamed, obstructed by cellular debris, altered by prolonged corticosteroid therapy, or covered by the iris — such as in iris bombe or anterior synechiae.

2.3. Examination of Ocular Adnexa:

The ophthalmologic exam should always begin with the assessment of the ocular adnexaandsclera.

2.4. Conjunctiva:

Ocular rednesswith conjunctival injection is common in anterior uveitis and panuveitis. It often predominates around the cornea, forming a perikeratic ring. Located deeply near the limbus, it reflects inflammation of the underlying ciliary body, and may appear as opaque inflammatory debris.

Other, less frequent anterior segment findings include conjunctival aphthae, episcleritis, cilioflush episodes, and circumferential perilimbal ciliary injection. [43]

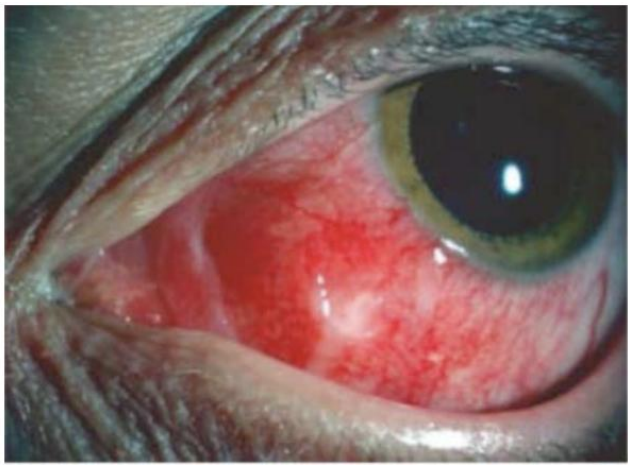

Figure 21:Conjunctival ulcer[43]

2.5. The cornea [44]:

Corneal examination is an important component in the diagnostic approach to uveitis. Analysis of keratic precipitates (KPs) is a key part of this assessment. Their size, shape, number, distribution, color, and composition must be evaluated using various magnifications with the slit lamp.

Retrodescemetic precipitates consist of inflammatory cells adhering to the posterior surface of the cornea. They are most commonly seen in the inferior half of the cornea, where they typically form a triangular pattern with the apex pointing upwards.

Neutrophilic polymorphonuclear cells, which have a low tendency to aggregate, produce KPs that appear as fine grayish dots, whereas lymphocytes, which aggregate more readily, form KPs that appear as small, whitish, round, well-defined clumps.

These keratic precipitates are often observed in anterior uveitis, and sometimes in intermediate uveitis.

They may be small and fine (fine KPs), which is characteristic of non-granulomatous uveitis, or large and confluent, resembling "mutton fat", which indicates granulomatous uveitis (see figure22).

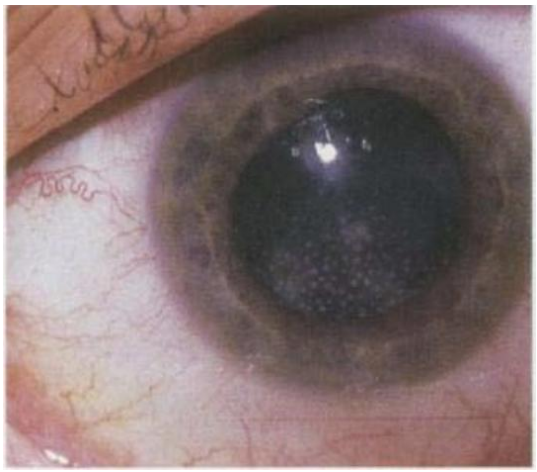

Figure 22: Triangularly arranged descemetic precipitates with the apex pointing upwards[44]:

2.6. The Anterior Chamber:

Under normal conditions, the anterior chamber is optically transparent. No cells are present in the aqueous humor, and the protein concentration is low.

However, when an inflammatory process disrupts the blood-aqueous barrier, the levels of proteins and cells increase enough for the slit-lamp light beam to become visible within the anterior chamber. Inflammation of the anterior chamber is reflected by two phenomena:

- Tyndall effect, which indicates the abnormal presence of inflammatory cells
- Flare, which reflects the increased protein concentration in the aqueous humor.

When the number of inflammatory cells is very high, they may sediment in the lower part of the anterior chamber, forming a hypopyon. [45]

The presence of hypopyon may indicate the severity of the inflammatory flare. However, it typically resolves without sequelae. It is observed in approximately 12% [46] of patients with ocular involvement, either visible to the naked eye or more frequently through biomicroscopy or gonioscopy. [47]

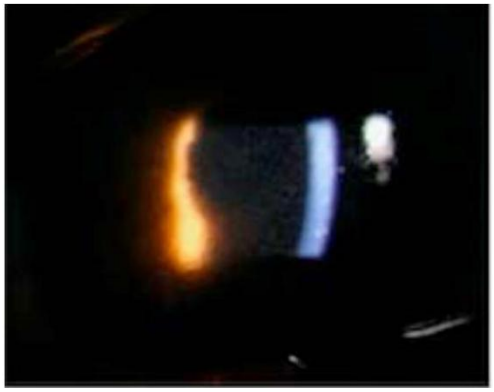

Figure 23: Inflammatory cells in the anterior chamber [48]

Table XII: Grading of the protein tyndall effect in the anterior chamber [49]

Grade	Number of cells	Flare
0	<1	None
Trace / 0.5+	1-5	-
1+	6-15	Mild
2+	16-25	Moderate
3+	26-50	Present
4+	>50	Intense

2.7. The iris and pupil:

Examination of the iris provides essential information in the evaluation of uveitis. The presence of nodular, granulomatous lesions on the iris indicates that the uveitis belongs to the granulomatous type.

The structure of the iris must also be assessed, and areas of atrophy should be looked for before pupil dilation or during mild pharmacological mydriasis.

Sometimes, pupil dilation is difficult or even impossible due to iridolenticular synechiae (adhesions between the iris and the lens). When these adhesions are localized to specific segments of the pupil, they are called partial synechiae. When they extend around the entire 360-degree circumference of the pupil, they are called complete or annular posterior synechiae.

Annular and total posterior synechiae can lead to pupillary seclusion with increased intraocular pressure due to accumulation of aqueous humor behind the iris.

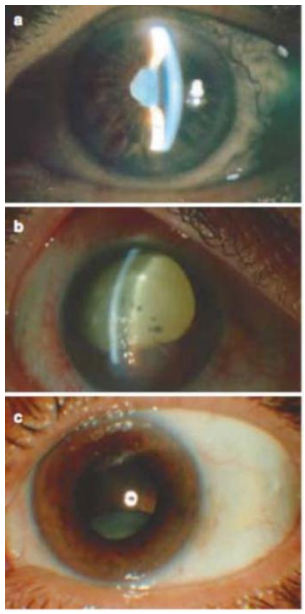

Figure 24 :Slit-lamp photographs show structural damage to the anterior segment in patients with Behçet's disease, including posterior synechiae, peripheral anterior synechiae, a shallow anterior chamber, and elevated intraocular pressure (b); and a mature subluxated lens due to zonular defect (c). [49]

2.8. The Lens:

The evaluation of the lens begins with the search for pigment deposits on the anterior capsule. These are usually arranged parallel to the pupil or in a circular pattern when they reflect the rupture of synechiae. The various lens components must then be examined to look for cataract formation. Outside of the clinical context, it is not possible to definitively determine whether a posterior subcapsular cataract is of uveitic or corticosteroid origin.

2.9. The Vitreous:

Examination of the vitreous is essential in cases of intermediate uveitis. There is a diffuse vitreous haze with cellular and proteinaceous Tyndall phenomenon. Inflammatory signs in the vitreous, in the form of haze or cells, are the main indicators of posterior segment involvement and suggest a breakdown of the blood-retinal barrier (Figure 23). Cells are also visible in the vitreous during an acute attack (Table 25). However, they are not as pathognomonic for active inflammation as they are in the anterior segment and often persist for a long time in many different and nonspecific forms.

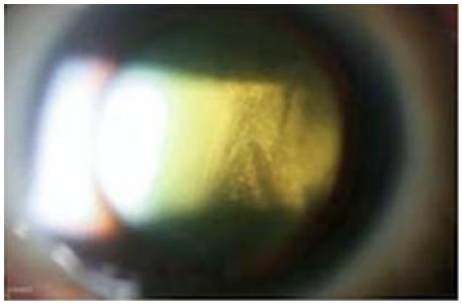

Figure 25: Inflammatory cells in the vitreous [50]

Table XIII: Classification of vitreous cells by slit-lamp examination [49]

Grade	Number of Cells	Haze Description
0	<1	None
Trace / 0.5+	1-5	-
1+	6-15	Hazy nerve fiber layer
2+	16-25	Blurred optic disc and vessels
3+	26-50	Optic disc only visible
4+	>50	Optic disc not visible

The analysis also focuses on detecting vitreous traction, posterior vitreoretinal adhesions, or epiretinal membranes that may induce or maintain cystoid macular edema.

The clinical assessment of these particular features, which is more challenging in an inflamed eye with altered structures, has been transformed by the recent use of optical coherence tomography (OCT).

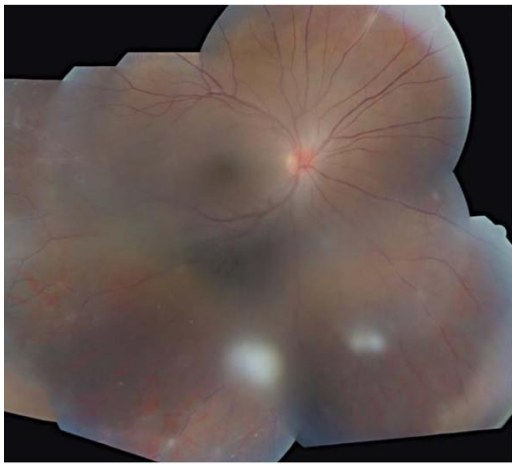

Figure 26:vitreous condensations (snowballs) and peripheral vascular sheathing (periphlebitis) [51]

3. Uveitis: (52, 53, 54):

Uveitis is an inflammation of the vascular tunic of the eye, called the uvea because of its resemblance to a grape, encompassing the iris, ciliary body, and choroid. Today, the term uveitis applies to most intraocular inflammatory manifestations. The incidence of uveitis is estimated in Northern Hemisphere countries at just over 50 cases per 100,000 inhabitants per year, with a prevalence of a little more than 100 cases per 100,000 inhabitants.

According to the Standardization of Uveitis Nomenclature Working Group criteria (Jabs et al., 2005), uveitis can be classified based on its anatomical location: anterior, intermediate, posterior, and panuveitis.

3.1. Chronological Classification:

The onset of uveitis can be latent or apparent. The duration of inflammation is highly variable, with an evolution that can sometimes be slow and insidious or, alternatively, sudden and severe.

According to the SUN (Standardization of Uveitis Nomenclature) [49]:

- Acute uveitis: sudden onset uveitis that resolves within 3 months.
- Chronic uveitis: persistent uveitis with a relapse occurring less than 3 months after stopping treatment.
- Recurrent uveitis: repeated episodes of uveitis separated by inactive periods without treatment.

3.2. Anterior Uveitis:

It is defined as inflammation located in the anterior part of the ciliary body and/or the iris. It includes iritis, anterior cyclitis, and iridocyclitis [55]. It is very rarely isolated (5–10%) [56].

Functional signs include ocular redness with a perilimbal (ciliary) flush, mild eye pain, and a decrease in visual acuity, which is often moderate. Irritative signs are often absent, hence the necessity of systematic ophthalmologic examination during Behçet's disease.

The intensity of anterior uveitis is assessed by the Tyndall phenomenon, retro-descemet precipitates, and flare.

This anterior uveitis may spontaneously regress initially leaving minimal sequelae, but recurrent flares eventually cause structural changes in the anterior chamber of the eye, such as irido-lenticular synechiae, glaucoma, or choroidal cataract. The latter makes monitoring of posterior lesions impossible [49].

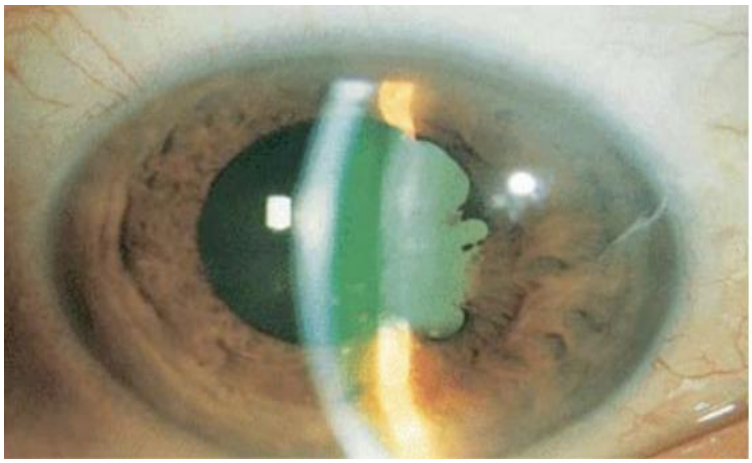

Figure 27:Irido-lenticular synechiae[56].

3.3. Intermediate Uveitis:

Defined as inflammation primarily involving the vitreous body; this includes pars planitis, hyalitis, and posterior cyclitis [55]. Its frequency ranges from 4 to 7% [57].

Functional signs include floaters (myodesopsia), defined as the perception of flying spots, and progressively developing blurred vision. However, many cases are asymptomatic and discovered during routine examination. Rarely, intermediate uveitis may be identified due to decreased visual acuity.

Examination of the vitreous reveals the three main manifestations of hyalitis: inflammatory cells, proteinaceous Tyndall effect, and sometimes vitreous remodeling.

The course is most often chronic, with periods of exacerbation and remission. The main complications are macular edema and posterior subcapsular cataract, which are the leading causes of visual acuity loss in intermediate uveitis. Less commonly, retinal detachment and secondary glaucoma due to peripheral anterior synechiae may complicate the course of the disease [58].

3.4. Posterior Uveitis:

An inflammation of the retina, the choroid, or both, resulting in chorioretinitis. The involvement can be focal or diffuse, and depending on etiology, posterior uveitis may be associated with vasculitis or optic neuritis.

In posterior uveitis, there is little to no redness, pain, or photophobia. Floaters (myodesopsia) are frequently reported; they increase with relapses and decrease with effective treatment.

Vasculitis affects vessels of all calibers, particularly veins. It is occlusive and may lead to ischemic areas. It is usually clearly visible on fundoscopic examinations as white sheathing around irregularly sized vessels dispersed throughout the fundus. Hemorrhages may also be present.

Retinitis foci appear white and hemorrhagic, highly variable in number and size, and are often accompanied by yellow-white exudates. Significant bilateral papilledema should prompt neuroimaging to search for cerebral venous thrombosis causing intracranial hypertension.

Macular edema is a key determinant of long-term visual prognosis and is associated with poorly controlled inflammation.

After several episodes of posterior uveitis, inflammation may subside, leaving an atrophic retina, empty (attenuated) vessels, a pale optic nerve, and alterations of the retinal pigment epithelium [59].

3.5. Panuveitis:

The frequency of total uveitis (panuveitis) in Behçet's disease ranges between 24% and 70% [60]. It is characterized by severe inflammation of the anterior, intermediate, and posterior segments, without a predominant site of inflammatory activity.

4. Retinal Vasculitis:

Retinal vasculitis in Behçet's disease is a panvasculitis. In the acute phase, there is lymphocytic inflammatory infiltration invading the media and adventitia of the vessels. In later stages, a significant fibrotic scarring reaction develops.

It is the second most frequent ocular manifestation after uveitis [61]. Retinal vasculitis (RV) in Behçet's disease is a feared sign, as it can progress rapidly to blindness [62].

Retinal vascular lesions are primarily venous, with periphlebitis being the most common manifestation. It may occur both in the posterior pole and in the peripheral retina.

Arterial involvement can also occur alongside venous lesions, although it is less common and tends to appear at a later stage.

On fundus examination, an occlusive periphlebitis is observed (the outer wall of the veins is the primary site of inflammation). This appearance is characterized by a lymphoplasmacytic infiltrate originating from the vascular lumen due to disruption of the blood-retinal barrier. The fundus examination helps to specify the topography, the type of capillaropathy, associated ocular involvement, and complications (such as macular edema, branch retinal artery or vein occlusion, optic atrophy, cataract, retinal detachment, vitreous hemorrhage, neovascular glaucoma, and ischemic neovascularization).

Fluorescein angiography allows a comprehensive assessment of retinal involvement and can detect subclinical abnormalities. It can demonstrate dye leakage from vessels, macular edema, or retinal edema spaces, hemorrhages, or exudates. This examination is particularly useful for early diagnosis and monitoring [63].

Other manifestations may include retinitis and choroiditis.

5. Retinitis:

Active lesions appear as whitish opacities with poorly defined borders due to surrounding edema, which become more well-demarcated as the inflammation subsides. The presentation may be focal, multifocal, geographic, or diffuse.

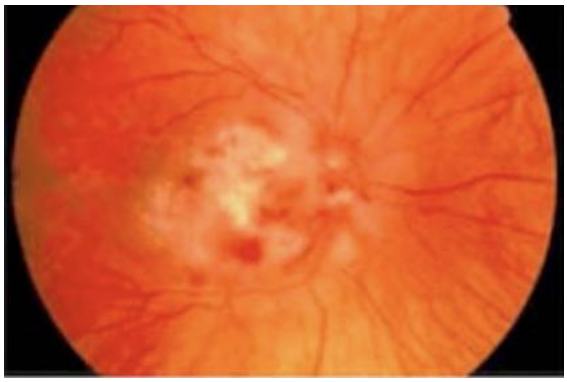

Figure 28: retinitis[64].

6. Choroiditis:

Its appearance may vary depending on the underlying disease. In imaging, round, yellowish nodules can be seen deep within the retina. A helpful clue is that choroiditis typically does not cause vitritis unless there is associated retinitis—this makes sense anatomically, as the retina lies between the choroid and the vitreous.

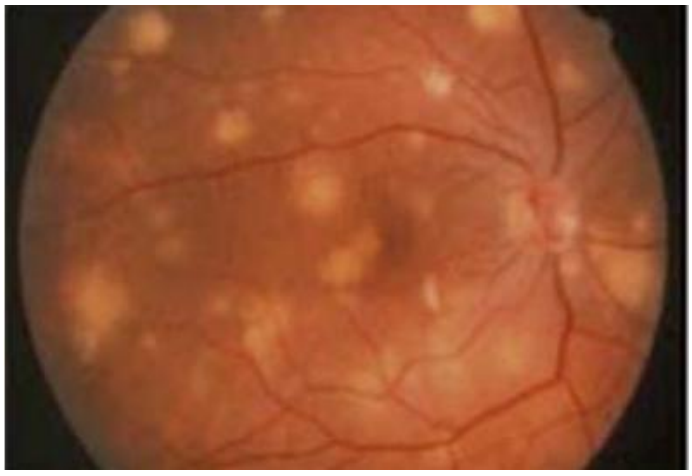

Figure 29: Choroiditis [65]

7. Retinal Vein Occlusions:

Retinal vein occlusions are relatively rare [66] in Behçet's disease (BD), but they differ from atherosclerotic vein occlusions by certain clinical and evolutionary characteristics [67].

The occlusion can affect either the central retinal vein (CRVO) or a branch of the central retinal vein (BRVO), two mutually exclusive forms that rarely occur in the same individual [68].

The severity of visual loss depends on the associated capillary involvement, leading to three clinical forms with different presentations and prognoses:

- Ischemic form: severe functional impairment with visual acuity often worse than 20/200.
- Edematous form: less severe visual impairment.
- Mixed form: the most frequent, combining ischemic and edematous areas. This form may be present from the outset or develop following the conversion of an edematous form [69].

At fluorescein angiography, there is most often a delayed dye transit in the venous network. The venous walls also allow leakage of the dye, mainly at the venous curves. Areas of retinal ischemia appear as zones of non-perfusion of the dye [70].

8. Maculopathy:

Macular alterations in Behçet's disease are frequent but not specific. Their occurrence significantly affects visual prognosis. Clinical and angiographic diagnosis of these lesions may be hindered by media opacities (uveitis, cataract) or posterior synechiae. These lesions primarily present a therapeutic challenge. Maculopathy is frequent, observed in 12 to 50% of cases depending on the authors [71,72]. Various types of maculopathies exist, ranging from macular edema—which is the most common manifestation—to macular hole, ischemic maculopathy, and neovascularization reported by some authors, as well as epiretinal membranes associated with certain vasculitides.

8.1. Macular edema:

Macular edema is defined by thickening of the macular retina related to the accumulation of extracellular fluid that exceeds the resorptive capacity of the retinal pigment epithelium, autoregulation of blood flow (decreased hydrostatic pressure), and tissue compliance. The formation of intraretinal cystoid spaces defines cystoid macular edema (CME) [73]. Slit-lamp examination reveals retinal thickening manifested by loss of the foveolar reflex and the presence of a yellow subretinal spot in cases of CME.

On angiography, only the visualization of dye pooling in the central cystoid spaces, creating the characteristic "flower petal" pattern, confirms the presence of CME.

Cystoid macular edema (CME) appears on optical coherence tomography (OCT) as well-defined hyporeflective cavities corresponding to the angiographic cystoid spaces, associated with retinal thickening. OCT has the advantage of detecting subclinical serous retinal detachments, which may be associated with macular edema in some cases.

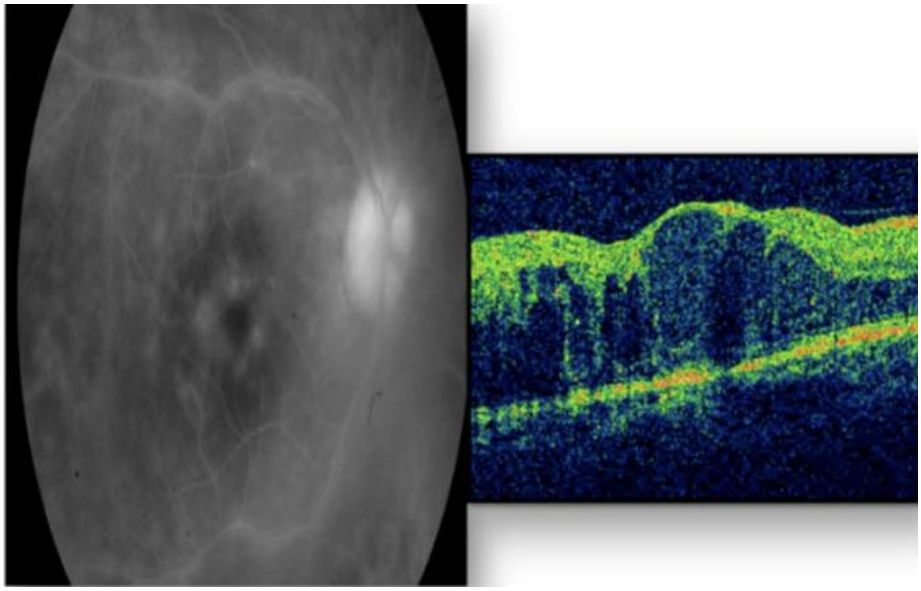

Figure 30 : Cystoid macular edema [73]

8.2. Macular hole:

The macular hole is a rare complication [74]. It results from the centrifugal displacement of photoreceptors due to a central dehiscence of the fovea. Its pathophysiology is likely multifactorial. Intraocular inflammation related to Behçet's disease alters the vitreoretinal interface, leading to vitreoretinal traction and cellular proliferation at the level of the internal limiting membrane. This causes retraction of the membrane and subsequently the formation of a macular hole.

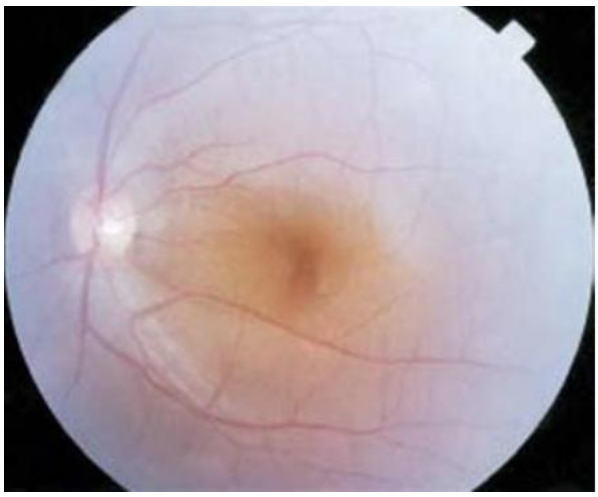

Figure 31 : Macular hole[74].

8.3. Macular epiretinal membranes [75]:

Macular epiretinal membranes are benign, non-vascular cellular proliferations with a self-limiting course. They have a contractile epicenter located in the macular or paramacular region and usually extend only slightly beyond the posterior pole.

MEM can cause a functional macular syndrome of varying severity, characterized by decreased visual acuity, floaters (myodesopsia), and a relative central scotoma. The diagnosis of MEM is primarily biomicroscopic; slit-lamp examination allows clear visualization of the membrane's shiny reflex.

9. Neuro-ophthalmological manifestations:

9.1 Cranial nerve involvement:

Reported manifestations in neuro-Behçet include ocular motor paralysis and internuclear ophthalmoplegia [75,76].

9.2 Optic neuropathy:

Optic neuropathies are disorders of the optic nerve fibers occurring due to impairment of axoplasmic flow.

Optic nerve inflammation may persist between inflammatory episodes. It generally presents as an optic neuropathy evolving chronically towards optic atrophy [77]. Optic neuropathy is rare in Behçet's disease [78]. Decreased visual acuity and ocular pain are the most frequently reported symptoms by patients.

Slit-lamp examination can be normal or may reveal inflammation of the anterior segment, vitreous involvement, or retinal vasculitis lesions.

Fundus examination allows description of papillary lesions and may show:

- Papilledema due to stasis, ischemia, or inflammation of the optic nerve
- Papillary pallor or sequelae optic atrophy
- Normal fundus in cases of retrobulbar neuropathies

Fluorescein retinal angiography has three main uses:

- Confirm possible papilledema by showing papillary hyperfluorescence
- Help determine the etiology of papillary involvement:
    - Ischemic: papillary hypofluorescence, vascular occlusion
    - Inflammatory: dye leakage at the posterior pole
- Detect associated signs such as vasculitis or posterior edema

Visual evoked potentials (VEP) are consistently abnormal, indicating inflammatory involvement.

Neuroimaging studies (MRI and cerebral MR angiography) are essential to rule out cerebral venous thrombosis and intracranial expansive processes [79].

10. Minor ocular manifestations: [80][81]

Minor ocular manifestations have been described in Behçet's disease, including keratitis, conjunctivitis, episcleritis, conjunctival ulcers, and orbital myositis.

10.1 Episcleritis:

Episcleritis is a localized inflammation, most often affecting the perilimbal area with rapid onset. It presents as ocular discomfort sometimes accompanied by photophobia and tearing. On slit-lamp examination, episcleral redness appears as a violaceous congestion visible through the hyperemic conjunctiva. The redness blanches upon pressure, which is painful, but quickly reappears once the pressure is released.

10.2 Conjunctival ulcers:

Conjunctival ulceration is rare but possible in Behçet's disease. Systematic examination of the conjunctiva is recommended in patients with Behçet's disease, and Behçet's should be included in the differential diagnosis of conjunctival ulcers. These ulcers are most often observed in association with exacerbations of oral mucosal ulcers but are not associated with intraocular inflammation.

Clinical examination specifies the location of the ulceration, and conjunctival scrapings help exclude infectious causes. Histologically, there is infiltration of the conjunctiva by inflammatory cells, particularly lymphocytes and plasma cells, as well as intraepithelial and perivascular infiltration by neutrophils.

10.3 Orbital myositis:

Orbital myositis, or chronic orbital inflammation, is one of the rarest ocular manifestations of Behçet's disease. Clinically, it manifests as a relatively sudden onset of pain exacerbated by eye movements, diplopia in the field of action of the affected muscle(s), and periorbital inflammation. Clinical examination looks for axial proptosis and conjunctival hyperemia, especially at the insertion of the extraocular muscles. CT scan and orbital/cerebral MRI may reveal abnormal signal intensity in the extraocular muscles.

11. Ophthalmologic complications in ocular Behçet's disease:[82]

11.1 Anterior segment complications:

- **Glaucoma**:[83]

From a pathophysiological perspective, glaucoma is secondary to the occurrence of associated trabeculitis, trabecular blockage by inflammatory cells, or the presence of inflammatory sequelae such as peripheral anterior synechiae or posterior synechiae It can also complicate neovascular glaucoma secondary to retinal ischemia caused by occlusive vasculitis or be secondary to prolonged corticosteroid use leading to impaired uveoscleral outflow.

- **Cataract**:

One of the main sequelae of the disease [84]. Inflammatory mediators released during recurrent attacks in the anterior segment, as well as prolonged corticosteroid therapy, can induce metabolic changes in the lens leading to cataract formation. These cataracts are mainly located in the posterior subcapsular region. Mature and cortical cataracts due to prolonged inflammatory activity and corticosteroid use can also be observed.

11.2 Posterior segment complications:[82]

- **Vitreous hemorrhage**:

Responsible for a rapidly progressive decrease in visual acuity, it begins with the sensation of "floaters" described as a "rain of soot," followed by a partial to complete obscuration of vision.

This is either a complication of retinal neovascularization or a retinal tear. A thorough examination of the entire retina after pupil dilation is essential. When the retina is obscured by the hemorrhage, B-scan ultrasonography provides diagnostic assistance by enabling the detection of retinal detachment.

- **Retinal Detachment:**

The prodromal signs of retinal detachment include floaters (myodesopsia), reflecting the onset of a posterior vitreous detachment, and photopsia indicating traction exerted on the retina by a detaching vitreous.

Initially, it presents as a visual field defect corresponding to the area of detached retina, followed by a sudden decrease in visual acuity if the detachment involves the macula. Ophthalmologic examination reveals decreased intraocular pressure. Fundus examination assesses the extent of the detachment and the presence of vitreoretinal proliferation, which is a poor prognostic factor.

Examination of the fellow eye seeks lesions that could predispose to retinal tears, which should be treated preventively by laser photocoagulation.

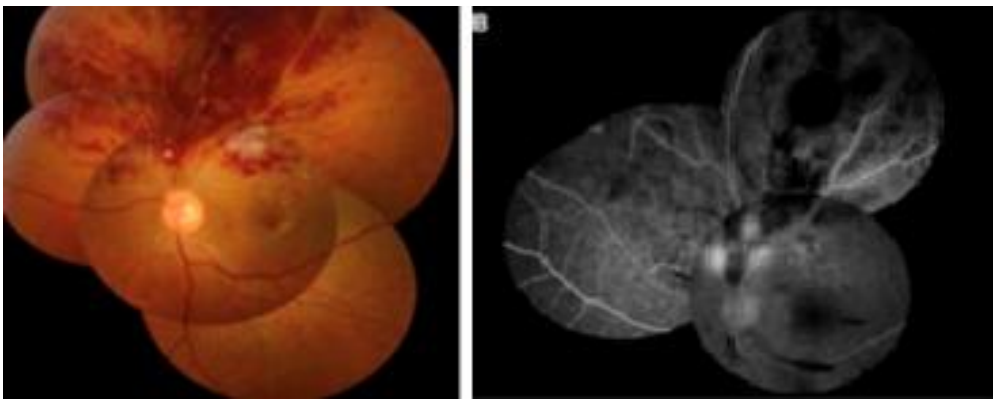

Figure 32: a. Fundus photograph showing periphlebitis complicated by a superotemporal branch retinal vein occlusion with macular involvement including retinal edema, serous retinal detachment, and hard exudates. B. Fluorescein angiography of the same patient one month after the initial examination demonstrating preretinal neovascularization with preretinal hemorrhages associated with extensive areas of capillary non-perfusion.[85]

- **Retinal Ischemia [86]:**

In our context, retinal ischemia may have two etiologies: a purely vascular origin when the ischemia is secondary to arterial or venous occlusions in the setting of retinal vasculitis, or a circulatory disorder when secondary to chronic glaucoma. Recurrent vaso-occlusive attacks progressively lead to attenuated retinal vessels, retinal atrophy and fibrosis, degenerative macular changes, epiretinal membrane formation, optic disc atrophy, varying degrees of chorioretinal scarring, and alterations of the retinal pigment epithelium.

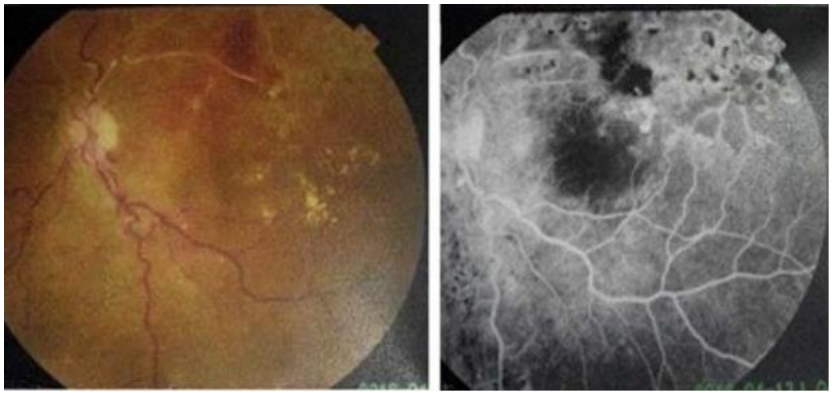

Figure 33: The left eye of a patient with Behçet's disease shows permanent damage resulting from recurrent vaso-occlusive attacks, which have led to optic atrophy, ghost retinal vessels, diffuse retinal atrophy, fibrosis, and pigmentary changes[86]:

VIII. Extra-ocular manifestations:

1. Mucocutaneous Manifestations:

Recurrent oral aphthous ulceration is the most common manifestation of the disease. These ulcers are distinct from simple aphthous stomatitis or common canker sores. They typically appear as minor (<10 mm), major (≥10 mm), or herpetiform ulcers that are oval or round, superficial, non-scarring, and covered with a white or grayish pseudomembranous necrotic base surrounded by an erythematous halo [87].

Although oral ulcers usually precede other symptoms—especially in children—by several years, up to 15–20% of patients may not develop aphthous ulcers at the onset of the disease. Smoking may suppress their occurrence, while local trauma and poor oral hygiene may increase the frequency of attacks.

Genital aphthous ulcers are less common but tend to leave scars (Fig.32) These ulcers most often occur on the scrotum in males and the labia majora in females, but they may also appear in the perianal and perineal regions, as well as on the thighs [87].

Papulopustular skin lesions are also common manifestations and may resemble acneiform eruptions or folliculitis. These lesions are similar in appearance to typical acne but are considered more specific to Behçet's disease (Fig. 32).

Erythema nodosum-like lesions occur more frequently in women (Fig. 32). They typically develop on the pretibial area as painful, erythematous nodules but may also be seen on the face, neck, arms, and buttocks. These lesions usually resolve spontaneously within 3 weeks and often leave behind residual pigmentation [87].

Superficial thrombophlebitis may also present as painful, erythematous nodular lesions, appearing as linear or nodular swellings along inflamed subcutaneous veins.

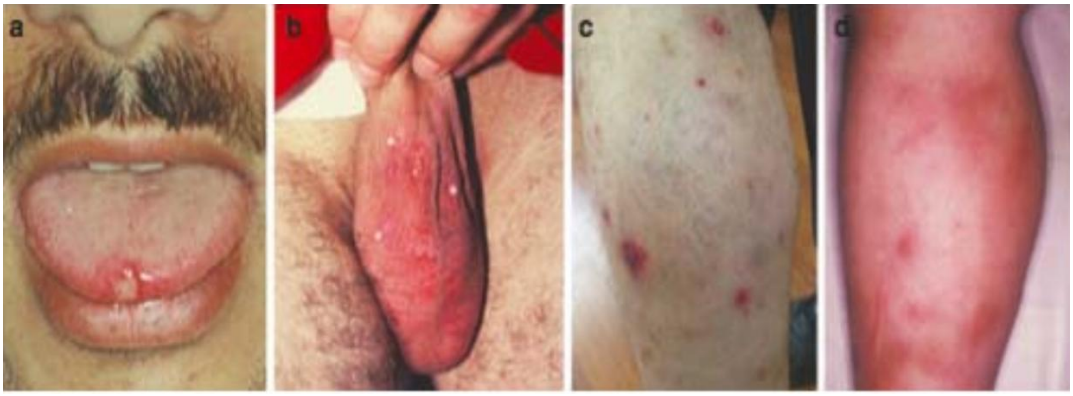

Figure 34: Mucocutaneous manifestations of Behçet's disease: (a) Oral aphthous ulcer on the tongue (b) Genital ulcers on the scrotum – asterisks indicate scars from previous ulcers (c) Pustular lesions (d) Nodular skin lesions on the calf[87].

- **Pathergy Test:**

The cutaneous pathergy reaction has historically been considered useful in the diagnosis of Behçet's disease, although a declining trend in positivity has been observed in recent years. A positive pathergy reaction can be seen in up to 60–80% of patients in endemic regions and much less frequently in non-endemic areas. It supports the diagnosis of Behçet's disease depending on the clinical context, as pathergy is rarely observed in other neutrophilic dermatoses such as Sweet syndrome and pyoderma gangrenosum [88].

Following minor skin trauma on the forearm via oblique insertion of a hypodermic needle (Fig. 33), patients with Behçet's disease may develop an erythematous papule, or more rarely a pustule, resembling the spontaneously occurring cutaneous lesions (Fig. 33).

The extent of trauma induced—affected by the thickness and bluntness of the needle—may influence the result.the extent of the inflammatory reaction and the persistence of the erythematous induration at 48 hours is necessary for a positive test[89]

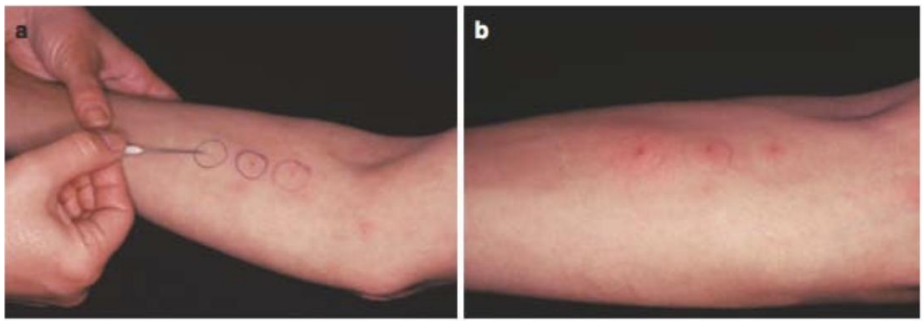

Figure 35: Pathergy test[89]

2. Articular Manifestations [90]:

Joint involvement is often early and may even be the initial presentation, sometimes preceding other manifestations by several years. It typically consists of arthralgia and/or, less commonly, inflammatory oligoarthritis, usually fixed and affecting weight-bearing joints.

Temporomandibular, sternoclavicular, manubriosternal, and atlantoaxial involvement are rare.

The most commonly affected joints are the knees, followed by the ankles, wrists, elbows, and hands. Other joints, such as the hips and shoulders, are less frequently involved [91-92].

The clinical course is recurrent and asymmetric. Polyarticular forms are rare (2%). Radiographic findings are usually normal; in rare cases, osteocartilaginous erosions or minor joint space narrowing may be observed. Joint destruction is exceptional. Deformities may be seen in such cases.

Synovial fluid aspiration typically reveals viscous, inflammatory fluid rich in polymorphonuclear cells.

The development of popliteal cysts is possible, and rupture of such cysts can be difficult to distinguish from deep vein thrombosis, especially since associations between the two have been reported. Sacroiliac joint involvement has been observed with varying frequency among authors (1% to 34%). There is also a reported association with true ankylosing spondylitis in HLA-B27 positive patients (2%).

Osteonecrosis has been reported, usually in patients undergoing corticosteroid therapy.

Muscular involvement is rare but indisputable and may occur in conjunction with joint manifestations. It mainly presents as diffuse myalgia or muscle pain predominant in the proximal muscles; true myositis is possible. Localized forms may raise diagnostic challenges, particularly in differentiating them from deep vein thrombosis.

On clinical examination, painful swellings may be observed. Biopsy typically shows degeneration of muscle fibers and infiltration by mononuclear and polymorphonuclear cells. CPK levels are rarely elevated, and if markedly increased, myopathies or rare rhabdomyolysis secondary to colchicine (especially in patients with renal or hepatic impairment) should be considered.

3. Neurological Manifestations [90]:

Neurological manifestations occur in approximately 25–30% of patients.

These manifestations arise randomlyin relation to the onset of Behçet's disease. Most often, they appear **several years** into the disease course, with an average delay ranging from **2.17 to 5.6 years** [93,94].

The neurological involvement in Behçet's disease (BD) primarily affects the **central nervous system (CNS)** and is typically classified as either:

- **Parenchymal involvement** (affecting white matter, most commonly at the **mesodiencephalic junction**), or
- **Extraparenchymal involvement** (vascular involvement of **veins or arteries**).

Peripheral nervous system involvement has been **rarely reported**, and its true association with BD remains **controversial**.

Parenchymal forms are more frequent, occurring in **70-80%** of patients with neurological involvement, compared to extraparenchymal forms. The **coexistence of both types** in a single patient is **exceptional**.

The **onset** of neurological manifestations in Behçet's disease is **highly variable**, presenting in either a **progressive** or **acute** manner [95,96]. A distinctive feature of neurological involvement is that it may be the **initial presentation** of the disease, even **before the onset or diagnosis** of mucocutaneous manifestations.

Parenchymal Manifestations: Parenchymal involvement typically presents as a subacute [97]. In two-thirds brainstem syndrome. Inflammatory parenchymal lesions can be unifocal or multifocal [98], of cases, neurological manifestations are acute and follow a relapsing-remitting course, with episodes interspersed with periods of remission (which may or may not leave residual deficits). However, primary progressive or secondary progressive forms may also occur. Extraparenchymal involvement mainly consists of **cerebral venous thrombosis**. A **smaller subset of patients** (around **20%**) with neurological involvement may develop **intracranial hypertension**and **papilledema** due to **cerebral venous thrombosis.**

This **vascular subtype** tends to have a **better prognosis** than parenchymal neurological involvement.

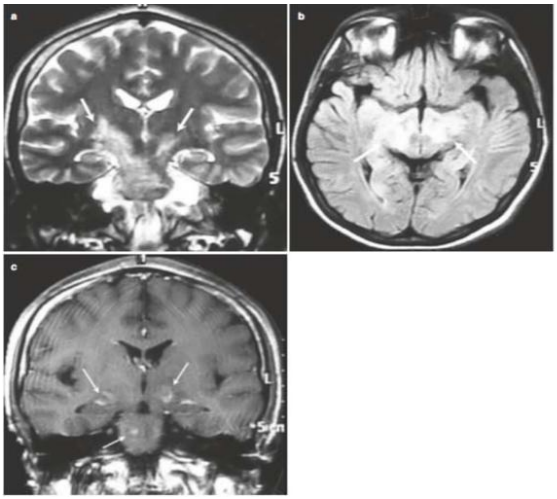

Figure 36: Parenchymal Neurological Involvement (arrows indicate the location of the lesions) (Courtesy of Professor Murat Kürtüncü) (a) Coronal T2-weighted image of the patient: the bilateral lesion extends from the thalamus to the midbrain. (b) Axial FLAIR-weighted image of the patient at the midbrain level: the cerebral peduncles and substantia nigra are involved. (c) Axial contrast-enhanced T1-weighted images: there is heterogeneous contrast enhancement of the lesion[97]..

4. Vascular manifestations of Behçet's disease:

Behçet's disease holds a distinct position among systemic vasculitides due to its capacity to affect blood vessels of all types and calibers, with a predilection for the venous system [99].

Vascular wall inflammation is commonly associated with thrombosis; however, the risk of thromboembolic disease remains low due to the thrombus adhering tightly to the underlying endothelium. Superficial thrombophlebitis, often presenting as painful nodular skin lesions, is the most frequent vascular finding and occurs more commonly in men. It has prognostic value as it may be the initial sign of vascular involvement in Behçet's disease.

Deep vein thrombosis is most commonly observed in the lower limbs [100], but any venous territory may be affected, including the inferior and superior vena cava, hepatic veins, and cerebral venous sinuses. Recurrent thrombotic episodes can lead to post-thrombotic syndrome and chronic venous ulcers. Patients with Budd-Chiari syndrome tend to have a worse prognosis.

Arterial involvement usually manifests as aneurysms rather than occlusions. Aneurysms in Behçet's disease are typically irregularly shaped saccular pseudoaneurysms with mural thrombus. Vascular manifestations can be classified into the following categories:

- ✓ Venous thromboses
- ✓ Deep vein thrombosis
- ✓ Arterial involvement
- ✓ Cardiac involvement

5. Gastrointestinal Involvement [90]:

Gastrointestinal manifestations in Behçet's disease often resemble those of Crohn's disease on macroscopic examination, and less commonly those of ulcerative colitis (limited to rectal and colonic involvement), creating diagnostic challenges. The reported frequency varies widely, ranging from 30% in Japanese series to less than 5% in European cohorts.

Clinical symptoms are nonspecific and may include flatulence, nausea, bloating, belching, diarrhea, anorexia, or rectal bleeding. No specific endoscopic or histological features have been identified. However, the presence of deep, few (<5), oval-shaped lesions localized to the ileocecal region favors a diagnosis of Behçet's disease. Unlike Crohn's disease, granulomas are never seen on biopsy. Histopathological findings often show nonspecific inflammatory changes. A few cases of pancreatitis have also been reported.

When gastrointestinal involvement is the predominant presentation, differential diagnoses such as inflammatory bowel disease (IBD) or genetic causes should be considered

6. Pulmonary Involvement:

Pulmonary involvement is rare and mainly presents as nodular lesions resulting from pulmonary infarctions, which tend to cavitate overtime. In some cases, ground-glass opacities indicative of alveolar hemorrhage may be observed. Vasculitis has occasionally been confirmed. CT pulmonary angiography and ventilation/perfusion scans are useful for detection.

7. Renal Involvement [90]:

Renal involvement is exceptional and is primarily represented by amyloid nephropathy, which typically occurs in uncontrolled patients after many years of disease evolution. Rare cases of glomerular disease have also been described, mainly proliferative glomerulonephritis with crescent formation or IgA nephropathy. Complications related to thrombosis of renal veins and/or arteries have also been reported.

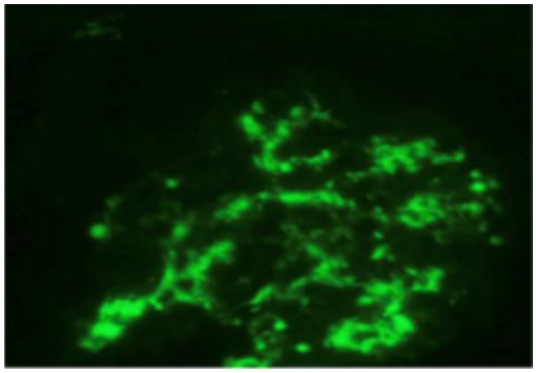

Figure 37: Direct immunofluorescence using fluorescein-labeled anti-iga antibodies [101]

IX. Inflammatory biomarkers:

C-reactive protein (CRP) is a well-known acute-phase reactant. It is also a highly sensitive marker of acute inflammation and tissue damage. CRP is used to monitor the severity of diseases or response to treatment in infectious, inflammatory, autoimmune, or rheumatologic diseases. CRP is also used as a biomarker for predicting mortality and morbidity in cer- ebral and cardiovascular diseases [8]

Albumin is a negative acute-phase reactant that is reduced in inflammatory condi- tions (Its levels maydecrease in various inflammatory diseases, liver, and kidney diseases, or in cases of malnutrition.)[8]

The CRP/albumin ratio (CAR) is the combination of these two acute-phase reactants and could provide more accurate information on inflammatory status . The CAR is used as a marker for determining the severity of inflamma- tion and for predicting mortality in sepsis or coronary artery disease [8]

The neutrophil/albumin ratio (NAR) has been reported as a new inflammatory indicator in severe infection, cancer, and schizophrenia. In patients with cancer, a higher level of NAR was found to represent an increased inflammatory state, which poorly affects prognosis and treatment response.Neutrophils, the key components of the innate immune system, are activated and recruited to the target tissue by inflammatory mediators due to the chronic inflammatory status of BD, causing damage and organ dysfunction [153]

Neutrophils, lymphocytes, and **platelets** play a role in the con- trol of inflammation, and systemic inflammation is associated with alterations in the quantity and composition of circulating blood cells, such as neutrophilia, lymphopenia, and thrombocytosis [152]

MPV is the volume of the average circulat- ing platelets in femtoliters and is a marker of platelet activation that is known to be associated with inflammation.

NLR is calculated as the absolute count of neutrophils divided by the absolute count of lymphocytes and may be useful to estimate the activity of autoimmune and inflammatory diseases.

PLR is calculated as the absolute platelet count divided by the absolute lymphocyte count. also used as an index for inflammatory status in diverse dis- eases

MPV is a potential marker that signifies platelet count and activity and has been associated with inflammation and inflammation severity.[152]

X. Differential diagnosis [102]:

It is important to differentiate acute anterior uveitis in Behçet's disease from HLA-B27-associated uveitis, whether isolated or associated with systemic involvement. In cases of cold hypopyon, the differential diagnosis also includes acute lymphoblastic leukemia and other masquerade syndromes such as intraocular foreign bodies and ocular tumors. Clinical examination, blood count, and sometimes anterior chamber paracentesis help establish the definitive diagnosis.

Other important causes of anterior uveitis, such as sarcoidosis, herpes, tuberculosis, and syphilis, usually present with granulomatous inflammation, unlike Behçet's uveitis.

The differential diagnosis also includes other etiologies of intermediate uveitis, retinal vasculitis, retinitis, and optic neuropathy. Regardless of the nature of the posterior segment involvement, the presence of granulomatous anterior uveitis excludes the diagnosis of Behçet's disease and requires investigation of another infectious or non-infectious cause. A detailed clinical analysis is essential for differential diagnosis, selection of complementary tests, and therapeutic management.

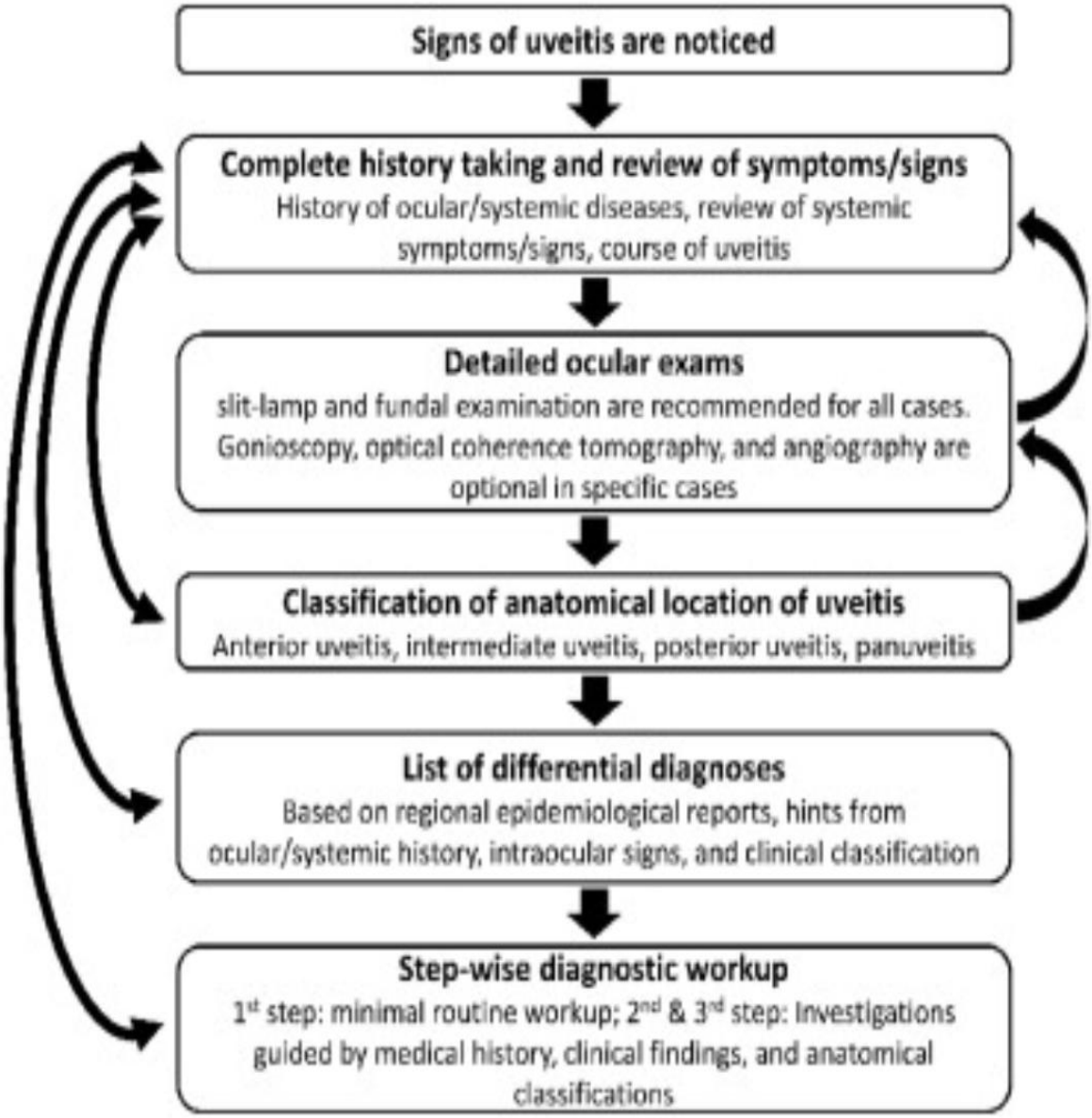

Figure 38: General algorithm for managing uveitis[102]:

Table XIV: Functional and clinical signs, and main etiologies according to the location of uveitis

Topography	Associated Signs	Main Etiologies
Anterior	**Functional signs**: photophobia, redness, pain, epiphora, decreased visual acuity (DVA)	-
	Clinical signs: conjunctival hyperemia	-
	Keratic precipitates: granulomatous (G) or non-granulomatous (NG), localized or diffuse, pigmented or non-pigmented	**G**: Infectious: HSV, VZV, CMV, TB, syphilis, Lyme disease, toxoplasmosis, Fuchs, Posner-Schlossman syndrome.
		Autoimmune: VKH, sympathetic ophthalmia, sarcoidosis, MS, phacoantigenic uveitis.
		NG: HLA-B27 (psoriasis, IBD, ankylosing spondylitis, reactive arthritis), seronegative spondyloarthritis, Behçet's disease
	Iris nodules (IN)	Sarcoidosis, TB, Fuchs
	Iris atrophy (IA) diffuse or sectoral	HSV, VZV, CMV, Fuchs
	Iris heterochromia (IH)	Fuchs
	Anterior chamber Tyndall	-
	Hypopyon (H)	HLA-B27, Behçet, HSV, VZV, rifabutin
	Irido-lenticular synechiae (ILS)	Sarcoidosis, TB, juvenile idiopathic arthritis, herpes virus, MS
	Ocular hypotony	-
	Ocular hypertension (OHT)	HSV, VZV, CMV, TB, syphilis, toxoplasmosis, sarcoidosis, Fuchs, Posner-Schlossman syndrome
	Cataract	-

Intermediate	**Functional signs**: blurred vision, decreased visual acuity, floaters	**Infectious**: TB, syphilis, Lyme disease, HTLV-1
		Autoimmune: sarcoidosis, MS
		Idiopathic: very common
	Clinical signs: vitritis with or without vitreous cellular aggregates ("snowballs"), vitreous sheets ("snowbanks"), peripheral retinal detachment	-
	Vascular sheathing	-
	Papillary or macular edema	-
Posterior	**Functional signs**: blurred vision, decreased visual acuity, visual field defects, signs of anterior involvement if associated anterior uveitis	-
	Retinitis (R)	HSV, VZV, CMV, syphilis, Behçet
	Retinochoroiditis or chorioretinitis (CR)	White spots, TB, syphilis, Lyme, sarcoidosis, toxoplasmosis, Birdshot retinochoroidopathy
	Hemorrhages (H)	Herpes viruses
	Hyalitis	-
	Serous retinal detachment (SRD)	VKH, sympathetic ophthalmia, posterior scleritis
	Neuroretinitis (NR), papillitis	Syphilis, cat scratch disease, IRVAN (Idiopathic retinal vasculitis, aneurysms, and neuroretinitis)
	Macular edema	-
	Vascular sheathing, vasculitis (V)	Behçet, sarcoidosis, syphilis, TB, SUSAC syndrome, Cogan syndrome, Eales disease, systemic vasculitis (granulomatosis with polyangiitis, PAN, Churg-Strauss syndrome)

XI. Treatment:

1. Objective:

Although the treatment of Behçet's disease remains largely empirical to date, it has been clearly demonstrated that early and effective treatment of acute inflammatory flares and the prevention of relapses significantly improve the disease outcome. It is widely accepted that intraocular inflammation requires prolonged corticosteroid therapy combined with an immunosuppressant to prevent recurrences that may threaten visual prognosis [103].

2. Management:

2.1. General measures: [104]

Corticosteroid therapy increases the risk of infections and may trigger latent infections, which should be prevented by vaccination or prophylactic anti-infective treatments.

- Seasonal influenza vaccination should be offered to patients with Behçet's disease. Pneumococcal vaccination is also recommended. Vaccines recommended for patients treated with immunosuppressants, biologics, and/or corticosteroids for chronic autoimmune or inflammatory diseases correspond to the current vaccination schedule.Additionally, specific vaccinations against influenza and pneumococcal infections are advised; in adolescent girls and even from 9 years of age, vaccination against human papillomavirus (HPV) should be added.

It is recommended to update vaccinations as early as possible during the course of the disease, preferably before starting immunosuppressive treatment, especially for live attenuated vaccines which cannot be administered afterward.

Live attenuated vaccines are contraindicated in patients receiving immunosuppressive therapy, biologics, and/or corticosteroids at immunosuppressive doses.

Pneumococcal vaccination should be administered using the 13-valent conjugate polysaccharide vaccine according to the age-appropriate schedule, followed by the 23-valent non-conjugate polysaccharide vaccine (if age > 2 years).

- A recent contact with a person affected by tuberculosis, a history of untreated and spontaneously cured tuberculosis, a tuberculin skin test ≥ 10 mm in the absence of BCG vaccination, or a positive Quantiferon® test should prompt consideration of antituberculous prophylaxis alongside the initiation of corticosteroid therapy. In case of rifampicin prescription, corticosteroid doses should be increased by approximately 30% to counteract the enzyme-inducing effect of rifampicin.
- Hyperinfection or malignant strongyloidiasis must be prevented by administering eradication antiparasitic treatment at the start of corticosteroid therapy in any patient who has stayed in an endemic area (tropical, subtropical regions, southern Europe).
- Prevention of secondary metabolic effects of long-term corticosteroid therapy (other than osteoporosis) represents another major aspect of corticosteroid prescription. Corticosteroid-induced diabetes is frequent in older populations and should be screened from the initiation of corticosteroid therapy. Referral to a dietitian should be systematically proposed to implement an appropriate diet in terms of carbohydrate intake and also to prevent weight gain or fluid retention by counseling on calorie and sodium intake.
- For the prevention of corticosteroid-induced myopathy, patients are advised to engage in regular physical activity (brisk walking 30 to 45 minutes per day) and, in case of established muscle wasting, to undergo physiotherapy sessions for muscle strengthening.

Consultation with a psychiatrist may be useful for patients with a psychiatric history to assess the risk of psychiatric decompensation under corticosteroid and/or interferon-α treatment.

The importance of preventing corticosteroid-induced osteoporosis is often underestimated. This prevention aims to reduce the risk of fractures in patients on long-term corticosteroid therapy (≥ 7.5 mg/day prednisone equivalent for ≥ 3 months). French guidelines published in 2014 address women who are premenopausal and men under 50 years old— the main population affected by Behçet's disease— for whom osteoporosis prevention strategies are less well defined than for older populations:

- Bone mineral density (BMD) measurement is recommended for patients starting prolonged corticosteroid therapy (≥ 7.5 mg/day prednisone equivalent for ≥ 3 months) or for those on corticosteroids for more than 3 months without an initial BMD assessment.
- Screening for subclinical fractures by spinal radiographs should be performed if there is a loss of height ≥ 4 cm compared to height at age 20, or a height loss ≥ 2 cm during follow-up, or if spinal pain occurs, including in children.
- The FRAX® score (10-year fracture risk assessment) is not validated in premenopausal women and men under 50 years old.
- Measurement of bone remodeling markers is not useful.
- Prescribe the minimum effective corticosteroid dose.
- Encourage adequate daily calcium intake preferably through diet; routine calcium supplementation is not systematically recommended.
- Measurement of 25-OH vitamin D levels and maintenance above 30 ng/mL.
- Encourage physical activity.
- Encourage smoking cessation.
- Avoid excessive alcohol consumption.

In case of arterial lesions, blood pressure should be monitored according to current guidelines. Smoking is a risk factor for vascular complications, and cessation is mandatory for all patients.

3. Medical treatment:

3.1. Anti-inflammatory steroids: corticosteroids :[105]

In cases of anterior uveitis, corticosteroid therapy is administered locally as eye drops. It should be initiated with a potent corticosteroid, dexamethasone, at a frequency proportional to the severity of anterior segment inflammation. For severe inflammation, hourly instillations can be recommended, followed in the evening by a corticosteroid ointment. This frequency is gradually reduced as ocular inflammation subsides.

A maintenance dose of one drop three times daily may be necessary to prevent potential relapse. In all cases, the total duration of topical treatment should be 4 to 6 weeks. Clinical monitoring of local corticosteroid therapy must be close, assessing the anterior chamber Tyndall effect, preferably by automated photometry.

Intraocular pressure measurement must be systematic due to the frequency of corticosteroid-induced ocular hypertension.

Mydriatic and cycloplegic eye drops (tropicamide, neosynephrine, atropine) are often prescribed alongside topical corticosteroids to release posterior synechiae or prevent their formation.

In cases of posterior segment involvement, systemic corticosteroid therapy by oral route is prescribed at a dose of 1 mg/kg/day.

It may be preceded by intravenous methylprednisolone boluses at a dose of 0.5 to 1 g/day for 3 days. Corticosteroid therapy must be tapered gradually due to the risk of rebound or relapse upon discontinuation.

3.2. Periocular injections:

If the uveitis is anterior, acute and does not respond to corticosteroid eye drops, or if the uveitis is intermediate, posterior, or pan-uveitis with an initially severe cataract, unilateral or immediately complicated by macular edema responsible for decreased visual acuity, a periocular injection is recommended, as it allows limiting systemic side effects and avoiding complications associated with intraocular injections [106].

3.3. Immunosuppressive treatment:

*a. **Colchicine:** [107]*

Colchicine is a drug with anti-inflammatory and immunomodulatory properties. It is indeed capable of inhibiting chemotaxis, adhesion, and mobilization of neutrophils, reducing free radical production and the activation of inflammation. It is used in Behçet's disease at a dose of 0.5 to 2 mg/day [108] to prevent mucocutaneous involvement and, according to some authors, to prevent ocular relapses.

b. Azathioprine: Imurel

Azathioprine (AZA) is an antimetabolite with a cytostatic effect on dividing cells, used in the treatment of many autoimmune and rheumatic diseases, including Behçet's syndrome with ocular involvement.

Its usual dose is 2.5 mg/kg/day (not exceeding 200 mg/day), and an average delay of 3 months is needed for its effect to fully manifest [108]. It is often prescribed in combination with anti-TNF-alpha agents, but one study [109] did not show superior efficacy with this combination.

c. Cyclosporine:

The main indication for cyclosporine A in Behçet's disease is ocular involvement, but the introduction of IFN-alpha and anti-TNF-alpha agents in the treatment of Behçet's disease has reduced the use of this drug over time. The dose of cyclosporine A should not exceed 5 mg/kg/day, and patients must be closely monitored for adverse effects, particularly irreversible nephrotoxicity. [109]

Combination with infliximab was well tolerated and led to better long-term prognosis. [110]

d. Methotrexate:

Methotrexate is a folic acid analogue that competitively inhibits intracellular dihydrofolate reductase, thereby inhibiting the synthesis of purines, nucleic acids, and certain amino acids. Methotrexate also has anti-inflammatory and immunomodulatory effects by inhibiting neutrophil chemotaxis through suppression of IL-8 production, reducing the density of epidermal Langerhans cells, and exerting a cytotoxic effect predominantly on lymphocytes. [112]

- ✓ **Dosage:**

The usual dose ranges from 7.5 mg to 25 mg given orally once weekly. It can also be administered via intramuscular (IM) or subcutaneous (SC) routes. Methotrexate is generally well tolerated at these doses; concomitant folinic acid reduces side effects.

- ✓ **Adverse effects and contraindications:**

Methotrexate has hematological, renal, hepatic, gastrointestinal, cutaneous-mucosal, and pulmonary toxicities.

e. Cyclophosphamide:

Cyclophosphamide is a cell cycle nonspecific alkylating agent that exerts its antiproliferative effects by cross-linking nucleic acids, thereby damaging DNA and disrupting its replication, leading to apoptosis of cells .Besides its common use in oncology, it has been used in the treatment of several inflammatory diseases, notably systemic autoimmune diseases such as systemic lupus erythematosus (SLE), and vasculitides such as ANCA-associated vasculitis (AAV) and Behçet's disease.

Oral cyclophosphamide (CYC) is prescribed at a dose of 2 mg/kg/day or as a monthly intravenous bolus of 750 mg/m² during the first 9 months. It has shown beneficial results in the vascular manifestations of Behçet's disease, such as pulmonary artery aneurysms and thromboses,

aortic aneurysms, peripheral arterial aneurysms, and Budd-Chiari syndrome, which are associated with high mortality. [113] CYC was also a therapeutic option for patients with Behçet's syndrome with ocular or neurological involvement before the availability of other agents such as TNF-α inhibitors and IFN-α.

f. Other immunosuppressive treatments:

Tacrolimus [114], a calcineurin inhibitor derived from the bacterium Streptomyces tsukubaensis, has become a reliable agent in the therapeutic arsenal for uveitis. Tacrolimus works by decreasing interleukin-2 levels, which in turn inhibits the action of CD4+ T cells. Its superiority in preventing solid organ transplant rejection is well established, and its use has increased over the last decade in inflammatory ocular diseases such as birdshot choroidopathy and Behçet's disease.

Tacrolimus is administered at a dose of 0.05 to 0.20 mg/kg/day in two divided doses.

Alkylating agents such as chlorambucil (Chloraminophene®) are cytotoxic drugs that cause rapid destruction of B and T lymphocytes.

Their toxicity is mainly hematological, hepatic, pulmonary, ovarian, and bladder related. They are very rarely used nowadays in the treatment of ocular involvement in Behçet's disease.

g. Biologic therapy:

The use of immunosuppressants has decreased since the emergence of biologic therapies. Due to their powerful and rapid effects, biologic agents are now used alone or in combination in refractory ocular Behçet's disease or sometimes even as first-line treatment in severe vision-threatening flares [115].

- **Interferon alpha-2a (IFN-α2a):**

Interferon alpha is a cytokine naturally produced in response to viral infection or tumors, with variable antiviral, antiproliferative, antiangiogenic, and immunomodulatory effects. In clinical practice, interferon alpha-2a is generally indicated as a second-line treatment in resistant cases or as first-line therapy in very severe posterior uveitis or in cases of intolerance to conventional

immunosuppressive drugs. Studies have shown that it improves visual acuity, reduces macular edema, significantly decreases relapse rates, and sometimes allows complete corticosteroid discontinuation [116,117]. There is no standardized consensus regarding the initial dosing up to maintenance dose, which permits remission and disease quiescence for at least 6 to 9 months. However, oral steroids should be tapered to a maintenance dose of 10 mg/day from the start of treatment [118,119].

The main side effects of interferon include flu-like syndrome, psoriasis, epilepsy, depression, leukopenia, varicella-zoster virus (VZV) reactivation [120], and autoimmune manifestations.

- **Tumor necrosis factor alpha (TNF-α) inhibitors:**

In Behçet's disease, there is an increased production of TNF-alpha by macrophages, CD4+ and CD8+ T cells, and natural killer cells [121].

The reduction of circulating TNF-alpha by blocking agents has led to a dramatic improvement in disease activity, as demonstrated by numerous trials, particularly in patients with severe panoramic posterior uveitis. The anti-TNF-alpha drugs used are recombinant monoclonal antibodies targeting TNF-alpha. Therefore, the pre-treatment workup must include a complete blood count, liver function tests, hepatitis B and C serology, chest X-ray, tuberculin skin test (PPD), Quantiferon test, and antinuclear antibody (ANA) titers [122]. In case of failure of a first anti-TNF-alpha agent, switching to another anti-TNF agent may be considered, or combining an immunosuppressant with an anti-TNF agent can be useful to prevent the formation of antibodies against the anti-TNF agent itself and to ensure better efficacy [123].

Adalimumab (ADA) is a human monoclonal antibody directed against TNF-alpha. It is one of the few drugs tested in randomized controlled trials (RCTs) against placebo in active and quiescent non-infectious uveitis (VISUAL I and VISUAL II studies, respectively) [124,125], where Behçet's disease accounted for 7% of uveitis etiologies.

Due to its superiority over placebo in improving central retinal thickness and controlling disease activity (but not macular edema), the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) approved ADA for non-infectious uveitis in 2016. Adalimumab is administered by subcutaneous injection at an adult dose of 40 mg every 2 weeks.

Numerous uncontrolled studies, such as those reported by Fabiani et al. and Urruticoechea-Arana et al., have also shown significant results regarding ADA's efficacy in improving uveitis [126,127]. Not only was ADA superior to placebo in controlling disease activity, but a higher percentage of patients on ADA were able to discontinue oral steroids [128]. Adalimumab has also been tested in the pediatric Behçet's subgroup, where early initiation of the drug in two children allowed disease control while reducing topical and systemic steroids, thus preventing complications [121].

Humira is the reference drug for adalimumab studied in all the above trials. Several adalimumab biosimilars (bio-ADA) are still under investigation for their efficacy in ocular Behçet's disease. A very recent study by Soheilian et al. reports significantly positive outcomes with bio-ADA in improving visual acuity, reducing vitreous haze, and improving anterior chamber activity in 48 patients with refractory Behçet's disease [128]. Sota et al. also report favorable results in controlling retinal vasculitis and disease activity while preserving visual acuity [129,154].

Infliximab (IFX) is another TNF-alpha blocker in the form of a chimeric monoclonal antibody. It is generally reserved for refractory cases or used as a first-line treatment in severe posterior uveitis with a higher risk of tissue damage or vision loss. Infliximab is administered at a dose of 3 to 5 mg/kg by slow intravenous infusion over 2-3 hours. The loading regimen includes repeated doses at week 2, then week 6, followed by maintenance infusions every 6-8 weeks to maintain disease control. Numerous trials have demonstrated the rapid and potent effect of infliximab on Behçet's uveitis. The drug induces rapid remission of the disease and improvement in visual acuity. It also reduces the frequency and severity of flares compared to other immunosuppressants during the first 6 months of treatment as well as long-term therapy [131].

Early administration within the first 36 months, compared to 72 months, appears to confer a protective effect on visual outcome and disease control [132].

As with ADA, IFX is typically combined with another immunosuppressant to prevent the formation of antibodies against the anti-TNF-alpha agent itself and may be associated with reactivation of tuberculosis and hepatitis B or C. Numerous adverse effects have been reported with IFX, including allergic reactions, drug-induced lupus, worsening of multiple sclerosis, optic neuritis, and pulmonary embolism, sometimes necessitating treatment discontinuation.

Several comparative studies between ADA and IFX have been conducted [133]. In particular, a multicenter study involving 177 patients compared ADA and IFX as first-line biologic treatments in refractory Behçet's uveitis and found that both groups achieved significantly better disease activity control, but the ADA group had a higher percentage of patients with better best corrected visual acuity (BCVA) and higher drug retention rates with fewer drug-related reactions [134].

Regarding infliximab biosimilars (bio-IFX), conflicting reports exist about their efficacy in ocular Behçet's disease management. While bio-IFX was disappointing in 3 patients with ocular and neurological Behçet's disease, leading to recurrence of disease activity after switching from the reference drug to biosimilars [135], another study reported success of bio-IFX in achieving remission in 4 out of 6 patients with Behçet's involving uveitis, nervous system, vessels, and joints [128].

Golimumab is another fully humanized anti-TNF alpha monoclonal antibody that appears to have promising efficacy, particularly in refractory Behçet's disease cases [136,137].

Further studies are needed to better evaluate its efficacy and safety profile.

❖ **Interleukin receptor antagonists:**

- **Interleukin-6 (IL-6) antagonists:**
  - **Tocilizumab (TCZ):**

In recent years, several reports have demonstrated the efficacy of TCZ, an interleukin-6 inhibitor, in controlling cases of uveitis refractory to conventional treatment and TNF-alpha antagonists [136,138].

The drug has achieved complete remission in some cases of ocular Behçet's disease, although it has failed to control systemic disease in the same patients [163,164]. TCZ may be considered for some patients with refractory uveitic macular edema (STOP-Uveitis study) [141,142].

The SATURN and SARIL-NIU trials investigated sarilumab, a newer IL-6 antagonist, in non-infectious uveitis. However, sarilumab has not yet been approved for ophthalmic involvement management in Behçet's disease [143].

- **Interleukin-1 (IL-1) antagonists:**
- **Anakinra (ANA) and canakinumab (CAN):**

ANA and CAN are currently under investigation. A retrospective multicenter Italian study conducted in 2017 indicated that these two IL-1 antagonists successfully managed intraocular inflammation in a small cohort of patients with Behçet's disease [144,145]. This finding was confirmed by another study reporting a better response to IL-1 treatment in patients with ocular Behçet's, especially those with uveitis, compared to those without ocular involvement [137]. The rationale for IL-1 inhibition and its reported success is based on the potential role of IL-1β, expressed by retinal dendritic cells, macrophages, and neutrophils, as a mediator of the local inflammatory process [146].

- **Interleukin-17A (IL-17A) antagonists:**

The SHIELD trial was conducted to evaluate the efficacy of secukinumab in Behçet's disease uveitis. The trial did not meet its primary endpoint compared to placebo regarding uveitis relapses but significantly reduced the need for concomitant immunosuppressive treatment [140].

- **Janus kinase inhibitors (JAKi):**

Several recent studies have reported the success of JAK inhibitors in the treatment of non-infectious autoimmune uveitis refractory to conventional immunomodulators and anti-TNFα agents, suggesting that they may be an alternative to the aforementioned therapies [147,148]. Some have also reported a steroid-sparing effect. JAK inhibitors have already been approved for several autoimmune rheumatologic, gastrointestinal, and dermatologic diseases. They act by inhibiting the phosphorylation of the transmembrane JAK protein, thereby blocking or reducing the cytokine signaling cascade prior to its activation [149]. Zou et al. reported positive outcomes with tofacitinib in patients with refractory uveitis, highlighting the need for larger prospective studies [149].

h. Other Treatments:

Surgery is recommended for the treatment of ocular complications of Behçet's disease such as cataract or glaucoma.

Panretinal photocoagulation is used in ophthalmology to treat retinal vascular lesions that do not respond to anti-inflammatory and immunosuppressive treatment. Photocoagulation can cause structural damage to the retina and choroid. Consequently, the blood-retinal or blood-aqueous barrier may be disrupted, leading to the release of pro-inflammatory cytokines and thereby triggering a uveitis relapse, known as laser-induced hypopyon. The underlying mechanism may correspond to an "ocular pathergy test" in patients with Behçet's syndrome [150].

4. Indications:

Management and follow-up must be conducted with an ophthalmologist experienced in the care of chronic inflammatory eye diseases. Ophthalmologic involvement in Behçet's disease is severe, impacting functional prognosis and frequently recurrent. Reduction (or discontinuation) of immunosuppressive or immunomodulatory treatment should only be considered in exceptional cases, and only after at least 2 years of remission in severe Behçet's disease; expert opinion is recommended.

For anterior uveitis, corticosteroid therapy is administered topically as eye drops. Treatment should be initiated with a potent corticosteroid, such as dexamethasone, with dosing frequency proportional to the severity of anterior segment inflammation. Clinical monitoring of topical corticosteroid therapy should be close (initially every 48 hours, then every 1 to 2 weeks depending on severity), assessing anterior chamber Tyndall effect and measuring intraocular pressure systematically due to the common occurrence of steroid-induced ocular hypertension. Mydriatic and cycloplegic eye drops (tropicamide, neosynephrine, atropine) are often prescribed alongside topical corticosteroids to resolve or prevent posterior synechiae formation. In cases of ocular hypertension, one or more hypotensive eye drops should be prescribed, avoiding prostaglandin analogues if possible, due to their pro-inflammatory effects.

Hypopyon uveitis generally requires systemic corticosteroid therapy. Some authors recommend the use of an immunosuppressant (azathioprine) for anterior uveitis in Behçet's disease, especially in young male patients or in recurrent uveitis.

All cases of posterior uveitis in Behçet's disease should be treated systemically with corticosteroids and immunosuppressants. Posterior segment involvement requires systemic corticosteroids and immunosuppressive therapy, such as azathioprine in non-severe cases.

Severe posterior uveitis (characterized by decreased visual acuity, occlusive vasculitis, and/or macular edema) justifies systemic treatment with corticosteroids and anti-TNFα antibodies. Interferon-alpha (IFN-α) may be proposed as an alternative therapeutic option.

Oral systemic corticosteroid therapy is prescribed according to severity at a dose of 0.5 to 1 mg/kg/day and may be preceded by methylprednisolone pulses at a dose of 500 mg/day for 3 days. Azathioprine at a dose of 2 mg/kg/day or cyclosporine (3 mg/kg/day) are effective corticosteroid-sparing treatments and appear useful in preventing relapses of Behçet's disease. However, this treatment alone does not seem sufficient for severe uveitis with decreased visual acuity, macular edema, and/or retinal vasculitis, which represent therapeutic emergencies.

In cases of acute flare-up of posterior uveitis with macular edema and/or retinal vasculitis, intravenous infusions of infliximab at 5 mg/kg or subcutaneous injections of adalimumab (initial dose of 80 mg followed by 40 mg every 15 days) lead to rapid improvement in the majority of cases. IFN-α (Roferon: 3 million units, subcutaneously, three times a week) may be proposed as an alternative therapy. In contrast, etanercept is not indicated for the treatment of uveitis in Behçet's disease. Currently, there are limited data available regarding certolizumab and golimumab for this indication. Other treatments that may be of interest for ocular involvement include IL-6 inhibitors.

4.1 Recommendations for the management of ocular involvement in Behçet's disease:

- Initial management and follow-up of patients with Behçet's disease and uveitis require close collaboration with an ophthalmologist.
- Any patient with Behçet's disease and posterior segment ocular involvement should be treated with an immunosuppressant or biologic therapy (azathioprine, cyclosporine A, interferon-α, or anti-TNFα agents).
- Any severe involvement threatening visual acuity must be treated with high doses of corticosteroids combined with anti-TNFα therapy or IFN-α.
- All systemic corticosteroid therapy should be combined with the administration of an immunosuppressant.
- Intra-vitreal corticosteroid injections combined with systemic treatment may be considered in cases of unilateral involvement.

- Patients refractory to azathioprine or cyclosporine can be treated with IFN-α or monoclonal anti-TNFα agents. The choice between these two treatments depends on the patient's infectious risk (e.g., tuberculosis), tolerance to IFN-α, and the clinician's experience.
- Regarding isolated anterior segment involvement, systemic immunosuppressive therapy may be considered in the presence of poor prognostic factors such as young age, early disease onset, and male sex.

4.2 Indications for Surgical Treatment:

Cataract and glaucoma surgeries can be performed safely in patients with Behçet's syndrome (BS) after effective control of intraocular inflammation, particularly with the use of IFN-alpha or anti-TNF therapy.

Cataract surgery should be conducted on a quiet eye, with uveitis in complete remission for at least 3 months.

Visual recovery after cataract surgery depends on the degree of preoperative retinal damage, which may be predicted by electroretinography.

Pars plana vitrectomy may be necessary for vitreoretinal complications such as persistent vitreous hemorrhage, epiretinal membrane, macular hole, or retinal detachment. There is no evidence that this procedure could be a therapeutic option for preventing ocular Behçet's disease exacerbations.

5. Treatment of Other Manifestations

5.1 Mucocutaneous Involvement:

Colchicine is the first-line treatment in the absence of contraindications to prevent recurrence of mucocutaneous lesions, particularly oral and genital aphthae or erythema nodosum-like lesions, usually at a dose of **1 to 2 mg/day**. **Good oral hygiene** is essential. **Topical corticosteroids** (class I or II) may be used to treat oral and genital aphthosis, although a **short course of oral corticosteroids** may sometimes be required.

In cases of **disabling and treatment-resistant oral aphthosis**, corticosteroid mouthwashes can be useful.

Topical lidocaine gel may provide relief for **very painful genital ulcers**.

In **highly selected cases** (patients with severe, refractory mucocutaneous disease), alternative treatments such as:

- **Apremilast** (a phosphodiesterase-4 inhibitor),
- **Anti-TNFα agents**,
- **Azathioprine**,
- **Thalidomide**, or
- **Ustekinumab** may be considered.

A **phase II randomized clinical trial** including **111 adult patients** with recurrent oral ulcers showed that **apremilast (Otezla®)** at **30 mg twice daily** significantly reduced the **mean number of oral ulcers per patient** compared to placebo.

Anti-acne treatments have limited effectiveness on pustular skin lesions.

5.2 Articular Involvement

Colchicine is the first-line treatment, typically at doses of **1 to 2 mg/day**. **Intra-articular corticosteroid injections** are a useful adjunct, especially given the oligoarticular pattern involving large joints. **NSAIDs** or **short courses of oral prednisone** may also be considered during acute flares.

In **refractory and/or recurrent forms**, **disease-modifying therapy** is necessary. Options include:

- **Anti-TNFα agents**,
- **Azathioprine** (**2 mg/kg/day**), or
- **Methotrexate** (**7.5–25 mg/week orally**).

5.3 Neurological involvement:

a. Parenchymal forms:

The treatment of parenchymal forms is based on glucocorticoids, at high doses as induction therapy (intravenous boluses of methylprednisolone, 500 mg/day for 3 days), followed by oral corticosteroid therapy at 1 mg/kg/day (not exceeding 80 mg/day) of prednisone equivalent for 3 weeks with progressive tapering (15 to 20 mg/day at 3 months and ≤ 0.1 mg/kg/day at 6 months).

Neurological involvement is a severe manifestation of BD that threatens life and function, and relapses are frequent. A reduction (or discontinuation) of immunosuppressive or immunomodulatory treatment should not be considered, except in exceptional cases, before at least 2 years of remission in the context of severe Behçet's disease, and expert opinion is recommended.

In severe parenchymal involvement (Rankin score ≥ 2), an immunosuppressant should be added from the start of treatment, such as intravenous cyclophosphamide (0.7 g/m² not exceeding 1.2 g) in boluses every 4 weeks with a switch to oral azathioprine (2 mg/kg/day) after 6 cycles.

Anti-TNFα antibodies such as infliximab (5 mg/kg at weeks 0, 2, 6, then every 6 weeks) may be proposed as an alternative to cyclophosphamide. For less severe parenchymal forms (Rankin score < 2), oral azathioprine (2 mg/kg/day) is recommended. Methotrexate (0.3 mg/kg/week) or mycophenolate mofetil (2 g/day) can also be used. The treatment of isolated meningitis is based on high-dose glucocorticoids. The immediate addition of an immunosuppressant (such as azathioprine) is not recommended for a first episode but can be discussed in case of relapse under corticosteroids. Cyclosporine no longer has a place in the treatment of these forms due to an increased risk of neurological worsening.

b. Extra-parenchymal forms (cerebral thrombophlebitis):

The treatment of cerebral thrombophlebitis in BD also relies on high-dose glucocorticoids as induction therapy, with intravenous boluses of methylprednisolone (500 mg/day for 3 days), followed by oral corticosteroid therapy at 1 mg/kg/day (not exceeding 80 mg/day) of prednisone equivalent for 3 weeks with progressive tapering (15 to 20 mg/day at 3 months and ≤ 0.1 mg/kg/day at 6 months).

The immediate addition of an immunosuppressant (such as azathioprine) is not recommended during a first episode but can be discussed in case of relapse under corticosteroids.

The prescription of anticoagulants at curative doses is recommended. The duration of anticoagulation is debated but is generally 12 to 18 months. The hemorrhagic risk must always be assessed, notably by verifying the absence of arterial aneurysmal involvement.

5.4 Vascular involvement:

It is now clearly established that immunosuppressive treatment is the cornerstone of the therapeutic strategy in these severe forms of Behçet's disease (BD); this is based on the fact that inflammation of the vascular wall very likely plays a predominant role in the occurrence of vascular thrombotic lesions.

Curative anticoagulation is indicated in venous thrombosis after assessing the hemorrhagic risk and verifying for potential arterial aneurysmal lesions. The duration of anticoagulant treatment is 3 to 6 months except in severe forms such as thrombosis of the hepatic veins and/or the vena cava, which require prolonged anticoagulation. Vascular involvement is a severe manifestation of BD that is life-threatening and prone to frequent relapses. A reduction (or discontinuation) of immunosuppressive or immunomodulatory treatment should not be considered, except in exceptional cases, until after at least 2 years of remission in the context of severe BD, and expert opinion is advised.

For acute deep vein thrombosis without severity criteria (lower limbs), treatment with glucocorticoids (prednisone as induction therapy) and effective anticoagulation for 3 to 6 months is recommended. The treatment of severe cardiovascular involvement (thrombosis of hepatic veins, vena cava thrombosis, arterial aneurysms, myocarditis, etc.) is based on high-dose glucocorticoids as induction therapy (intravenous boluses of methylprednisolone, 500 mg/day for 3 days), followed by oral corticosteroid therapy at 1 mg/kg/day (not exceeding 80 mg/day) of prednisone equivalent for 3 weeks with progressive tapering (15 to 20 mg/day at 3 months and ≤ 0.1 mg/kg/day at 6 months).

An immunosuppressant should be added from the beginning of treatment, such as intravenous cyclophosphamide (0.7 g/m² not exceeding 1.2 g) in boluses every 4 weeks, or anti-TNFα antibodies such as infliximab (5 mg/kg at weeks 0, 2, 6, then every 6 weeks).

Oral azathioprine (2 mg/kg/day) or anti-TNFα antibodies (adalimumab or infliximab) are recommended in the management of recurrent vascular involvement. Surgical or endovascular management should not, however, be delayed if the patient is symptomatic.
It is essential to initiate corticosteroid therapy and an immunosuppressive treatment before surgical management in order to reduce the risk of postoperative complications. Postoperative complications are indeed significantly less frequent in patients receiving immunosuppressants.

A multidisciplinary approach in an expert center is essential to decide the optimal timing for the intervention. Long-term follow-up is essential to detect complications and recurrences. In the case of **pulmonary aneurysms** and the occurrence of **life-threatening hemoptysis**, it is important to determine the location and mechanism in order to propose relevant targeted interventional radiology either on the **pulmonary aneurysm** (pulmonary vasocclusion) or on the **peri-aneurysmal bronchial hypervascularization** (bronchial arteriography with embolization). Surgery during the active phase of hemoptysis carries a very poor prognosis. This management must be carried out in multidisciplinary consultation and in an expert center

5.5 Digestive involvement:

Digestive involvement in Behçet's disease must be confirmed by endoscopy and/or imaging. Digestive ulcers related to NSAIDs or of infectious origin must be ruled out. The treatment of digestive involvement combines glucocorticoids (0.5 mg/kg/day as induction therapy) and 5-ASA or azathioprine (2 mg/kg/day).

In severe and/or refractory forms, anti-TNFα treatment is recommended.

In cases with digestive involvement and diarrhea, and due to the frequent gastrointestinal side effects of colchicine (diarrhea in 1 to 10% of cases), initiation of colchicine treatment should be discussed with a gastroenterologist.

This treatment may, for example, be delayed until inflammation is controlled.

XII. Discussion of ourresults:

1. Epidemiological Data:

Ocular involvement is common in Behçet's disease.The reported frequency varies across studies depending on the authors and the method of patient recruitment. In our study onthe impact ofinflammatory markers in activity of ocular Bechet's disease, the number of patients included was 92.

This sample size is comparable to international studies, although there are some differences in the sample sizes used, ranging from 104 cases in the series byLetifi and al [10]to 27 cases in the study by BAYRAKTAR and al [9].

Table XV: Reported sample sizes of ocular manifestations in the literature and in our study

Authors	Country	Year	Number of cases
Kim and al [8]	Korea	2021	50
E. Kamal and al [153]	Egypt	2022	38
BAYRAKTAR and al [9]	Turkey	2024	27
Balbaba and al [155]	Turkey	2019	48
Letifi and al[10]	Tunisia	2022	104
Sakamoto and al[11]	Japan	1995	52
Sota and al[154]	Italy	2020	47
Our series	Morocco (Marrakech)	2025	92

1.1. Gender Distribution:

Sex distribution in our study showed a clear male predominance, with 70 % of patients being male and 30% female, corresponding to a male-to-female ratio (M/F) of 2.3.

This male predominance is consistent with findings reported in most other studies in the literature, with the exception of the series by Sota et al. [154], where the sex ratio was close to 1, indicating a balanced distribution. This may be explained by the relatively small sample size.

Table XVI: The Gender distribution of patients

Authors	Country	Year	male-to-female ratio
Kim and al [8]	Korea	2021	1,6
Balbaba and al [155]	Turkey	2019	1,5
Letifi and al. [10]	Tunisia	2022	3,5
Sota and al [154]	Italy	2020	0,96
Sakamoto and al [11]	Japan	1995	2,3
µOur series	Morocco(Marrakech)	2025	2,3

1.2. The Mean age of patients :

In our study, the mean age of patients was 41 years, with a range from 18 to 68 years, which is consistent with the results reported in the previously cited studies.

Table XVII: The mean age of patients

Authors	Country	Year	Mean age
Kim and al [8]	Korea	2021	43.7[33-54]
Balbaba and al [155]	Turkey	2019	35,12[23-48]
Sota and al[154]	Italy	2020	33,9[19-48]
Sakamoto and al [11]	Japan	1995	35[17-55]
Letifi and al. [10]	Tunisia	2022	35 [14-68]
Our series	Morocco(Marrakech)	2025	41 [18-68]

2. Clinical diagnosis:

2.1. Onset characteristics:

In our study, the frequency of cases with initial presentation was 36 %. This rate is lower than the rate observed by Sota and al [154] (62%) and Letifi and al[10] (55%).

Table XVIII: Onset characteristics

Authors	Country	Year	Onset characteristics
Sota and al[154]	Italy	2020	Inaugural in 62%
Letifi and al [10]	Tunisia	2022	Inaugural in 55%
Our series	Morocco (Marrakech)	2025	Inaugural in 36%

2.2. Revealing clinical signs:

In our serie, Decreased Visual Acuity (DVA) was the most common presenting symptom, followed by Ocular redness and periocular pain.

Similarly, Letifi and al. found that decreased visual acuity was more predominant than ocular redness as the initial clinical manifestation of the disease.

Table XIX: Revealing clinical signs

Authors	Country	Revealing signs	Frequency
Letifi and al [10]	Tunisia	Decreased Visual Acuity Ocular redness periocular pain	95 % 58,8% 11,1%
Our series	Morocco (Marrakech)	Decreased Visual Acuity Ocular redness periocular pain	94.57% 58.70% 33.70%

2.3. Bilateral involvement:

In our serie, bilateral involvement was observed in 77% of cases. This rate is comparable to that reported by Letifi and al [10](79%), and higher than that reported by Sota and al [154] (49.4%) and Sakamoto and al [11] in (66%).

Table XX: Bilateral involvement

Authors	Country	Year	Bilateral involvement
Sota and al[154]	Italy	2020	49,4%
Sakamoto and al [11]	Japan	1995	66%
Letifi and al. [10]	Tunisia	2022	79%
Our series	Morocco (Marrakech)	2025	77%

2.4. Visual acuity:

In our serie, 64% of patients had visual acuity ≤ 20/40, while 36% had visual acuity better than 20/40. This distribution shows a higher proportion of patients with reduced visual acuity at the admission time, possibly due to delayed diagnosis related to economic issues or lack of awareness, compared to the studies by Sota and al [154]and Sakamoto and al [11].Letifi and al [10]reported nearly an equal distribution between patients with visual acuity ≤ 20/40 (50.42%) and those with better visual acuity (49.58%).

Table XXI: Visual acuity

Authors	Country	Visual acuity	frequency
Sota and al [154]	Italy	VA ≤20/40	18%
		VA ≥20/40	82%
Sakamoto and al [11]	Japan	Normal VA	56,4%
		Reduced VA	43,6%
Letifi and al. [10]	Tunisia	VA ≤20/40	50,42%
		VA ≥20/40	49,58%
Our series	Morocco (Marrakech)	VA ≤20/40	64%
		VA ≥20/40	36%

3. Clinical Features of Ocular Involvement:

In our serie, uveitis was the most dominant ocular manifestation, observed in 64% of patients. This predominance was also noted in the study by Sota and al [154], where uveitis affected 65.96% of patients.

In comparison, lower frequencies were reported by Kamal and al[153] (38.6%) and Sakamoto andal[11] (28%). Retinal vasculitis was present in 47% of our patients, though corresponding data were not available in the other studies. Maculopathy was observed in 10% of our cases, which is notably lower than the 30% reported in the Japanese series. Optic neuropathy was found in 5% of patients in our study, also less frequent than the 9% observed by Sakamoto and al [11].

Table XXII: Clinical features of ocular involvement

Authors	Uveitis	Retinal vasculitis	Maculopathy	Optic neuropathy
e. Kamal and al; Egypt [153]	38,60%	-	-	-
Sota and al [154] Italie	65,96%	-	-	-
Sakamoto and al [11] Japan	-	-	30%	9%
Bayraktar and al [9] Turkey	28%	-	-	-
Our series Morocco(Marrakech)	64%	47%	10%	5%

3.1. Characteristics of Uveitis:

In our series, posterior uveitis was the predominant anatomical form observed. This is consistent with the findings of E. Kamal et al. [153], who also reported posterior uveitis as the most common localization. In contrast, pan uveitis was the most frequently reported form in the studies by Sota et al. [154] and Letifi et al. [10], while Kim et al. [8] identified anterior uveitis as the most prevalent subtype.

Table XXIII: Uveitis characteristics

Authors	Localization of uveitis
Kim and al [8]	Anterior uveitis 50%
E. Kamal and al [153]	Posterior uveitis 45.3%
Sota and al[154]	Pan uveitis 48%
Letifi and al [10]	Pan uveitis 32.23%
Our series	Posterior uveitis 66%

4. Extra-ocular Manifestations of Behçet's Disease:

Extra-ocular manifestations were consistently present in all patients. **Oral aphthosis**, a key diagnostic criterion, was observed in **100% of patients** in our study and reported in more than 50% of cases across all referenced series. In contrast, the frequency of **genital aphthosis** showed wide variation, ranging from **19.1%** in the studies by Sota and al. [154] and Ghavidel eand al., to **69.3%** in the study by E. Kamal and al. [153].

Regarding other cutaneous manifestations, a predominance of **pseudofolliculitis** over **erythema nodosum** was consistently observed in the literature as well as in our study.

Most reviewed studies also reported the presence of systemic manifestations, including neurological, gastrointestinal, and articular involvement, with variable frequencies(TableXXIV)

Table XXVI: Extra-ocular manifestations of behçet's disease

Authors	Oral ulcer	Genital ulcers	Other Cutaneous Manifestations	Other Manifestations
E. Kamal and al [153]	77.3%	69.3%	Erythema nodosum 2.6% Papulopustular lesions 4%	Articular manifestations 29.3% Neurological involvement 6.6%
Bayraktar and al [9]	44.7%	18.7%	Erythema nodosum 13.3% Papulopustular lesions 36.7%	Articular manifestations 14%
Sakamoto and al [11]	56,4%	27%	53,4%	39%
Sota and al[154]	72,34%	19,15%	Erythema nodosum 4.25% Papulopustular lesions 14.89%	Neurological involvement 4.25% Gastrointestinal involvement 8.51 % Vascular involvement 4.25%
Our series	100%	47%	Erythema nodosum 17% Papulopustular lesions 28%	Articular involvement 35% Neurological involvement 8% Vascular involvement 12% Gastrointestinal involvement 1%

5. Treatment :

Oral and intravenous corticosteroid therapy (bolus) were first-line treatments, administered to the majority of the patients across various studies.

With regard to immunosuppressive therapy, a high rate of prescription was observed, particularly in our study (93%) and by E. Kamal and al [153] (46,7%). In contrast, Biologicswere preferred in the series by Sota et al [154].

Table XXV: Treatment received by the patients

Authors	Oral corticosteroids	Methylprednisolone bolus	immunosuppressant	Biologics
E. Kamaland al [153]	70.6%	-	46.7%	29.3%
Sota and al[154]	-	-	29%	40,4%
Letifi and al [10]	69%	42,30%	16,34%	-
Our series	100%	82%	93%	15%

6. Outcome after treatment:

The majority of our patients showed a favorable progression, which is consistent with the findings of Sakamoto et al. [11] and Letifi et al. [10], but contrasts with the results reported by Sota et al. [154], where 89% of patients experienced an unfavorable outcome.

Table XXVI: Unfavorable outcome of patients

Authors	Country	Year	Unfavorable outcome
Sota and al[154]	Italy	2020	89%
Sakamoto and al [11]	Japan	1995	35%
Letifi and al. [10]	Tunisia	2022	43,8%
Our series	Morocco (Marrakech)	2025	44%

7. Ophthalmologic complications after treatment :

The two most frequent complications in our serie were Iris-lens synechiae and blindness, with rates of 45% and 29%, respectively.

Cataract is one of the most commonly reported complications in various studies: Letifi and al [10]: 27.2%, and Sota and al [154]: 21%. In contrast, in Japan, maculopathy is reported as the most frequent complication, with a rate of 29.7%.

Table XXVII: The frequency of different complications

Authors	Complications	Frequency
Sota and al[154]	Iris-lens synechiae	10 %
	Cataract	21 %
	Macular hole	2%
	Macular edema	11%
	Retinal detachment	2%
	Blindness	3,5%
Sakamoto and al [11]	Maculopathy	29.7%
	Glaucoma	19%
	Neovascularization	8.91%
Letifi and al. [10]	Cataract	27.2%
	Optic atrophy	17.3%
	Iris-lens synechiae	16%
	Maculopathy	9.8%
	Glaucoma	2.4%
Our series	Iris-lens synechiae	45%
	Cataract	15%
	Optic atrophy	4%
	Macular hole	8%
	Macular edema	12%
	Posterior vitreous detachment	17%
	Retinal detachment	9%
	Blindness	29%

8. Inflammatory biomarkers:

We note that certain significant p-values were common across the different studies, including ours, CAR was significantly associated with the activity of ocular Behçet in our study (p=0.014) and the studies from Korea [8] ($p < 0.001$), Turkey [9] (BAYRAKTAR, $p < 0.001$), Egypt[153] ($p = 0.0349$), CRP was also a commonly significant marker, with p-values < 0.001 (Korea[8]), 0.008 (BAYRAKTAR[9]), < 0.0001 (Egypt[153]), 0.003 (Balbaba[155]), and 0.007 (our series), NAR, although less frequently assessed, showed significance in both the Egyptian [153] ($p = 0.0108$) and our serie ($p < 0.001$. In contrast, other markers such as PLR and NLR yielded inconsistent results; for instance, PLR was not significant in our study or the Korean [8] & Egyptian studies [153], NLR was only significant in Balbaba's study [155] ($p = 0.001$).

Table XXVIII: P-Value analysis of inflammatory biomarkers

Authors	Country	Inflamatory Biomarkers	P value
Kim and al [8]	Korea	CAR	< 0.001
		NLR	0.280
		PLR	0.110
		CRP	< 0.001
BAYRAKTAR and al [9]	TURKEY	CAR	< 0.001
		CRP	0.008
E. Kamal and al [153]	Egypt	CAR	0.0349
		NAR	0.0108
		CRP	< 0.0001
		PLR	0.18
Balbaba and al [155]	Turkey	NLR	0.001
		CRP	0.003
Our series	Morocco (Marrakech)	MPV	<0.001
		NAR	<0.001
		LMR	0.023
		CRP	0.007
		CAR	0.014
		PLR	0.910
		NLR	0.222

CONCLUSION

Behçet's disease is a chronic, multisystemic inflammatory disorder of unknown cause. It is characterized by recurrent oral and genital aphthosis, skin lesions, and ocular, articular, vascular, and neurological involvement.

Ocular involvement is one of the major diagnostic criteria for Behçet's disease and must therefore be systematically assessed. Uveitis is the most common ocular manifestation and poses a serious threat to visual prognosis. Various ophthalmological features such as macular edema, retinal vasculitis, and papilledema must be recognized, especially since they can be revealing signs of Behçet's disease.

According to the criteria established by the International Study Group for Behçet's Disease (ISG), the diagnosis is clinical.

Treatment includes both local and systemic corticosteroids, in combination with disease-modifying therapy based on immunosuppressive agents.

Our study enabled the analysis of the biological markers of inflammation and their impact on the activity of ocular Behçet's disease.

We found that certain inflammatory markers have significant value, which is consistent with findings reported in the literature: the blood indices CRP, NAR and CAR are potential inflammatory markers that can be used to evaluate disease activity in patients with ocular involvement of BD.

ABSTRACT

Abstract

Behcet's disease (BD) is an inflammatory, systemic, dysimmune, chronic vasculitis that progresses by relapses. The initial diagnosis is clinical, based on criteria defined by the ISG, which include ophthalmological manifestations.

This study aimed to evaluate the impact of inflammatory biomarkers on the activity of ocular Behçet's disease.

A retrospective, descriptive, and analytical study was conducted on 92 patients diagnosed with ocular BD, hospitalized in the Internal Medicine Department of The university hospital Errazi (Marrakech) between 2010 and 2023. Data were collected from medical records and supported by clinical and paraclinical evaluations

The cohort showed a male predominance (70%) with a mean age of 41.3 years. Bilateral ocular involvement was observed in 77% of cases. The main clinical manifestations included uveitis (64%), retinal vasculitis (47%), and maculopathy (10%). Severe visual acuity loss was frequent at diagnosis.

Systemic corticosteroid therapy was administered to all patients, with 93% receiving additional immunosuppressive therapy. Biologic therapies were used in 15% of cases. Clinical improvement was noted in 57% of patients, while 30 % had stable disease. However, 29%progressed to blindness.

The analytical part of the study investigated several blood-based inflammatory markers: CRP, CAR (CRP/albumin ratio), NAR (neutrophil/albumin ratio), LMR (lymphocyte/monocyte ratio), PLR (platelet/lymphocyte ratio), NLR (neutrophil/lymphocyte ratio), and MPV (mean platelet volume). Statistically significant differences between active and inactive disease phases were found for MPV, NAR ($p<0.001$), LMR ($p=0.023$), CRP ($p=0.007$), and CAR ($p=0.014$). PLR and NLR were not statistically significant.

In conclusion, this study highlights the potential of specific inflammatory biomarkers (especially MPV, NAR, CAR, and CRP) as indicators of ocular disease activity in BD. Their integration into clinical practice could enhance monitoring and allow early therapeutic intervention, thereby improving visual prognosis and reducing long-term complications.

Résumé

La maladie de Behçet (MB) est une vascularite inflammatoire, systémique, dysimmunitaire et chronique, évoluant par poussées. Le diagnostic initial est clinique, basé sur les critères définis par l'ISG, incluant des manifestations ophtalmologiques.

Cette étude avait pour objectif d'évaluer l'impact des biomarqueurs inflammatoires sur l'activité de la maladie de Behçet oculaire.

Une étude rétrospective, descriptive et analytique a été menée sur 92 patients atteints de MB oculaire, hospitalisés au service de médecine interne du The university hospital Errazi (Marrakech) entre 2010 et 2023. Les données ont été recueillies à partir des dossiers médicaux et complétées par des évaluations cliniques et paracliniques.

La population montrait une prédominance masculine (70 %) avec un âge moyen de 41,3 ans. Une atteinte oculaire bilatérale était observée dans 77 % des cas. Les principales manifestations cliniques étaient : uvéite (64 %), vascularite rétinienne (47 %) et maculopathie (10 %). Une perte sévère d'acuité visuelle était fréquente au moment du diagnostic.

Tous les patients ont reçu une corticothérapie systémique, avec un traitement immunosuppresseur associé dans 93 % des cas. Une biothérapie a été utilisée chez 15 % des patients.Uneamélioration cliniqueaéténotéechez57%,30%sontrestésstables,tandisque29% ont évolué vers la cécité.

L'étude analytique a porté sur plusieurs biomarqueurs inflammatoires sanguins : CRP, CAR (rapport CRP/albumine), NAR (rapport neutrophiles/albumine), LMR (rapport lymphocytes/monocytes), PLR (rapport plaquettes/lymphocytes), NLR (rapport neutrophiles/lymphocytes), et MPV (volume plaquettaire moyen). Des différences significatives ont été trouvées entre les phases active et inactive pour le MPV, NAR ($p<0,001$), LMR ($p=0,023$), CRP ($p=0,007$), et CAR ($p=0,014$). Le PLR et le NLR n'étaient pas significatifs.

En conclusion, cette étude met en évidence l'intérêt de certains biomarqueurs inflammatoires (notamment MPV, NAR, CAR et CRP) comme indicateurs de l'activité oculaire de la MB. Leur intégration dans la pratique clinique pourrait améliorer le suivi et permettre une intervention thérapeutique précoce, améliorant ainsi le pronostic visuel et réduisant les complications à long terme.

ملخص

مرض بهجت هو التهاب أوعية مزمن، جهازي، ذو منشأ مناعي ذاتي، يتسم بتطور على شكل نوبات. يتم التشخيص الأولي سريريًا اعتمادًا على معايير مجموعة الدراسة الدولية (ISG) ، والتي تشمل المظاهر العينية.

هدفت هذه الدراسة إلى تقييم تأثير المؤشرات الحيوية الالتهابية على نشاط مرض بهجت العيني.

تم إجراء دراسة استعادية، وصفية وتحليلية على 92 مريضًا تم تشخيصهم بمرض بهجت العيني، وتمت معالجتهم في قسم الطب الباطني بمستشفى الرازي الجامعي بمراكش بين عامي 2010 و2023. تم جمع البيانات من الملفات الطبية واستكمالها بالفحوص السريرية والمخبرية.

أظهرت العينة تفوقًا للذكور بنسبة 70٪، بمتوسط عمر 41.3 سنة. وُجدت إصابة عينية ثنائية في 77٪ من الحالات. تمثلت الأعراض السريرية الرئيسية في التهاب العنبية (64٪)، التهاب الأوعية الشبكية (47٪)، واعتلال البقعة (10٪). وكانت خسارة حدة البصر الشديدة شائعة عند التشخيص.

تلقى جميع المرضى علاجًا بالكورنيكوستيرويدات الجهازية ،مع علاج مثبة للمناعة في 93% من الحالات و تم استخدام العلاج البيولوجي في 15% من المرضى لوحض تحسن سريري لدى 57% وثبات لدى 30% بينما تطورت الحالة الى العمى في 29٪ من الحالات

شملت الدراسة التحليلية عدة مؤشرات التهابية دموية: البروتين التفاعلي C (CRP)، نسبة CRPإلى الألبومين (CAR)، نسبة العدلات إلى الألبومين (NAR)، نسبة اللمفاويات إلى الوحيدات(LMR)، نسبة الصفيحات إلى اللمفاويات (PLR)، نسبة العدلات إلى اللمفاويات (NLR)، وحجم الصفائح الدموية المتوسط (MPV). ظهرت فروقات ذات دلالة إحصائية بين المراحل النشطة وغير النشطة للمرض في MPV، (p<0.001) NAR، (p=0.023) LMR، (p=0.007) CRP، و (p=0.014) CARأما PLR و NLRفلم تكن دالّة إحصائيًا.

في الختام، تؤكد هذه الدراسة على فائدة بعض المؤشرات الحيوية الالتهابية خصوصًا (MPV، NAR، CAR، و CRP)كمؤشرات على نشاط المرض العيني في بهجت. وقد يساعد دمجها في الممارسة السريرية في تحسين المتابعة والتدخل العلاجي المبكر، مما يساهم في تحسين التنبؤ البصري وتقليل المضاعفات طويلة المدى.

APPENDIX

Operating sheet

I. Patient identity

- Name :
- Age :
- Gender :
- Origins :
- Profession :
- Social Status :

II. medical History

- Personal medical history
- Onset age of Behçet's disease
- Onset age of ocular Behçet's disease
- Family medical history

III. Ophtalmologic manifectations :

- Chief Complaint :
    - Decreased visual acuity
    - Ocular redness
    - Ocular pain
    - Headache
    - Visual blurring

  - Floaters
- Duration of progression
- Location
  - Unilateral
  - Bilateral
- Ophthalmologic examination findings
  - visual acuity
  - Retinal vasculitis :
    - Venous
    - Arterial
  - Uveitis :
    - Anterior uveitis
    - Intermediate uveitis
    - Posterior uveitis
    - Panuveitis
- Clinical Features of Ocular Involvement
- Complementary examination
- B-mode ultrasound
- Retinal angiography
- Macular OCT
- Others

IV. Extra-ocular manifestations

- Mucocutaneous manifestations
- Articular manifestations
- Neurological manifestations
- Vascular Manifestations
- Others

V. Treatment

- Laser
- Corticotherapy
- Immunosuppressant
- Biologics
- Colchicine

VI. Evolution

- visual acuity
- Complete recovery
- Partial recovery
- Stable
- Exacerbation
- Blindness

VII. Biological findings

- Complete blood count
- C-reactive protein
- Albumin

Appendix II :

Anatomic Classification of Uveitis (IUSG)

Type	Primary Site of Inflammation	Includes
Anterior uveitis	Anterior chamber	Iritis, iridocyclitis, anterior cyclitis
Intermediate uveitis	Vitreous	Pars planitis (posterior cyclitis, hyalitis)
Posterior uveitis	Retina or choroid	Focal, multifocal or diffuse choroiditis; chorioretinitis; retinitis; neuroretinitis

Appendix III :

Fluorescein Angiography Grading System (Keorochana et al., 2021)

Criterion	Categories
Anatomical Location of Leakage	**• Posterior pole (macula ± optic disc) • Peripheral retina • Both (posterior + peripheral)**
Extent of Leakage	**• Focal (limited/single region) • Diffuse (broad, widespread leakage)**
Severity of Leakage (late-phase)	**• Mild • Moderate • Severe**
Ischemic Angiographic Signs	**• Macular ischemia • Arteriovenous vascular remodeling (AVR)**

Appendix IV:

BEHCET'S DISEASE OCULAR ATTACK SCORE 24 [157]

Behçet's disease ocular attack score 24

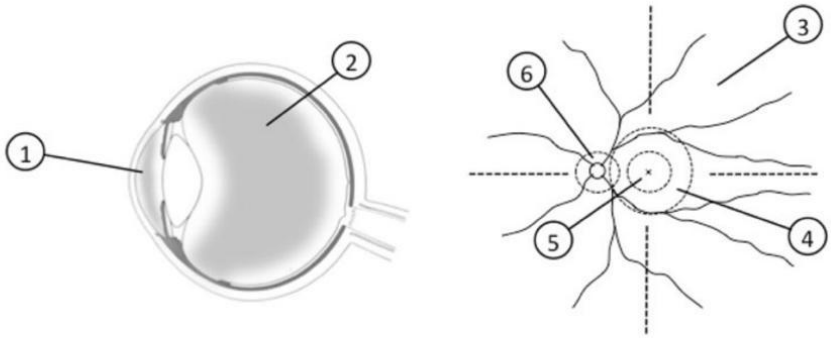

Fig. 1 BOS24 scoring system. The BOS24 consists of a total 24 points summarized from 6 parameters of ocular inflammation symptoms, including anterior chamber cells (maximum 4 points), vitreous opacity (maximum 4 points), peripheral fundus lesions (maximum 8 points), posterior pole lesions (maximum 4 points), subfoveal lesions (maximum 2 points), and optic disc lesions (maximum 2 points). For scoring retinal inflammatory signs, the retinal field is divided into the posterior pole (areas *inside* of arcade vessels) and peripheral retina (areas *outside* of arcade vessels), with the latter further divided into 4 areas for each quadrant; temporal superior, temporal inferior, nasal superior, and nasal inferior

1. Anterior chamber cells	0, 1, 2, 3, 4 point
2. Vitreous haze	0, 1, 2, 3, 4
3. Peripheral retina lesions	0, 2, 4, 6, 8
4. Posterior pole lesions	0, 2, 3, 4
5. Foveal lesions	0, 2
6. Optic disc lesions	0, 2
	total 24 points

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قسم الطبيب

أقسم بالله العظيم

أن أراقب الله في مهنتي

وأن أصون حياة الإنسان في كافة أطوارها في كل الظروف والأحوالباذلة وسعي في إنقاذها من الهلاك، والمرض، والألم، والقلق.

و أن أحفظ للناس كرامتهم و أستر عورتهم و أكتم سرهم.

وأن أكون على الدوام من وسائل رحمة الله، مسخرة كل رعايتي الطبية للقريب و البعيد، للصالح و الطالح، و الصديق و العدو.

و أن أثابر على طلب العلم و أسخره لنفع الإنسان لا لأداه.

وأن أوقر من علمني وأعلم من يصغرني وأن أكون أختا لكل زميل(ة) في المهنة الطبية متعاونين على البر و التقوى.

وأن تكون حياتي مصداق إيماني في سري وعلانيتي، نقية مما يشينها تجاه الله ورسوله والمؤمنين.

و اللهعلى ما أقول شهيد.

كليـــــــة الـطب
و الصيدلة - مراكش
FACULTÉ DE MÉDECINE
ET DE PHARMACIE - MARRAKECH
جامعة القاضي عياض
UNIVERSITÉ CADI AYYAD

سنة 2025 أطروحة رقم 193

تأثير المؤشرات البيولوجية الالتهابية على نشاط داء بهجت العيني

الأطروحة

قدمت ونُوقشت علانية يوم 2025/07/04

من طرف

السيدة بشرى بويكنيفن

المزدادة في 04 يناير 2000 بمدينة جرادة

لنيل شهادة الدكتوراه في الطب

الكلمات الأساسية:

داء بهجت – داء بهجت العيني – المؤشرات الالتهابية البيولوجية

اللجنة

السيد	م. زياني أستاذ في الطب الباطني	الرئيس
السيدة	ل. السعدوني أستاذة في الطب الباطني	المشرف
السيد	ف. العسري أستاذ طب و جراحة العيون	الحكام
السيدة	م. زحلان أستاذة في الطب الباطني	
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