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Eye Manifestations in Behcet's Syndrome

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ABSTRACT

Behcet's syndrome is an inflammatory, chronic, recurrent, multisystemic disease, common in men 25-40 years of age, with immunological determinism (including autoimmune) in the presence of infectious (bacterial) triggering agents and genetic involvement through the presence of HLA-B51. Behcet's syndrome is characterized by a symptomatic triad of: recurrent nongranulomatous uveitis with hypopyon, oral and genital ulcers, and skin changes. Iridocyclitis (anterior uveitis) with acute, recurrent hypopyon is the most common ocular manifestation in Behcet's syndrome and progresses to unpredictable outbreaks with sequelae and severe complications that cause loss / loss of vision. Ocular manifestations in Behcet's syndrome are also accompanied by posterior pole involvement with posterior uveitis, venous and arterial occlusive vasculitis, necrotizing retinitis, macular edema, cystoid macular edema, which accentuates the decrease / loss of vision.Treatment of Behcet's syndrome should be adapted to the chronic course of the disease and should be aggressive from the outset through systemic drug combinations: corticosteroid / immunosuppressive / immunomodulatory therapy and appropriate ophthalmic treatment: cycloplegics, antiglaucoma eye drops, filter surgery, cataract surgery, cataract surgery under cortisone protection, endoocular surgery, laser photocoagulation. Ophthalmologist / internist interdisciplinary collaboration is required.

Keywords: Behcet's syndrome, Acute iridocyclitis with hypopyon, Posterior uveitis, Occlusive vasculitis, Corticosteroid therapy, Immunosuppressants

I. INTRODUCTION

Behcet's syndrome is a somatic dermato-ophthalmic syndrome, with multiple organ lesions, with rare complete remission. Behcet's syndrome is a chronic, multisystemic, recurrent condition that clinically manifests as occlusive arterial and venous vasculitis. Eye disease has a chronic, recurrent course over a long period of time (years) and can lead to blindness through uveal and retinal damage.The disease is more common in men, young adults (25-40 years), predominates in the Mediterranean basin (Turkey), Iran, Japan, Korea, China and manifests itself with acute explosive episodes, unpredictable lasting 2-4 weeks.

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Behcet's syndrome has an etiology partially known as immunological determinism (including autoimmune), with the presence of bacterial or viral infectious triggers with pathogenic influences caused by a possible imbalance of the microbial population in the intestinal tract [1,2].

The disease is triggered by exogenous agents with concomitant disruption of the autoimmune and autoinflammatory response with the involvement of inflammatory cytokines (IFN-γ, IL-1, IL-18, TNF-α that activate naive neutrophils and endothelial cells [3]. Behcet's disease is triggered in people with genetic susceptibility, being associated with HLA-B51, HL-B5 (ocular), HLA-B12 (oral and cutaneous HLA-B27 (articular) present, with histopathological changes of vasculitis and thrombosis similar in multiple organs affected. Behcet's syndrome is a multisystem idiopathic condition characterized by a symptomatic triad: anterior, acute, nongranulomatous uveitis with hypopyon, recurrent, ulcerated mouth sores, genital ulcers, and erythema multiforme.

Clinical Aspects in Behcet's Syndrome

Ocular manifestations in Behcet's syndrome eventually lead to blindness and are associated with neurological, digestive, venous thrombosis and arterial aneurysms.

The clinical diagnosis of the disease is made on the basis of international I.C.B.D. (Criteria for Behcet's Disease) 2014 [4].

- Ocular lesions 2
- Cutaneous lesions 1
- Pathergic test 1
- Genital aphthosis 2
- Neurological manifestations 1
- Oral aphtosis 2
- Vascular manifestations 1

Each event has a score number > 4 points - a positive diagnosis of Behcet's disease.

Major criteria for Behcet's disease [5,6].

- stomatitis with round, slightly hypertrophic peripheral mouth ulcers
- recurrent genital ulcers
- skin lesions:
    - erythema nodosum
    - hypersensitivity (dermatographism)
    - acneiform lesions (folliculitis)
    - dermal vasculitis
- ocular manifestations 75% of cases:
    - nongranulomatous anterior uveitis (iridocyclitis) with hypopyon, sterile, recurrent

- secondary glaucoma by uveitic pupillary block
- cataract
- posterior ocular damage with necrotizing retinal vasculitis and hyalitis in young man, retinal periphlebitis, retinitis with foci of hemorrhagic retinal necrosis
- tractional retinal detachment

Minor criteria for Behcet's disease [5,6]

- 50% self-limiting and non-destructive arthritis - knee, ankle, occasionally sacroiliac
- epididymitis
- obliterating vascular lesions
  - migratory thrombophlebitis, recurrent, superficial, deep, obliterative
  - arterial occlusions, formation of aneurysms
- CNS lesions – 25%
  - meningoencephalitis
  - brain damage, spinal cord, peripheral nervous system (NS)
  - cranial nerve palsies - 6, 7
  - central scotoma due to papillary edema
  - idiopathic intracranial hypertension with papillary edema
- psychic manifestations
- digestive manifestations
  - abdominal discomfort and diarrhea
  - intestinal ulcerations similar to those of Crohn's disease
- renal manifestations
  - acute glomerulonephritis (rare)
- pulmonary manifestations
  - pulmonary artery aneurysm
- musculoskeletal manifestations
  - 50% arthritis in the knee

4 types of Behcet's disease were identified according to major and minor criteria (Japan)

- complete – 4 major criteria
- incomplete – 3 major criteria or 1 major + ocular
- suspect - 2 major criteria, without eye damage
- possible – 1 major criteria
- HLA-B51 present

Ocular Manifestations in Behcet's Syndrome

Ocular manifestations in Behcet's disease are present in 75% of patients, are multiple, recurrent, some with acute onset, others with unpredictable chronic evolution [7]:

- the onset of Behcet's syndrome only by eye signs is possible in 20% of patients.

Ocular manifestations in Behcet's syndrome [7,8]:

- progressive decrease in vision to blindness
- muscle paralysis, nystagmus
- conjunctivitis, keratoconjunctivitis sicca
- keratitis
- non-granulomatous anterior uveitis, acute recurrent with hypopyon, typical of Behcet's disease and the most common clinical manifestation of the disease.
- necrotic, hemorrhagic posterior uveitis
- panuveitis
- retinal edema and retinal ischemia that promotes neovascularization (possibly complicated by neovascular glaucoma)
- retinitis, $\pm$ retinal necrosis, retinal hemorrhages
- retinal edema and optic atrophy
- periphlebitis, retinal periarteritis
- macular edema, cystoid macular edema
- aneurysms, venous occlusions due to necrotizing occlusive vasculopathy on vessels of different caliber
- vitreous hemorrhage, vitreous degeneration
- ischemic optic neuropathy
- paralysis of cranial nerves - 6
- intermittent ophthalmoplegia
- intracranial hypertension

Anterior uveitis in Behcet's disease is present in 75-80% of cases, is frequently bilateral, 60-100% initially, or successively [4,7,8].

- Anterior uveitis has an acute onset with spontaneous regression in a few weeks
- Anterior uveitis is always severe and recurrent negranulomatous
- At the first outbreak, the anterior uveitis from Behcet's disease is unilateral, with a tendency to evolve to posterior uveitis 30-50% with retinal occlusive vasculitis or total uveitis 40-80%.

Symptoms in Previous Uveitis:

- ocular, periocular pain of variable intensity
- progressive decrease in vision
- photophobia
- red eyes with intense pericherial conjunctival hyperemia, purplish

Anterior uveitis - iridocyclitis in Behcet's disease may be the first initial, isolated clinical manifestation (sometimes several years), which delays the diagnosis of Behcet's disease.

- iridocyclitis is accompanied by inflammation of the anterior chamber, positive Tyndal and hypopyon which may disappear spontaneously in days, weeks
- sometimes the ciliary injection is NOT present
- posterior iridocrystalline, iridocrystalline synechia are present
- ocular hypertension is possible by pupillary block by pupillary secretion and / or peripheral anterior synechiae or by trabeculitis induced by cortisone treatment
- -irian atrophy at the end of the inflammatory process

Posterior uveitis present in 80-90% is a determining factor of vision loss in Behcet's disease and may progress to blindness [5,7,8]:

- posterior uveitis may be isolated or concomitant with anterior uveitis - panuveitis
- is associated with arterial and venous vasculitis, frequently with occlusive character generating retinal ischemia and secondary neovascularization
    - vessels with irregular caliber are surrounded by white sleeves
    - Retinal hemorrhages are sometimes present
- there are foci of yellowish-white retinitis, which can be resolved without scarring, numerically and superficially variable hemorrhages, located up to the periphery of the retina
- unilateral or bilateral inflammatory or ischemic papillary edema, sometimes secondary to intracranial hypertension
- macular edema, cystoid macular edema that accentuates vision loss

The evolution of ocular determinations is severe, with multiple recurrences, long periods of time (sometimes years) and is often accompanied by complications.

Ocular Complications in Behcet's Disease

Eye complications in Behcet's disease are common in the late stages of the disease with:

- posterior subcapsular cataract due to recurrent uveal inflammation
- anterior post-uveitis secondary glaucoma with chronic recurrent course, frequently by posterior iridial synechiae with pupillary blockage (possible pupillary occlusion / occlusion) and / or synechiae in the iridocorneal angle with trabecular blockage (both or more frequently pupillary block)
- neovascular glaucoma by preretinal neovascularization
- epimacular membrane, macular hole, macular edema that significantly changes the long-term visual prognosis
- preretinal, papillary and iridial neovascularization (with secondary neovascular glaucoma)

Ocular manifestations in Behcet's disease progress to major retinal atrophy, pigmented reshaping, papillary atrophy.

- **The visual prognosis in Behcet's syndrome is reserved by the recurrent evolution of ocular manifestations associated with complications and sequelae.**

Laboratory examination helps confirming the positive diagnosis of Behcet's syndrome by correlating with clinical manifestations and therapeutic response

- examinations specific to the inflammatory syndrome
    - increase in C-reactive protein
    - increase in ESR sedimentation rate - (elevated erythrocyte sedimentation)
    - increase in the number of leukocytes
    - inflammatory anemia
    - increased fibrinemia
    - hyperalpha 2 and hypergammaglobulinemia
    - HLA-B51 research

- **skin biopsy after pathergy test** showing vasculitis with complementary deposits [4].

Fluorescein angiography shows vessel wall, ischemic areas, areas of hyperfluorescence, papillary edema, macular edema and macular ischemia, retinal capillaries.

OCT (optical coherence tomography) shows macular thickness and vitreoretinal interface.

Treatment of Behcet's Syndrome

Treatment of Behcet's syndrome is adapted to the clinical course of the disease, requiring immediate treatment of acute onset, treatment of relapses, and reduction (as far as possible) of complications and sequelae (as recommended by Euler 2008) [7,9].

Corticosteroid therapy has immediate anti-inflammatory action in acute onset

- local
  - effective corticosteroid eyewash in the anterior uveitis
  - subtenon injections
  - intravitreal injections with dexamethasone implant for severe anterior uveitis or panuveitis with cystoid macular edema
- generally indicated in posterior uveitis
  - intravenous bolus with methylprednisolone 1g - 3 days, followed by prednisone 1 mg / kg / day, with progressive dose reduction (rebound will be avoided).

From the onset of Behcet's disease, an aggressive therapeutic attitude is required with drug combinations with corticosteroid therapy combined with immunosuppressants and immunomodulators.

Immunosuppressants - indicated in severe multiple recurrent forms of Behcet's disease.

- **Azathioprine** 2-2,5 mg/kg/day and **Cyclosporine** 3-5 mg/kg/day could prevent ocular recurrences
  - cyclosporine is limited for the side effects of nephrotoxicity and hypertension
  - cyclosporine - contraindicated in neurological determinations in Behcet's disease
  - side effects - risk of infection, oncogene, sterility
- If occlusive vasculitis occurs that could result in permanent sequelae, treatment with Azotioprin should be started immediately, and in case of failure - cyclophosphamide injection.
- Systemic immunosuppressive therapy is used for at least 2 years, with periodic reassessment of inflammation.

Immunomodulatory Therapy

- **Colchicine**
  - 0,5 – 2 mg/day
  - indicated for cutaneous-mucosal, articular lesions, without proven efficacy on ocular lesions
- **Thalidomide**
  - it is effective for mucous forms, but its action stops when treatment is stopped
  - major teratogenic risk
- **Interferon alfa**

- 1-3 times/week
- decreases the number of outbreaks, with limited long-term effects

Biological Agents – antiTNF – alfa (recombinant monoclonal antibodies)

- **Infliximab**
  - 5 mg / kg infusion at 0, 2, 6, 8 weeks or subcutaneously
  - decreases uveitis outbreaks, but treatment should be prolonged
  - effective in 24 h in the outbreak of acute refractory uveitis
- **Adalimumab**
  - 40 mg every 2 weeks, alternative to failure or intolerance to infliximab
  - side effects - reactivation of tuberculosis, infections
  - sometimes requires combination with azotioprine or methotrexate
- **Etanercept**

New Treatments

- **antiinterleukin 1** (anti – IL-1)
  - indicated in acute onset and recurrence
  - humanized monoclonal antibody administered by intravenous infusion

Associated Ophthalmic Treatment

- Mydriatic and cycloplegic eye drops - locally, associated with corticosteroid eye drops and systemic medication
- Treatment of ocular hypertomy with antiglaucoma eye drops, if necessary filtration surgery, laser iridotomy, surgical iridectomy under local and general corticosteroid therapy
- Cataract surgery by phacoemulsification with implant under cortisone protection
- Endoocular surgery as needed for retinal detachment, epiretinal membrane, tractional macular edema
- Laser photocoagulation for ischemic areas

Indication of Treatment [10,11]:

- Corticosteroids
  - local:
    - oral ulcers, skin lesions, eye determinations

  - systemic
    - 1 mg/kg cp
    - intravenous bolus 1g/day x 3 days
    - oral, genital ulcers, erythema nodosum, arthritis, vascular, neurological, ocular lesions
  - intravitreal – uveitis
  - intrarticular – arthritis
- Azathioprine: oral 0,5-2 mg/kg/day – oral, genital ulcers, erythema nodosum, arthritis
- Colchicine
  - oral 0,5 – 2 mg/day
  - oral and genital ulcers, erythema nodosum, arthritis
- Thalidomide
  - 100-300 mg/day
  - oral, genital ulcers, arthritis, gastrointestinal disorder
- Cyclophosphamide
  - parenteral 15 mg/kg/day
  - vasculitis
- Cyclosporine
  - 5 mg/kg/day
  - uveitis
- TNFα inhibitors
  - Infliximab 5mg/kg/day
  - Adalimumab 40 mg every 2 weeks
  - Etanercept 50 mg/week
- Interferon α
- Other drugs
  - Anakinra (IL-1)
  - Tocilizumab (inhibitor IL-6)

- Ustekinumab (inhibitor IL-12)

- Suprasalazin – 4 mg/day

-gastrointestinal disorders

The treatment algorithm in Behcet's syndrome includes the treatment of cutaneous-mucosal, articular, ocular, vascular, neurological, gastrointestinal determinations [10-12].

- **Mucosal Skin Lesions**

  - **Corticosteroids -** prednisolone initially 40-60 mg / day, 2, 4, 6 weeks
  - If they do NOT respond to treatment, **colchicine** is associated

- **Eye determinations** require immediate treatment of uveitis, retinitis, vasculitis
  - **in the acute phase** of local **mydriatic inflammation, cycloplegic, topical corticosteroids, subconjunctival injections**
  - in **severe forms** it is rapidly associated with **systemic corticosteroids** (urgently affecting the posterior segment), with **Azothioprin** or **Cyclosporine** in addition
  - in **non-responsive patients** - TNFα or IFNα agents
  - **in addition to the acute inflammatory attack**, the patient should be monitored and depending on the clinical appearance and evolution, **Azathioprine** should be administered with / without low doses of corticosteroids, in order to reduce the recurrence
  - if **recurrent attacks** occur and vision decreases, **Cyclosporine anti TNFα (infliximab, adalimumab) or IFNα with / without cyclosporine is indicated**

- venous lesions with **vascular thrombosis** require treatment with immunosuppressive corticosteroids associated with **azathioprine, cyclosporine**
  - in **refractory** forms with extensive venous thrombosis - **anti TNFα, IFNα**
  - **immunosuppressants** may be associated with **anticoagulants in large thrombosis** of large vessels (vena cava) with possible indication for **cyclophosphamide**
  - depending on the clinical appearance and evolution, it is possible to combine **colchicine with azathioprine, cyclophosphamide and anticoagulants.**

- **Articular Lesions**
  - **colchicine** in addition to **benzathine penicillin** is required in **arthritis attacks** if patients DO NOT respond to colchicine
  - in recurrent attacks and / or resistance, **azathioprine** is indicated

- in **severe** forms **TNFα, IFNα**
- symptomatic treatment with **non-steroidal anti-inflammatory drugs and / or corticosteroids** - methylprednisolone
- **intraarticular corticosteroids** in patients with **monoarteritis**
- therapeutic alternatives: **ustekinumab, secukinumab, anti IL-1**

- in **gastrointestinal** disorders **– sulfasalazine**
- **Neurological determinations** - in Behcet's syndrome, high doses of intravenous corticosteroids (methylprednisolone 500-1000 mg/day, 3-5 days) are initially required followed by **oral corticosteroids** with slow dose reduction, duration of treatment and the rate of decrease in corticosteroid doses depend on the clinical response
  - **corticosteroids** are associated with **immunosuppressants - azathioprine** 1-1.5 mg / kg / day and may increase up to 2.5 mg / kg / day
  - in **severe forms** with a reserved prognosis **antiTNFα** is indicated or oral **cyclophosphamide** 1-3 mg / kg / day or intravenous pulse (500-1,000 mg / m^2 at 6-9 months)
  - in **selected cases IFNα, methotrexate, mycophenolate mofetil, anti IL-6, anti IL-1** are indicated

II. CONCLUSIONS

Behcet's syndrome is a severe multisystemic disease, with an acute onset, with unpredictable chronic evolution, associated with serious complications. Behcet's syndrome is associated with ocular determinations, initially with anterior iridocyclitis nongranulomatous with hypopyon, acute, recurrent, accompanied by ocular complications and sequelae, associated with progressive vision loss, followed or accompanied by posterior uveitis and occlusive retinal vasculitis that increase vision decrease up to blindness. The therapeutic approach must be adapted to the evolution of the disease and requires systemic drug combinations between corticosteroids / immunosuppressants / immunomodulators / biological agents.

The ocular manifestations of Behcet's syndrome, almost always present, evolve with multiple complications and require, in addition to the well-controlled systemic treatment, an adequate ophthalmological treatment. Ophthalmologist / internist interdisciplinary collaboration is required.

III. CONFLICT OF INTEREST

The authors report no potential conflicts of interest in research, authorship, and / or publication of this article.

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