FROSTED BRANCH ANGIITIS

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Frosted branch angiitis was originally described in the Japanese literature by Ito in 1976 in a six-year-old child presenting with severe sheathing of all retinal vessels producing the appearance of frosted branchs of a tree.

This entity is an acute panuveitis with severe vasculitis affecting the whole retina. Since veins are more involved than arteries, it is also called diffuse acute retinal periphlebitis.

Epidemiology

Frosted branch angiitis is a rare disease, being described in only 58 cases in the literature most from Japan, but also some in North America, Turkey and India.

This entity usually affects young patients; in Japan the disease tends to affect children (range: 6-16 years old) with higher frequency, while in the other countries where this disorder has been described, the affected population is older, ranging from 23 to 29 years old .Slighthly more males have been reported than females (52% versus 48%). This condition is typically bilateral, but unilateral cases (28%) have been reported.

Classification

Frosted branch angiitis can be an idiopathic disorder or can be associated with ocular and systemic diseases.

Cytomegalovirus retinitis (CMV), AIDS retinitis and Toxoplasmic chorioretinitis are the most frequent ocular associations, while systemic lupus erythematosus, Crohn's disease, large cell lymphoma and acute lymphoblastic leukemia have been described as systemic disorders associated with frosted branch angiitis.

The increasing use of the term frosted branch angiitis in the ophthalmic literature raises questions about what this disorder is and when the term should be used to describe a distinct clinical syndrome or merely a clinical sign that is being recognized in an increasing number of inflammatory conditions.

This led Kleiner to divide patients with a similar retinal appearance into three different subgroups. The first comprises patients affected by lymphoma and leukemia that can present with a frosted branch-like appearance in the fundus. The second group includes patients with associated autoimmune or viral disease which can have frosted branch angiitis as a clinical sign of the underlying disease. Finally the clinical syndrome comprises patients with the acute idiopathic disorder. These latter patients , are typically described as young and healthy patients (10-30 years old), presenting with an acute bilateral visual loss and panuveitis. Despite the acute onset, they have a prompt response to cortico-steroid treatment with an excellent recovery of visual acuity. The frosted branch angiitis in AIDS patients is always associated with active widespread CMV retinitis and the periphlebitis affects vessel's wall away from areas of retinitis. Approximately 6% of patients with CMV retinitis are estimated to have frosted branch angiitis.

Symptoms

The most common ocular symptom is acute visual loss. The visual acuity in acute stages can range from 20/100 to light perception. Blurred vision, floaters and flashing lights can also be

present at onset. Associated systemic symptoms are rare or non-specific, such as flu-like syndrome including upper respiratory infection, sore throat, fever and malaise, back pain and headache.

Clinical Characteristics

The clinical characteristics that describe frosted branch angiitis include:

1. Severe vascular sheathing and retinal edema.

2. Acute visual loss.

3. -*Vitritis and iridocyclitis.

4. Dye leakage from sheathed vessels in the late phase of fluorescein angiogram and no signs of stasis or occlusion.

5. Otherwise healthy patients.

6. Prompt coticosteroid response.

7. Persistent retinal geographic depigmentation.

The inflammation of the anterior segment is usually mild and may include conjunctival and ciliary injection. Occasionally filiform keratic precipitates can be noted. The grade of anterior chamber inflammation is low, ranging from 0.5 to 1.5 + flare/ cells. In patients with associated systemic lupus erythematosus, hypopyon can occasionally be seen. A positive afferent pupillary defect is rarely noted. Conversely, the grade of posterior segment inflammation is always severe. The vitiitis contributes to create hazy appearance of the fundus. The whole retina is edematous with the characteristic findings of uninterrupted white and thick sheathing of vessels which start from the optic disc and extend to the periphery. The veins are more dramatically affected by the vasculitis. Retinal exudates and hemorrhages are also noted. Atrophic depigmented lesions in the periphery are present during the recovery phase and are though to be the consequence of poor blood perfusion of the peripheral retina; serous retinal detachment and yellowish placoid lesions at the retinal pigment epithelium layer have been described. The choroid can present circulation abnormalities and neovascularization, and the optic disc is frequently edematous and hyperemic.

Diagnosis

1. Ophthalmoscopy

2. Fluorescein angiogram

3. Visual field test

4. Electrophysiological tests: ERG/VECPs

The typical ophthalmoscopic appearance of frosted branchs of a tree is the first important feature that helps in making the diagnosis. Moreover, some characteristic reports on specific ophthalmologic tests can help in confirming the diagnosis and in excluding other causes of retinal vasculitis.

The fluorescein angiogram shows normal venous flow and delayed filling of arteries in the early phases, while in the late stages the leakage from vessels (veins more than arteries), perivenular leakage and optic disc hyperfluorescence are characteristic. There are no signs of vascular occlusion or stasis.Nevertheless, vessel narrowing or dilation, areas of capillary non-perfusion and artero-venous anastomoses can be noted in the angiogram. As a confirmation of the choroidal involvement, the indocyanine angiogram shows leakage from choroidal vessels. The yellowish placoid lesions at the retinal pigmented epithelium layer appear like hypofluorescent spots in both fluorescein and indocyanine angiogram.

Abnormalities of the visual field test including blind spot enlargement, central scotomata within the 30 degrees, concentric constriction and general deterioration of sensitivity are noted in patients with frosted branch angiitis. The cause of central scotoma similar to optic neuritis is likely to be macular edema and exudates rather than direct damage to the optic nerve. The ERG shows reduction in the amplitude of a- and b- wave. Almost no electroretinogram response could be elicited on the first week after the patient's initial presentation. The pattern visually evoked cortical potentials (VECPs) are also reduced.

PATHOGENESIS

1. Idiopathic: the pathogenesis of idiopathic frosted branch angiitis is unknown. Many observations led to the hypothesize an immune-mediated mechanism. The the evidence of a localized ocular vasculitic process sparing other systemic organs, suggests that the immune response is directed to an inciting antigen in the eye. The presence of positive titers for HSV, VZV, EBV, CMV, Rubella and anti-streptolysin O in some patients affected by frosted branch angiitis, suggested that viral or bacterial infection can be the triggering antigen source. In addition, it has been postulated that low immunoglobulin levels in young patients might be insufficient to suppress the immune response caused by the infection. Finally, the prompt response to steroids suggests a probable immune-mediated mechanism.

2. Non idiopathic: in cases of frosted branch angiitis associated with viral diseases(CMV, AIDS) it has been hypothesized that viral antigens form immune-complexes and deposit in retinal vessels causing vasculitis. A direct viral invasion (CMV has particular tropism for endothelial cells), is also thought to be responsible for the pathogenesis. Immune complexes are also responsible for retinal vasculitis secondary to autoimmune disorders (SLE, Crohn's). Conversely in patients affected by lymphoma and leukemia, frosted branch angiitis is caused by infiltration of retinal vessels from malignant cells.

Laboratory tests in patients with frosted branch angiitis do not show abnormalities and are mostly useful to rule out the possibility of systemic associated diseases.

DIFFERENTIAL DIAGNOSIS

Although frosted branch angiitis has been described as a type of vasculitis that affects both arteries and veins, it is predominantly a periphlebitis. Therefore, the differential diagnosis must include all diseases presenting with retinal vasculitis involving veins. In addition, treatable causes of retinal vasculitis should be excluded before the initiation of corticosteroid treatment. In the following Table are listed the most important disease that should be considered in the differential diagnosis of frosted branch angiitis. Laboratory tests and the specific investigations commonly used to rule out possible associated diseases are also shown.

Disease	Laboratory test

Sarcoidosis	Chest X-ray; ACE; serum calcium and phosphorus; serum lisozyme
Syphilis	VDRL; FTA-ABS; MHA-TP
Tuberculosis	Chest X-ray; PPD
Multiple sclerosis	MRI; CSF
Systemic lupus erythematosus	ANA; anti-DNA
Pars planitis	
Eales'disease	
Viral	Viral titers; PCR(aqueous/vitreous)
Lymphoma/Leukemia	Complete blood count and differentiation; vitreous biopsy; CSF; MRI

Although clinical symptoms and laboratory tests can help in confirming the diagnosis of sarcoidosis , associated ophthalmic findings such perivascular sheathing in the midperiphery, vitreous snowballs and granuloma in retina or choroid, may better help to differentiate this disease from frosted branch angiitis. The vasculitis of ocular syphilis is generally a periarteritis with arteriolar sheathing, exudates and intra-retinal hemorrhages, although isolated venous periphlebitis has also been described. Tuberculosis commonly produces focal perivenous sheathing in the peripheral venules, which occasionally involves the central retinal vein. Retinal venous sheathing seen in patients with multiple sclerosis consists of patchy small and interrupted cuffs surrounding the blood vessels, in contrast to the uninterrupted widespread sheathing present in frosted branch. In addition,the periphlebitis in multiple sclerosis frequently resolves spontaneously without visual symptoms. In systemic lupus erythemotosus the most common findings are cotton wool spots and hemorrhages and an arteritis. Nevertheless, occasionally periphlebitis with or without vein occlusion can occur. The fluorescein angiogram shows venous leakage in the late stages, but usually the retinal vascular tree involvement is more limited than in frosted branch angiitis. Retinal periphlebitis can be found in association with pars planitis. The peripheral terminal branches of the retinal veins are cuffed with white inflammatory exudates, differentiating this entity from the diffuse periphlebitis of frosted branch angiitis. Eales' disease can present as a low-grade periphlebitis with characteristic areas of capillary occlusion in the peripheral retina and fluorangiographic evidence of vascular obliteration. Retinal vasculitis of viral etiology like acute retinal necrosis, affects more frequently arteries than veins and is associated with areas of retinitis. In contrast to frosted branch angiitis, the patients are rarely young and have a very poor prognosis.

Lymphoma can present with perivenular sheathing, but the typical clumps and sheets of malignant cells in the vitreous and the non-response to steroids must help in the differential diagnosis.

TREATMENT

Systemic steroids (initial dose 80 to 100mg oral prednisone for 10 days) should be initiated once treatable causes are excluded. Recovering of visual acuity starts approximately two to three week after treatment institution. The visual acuity during recovering phases ranges from 20/20 to 20/40. There are controversial opinions in the literature about the use of corticosteroids. The majority of authors suggest early institution of high doses of steroids to prevent macular scarring, while others think that the natural course of the disease is self-limiting and does not require steroid treatment.

COMPLICATIONS AND PROGNOSIS

Capillary non perfusion and neovascular glaucoma , macular scarring, retinal detachment and neovascularization are the most severe complications described in frosted branch angiitis. Nevertheless, despite the severe retinal appearance, the prognosis is usually good, with rapid recovering of visual acuity after prompt steroid treatment. Visual field and electrophysiological tests return completely normal after one or two months from onset.

The disease is frequently limited to an isolated acute episode, although rare cases of recurrence have been described.

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Review Questions for Frosted Branch Angiitis

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1.Which statement best describes frosted branch angiitis?

a) Retinal arteritis associated with hard exudates and hemorrhages.

b) Chronic vascular leakage associated with presence of yellowish placoid lesions at the retinal pigment epthelium, leading to macular edema and macular scarring.

c) Retinal vasculitis in 30% of patients with sarcoidosis.

d) Acute retinal periphlebitis characterized by severe vascular sheathing.(*)

e) Non granulomatous uveitis associated with retinal periphlebitis.

2.Clinical case:

A six-year-old boy presented with acute visual loss in both eyes (VA 20/200: OD; CF: OS) anterior segment inflammation , severe vitritis and dramatic vascular sheathing in all retinal vessels. What would suggest ?

a) Order a fluorescein angiogram and a complete uveitis work-up.

b) Start antiviral treatment in the suspicion of an acute retinitis and vasculitis from viral etiology.

c) Order a visual field.

d) Order an MRI of the head.

e) Start immediately with oral prednisone after exclusion of major potential contraindications for the therapy.

Choose one:

a) a and d are correct

b) a, c and e are correct (*)

c) all are correct

d) only b is correct

e) a and c are correct

3.The fluorescein angiogram in frosted branch angiitis.

a) Shows optic disc hyperfluorescence and venous leakage in the early phases.

b) Shows macular edema, macular exudates and arteriolar occlusion.

c) Is the only diagnostic test necessary to make the diagnosis.

d) Shows normal venous flow in the early stages and vessel leakage predominantly from veins in the late stages.(*)

e) Is not recommended if the patient is young.

4.What are the most important laboratory investigations in a patients with idiopathic frosted branch angiitis syndrome?

a) ESR, CRP and A-1 acid glycoprotein.

b) ANA, anti-DNA and total complement.

c) Anti HSV, VZV, CMV antibodies.

d) ACE, serum calcium and phosphorus levels.

e) None. (*)

5. What is the difference between primary frosted branch syndrome and secondary frosted branch angiitis?

a) The primary syndrome is idiopathic. (*)

b)The secondary frosted branch affects predominantly young and healthy patients.

c) The primary syndrome is more diffuse in patients in Japan and India.

d) The primary syndrome has a prompt corticosteroid response, while the secondary disorder responds only to the specific therapy.

e) The secondary frosted branch angiitis is associated with ocular and systemic diseases.(*)

6. If you see a 60 y.old patient with frosted branch funduscopic appearance in the right eye and severe vitritis with multiple vitreous clumps and pigmented cells, that has been treated for the previous three months with 50mg prednisone PO without any improvement of visual acuity and ophthalmoscopic findings, what is your approach?

a) I will quickly plan a vitreous biobsy. (*)

b) I will start immune suppressive therapy.

c) I will boost the doses of oral cortico steroids.

d) I will send the patient for an MRI and CT scan of the head. (*)

e) I will do a periocular injection of steroid.

7. What are the most important differential diagnoses to consider in case of frosted branch angiitis?

a) Sarcoidosis and tuberculosis.

b) Multifocal choroiditis and panuveitis.

c) Systemic lupus erythematosus and polyarteritis nodosa.

d) Wegeners' granulomatosis.

e) All ocular and systemic diseases presenting with retinal periphlebitis. (*)

8. Which sentences are correct?

a) Young patients affected by frosted branch angiitis have better prognosis than older patients

b) The yellowish placoid lesions present at retinal pigmented epithelium layer are hypofluorescent in the fluorescein angiogram and hyperfluorescent in the indocyanine angiogram.

c) The pathogenesis of idiopathic frosted branch syndrome is thought to be related to formation of immune complexes

d) The visual field in acute stages shows central scotoma similar to those seen in optic neuritis. (*)

e) The a- and b- waves in ERG are reduced in amplitude during the acute stages but return normal to after 3 months. (*)

9.The possible complications of frosted branch angiitis are.

a) Central retinal vascular occlusion.

b) Branch retinal vein occlusion.

c) Posterior inflammatory synechia.

d) Macular scarring and neovascular glaucoma. (*)

e) Macular hole and pseudohole.

10.Which sentences are correct about the pathogenesis of frosted branch angiitis?

a) In the idiopathic syndrome the pathogenesis is unknown. (*)

b) In frosted branch associated systemic lupus erythematosus the pathogenesis is thought to be related to vascular occlusion.

c) When frosted branch is associated with CMV retinitis, the periphlebitis can be caused by immune-complex deposition in vessel walls as well as by direct viral invasion. (*)

d) Malignant cell infiltration is responsible for the frosted branch appearance in the fundus in patients with lymphoma and leukemia. (*)

e) In some patients frosted branch angiitis can be triggered by drug ingestion, particularly penicillin and sulfamidics.