Neuroophthalmologic Aspects of the Vasculitides

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KEYWORDS

• Ophthalmology • Neuroophthalmology • Primary • Secondary • Vasculitis • Autoimmune • Nervous system

KEY POINTS

- There have been significant advances in the understanding of the vasculitides in the past several years, leading to more precise classification and nosology.
- Ophthalmologic manifestations may be the presenting feature of and a clue to the diagnosis of vasculitis.
- Neuroophthalmologic findings may develop in the course of the illness owing to a common disease mechanism.
- Precise diagnosis and prompt treatment of ophthalmologic vasculitis involvement prevents short- and long-term ophthalmologic sequel.

INTRODUCTION

Vasculitis is a term used to characterize a spectrum of diseases associated with vascular inflammation. Ophthalmologic manifestations may be the presenting features of primary and secondary systemic vasculitis and a clue to early diagnosis to prevent ischemic vascular sequela. Unrecognized and therefore untreated, the ophthalmologic and neuroophthalmologic features can be catastrophic with irreversible loss of function, particularly when visual involvement coincides with vasculitic brain infarction, hemorrhage, and aneurysm formation or ischemic involvement of the optic nerve or surrounding orbital structures. This article considers the ophthalmologic aspects of primary systemic vasculitis and primary central nervous system vasculitis (PCNSV) in children and adults.

CLASSIFICATION OF VASCULITIS

The revised Chapel Hill Consensus Conferences (CHCC) in 2012[1] provides consensus on nosology and definitions for the commonest forms of vasculitis in adults based on

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the caliber of vessels involved. The Pediatric Rheumatology European Society and the European League against Rheumatism proposed specific classification criteria for the commonest childhood vasculitis syndrome[2] based on vessel size similar to the CHCC nomenclature. The European League against Rheumatism, Pediatric Rheumatology European Society, and the Pediatric Rheumatology International Trials Organization defined the clinical, laboratory, and radiographic characteristics of several childhood systemic vasculitides in a validated classification of pediatric vasculitis.[3] There is a continuum of vasculitic disorders, with some occurring exclusively in childhood or in older adults, and others across the age spectrum, although with differing epidemiology, clinical and laboratory manifestations, and response to treatment.

LARGE VESSEL VASCULITIS

Giant Cell Arteritis

This granulomatous large vessel vasculitis involves cranial branches of the arteries arising from the arch of the aorta. The American College of Rheumatology (ACR) 1990 criteria for the classification of giant cell arteritis (GCA)[4] identified 5 criteria from which 3 or more in a given patient was associated with a sensitivity of 93.5% and a specificity of 91.2%, for the diagnosis of GCA: age equal to or greater than 50 years at disease onset, new localized headache, temporal artery tenderness or decreased temporal artery pulse, elevated erythrocyte sedimentation rate to 50 mm/h or more, and vascular tissue biopsy sample showing necrotizing arteritis with predominance of mononuclear cells infiltration or granulomatous multinucleated giant cell inflammation. The histopathology of biopsy-positive GCA includes vessel wall infiltration by mononuclear cells, $CD4^+$ T cells, activated macrophages, and multinucleated giant cells that form granulomas close to the internal elastic lamina of involved vessels in up to one-half of specimens.[5]

A prospective study of 170 patients with biopsy-confirmed GCA[6] noted ocular involvement in 85 patients (50%), including visual loss present in 83 (97.7%), amaurosis fugax in 26 (30.6%), eye pain in 7 (8.2%), and diplopia in 5 (5.9%). Ocular ischemic lesions consisted of arteritic anterior ischemic optic neuropathy (AION) in 69 cases (81.2%), central retinal artery and cilioretinal occlusions each in 12 cases (14.1%) cases, the latter after satisfactory fundus fluorescein angiography (FFA); as well as, posterior ischemic optic neuropathy in 6 cases (7.1%), and ocular ischemia in 1 case (1.2%). Among 42 other patients in Olmsted County Minnesota studied by Huston and coworkers,[7] visual symptoms preceded the clinical and histopathologic diagnosis of GCA in 15 patients (40%). Blurred vision was noted in 6 patients (19%), followed by diplopia in 5 patients (12%), transient vision loss in 5 patients (12%), permanent partial loss in 4 patients (10%), and permanent complete loss in 3 patients (10%). A follow-up Olmsted County cohort 25 years later totaling 168 patients with GCA[8] found visual disturbances at presentation in 16 patients (9.5%) and at the time of diagnosis in 37 patients (22%), of whom 14 patients (8.3%) had transient vision loss, 18 (10.7%) had permanent vision loss, and 14 (8.3%) had diplopia.

Of 18 patients with varying visual loss and occult GCA,[9] amaurosis fugax was noted in 6 patients (33.3%), diplopia in 2 patients (11.1%), and eye pain in 1 patient (5.6%). Ocular ischemic lesions included AION in 17 patients (94.4%) and central retinal artery occlusion and cilioretinal artery occlusions each in 2 patients (11.1%) after FFA. A high index of suspicion for GCA for patients older than 50 years who develop amaurosis fugax, visual loss, or AION in the absence of constitutional and systemic symptoms (**Fig. 1**).

A finding that supports the diagnosis of arteritic AION is chalky-white optic disc swelling. A small disc and cup may be associated with both arteritis and nonarteritic

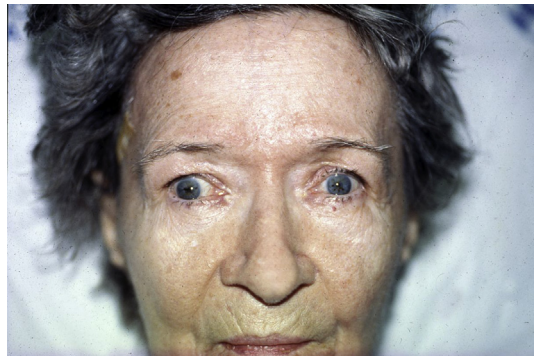

Fig. 1. Patient with giant cell arteritis and brainstem stroke demonstrating left gaze paresis.

AION, whereas a normal or large cup is highly suggestive of an underlying arteritic process. Color Doppler imaging of the central retinal and short posterior ciliary arteries is helpful in distinguishing GCA from nonarteritic AION.

The mainstay of treatment for GCA is corticosteroids (CS); however, the exact dosing regimen and mode of administration depends on the presence of visual involvement at the time of diagnosis. Salvarani and colleagues[10] used 40 to 60 mg oral prednisone for GCA, and intravenous methylprednisolone 1 g/day for 3 days for those with recent or impending visual loss. The addition of low-dose aspirin was beneficial in preventing cranial ischemic complications, including acute visual loss and cerebrovascular complications of GCA compared with CS alone. Such patients are 5-fold less likely to experience cranial ischemic complications as those who receive CS alone. Danesh-Meyer and colleagues[11] evaluated the incidence and extent of visual recovery of 34 patients with biopsy-proven GCA treated with high-dose systemic CS, noting that 27% of eyes suffered loss of visual acuity (VA) by 2 or more lines within 1 week of starting CS treatment, and 15% of eyes so treated showed an improved VA of 2 or more lines. Of the 15% of eyes that showed an improvement in VA, none showed further improvement in visual fields or color vision, leading the authors to conclude that the improvement in VA may reflect learning to view eccentrically.

Takayasu Arteritis

Takayasu arteritis (TAK) predominantly occurs in young Japanese females, typically before the age of 40 years. The ACR[12] selected 6 criteria for the classification of TAK, from which 3 or more in a given patient were associated with a sensitivity of 90.5% and a specificity of 97.8%, from among the following: age less than or equal to 40 years, claudication of an extremity, decreased brachial artery pulse, greater than 10 mm Hg difference in systolic blood pressure between arms, a bruit over the subclavian arteries or the aorta, and arteriographic evidence of narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities. Ocular features not formally part of the criteria of TAK occur in 35% to 68% of patients, typically owing to ischemia and hypoperfusion resulting from occlusive arteritis of the aortic arch branches, whereas those arising in the setting of hypertension result from vasculitic renal artery involvement.

The commonest ischemic ocular manifestation of TAK is retinopathy, first described by Takayasu,[13] who noted peculiar fundus changes consisting of dilated vessels around the optic disc owing to arteriovenous anastomoses in female patients without a palpable radial pulse. Less common manifestations of ocular ischemic include AION, central retinal artery occlusion, and ocular ischemic syndrome. The retinal changes in

TAK vary in symptomatology and severity depending on the location of carotid artery involvement, the rate and duration of ocular vascular hypoperfusion, and the presence of collateral blood supply to the eye. Uyama and Asayama[14] classified retinopathy into stages 1 to 4 wherein 20 patients (53%) with stage 1 had dilations of small vessels, 12 patients (32%) with stage 2 disease had microaneurysm formation, and 3 patients (8%) each with either stage 3 or 4 disease, respectively, manifested arteriovenous anastomoses or ocular complications of vitreous hemorrhages, proliferative retinopathy, and vision loss. The authors attributed retinal vascular changes to decreasing blood flow in the retinal vasculature, noting decreased intraocular pressure with disease progression. In contrast with type I TAK, hypertensive fundal changes predominated in patients with type III disease with 12 patients (86%) demonstrating hypertensive changes occurring in the fundus and 2 patients (14%) manifesting hypertensive retinopathy.

Kerr and colleagues[15] noted a 60% response rate to CS alone among 60 patients with TAK with an estimated time to remission of 22 months. Among 4 patients with TAK treated with CS described by Ishikawa,[16] one improved from stage 3 to stage 2 TAK, whereas another patient developed unilateral blindness, and 2 others, were stable. Panretinal photocoagulation is an adjunctive therapy used to treat cases of severe retinal ischemia,[17] whereas antiplatelet agents decreased the frequency of arterial ischemic events. The inflammatory process underlying ocular manifestations may lead to improvement; however, arterial stenoses require bypass surgery.

MEDIUM VESSEL VASCULITIS

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) predominantly affects medium-sized arteries. The pathologic findings of PAN include a hyaline-like necrosis in the media, which rapidly spreads to the adventitia and intima, with infiltration by neutrophils, eosinophils, lymphocytes, and plasma cells. This process is followed by proliferation of fibroblasts that can thicken the intima and occlude vascular lumina.

Although ocular manifestations are not a part of the diagnostic criteria for PAN, they occur in 10% to 20% of patients[18] either owing to the direct effects of arteritis that results in vascular ischemia, or as a secondary effect of renovascular hypertension with subsequent retinal edema, transudates, hemorrhages, and cystoid body formation. The most common arteries affected are the posterior ciliary arteries and choroidal vessels, which can result in choroidal infarcts and exudative retinal detachments. Conjunctival and anterior uveal involvement may occur. In an analysis of 393 patients with PAN,[19] 42 patients (10.7%) had ophthalmologic manifestations, of which blurred vision was the most common and noted in 13 of 42 patients (31%), followed by conjunctivitis in 8 patients (19%), retinal exudates in 8 patients (19%), and retinal vasculitis in 7 patients (17%). Other less common manifestations included uveitis in 5 patients (12%), episcleritis in 4 patients (10%), thrombosis in 4 patients (10%), keratitis and optic neuropathy each in 3 patients (7.1%), retinal hemorrhages in 2 patients (5%), and oculomotor nerve palsy in 1 patient (2%).

Reports of fundoscopic examination findings in patients with PAN variably include papilledema, macular star formation, cotton-wool spots, retinal or subhyaloid hemorrhages, retinal exudates, vascular occlusion of the central retinal artery, and irregularity of the retinal arteries with or without aneurysm formation.[20] Other common features on fluorescein angiography in PAN include retinal vasculitis with multiple arteriolar and capillary occlusions.

Akova and colleagues[21] described the responsiveness of a spectrum of ocular findings including scleritis, peripheral ulcerative keratitis, nongranulomatous uveitis, retinal vasculitis, pseudotumor of the orbit, and central retinal artery occlusion in 5 patients, 4 of whom responded to combination CS and cyclophosphamide or azathioprine therapy.

Kawasaki Disease

Kawasaki disease (KD) is a common vasculitis in children. There are 6 diagnostic features of KD, 5 of which are needed for the diagnosis, including fever of unknown origin lasting 5 days or more not responding to antibiotics, bilateral conjunctival hyperemia and indurated edema that spares the limbal region, orolabial lesions, redness and edema of palms and soles followed by fingertip desquamation, an erythematous polymorphous rash, and cervical lymph node enlargement.[22]

Ocular involvement in KD is typified by bilateral conjunctival hyperemia and indurated edema that spares the limbal region and the conjunctivitis that occurs in 83% to 92% of patients. The conjunctival lesion typically develops within a day or 2 of fever onset and lasts up to several months. Burke and Rennebohm[23] noted that anterior uveitis was a predominant finding during the acute phase of illness.

Posterior segment involvement in KD was documented in 2 patients with bilateral vitreous opacities and bilateral optic disc swelling,[24] unilateral retinal exudates, and macular and disc edema with severe visual loss, as well as in a patient with bilateral inner retinal ischemia diagnosed at postmortem examination.[25] Retinal vasculitis occurs rarely in KD owing to selective inflammation of the blood–ocular barrier. Several reported patients underwent FFA for retinal vasculitis, including one with retinal exudation, macular edema, and temporal disc swelling that showed no leakage,[26] and another with bilateral acute anterior uveitis, in whom FFA showed disc edema and leakage with localized areas of perivascular sheathing suggestive of periphlebitis and vasculitis.[27]

Rennebohm and associates[28] described 6 children with KD, 5 of whom developed anterior uveitis during the acute phase of KD. Both children treated with CS and cycloplegic drugs improved, as did the other 3 untreated children. Similarly, Puglise an colleagues[29] described a 4-year-old child with KD who presented with bilateral swelling and hyperemia of the conjunctiva unresponsive to intense topical steroid therapy; however, there was a decrease in conjunctival inflammation within 1 week of 30 mg/kg of aspirin therapy and complete resolution in 4 weeks.

SMALL VESSEL ANTINEUTROPHIL CYTOPLASMIC ANTIBODY-ASSOCIATED VASCULITIS

Granulomatosis with Polyangiitis

Granulomatosis with polyangiitis (GPA) is characterized by granulomatous inflammation of the upper and lower respiratory tract, and focal necrotizing glomerulonephritis with a triad of multinucleated giant cell granulomatous inflammation, vasculitis, and necrosis.[30] The ACR[31] identified 4 diagnostic criteria for GPA, 2 of which must be present to make the diagnosis from among the following, including nasal or oral inflammation, an abnormal chest radiographic showing nodules, fixed infiltrates, or cavities, urinary sediment showing microhematuria or red cell casts, and granulomatous inflammation on biopsy. The presence of 2 or more criteria imparts a sensitivity of 88.2% and specificity of 92.0% for the diagnosis of GPA. Although the serum antineutrophil cytoplasmic antibody (ANCA) level is not part of the ACR criteria, GPA is associated with ANCA seropositivity, particularly c-ANCA, the presence of which had a

99% specificity and 96% sensitivity for generalized GPA, and 67% sensitivity for the limited form. Ocular findings are not part of the diagnostic criteria for GPA; however, among patients with vasculitis, ocular inflammation, so noted as scleritis, episcleritis, and proptosis, have a sensitivity of 27.4% and a specificity of 96.9% for the diagnosis of GPA.

Ocular manifestations occur overall in 30% to 60% of patients with GPA, and are the presenting features in up to 16% of patients.[32] Ocular symptoms can be due to primary inflammation or focal vasculitis that affects the anterior and posterior segments of the eye, causing conjunctivitis, episcleritis, and keratitis, and optic nerve vasculitis, or as a result of the contiguous spread of longstanding granulomatous sinusitis leading to proptosis, orbital pseudotumor, and nasolacrimal duct obstruction. Vascular complications such as retinal artery occlusion can occur. Frequent symptoms of orbital disease included ocular pain, epiphora, and injection, although proptosis, vision loss, diplopia, and ophthalmoplegia can also occur.

Hoffman and colleagues[32] noted ocular manifestations of GPA among 15% of 158 patients at presentation, and in 52% of those in the course of the illness. Conjunctivitis and dacrocystitis each occurred in 20% of patients; however, they are considered nonspecific features. Painful proptosis, often associated with visual loss owing to optic nerve ischemia, and diplopia resulting from extraocular muscle entrapments, so noted in up to 2% of patients at the onset of disease and in 15% throughout the course of illness, are useful diagnostic features typically caused by retroorbital pseudotumor. Fauci and colleagues[33] identified proptosis in 15 of 49 patients (31%) with ocular involvement associated with GPA owing to retroorbital mass lesions.

Akikusa and colleagues[34] found eye involvement in 13 of 25 children (52%) with GPA at presentation, and in 15 children (60%) over the course of illness. The commonest ocular manifestations in affected children were conjunctivitis in 14 patients (56%), scleritis or episcleritis in 3 patients (12%), and proptosis in 2 patients (8%). Cabral and colleagues[35] reviewed the presenting clinical features of pediatric patients with GPA in 3 single-center cohorts and 1 multicenter cohort, noting ocular manifestations as common presenting features of GPA in children, with conjunctivitis occurring in up to 44% at presentation.

Fauci and colleagues[33] recommended remission induction treatment of GPA with 2 mg/kg/d of oral cyclophosphamide and 1 mg/kg/d of prednisone, followed by a tapering of prednisone to an alternate day administration, achieving complete remission rates of 93% for a mean duration of 48.2 months. Chan and colleagues[36] reported a patient with bilateral corneal ulcers and VA that decreased to 20/200 in the right eye and 20/70 in the left eye and was treated with 2 mg/kg/d of oral cyclophosphamide and 1 mg/kg/d of prednisone. Two years later, the VA in both eyes returned to 20/40, and the peripheral corneal ulcers healed, although shallow peripheral corneal thinning remained. Foster and colleagues[37] studied a patient with GPA and progressive blurred vision, diplopia, and increased supraorbital pressure who was found to have a VA of 20/200 in the right eye, 20/40 in the left eye, 90% ophthalmoplegia in the left eye, and a normal fundoscopic examination. The patient was treated with oral cyclophosphamide and prednisone, and 1 month later the VA improved to 20/40 with complete resolution of ophthalmoplegia. Vischio and McCrary[38] reported a 70-year-old man with left eye visual change, third nerve palsy, and orbital mass compressing the optic nerve that was biopsied with proven GPA. The patient was treated with prednisone 40 mg twice daily and cyclophosphamide 125 mg/d, without visual improvement 11 weeks later. There is substantial ocular morbidity associated with GPA despite efficacious immunosuppressant therapy so noted in 3 enucleations among 140 patients.[39] Sadiq and colleagues[40] identified a subgroup of patients

with GPA and orbital involvement with a poor prognosis as evidenced by permanent visual loss in 43% of patients. Patients with episcleritis, conjunctivitis, and anterior uveitis respond to topical therapy, but they should not be used because of secondary corneal thinning and perforation.[41]

Eosinophilic Granulomatosis with Polyangiitis

Eosinophilic GPA (EGPA) involves multiple organ systems, causing chronic rhinosinusitis, asthma, and eosinophilia. The ACR 1990 diagnostic criteria for EGPA[42] included 6 criteria, 4 of which were necessary from the following, including asthma, eosinophilia greater than 10%, neuropathy, pulmonary infiltrates, paranasal sinus abnormality, and extravascular eosinophils. The presence of 4 or more criteria yielded a sensitivity of 85.0% and a specificity of 99.7% for the diagnosis of EGPA. Although ANCA positivity is not part of the ACR's diagnostic criteria, it can be helpful in making the diagnosis in up to 70% of patients.[43] The characteristic changes of EGPA histopathology include necrotizing vasculitis and extravascular necrotizing granulomas with eosinophilic infiltrates; however, early cases may be characterized by tissue infiltration by eosinophils without overt vasculitis.[44]

Ocular features of EGPA can involve all parts of the eye and orbit. Takanashi and colleagues[45] classified the ocular manifestations into 2 types, pseudotumor or orbital inflammatory and ischemic vasculitis types. Patients with the pseudotumor type typically present with a chronically red eye, dacryoadenitis, mysositis, periscleritis, perineuritis, conjunctival granuloma, episcleritis, orbital abnormalities on imaging, and ANCA seronegativity. Those with the ischemic vasculitis present with sudden visual loss, amaurosis fugax, AION, central retinal artery or branch retinal artery occlusion, normal orbital imaging, and ANCA seropositivity.

Among 270 patients with EGPA,[19] 30 (11%) had ocular manifestations of which conjunctivitis was the most common, so noted in 13 patients (43.3%) followed by blurred vision in 9 patients (30%); oculomotor nerve palsy and sudden visual loss each in 4 patients (13.3%); retinal vasculitis in 3 patients (12%); orbital inflammatory disease, and retinal exudates each in 2 patients (6.7%); and episcleritis, keratitis, uveitis, retinal thrombosis, and retinal exudates present each in 1 patient (3.3%). Central retinal artery occlusion is another complication of EGPA, leading to sudden visual loss.

Among 96 patients with EGPA described by Guillevin and colleagues,[46] 3 patients (3.1%) presented with ophthalmic involvement. Two had episcleritis and 1 had bilateral exophthalmos. Jordan and colleagues[47] reported 2 patients with EGPA who presented with dacryoadenitis and diffuse orbital inflammation. Takanashi and colleagues[45] recommended enhanced orbital imaging to look for inflammatory lesions. Fundoscopy is useful in identifying patients with central retinal artery occlusion. There are no randomized, controlled studies of the efficacy of treatment on the ocular manifestations of EGPA.

Microscopic Polyangiitis

Microscopic polyangiitis (MPA) typically affects the kidney causing a pauci-immune focal necrotizing crescentic glomerulonephritis and pulmonary capillaritis. The histopathology of MPA is similar to GPA and EGPA; however, the absence of granulomatous inflammation distinguishes MPA from GPA, as does absence of asthma and eosinophilia from EGPA. Ocular findings are not part of the diagnostic criteria for MPA, and are much less common in MPA than other ANCA-associated vasculitis (AAV). Nevertheless, ocular involvement can occur in up to 24% of patients with MPA, most often presenting as episcleritis or conjunctivitis. Of those with ocular manifestations, the most common was conjunctivitis occurring in 7 (28%), episcleritis

occurring in 5 (20%), and blurred vision occurring in 4 (16%). Other less frequent ocular manifestations included retinal vasculitis in 3 patients (12%), retinal exudates, optic neuropathy, sudden visual loss and oculomotor nerve palsy in 2 patients (8%) patients each, and scleritis, keratitis, uveitis, retinal hemorrhage in 1 patient (4%) each.

Because ocular features in MPA are rare, the effects of treatment on ocular disease have been documented through single patient reports or small series. Mihara and colleagues[48] described 2 patients, one of whom had hypopyon iridocyclitis in the right eye, and ophthalmoscopy with retinal cotton-wool spots in the left eye, both of which responded to oral prednisolone, topical instillation of 1% atropine sulfate, and subconjunctival injections of betamethasone.

SMALL VESSEL IMMUNE COMPLEX-MEDIATED VASCULITIS

C1q-Associated Hypocomplementemia Urticarial Vasculitis

C1q/hypocomplementemia urticarial vasculitis (HUV) is a rare severe systemic form of urticarial vasculitis characterized by chronic nonpruritic urticarial lesions, angioedema, ocular inflammation, arthritis or arthralgia, obstructive lung disease, and glomerulonephritis. Its exact incidence is unknown, but it is two times more common in women than in men, and its peak incidence is seen in the fifth decade of life.[49] The histopathology of HUV is characterized by an interstitial neutrophilic infiltrate of the dermis, and a necrotizing vasculitis with immunoglobulin or C3 deposits in the blood vessels on immunofluorescence.

The diagnostic criteria for C1q/HUV were first described by Schwartz and colleagues.[50] The major criteria are urticaria for more than 6 months' duration and hypocomplementemia. The minor criteria, 2 of which are required for diagnosis, are dermal venulitis on biopsy, arthralgia or arthritis, uveitis or episcleritis, mild glomerulonephritis, recurrent abdominal pain, and a positive C1q precipitin test by immunodiffusion, with a decreased circulating C1q level. Exclusion criteria included significant cryoglobulinemia, elevated anti-DNA antibody titer, high titer of antinuclear antibody, hepatitis B virus antigenemia, decreased C-esterase inhibitor levels, and inherited complement deficiency. C1q/HUV and systemic lupus erythematosus share many clinical features; thus, it is important to note that uveitis is typically found in C1q/HUV, but not systemic lupus erythematosus.[51]

Ocular manifestations of C1q/HUV are found in up to 60% of patients. A study by Wisnieski and colleagues[51] in 18 patients with C1q/HUV found that 11 patients (61%) had ocular manifestations; 8 (44%) had conjunctivitis, episcleritis, and/or inflammation of the uveal tract; and 3 (16.6%) had scleral inflammation and photophobia. The treatment of C1q/HUV consists of dapsone and systemic CS and nonsteroidal antiinflammatory drugs.

Cryoglobulinemic Vasculitis

Cryoglobulinemic vasculitis (CV) is an small vessel vasculitis (SVV) that involves the skin, joints, peripheral nervous system, and kidneys. The histopathology of CV is characterized by a leukocytoclastic vasculitis, B-lymphocyte expansion, and tissue B-cell infiltrates. The 2012 CHCC defined CV as a vasculitis with cryoglobulin immune deposits affecting small vessels associated with serum cryoglobulins. Skin, glomeruli, and peripheral nerves are often involved. Ocular signs and symptoms are neither part of the diagnostic criteria for CV, nor are they very common.

The first ocular manifestation of CV was likely described by Wintrobe and Buell[52] in a patient suffering from multiple myeloma that had bilateral thrombosis of the central retinal veins and visual impairment. Other ocular manifestations included anterior

uveitis, scleritis, and peripheral ulcerative keratitis. Purtscher-like retinopathy was described by Myers and colleagues[53] in a 44-year-old man with chronic hepatitis C virus (HCV)-associated CV who developed sudden loss of vision in his left eye and abdominal pain. Fundoscopy revealed peripapillary cotton-wool spots and superficial retinal whitening in the macula. FFA revealed retinal vascular nonperfusion in the left macular and peripapillary region, but not in the periphery, consistent with Purtscher retinopathy. The authors proposed that retinopathy developed as a result of complement-mediated microembolism leading to vasoocclusion. Sauer and coworkers[54] documented a patient with Purtscher-like retinopathy associated with HCV-associated CV with complaints of visual loss.

Central serous chorioretinopathy is an ocular complication of CV reported in 2 patients by Cohen and colleagues.[55] These patients presented with serous retinal and retinal pigment epithelial detachments resembling central serous chorioretinopathy. The authors postulated that the increased protein content of the choroid in patients with CV caused an abnormal excess of interstitial fluid to accumulate in the subretinal pigment epithelium or subretinal space resulting in retinal pigment epithelial detachment.

The treatment of CV that consists of CS plus an alkylating agent is associated with induction of remission in up to 62% of patients compared with rituximab plus CS in promoting induction of remission in up to 64% of patients; in those with HCV-associated CV, treatment of HCV with pegylated interferon and ribavirin in addition to rituximab optimally treats most patients.[56] Myers and colleagues[53] described successful treatment of Purtscher retinopathy with plasmapheresis, prednisone and cyclophosphamide leading to improvement of left eye VA from 1/200 to 20/200, and resolution of retinal whitening, cotton-wool spots, and retinal hemorrhages observed on fundoscopy in 6 months. Central serous chorioretinopathy, another ocular manifestation of CV, responds to treatment with laser photocoagulation.

IgA Vasculitis/Henoch-Schönlein Purpura

IgA vasculitis (IgAV)/Henoch-Schönlein purpura (HSP) is characterized by IgA immune complex deposition, in addition to nonthrombocytopenic palpable purpura, abdominal pain, and arthritis. The pathology of IgAV/HSP includes infiltration of small blood vessels with polymorphonuclear leukocytes and leukocytoclasia. The ACR diagnostic criteria have found that the presence of 2 or more of the following criteria were 89.4% diagnostically sensitive and 88.1% specific for IgAV/HSP, including age at onset before 20 years, palpable purpura, acute abdominal pain, and biopsy showing granulocytes around arterioles or venules.[57]

Ocular manifestations of IgAV/HSP are rare, but case reports document a range of ophthalmologic complications. Recurrent episcleritis was one of the first ocular complications of IgAV/HSP in a 14-year-old girl who developed photophobia and intermittent ocular pain 5 weeks after the onset of joint symptoms,[58] ophthalmologic evaluation of whom revealed episcleritis and engorgement of the episcleral vessels.

The association between anterior uveitis and IgAV/HSP was first described by Yamabe and colleagues[59] in the description of a patient with nephritis, anterior uveitis, and keratitis later found to have IgAV/HSP. Muqit and colleagues[60] reported a 42-year-old man with IgAV/HSP complicated by keratitis and granulomatous anterior uveitis. Erer and colleagues[61] reported a 39-year-old man who presented with 3 episodes of anterior uveitis, one of which was bilateral, and unilateral episodes of each eye. Kaur and colleagues[62] documented bilateral anterior uveitis associated in an 11-year-old boy with IgAV/HSP and a 4-year history of eye pain and photosensitivity. Uveitis in IgAV/HSP is due to circulating immune complexes, which reach the eye and

deposit in uveal tissues. Immune complexes can deposit in vascular endothelial cells, pigmented epithelial cells, and corneal endothelial cells, expressing adhesion molecules that allows leukocytes to migrate to the uveal tissue and cornea causing injury.

Other rare ocular manifestations include AION[63] and acute visual loss owing to bilateral cystoid macular edema and cotton wool spots. The treatment of IgAV/HSP varies with disease severity with milder cases of IgAV/HSP responsive to supportive therapy and self-resolve in 6 to 16 weeks, and more severe involvement requiring systemic CS and intravenous immune globulin. Ocular manifestations of IgAV/HSP resolve with a combination of systemic and topical CS.

VARIABLE VESSEL VASCULITIS

Behçet Disease

Behçet disease (BD) is characterized by relapsing aphthous ulcers of the mouth, eye, and genitalia. The most widely used diagnostic criteria of BD were formulated by the International Study Group[64] and included recurrent oral ulcerations plus any 2 of genital ulceration, typical defined eye lesions, typical skin lesions, or a positive pathergy. Citirik and colleagues[65] described ocular findings in 34 pediatric patients that included panuveitis, and posterior and anterior uveitis in 53%, 32%, and 15% of patients, respectively. Other ocular findings included cataracts in 59%, posterior synechiae in 24%, postoperative capsular opacification 24%, vitreous condensation after vitritis in 50%, optic atrophy in 30%, cystoid macular edema 15%, narrowed or occluded retinal vessels after retinal phlebitis and branched retinal occlusions in 6%, and neovascularization of the disk and phthisis bulbi each in 3% of patients. Arai and colleagues[66] described the postmortem findings in a young man with BD with relapsing unilateral uveitis, sensorineural hearing loss, slight fever, and progressive CNS and autonomic nervous system involvement that included multifocal brainstem and cerebellar necrotic foci, perivascular neutrophilic inflammation, and perivasculitis.

Cortical venous sinus thrombosis in BD most commonly presents with symptoms and signs of increased intracranial pressure with a rarity of venous infarcts. Prothrombosis, when present, is presumed to commence as an endothelial disturbance. The treatment of BD-related cortical venous sinus thrombosis includes consideration of anticoagulation and CS alone or in association with another immunosuppressive agent.

Cogan Syndrome

Cogan syndrome was first described in a 26-year-old man with recurrent pain, spasm, and redness of the left eye with photophobia, excessive tearing, and marked conjunctival injection, followed by severe attack of dizziness, tinnitus, vertigo, nausea, vomiting, ringing in the ears, profuse perspiration, deafness, and nonsyphilitic interstitial keratitis.[67] Such symptoms tended to recur periodically for years before becoming quiescent. Vestibuloauditory dysfunction was manifested by sudden onset of Menière-like attacks of nausea, vomiting, tinnitus, vertigo, and frequently progressive hearing loss that characteristically occurred before or after the onset of interstitial keratitis. However, within 1 to 6 months of the onset of eye symptoms, auditory symptoms progressed to deafness over a period of 1 to 3 months, and certainly no longer than 2 years.

Gluth and associates[68] reviewed a cohort of patients with Cogan syndrome seen at the Mayo Clinic between 1940 and 2002. The commonest symptoms at presentation were sudden hearing loss in 50%, balance disturbance in 40%, ocular irritation in 32%, photophobia in 23%, tinnitus in 13%, and blurred vision in 10% of cases.

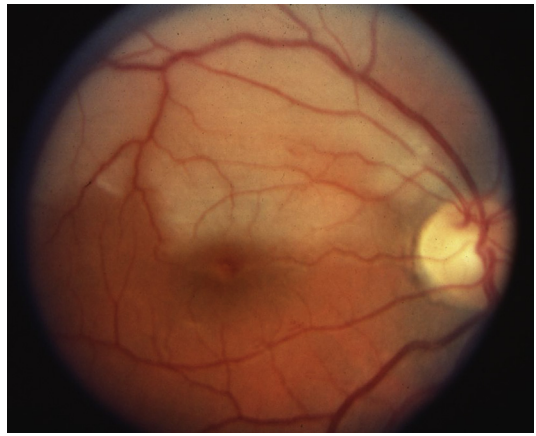

Fig. 2. Branch retinal artery occlusion in a patient with isolated central nervous system vasculitis.

Inflammatory eye findings that occurred in the course of disease included interstitial keratitis in 77%, iritis or uveitis in 37%, oscillopsia in 25%, scleritis or episcleritis in 23%, and conjunctivitis in 10%.

Most patients with Cogan syndrome (58%) are treated with CS with an overall favorable response in both vestibuloauditory and ophthalmologic manifestations, with the remainder demonstrating only ophthalmologic (23%) or vestibuloauditory improvement (19%) alone. Other therapies include methotrexate, cyclophosphamide, azathioprine, entanercept, hydroxchloroquine, and intravenous immune globulin therapy. Surgical cochlear implantation can led to objective and subjective benefits with improved hearing recognition.

Primary Central Nervous System Vasculitis

Primary angiitis of the CNS[69] and PCNSV[70] and granulomatous angiitis of the brain[73] are equivalent terms for a prototypical primary vasculitic disorder restricted to the CNS of diverse causes and clinicopathologic expressions. The diagnosis relies on the presence of the classic angiographic features of beading in cerebral angiographic studies and the histopathologic features of angiitis in brain and meningeal vessels in the absence of systemic vasculitis or another cause for the observed findings. Younger and colleagues[73] described symptoms and signs in 4 patients with granulomatous angiitis of the brain among whom visual symptoms included diplopia, amaurosis fugax, and blurring of vision. The one patient with granulomatous angiitis of the brain and herpes zoster ophthalmicus had contiguous involvement of the eye in in association with V1 dermatomal varicella zoster virus lesions. Among 4 patients described by Cupps and colleagues,[74] neuroophthalmologic involvement was noted in 2 patients. Patient 1 had transient hemifield visual loss accompanied by headaches before the angiographic diagnosis of isolated angiitis of the central nervous system with the involvement of named cerebral vessels, followed several months later after the commencement of a combination immunosuppressant therapy by a 1-week period of altered VA. Patient 3 had a unilateral fundus Roth spot, with markedly decreased VA and normal pupillary response before diagnostic cerebral angiography of isolated angiitis of the central nervous system showed narrowing of named cerebral vessels, followed months later after commencement of combination

immunosuppressant therapy by occipital headaches, transient decreased VA, and a starburst image of the central visual field.

Calabrese and Mallek[69] reported eye signs in 15% of literature cases with angiographically or pathologically defined primary angiitis of the CNS, but in none of the 8 Cleveland Clinic patients. Among 70 patients with angiographically defined PCNSV and 31 patients with pathologically verified proven PCNSV described by Salvarani and colleagues,[70] blurred vision and decreased acuity were most common in those with angiographically defined PCNSV overall in 68% of patients. Lanthier and coworkers,[71] who described histologically proven isolated angiitis of the central nervous system in 2 children, described 1 child with bilateral optic disk swelling and persistent conjugated gaze-evoked nystagmus at presentation. Among 4 children with angiographically negative childhood primary angiitis of the CNS described by Benseler and colleagues,[72] 1 child was noted to have gaze-evoked nystagmus (**Fig. 2**).

SUMMARY

Ophthalmologic and neuroophthalmologic manifestations of primary systemic and isolated CNS vasculitis typically arise in association with ischemic vascular disease of the CNS. Although uncommon, such manifestations may be the first clue to underlying ischemic disease owing to primary or secondary involvement of visual and eye movement pathways warranting further evaluation for CNS vasculitis.

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