A Review Article on Neuroretinitis

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ABSTRACT

Neuroretinitis is an inflammatory optic neuropathy with a classic fundoscopic appearance of optic disc swelling and hard exudates on the macula in a star formation. It can be a manifestation of systemic, infectious or autoimmune disease. In nearly half of cases, the etiology is idiopathic. This review aims to summarize the clinical presentation, fundoscopic mimics, etiologies, investigation, and treatment of neuroretinitis. Cat-scratch disease, the most common cause of infectious neuroretinitis, and recurrent idiopathic neuroretinitis, which can cause ocular morbidity, are discussed in detail.

Keywords: neuroretinitis, cat-scratch disease, idiopathic neuroretinitis
Neuroretinitis is an inflammatory disorder of the optic nerve characterized by optic disc swelling and macular star formation. It was first described by Leber in 1969 as a form of idiopathic stellate maculopathy. This was challenged by Gass in 1977 who argued that the disc edema in neuroretinitis precedes macular exudates. Using fluorescein angiography, Gass demonstrated the disease to be primarily an optic neuropathy. The condition was renamed to Leber’s idiopathic stellate neuroretinitis.

I. CLINICAL PRESENTATION

Neuroretinitis causes sudden-onset, painless loss of vision. It is usually unilateral, but bilateral simultaneous or sequential involvement has been reported. Examination reveals decreased visual acuity, visual field defects, and, oftentimes, an ipsilateral relative afferent pupillary defect (RAPD). The characteristic appearance of neuroretinitis on fundoscopy is optic disc swelling plus hard exudates on the macula in a complete or partial star arrangement. In the early phase of the disease, prior to appearance of the macular star, there may be a mild serous detachment of the macula associated with optic disc edema. Vision loss in neuroretinitis is due to a large central scotoma thought to be related to the maculopathy rather than to the optic nerve dysfunction.

II. PATHOPHYSIOLOGY

The earliest clinical abnormality in neuroretinitis is optic disc edema from inflammation. It typically precedes the development of macular star by 1-3 weeks and resolves spontaneously after 8-12 weeks. The optic disc swelling results to leakage of lipoproteinaceous material from the optic disc vasculature and accumulation of fluid and lipoprotein in the macula, particularly in the outer retinal layers. The disc swelling and macular fluid subside over a few weeks leaving behind the lipoprotein deposits (or hard exudates) in the macula. The characteristic star appearance is due to the radial arrangement of the Henle’s fiber in the outer plexiform layer of the retina. The hard exudates take 6-12 months to resorb.

III. DIFFERENTIAL DIAGNOSES

Neuroretinitis can be fundoscopically confused with other optic neuropathies that present with disc swelling such as florid papilledema (Figure 1) and non-arteritic ischemic optic neuropathy (NAION). Although the exudates in papilledema and NAION are often limited to the retina immediately surrounding the disc, they may extend to the macula, but rarely form a macular star. Additionally, papilledema is accompanied by other neurologic signs and symptoms of increased intracranial pressure (ICP) such as headache, vomiting, and abducens nerve palsy. Neuroretinitis may also mimic retinal vascular disorders such as malignant hypertensive retinopathy and diabetic papillopathy in the background of diabetic retinopathy. Presence of retinal vessel abnormalities and findings in the retinal periphery (microaneurysms, hemorrhages, cotton-wool spots, and exudates) differentiate these two disorders from neuroretinitis. Other causes of posterior uveitis may also be mistaken for neuroretinitis. Presence of chorioretinal findings, such as focal areas of chorioretinitis, vasculitis, or peripheral retinal hemorrhages, suggest a different diagnosis other than neuroretinitis. Posterior scleritis may also present with optic disc edema and macular exudates. It can be differentiated from neuroretinitis by the presence of severe pain on history and characteristic ocular ultrasonography findings (i.e., T-sign, thickened choroid).

IV. ETIOLOGY

Neuroretinitis can be a manifestation of a systemic infectious or autoimmune disease.
Table 1 lists the variety of infectious etiologic agents and systemic disorders associated with neuroretinitis. The leading cause of infectious neuroretinitis is Bartonella henselae, a gram-negative bacterium, frequently acquired through a scratch or bite from an infected kitten. Very rarely, B. henselae can be transmitted by a bull ant sting or a flea bite. Three other species of Bartonella have been reported to cause neuroretinitis in humans: B. quintana, B. elizabethae, and B. grahamii. Another important cause of neuroretinitis in the Philippines is Mycobacterium tuberculosis (TB). Unlike optic neuritis, neuroretinitis is not associated with the development of multiple sclerosis. Nevertheless, neuroretinitis has been reported in 3 patients who were receiving treatment for multiple sclerosis. In 25-50% of cases, no cause can be readily identified from the clinical history and laboratory examination. These are labeled as idiopathic neuroretinitis.

**Table 1. Causes of Neuroretinitis**

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Autoimmune</th>
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</thead>
<tbody>
<tr>
<td>Bacteria: Bartonella sp. (B. henselae, B. quintana, B. elizabethae, B. grahamii), Brucella, Mycobacterium tuberculosis, Rickettsia rickettsii (Rocky Mountain spotted fever), Salmonella</td>
<td>Sarcoïdosis</td>
</tr>
<tr>
<td>Spirochetes: Borrelia burgdorferi (Lyme disease), Leptospira interrogans (leptospirosis), Treponema pallidum (syphilis)</td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>Virus: Chikungunya, cytomegalovirus, Coxsackie, dengue, Epstein-Barr virus, hepatitis B, herpes zoster virus, influenza A, measles, mumps, rubella, varicella, West Nile virus</td>
<td>Polyarteritis nodosa</td>
</tr>
<tr>
<td>Nematode: Toxocara</td>
<td>Tubulointerstitial nephritis and uveitis (TINU)</td>
</tr>
<tr>
<td>Fungus: Coccidioidomycosis, histoplasmosis</td>
<td>Systemic lupus erythematosus</td>
</tr>
</tbody>
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**VI. INVESTIGATIONS**

Evaluation of a patient with neuroretinitis begins with a focused clinical history taking. Inquiries on pet cats, cat bite or scratch, tick bites, sexual promiscuity, TB, travel to endemic areas (Lyme disease), rashes, lymphadenopathy, exposure to flood water, chronic cough, fever, or flu-like illness should be made. Due to the delay in appearance of the macular star, patients who present with papillitis or inflammatory disc swelling may be re-examined after 2 weeks for fundus findings that may be more consistent with neuroretinitis. In bilateral cases of optic disc edema associated with macular star, blood pressure should be measured and raised ICP should be ruled out. Laboratory testing should be tailored for each individual depending on the history and physical examination findings. Minimum laboratory work-up should include tests for TB, syphilis, and Bartonella species. Other tests that may be requested include serologies against viruses, bacteria, or protozoa (such as human immunodeficiency virus [HIV], toxoplasmosis, and Lyme disease), erythrocyte sedimentation rate (ESR), urinalysis, autoimmune panel, and blood cultures (Table 2). In select cases, neuroimaging and lumbar tap with cerebrospinal fluid analysis may be warranted.

**Table 2. Diagnostic Work-up for Neuroretinitis**

| Chest x-ray, tuberculin skin testing (PPD), interferon-gamma release assay | FTA-ABS, VDRL, RPR, MHA-TP |
| Serologies: B. henselae, B. quintana, Toxoplasma, Toxocara, B. burgdorferi, viral serum antibodies | ESR, CBC, Urinalysis |
| Serum angiotensin converting enzyme | Lumbar tap with cerebrospinal fluid analysis (opening pressure, cytology, glucose, protein, staining, culture) |
| ANA | Cranial MRI with gadolinium |
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PPD: purified protein derivative; FTA-ABS: fluorescent treponemal antibody-absorption test; VDRL: venereal disease research laboratory test; RPR: rapid plasma reagin; MHA-TP: microhemagglutinin assay for Treponema pallidum; ESR: erythrocyte sedimentation rate; CBC: complete blood count; ANA: antinuclear antibody; MRI: magnetic resonance imaging.
or pustular skin lesions at the site of inoculation may be present. Other systemic organ involvement in CSD include meningitis, hepatosplenomegaly, arthritis, osteomyelitis, granulomatous conjunctivitis (Parinaud's oculoglandular syndrome), splenic abscess, pneumonia, and thrombocytopenic purpura. In immunocompromised individuals, the disease may be disseminated involving multiple organs.

Neuroretinitis from CSD is unilateral in majority of cases; however, simultaneous, bilateral involvement has been reported. Contrary to typical optic neuritis, eye pain is uncommon in neuroretinitis (7.7%). Visual acuity on presentation ranges from 20/20 to counting fingers. The most frequent visual field defect pattern is a central scotoma. Dyschromatopsia is not uncommon. A RAPD is present ipsilateral to the eye with neuroretinitis in 67.5%. Disc swelling may be diffuse or sectoral. Macular exudates may be sparse or form a complete star (Figure 2). The macular star resolves in approximately 8-12 weeks. Other intraocular findings include anterior uveitis, vitritis, cotton-wool spots, hemorrhages, focal retinitis, inflammatory optic nerve mass, marked peripapillary edema with Paton lines, angiomatous lesions, and choroidal inflammatory lesion.

VII. TREATMENT

Treatment of neuroretinitis is directed to the specific underlying cause. Appropriate antibiotic therapy is required for infectious etiologies. Idiopathic neuroretinitis exhibits good spontaneous visual recovery and does not require any treatment. On the other hand, long-term immunosuppressive therapy may be considered for recurrent idiopathic neuroretinitis (discussed below).

VIII. CAT-SCRATCH DISEASE

Cat-scratch disease (CSD) is the most common form of infectious neuroretinitis caused by infection with \textit{B. henselae}. Approximately two-thirds of patients demonstrate seropositivity for \textit{B. henselae} despite the fact that only 1-2% of patients infected with the organism develop neuroretinitis. While fleas serve as vectors for the transmission of the bacteria, domestic cats are major reservoirs. All patients with neuroretinitis should be asked for a history of recent cat-scratch or bite. The infection is not known to be transmitted from human to human. The pathogenesis of neuroretinitis in CSD is hypothesized to be either due to direct bacterial invasion of the optic disc vasculature or cross-reaction of Bartonella antibodies against proteins found in the optic nerve. CSD may affect all ages but it is more commonly diagnosed in children and young adults.

Systemic signs and symptoms usually precede ocular manifestations and are important in establishing the diagnosis. The onset of visual symptoms usually follows inoculation by approximately 1 month and it follows the onset of constitutional symptoms by approximately 2-3 weeks. Non-specific symptoms may include fever, malaise, myalgia, arthralgia, and headache. Regional lymphadenopathy and papular or pustular skin lesions at the site of inoculation may be present. Other systemic organ involvement in CSD include meningitis, hepatosplenomegaly, arthritis, osteomyelitis, granulomatous conjunctivitis (Parinaud’s oculoglandular syndrome), splenic abscess, pneumonia, and thrombocytopenic purpura. In immunocompromised individuals, the disease may be disseminated involving multiple organs.

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CSD-associated neuroretinitis, the average central macular thickness on presentation using Stratus® OCT machine was 460 microns (range: 170-906 microns). Fluorescein angiography most frequently shows late optic disc dye leakage. Occasionally, an angiomatous peripapillary lesion may be documented in the early phase of angiography as well as pooling of dye corresponding to an area of peripapillary serous retinal detachment. Fundus autofluorescence may show a radial pattern of hyperfluorescence at the macula in an eye with submacular fluid due to neuroretinitis. It may also demonstrate subtle areas of hyperfluorescence temporal to the disc in an asymptomatic, fellow eye suggesting subclinical disease. Visual field testing often demonstrates a cecocentral scotoma, a paracentral scotoma, or an enlarged blind spot. Although not necessary in the diagnosis of CSD-associated neuroretinitis, contrast MRI of the orbits may show enhancement of the intraocular and orbital segments of the affected optic nerve.

The most popular confirmatory test for CSD-associated neuroretinitis is serology. An elevated IgM titer against B. henselae indicates recent infection and confirms the diagnosis of CSD. When IgM is unavailable, consecutive IgG titers during acute and convalescent stages may be requested. A rise in the IgG during the convalescent stage supports the diagnosis of CSD. A single, elevated IgG measurement for the diagnosis of CSD is controversial due to a high seroconversion in the normal population (2-3%). However, Suhler demonstrated that the seropositivity rate to B. henselae in patients with neuroretinitis was much higher at 64%. He recommends that it is reasonable to diagnose CSD in a patient with neuroretinitis on the basis of a single elevated IgG measurement. Dilution titers of 1:64 or higher on indirect immunofluorescent assay are considered by some to be positive.

Other methods to confirm CSD include blood culture, skin tests, and lymph node biopsy. Blood cultures may document bacteremia, though are rarely done because B. henselae are fastidious growers. Skin testing using Bartonella antigens have high sensitivity and specificity rates but the test has limited availability. Lastly, lymph node biopsy may be examined using Warthin-Starry stain or polymerase chain reaction for the presence of Bartonella.

In the immunocompetent patient, CSD-associated neuroretinitis is a self-limited disease. Management in the past varied from observation to medical therapy with antibiotics alone or in combination with steroids. Antibiotic therapy in the immunocompetent individuals is controversial due to lack of controlled studies. Observational case series show that rifampin, gentamicin, ciprofloxacin, trimethoprim-sulfamethoxazole, doxycycline, and azithromycin shorten the course of systemic disease. In febrile patients, fever and constitutional symptoms abated 4-5 days after commencement of antibiotics. The use of antibiotics, however, have not shown to affect visual outcome. Of note, doxycycline and ciprofloxacin are best avoided in young children. Steroids have been used for CSD-associated neuroretinitis in the belief that it may hasten recovery of vision. However, there is no good evidence that it affects visual outcome.

Meanwhile, antibiotic treatment is mandatory in the immunocompromised hosts (HIV seropositive or post-transplant patients). Additionally, antibiotic therapy is administered over a prolonged period (2-4 months) to prevent recurrence.

Historically, the disease is characterized by good visual recovery. Majority of eyes have final visual outcomes of 20/40 or better. A good visual acuity at presentation has been identified to be associated with good visual outcomes. However, some patients may still report of permanent distortion, subtle color vision deficits, mild loss of contrast sensitivity or small scotomas. These deficits may be due to variable degree of optic disc atrophy or retinal epithelial defects on the macula.

Rarely, CSD-associated neuroretinitis is complicated with macular hole formation, branch vein retinal occlusion, secondary unilateral glaucoma, central retinal vein occlusion, central retinal artery occlusion, neovascular glaucoma, and corneal decompensation. These generally result to severe visual impairment.

VIII. IDIOPATHIC NEURORETINITIS

Idiopathic neuroretinitis frequently affects young adults. In more than half of the cases, it is preceded with a flu-like illness. Vision loss is usually painless or may be associated with mild ocular discomfort. It is mostly unilateral; bilateral involvement is rare. Visual acuity at presentation ranges from 20/20 to light perception. The most common visual field deficit
is a central or cecocentral scotoma. An ipsilateral RAPD may be appreciated. Posterior vitreous cells may be present as well as occasional anterior uveitis. Fundoscopy invariably reveals disc swelling that may be associated with peripapillary nerve fiber layer hemorrhages. Review of systems and laboratory work-up are negative for any obvious cause of neuroretinitis.

Idiopathic neuroretinitis is often a self-limited disease. The disc edema resolves at 8-12 weeks resulting to a normal-looking or variably pale optic disc. Over time, the macular fluid and exudates disappear leaving behind retinal pigment epithelium defects. Even without treatment, visual outcome is excellent, with >90% achieving a final visual acuity of 20/40 or better. Currently, there is no standard treatment for idiopathic neuroretinitis.

Idiopathic recurrent neuroretinitis was first described by Purvin in 1994. It is diagnosed when 2 or more episodes of neuroretinitis occur in one eye in an otherwise, healthy individual. A retrospective study involving 41 patients from one institution showed that this disease is more common among young adults with no gender predilection. Additionally, there is no viral prodrome or seasonal predilection. Eye pain is a rare symptom (2%). The disease tends to be bilateral with sequential involvement of the fellow eye within a month to several years. The number of recurrence per patient ranged from 2 to 13 (mean: 3.6). With each recurrence, there occurs incremental decreases in visual acuity and visual fields. An autoimmune vasculitis is hypothesized to be the underlying mechanism in idiopathic recurrent neuroretinitis. Laboratory examination failed to identify a specific cause in each of the cases. Similar to any autoimmune disorder characterized by relapses, treatment has 2 arms: (1) control of inflammation by corticosteroids, and (2) prevention of recurrence using immunosuppressive agents. Systemic steroids in the form of pulse methylprednisolone or oral prednisone have been shown to eliminate disc swelling quickly. However, they had no effect on vision. Azathioprine alone or given with low-dose prednisone has been shown to reduce recurrence rate by as much as 72% and protect the eye from further vision loss.

In summary, neuroretinitis is an inflammatory disorder characterized by disc swelling and macular star. It can be a manifestation of a systemic infection or autoimmune disorder. Cat-scratch disease is the most common cause of infectious neuroretinitis. In nearly half of the cases, the etiology is unknown and visual recovery is excellent. The use of multimodal imaging may aid in the early diagnosis of neuroretinitis.

REFERENCES