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Review

# Update on Bartonella neuroretinitis

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## Abstract

***Purpose***: To review the clinical features, diagnosis, treatment modalities, and prognosis of Bartonella-associated neuroretinitis.
***Methods***: This is a narrative review on Bartonella-associated neuroretinitis including general and ophthalmological aspects of the disease. A comprehensive literature review between January 1950 and September 2018 was conducted in PubMed database. Epidemiology, clinical features, diagnosis, treatment, and prognosis of Bartonella neuroretinitis were reviewed.
***Results***: Cat scratch disease (CSD) is a worldwide distributed systemic infectious disease caused by a bacterium, *Bartonella henselae (B. henselae)* which is usually transmitted to humans through contact with infected cats. Ocular manifestations of CSD are diverse, with neuroretinitis and superficial retinal infiltrates being the most common and typical manifestations. Neuroretinitis typically presents as optic disc edema with a partial or complete macular star in association with mild vitritis. Macular star may be absent at the initial presentation, becoming evident 1–2 weeks after the onset of optic disc edema. Diagnosis of CSD is confirmed by reliable laboratory tests. Neuroretinitis usually has a self-limited course. Antibiotic therapy is required for severe systemic disease and vision-threatening ocular involvement. The adjunctive use of oral corticosteroids may further improve the visual outcome.
***Conclusions***: The diagnosis of Bartonella-associated neuroretinitis is based on typical clinical findings and positive serology. The prognosis is usually favorable in immunocompetent individuals.


*Keywords:* Cat scratch disease; *Bartonella henselae*; Optic neuritis; Serology; Neuroretinitis

## Introduction

Cat scratch disease (CSD), also known as cat scratch fever, is a self-limited, systemic infectious disease caused by a small, fastidious, gram-negative intracellular bacillus *Bartonella henselae (B. henselae)*.[1,2]

CSD was first described in 1950 by Debré et al.[3] However, the causative agent was first identified in 1983 by Wear and associates.[4] Humans may catch the infection through scratches, licks, and bites of cats or kittens.[1] Humans transmission can also occur secondary to tick bites.[1] The most common systemic manifestation consists of lymphadenitis involving the lymph nodes draining sites of inoculation.[1]

Many ocular manifestations may be related to CSD, with neuroretinitis and focal retinochoroiditis/retinal infiltrates being the most common clinical forms of ocular CSD.[1,5–7] Conversely, *B. henselae* is among the most common causes of neuroretinitis.[8,9]

The primary aim of this article was to review the clinical features, diagnosis, treatment modalities, and prognosis of Bartonella-associated neuroretinitis.

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## Methods

The literature review for this study was based on a search in PubMed/Medline and Scopus databases to identify original articles, reviews, and case reports between January 1950 and September 2018 in English language regarding Bartonella neuroretinitis. The following keywords were used: ("Bartonella" OR "Bartonella henselae" OR "Bartonella Infection" OR "Cat-Scratch Disease") AND ("Neuroretinitis" OR "Eye" OR "Uveitis" OR "Optic Neuropathy"). All selected articles were reviewed thoroughly by the authors to review epidemiology, pathogenesis, clinical features, diagnosis, treatment, and prognosis of Bartonella neuroretinitis.

## Results

### *General aspects of cat scratch disease*

#### *Epidemiology*

CSD is a worldwide distributed zoonosis.[10] Cats are the primary reservoir for *B. henselae*, with the cat flea (Ctenocephalides felis) being the main transmission vector among cats[11,12] and occasionally to humans. The incidence of CSD in the United States is roughly 22,000 cases per year.[13] The seroprevalence ranges from 2.0 to 32.38% in Eastern China[14] and from 12.8 to 13.7% in Brazil.[15] Recent data show that the incidence of CSD is 4.7 per 100.000 persons less than 65 years of age.[16] *B. henselae* is usually transmitted from cats to humans through scratches or by the contamination of superficial injuries.[17,18] The infection is not known to be transmitted from human to human. CSD cases have been reported at all times of the year but may increase during fall and winter.[19] *B. henselae* infection is more common in children and young adults.[20] The veterinary profession is also a risk factor for CSD infection.[1,21]

#### *Pathogenesis*

Humans infection occurs secondary to scratches, licks, bites of cats or kittens, and rarely tick bites.[1] The infectious agent causes in the inoculation site a focal granuloma with necrosis at the center and surrounding histiocytes, lymphocytes, and giant cells. Systemic manifestations of CSD are influenced by pathogen-related factors and the host's immune status.[1] The exact pathogenesis of CSD-associated neuroretinitis remains to be elucidated. The optic nerve involvement might be caused by optic nerve or intraocular infection by Bartonella, an immune response to bacterial infection, or a combination of infectious and parainfectious mechanisms.[9] The inflammation of the optic disc causes exudation of fluid into the peripapillary retinal leading to serous retinal detachment and the subsequent appearance of macular exudates with a partial or complete star pattern around the fovea.

#### *Systemic disease*

Primary inoculation through a cat scratch or bite often results in a local infection. An erythematous papule, vesicle, or macule often develops at the site of inoculation. A few weeks later, systemic reaction including regional lymphadenitis, low-grade fever, malaise, chills, excessive sweating during sleep, fatigue, and headache occurs.[22,23] Most patients experience self-limited disease in the inoculation site with mild systemic symptoms that resolve within several months.[24] However, a small subset of individuals, particularly immunocompromised patients, may develop extra nodal dissemination with life-threatening complications, such as endocarditis,[1] meningitis,[25] encephalitis,[25] arthritis,[26] osteomyelitis,[26] pneumonia,[1] and hepatosplenic involvement.[26]

#### *Ocular disease*

Ocular involvement occurs in 5–10% of individuals with CSD.[27] The eye may be the primary site of inoculation leading to Parinaud oculoglandular syndrome, characterized by infection of the conjunctiva and eyelids, associated with regional lymphadenopathy. Different ocular manifestations may occur following the systemic disease by 2–3 weeks. These manifestations include neuroretinitis, optic neuropathy, and an array of other forms of intraocular inflammation (Table 1).[1,20,28,29]

### *Clinical features of neuroretinitis*

Neuroretinitis is defined as inflammation of the optic nerve and peripapillary retina and is characterized by optic disc edema and subsequent formation of a macular star. Neuroretinitis is usually unilateral but may be bilateral in both immunocompetent and immunocompromised patients.[19] Ocular complaints usually begin 2–3 weeks after the onset of systemic symptoms. The decrease in vision is the most common ocular symptom.[6] Visual acuity at presentation varies from light perception to 20/20. There are usually a relative afferent pupillary defect, a visual field defect, and dyschromatopsia.[30] Cells and flare in the anterior chamber are seen at times, and a mild vitritis is common. Fundoscopic findings typically include optic disc edema and lipid exudation in the macula arranged in a complete or incomplete star

Table 1
Ophthalmic manifestations of Bartonella infection.

| Eye compartment | Clinical findings |
|---|---|
| Adnexal manifestations | Parinaud oculoglandular syndrome |
| Vitreous changes | Intermediate uveitis |
| | Vitreous hemorrhage |
| Retinal/choroidal manifestations | Inner retinitis |
| | Chorioretinitis |
| Retinal vascular manifestations | Retinal vasculitis |
| | Angiomatous-like proliferation |
| | Branch retinal arteriolar occlusion |
| | Branch retinal vein occlusion |
| Macular complications | Serous macular detachment |
| | Macular star |
| | Macular edema |
| | Macular hole |
| Optic nerve manifestations | Neuroretinitis |
| | Optic disc edema |
| | Optic nerve head mass |

configuration (Fig. 1).[31] When a partial star pattern is seen, it is usually present in the nasal macula. The optic disc is the primary target of inflammation in neuroretinitis.[32] The macular star may be absent at initial presentation. It usually develops roughly 1–2 weeks after the onset of optic disc edema. The disc edema begins to decrease in 2 weeks and usually shows complete resolution in 8–12 weeks. The macular star decreases in 4 weeks but may be present for up to 1 year.[33]

The optic disc edema is usually accompanied by papillary and peripapillary telangiectatic vessels (Fig. 2). Besides, it is commonly associated with peripapillary retinal thickening and exudative retinal detachment (Fig. 3).[34] Intraretinal hemorrhages may be seen.[35] Patients may present with a prominent peripapillary angiomatous lesion or optic disc, which may mimic other conditions such as toxocariasis or tumors.[36]

*Other posterior segment changes*

Small or large white retinal lesions consistent with inner retinitis or retinochoroiditis represent another common ocular manifestation of CSD. Retinal infiltrates and retinochoroiditis were reported as the most common findings in some studies.[5–7]

These lesions have typically a juxtavascular location and may be associated or not with neuroretinitis (Fig. 3).[6,19,24,37] The lesions fade slowly, imparting atrophic chorioretinal scarring onto the damaged retina. Telangectasia or an angiomatous-like proliferation of retinal capillaries may be associated and are better shown by fluorescein angiography.[38,39] Retinal vascular occlusions, predominantly arteriolar occlusions, may develop in ocular bartonellosis.[40] Branch retinal artery occlusion[6,41] or less often branch retinal vein

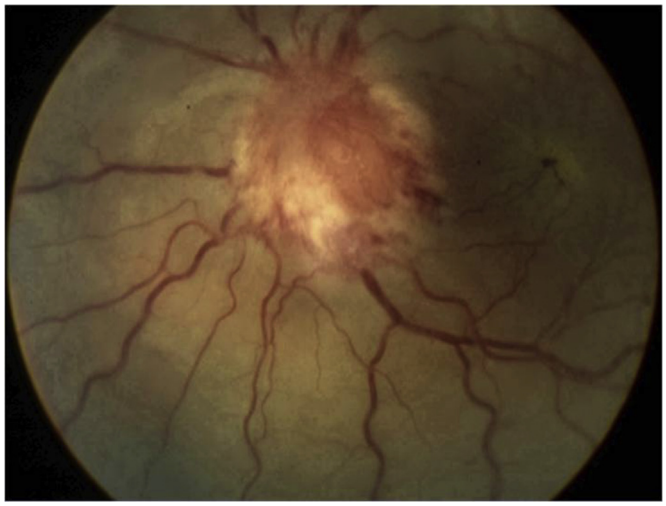

Fig. 2. Fundus photograph of the left eye of a patient with cat scratch disease (CSD) shows a prominent vascularized optic nerve head mass associated with peripapillary exudative retinal detachment (Courtesy, Andre Curi).

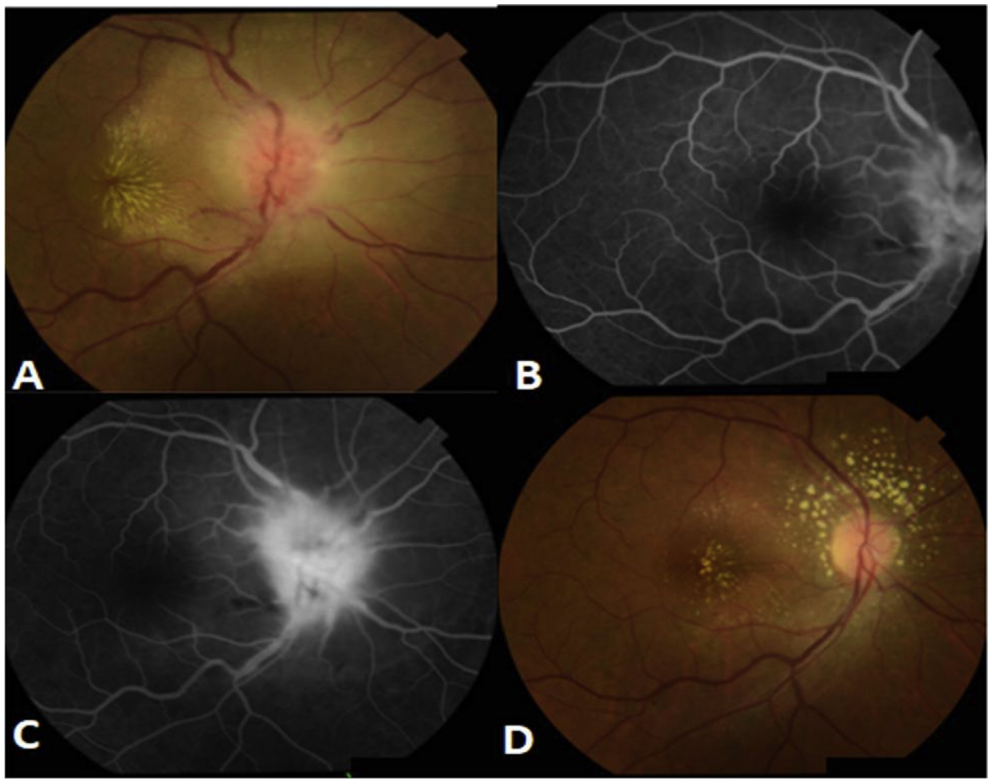


Fig. 1. (A) Fundus photograph of the right eye of a 44-year-old patient with a serologically confirmed cat scratch disease (CSD) shows a marked optic disc edema associated with a complete macular star and exudative retinal detachment. Early-phase (B) and late-phase (C) Fluorescein angiograms show progressive leakage and staining of the optic disc (D) Fundus photograph taken 4 weeks later shows a partial resolution of the macular hard exudates, with the appearance of new exudates around the optic disc.

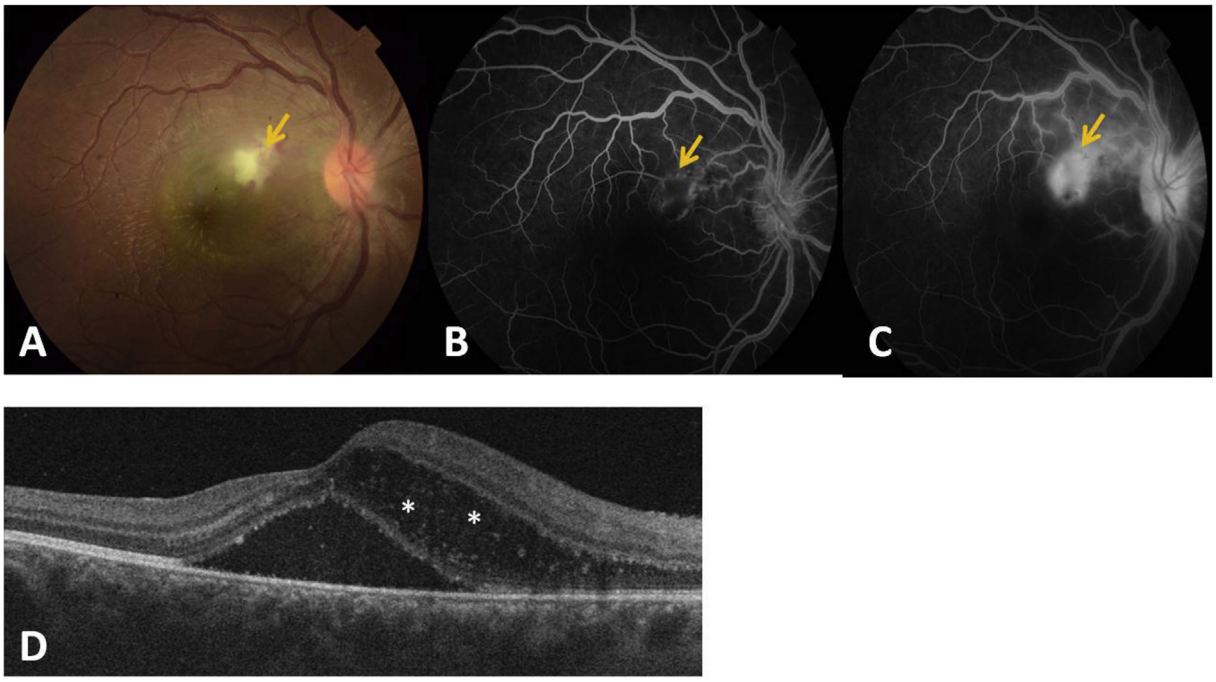


Fig. 3. Cat scratch disease (CSD) neuroretinitis in the right eye of a 19-year-old woman. (A) Fundus photograph shows optic disc edema with a partial macular star associated with a white retinal lesion (arrow) (B) Early-phase fluorescein angiogram shows hypofluorescence of the retinal lesion (arrow) (C) Late-phase fluorescein angiogram shows optic disc leakage and staining of the retinal lesion (arrow) (D) Swept-source OCT shows a marked retinal thickening nasally (white asterisk) associated with a macular serous retinal detachment (Courtesy, Walid Zbiba).

occlusion[29,41] may be a complication of CSD-related retinitis. A case of the central retinal artery and central vein occlusion has also been described.[7]

Other rare ocular findings associated with CSD may include inflammatory retinal mass,[42] subretinal mass associated with an abnormal vascular network among patients with human immunodeficiency virus infection,[7] intermediate uveitis and retinal vasculitis,[43] panuveitis with manifestations mimicking Vogt-Koyanagi-Harada disease,[44] exudative macular detachment without associated retinitis or neuroretinitis,[45,46] macular hole,[47] vitreous hemorrhage,[48] and endophthalmitis.[49]

*Imaging and ancillary testing*

Fluorescein angiography demonstrates early papillary and peripapillary telangiectasia with late marked fluorescein leakage from the optic disc and vessels (Figs. 1 and 3).[50] There is no associated perifoveal capillary leakage (Figs. 1 and 3).[51]

Indocyanine green angiography may also show optic disc hyperfluorescence without associated choroidal involvement.[52]

Fundus autofluorescence may be helpful for demonstrating hyperautofluorescent lesions corresponding to macular exudates.[53]

Optical coherence tomography (OCT) typically shows the thickening of the neurosensory retina in the peripapillary area and subretinal fluid accumulation.[50,54]

Retinal exudates appear as hyperreflective lesions in the outer plexiform layer. OCT can assist the clinicians to detect retinal findings that are not visible on clinical exam particularly in the early stages of Bartonella neuroretinitis (Fig. 3). Subclinical evidence of subretinal fluid accumulation and thickening of the neurosensory retina can be identified earlier on OCT compared with biomicroscopy.[54]

OCT angiography, a new non-invasive imaging modality, may be useful in detecting optic disc telangiectatic vessels (Fig. 4).

Visual field testing often demonstrates a cecocentral, central, or paracentral scotoma, or an enlarged blind spot.[29]

Other functional alterations include color vision abnormalities and reduction in average visually evoked potential (VEP) with normal electroretinogram.[19]

*Diagnosis*

The diagnosis of CSD-associated neuroretinitis is based on clinical findings including young age, history of contact with a cat, typical neuroretinitis, systemic symptoms, and positive serology.

The culture of *B. henselae* from blood patient is difficult and rarely successful.

Serological tests are more reliable based on immunoglobulin G (IgG) and immunoglobulin M (IgM) detection.

The indirect fluorescent antibody (IFA) test is the most reliable method with high specificity of 95%. However, cross reactivities have been reported in patients with *Coxiella burnetii* infection, *Chlamydophila* infection, *Brucella* sp and *non-henselae Bartonella* infections,[55] making the sensitivity less strong and variable in reports especially for IgM detection.

IgM detecting by enzyme-linked immunoassays (EIA) was found to have variable sensitivity in different reports, making

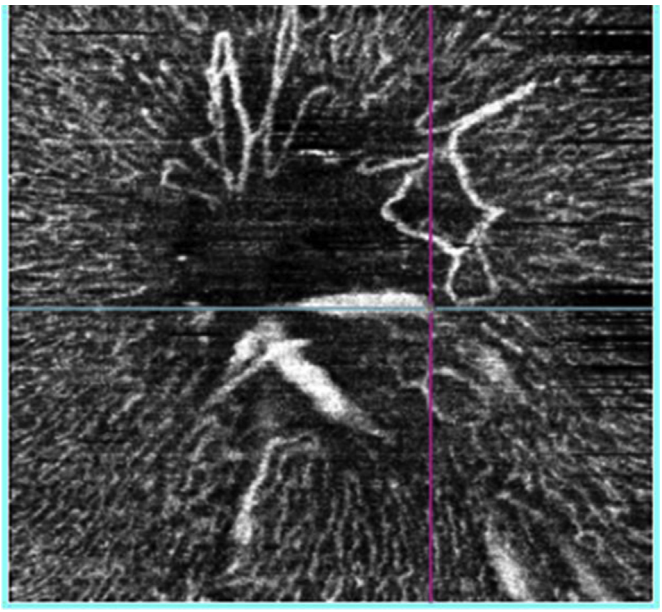

Fig. 4. Swept-Source OCT angiography showing peripapillary telangiectatic vessels in a patient with cat scratch disease (CSD)-associated neuroretinitis.

its clinical utility uncertain.[56] The usefulness of IgM-Western blot analysis for the diagnosis of CSD is not yet proven.

IgM positivity indicates acute disease. IgG titers exceeding 1:256 confirm CSD. Titers between 1:64 and 1:256 suggest possible CSD, and the serology should be performed again 10–14 days later.

Polymerase chain reaction (PCR) for the detection of *B. henselae* 16S ribosomal RNA gene in patients' tissues such as lymph nodes is a more advanced technique that has been recently used for CSD diagnosis.[57] There are few reports about PCR in aqueous humor.[58] Histological examination of iris specimen was reported in a child with iris nodule and showed granulomatous inflammation with a central necrosis.[59]

### *Differential diagnosis*

Etiologies of neuroretinitis can be divided into infectious and noninfectious diseases. Although CSD was found to be the leading cause of neuroretinitis, other infectious or inflammatory diseases should be considered in the differential diagnosis including toxoplasmosis, toxocariasis, tuberculosis, syphilis, Lyme disease, rickettsiosis, dengue fever, chikungunya, sarcoidosis, Behçet disease, and other conditions[31,32] (Table 2). The differential diagnosis is based on history, epidemiological data, systemic manifestations, and the pattern of ocular involvement. Other possible causes of optic disc swelling associated with macular star should be excluded including severe high blood pressure, diabetes mellitus, intracranial hypertension, branch retinal vein occlusion, and nonarteritic or arteritic anterior ischemic optic neuropathy (Table 2).[7,30,60–62] Small inner retinal infiltrates in the posterior pole may mimic cotton-wool spots. However, unlike these ischemic lesions, retinal infiltrates do not necessarily follow first-order arterioles and do not

Table 2
Differential diagnosis of cat scratch disease (CSD) neuroretinitis.

| Diagnosis | Main differentiating features |
|---|---|
| Toxoplasmosis | Unifocal retinochoroiditis, retino-choroidal scar, moderate to severe vitritis, granulomatous anterior uveitis |
| Toxocariasis | More common among children, unifocal vitreo-retinal granuloma, moderate to severe vitritis |
| Tuberculosis | Granulomatous anterior uveitis, occlusive periphlebitis, choroidal involvement |
| Syphilis | Great imitator, serological testing mandatory to exclude this condition |
| Lyme disease | Specific endemic area, erythema migrans, chronic arthritis, neurological involvement, array of non-specific ocular manifestations |
| Rickettsiosis | Specific endemic area, high fever with skin rash, small and large retinal infiltrates, mild vitritis |
| Dengue fever | Specific endemic area, systemic symptoms ranging from flu-like illness to hemorrhagic syndrome, foveolitis, diffuse retinal vasculitis |
| Chikungunya | Specific endemic area, flu like illness, polyarthralgia, non-granulomatous anterior uveitis, large retinal infiltrates |
| Sarcoidosis | Bilateral granulomatous anterior uveitis, segmental periphlebitis, multifocal choroiditis, vitreous snow balls |
| Behçet disease | Systemic involvement, acute non-granulomatous anterior uveitis, hypopyon, periphlebitis with occlusive complications, transient retinal infiltrates, severe diffuse vitritis |
| Other causes of optic disc edema with macular star<br>Systemic hypertension<br>Diabetes mellitus<br>Increased intracranial pressure<br>Branch retinal vein occlusion<br>Anterior ischemic optic neuropathy | Usually bilateral, lack of inflammatory reaction, associated features suggestive of specific entity |

correspond to areas of retinal capillary non-perfusion on fluorescein angiography.

*Treatment*

There is no *consensus* on the management modalities of CSD or its ocular manifestations. CSD is usually characterized by a self-limited course in immunocompetent patients. There is no recommendation to treat mild to moderate systemic CSD. However, severe ocular or systemic complications of CSD and immunocompromised patients should be treated. Antibiotic options may include doxycycline, azithromycin, erythromycin, ciprofloxacin, trimethoprim-sulfamethoxazole, gentamicin, or rifampin.[23,63]

Immunocompetent individuals aged more than 8 years are typically prescribed doxycycline, 100 mg per os twice a day for 2–4 weeks. This antibiotic may be given intravenously or used in association with rifampin (300 mg per os twice a day) in severe cases. A prolonged therapeutic regimen (4 months) is required in immunocompromised patients.[20] Children may be prescribed azithromycin. Paradoxical response to antibiotics is possible in CSD-associated ocular involvement.[64] Prescription of oral corticosteroids may be considered, in association with antibiotic therapy, in ocular CSD with severe inflammatory reaction. Recent data shows that patients treated with antibiotics and oral corticosteroids have better final visual acuity than patients treated by antibiotics alone.[65]

Preventive measures of CSD include washing hands after contact with cats, disinfection of injuries following a cat scratch or bite,[16] and limiting of the number of stray cats at greater risk for *B. henselae* bacteremia.[66]

Prolonged use of doxycycline or alternatively a macrolide may be helpful for prevention of CSD recurrences in HIV-positive patients.[20]

*Prognosis*

CSD-associated neuroretinitis is usually characterized by a self-limited course in immunocompetent patients, with gradual resolution of optic disc edema and hard exudates (Fig. 1). Most patients will recover a normal visual acuity within a few weeks to months.[19] Macular exudates usually disappear within approximately 8–12 weeks, but they may persist for up to one year. A mild or moderate optic disc pallor may rarely persist.[30] Retinal atrophy or residual retinal pigment epithelium changes may also occur as sequelae of severe exudative maculopathy, dense retinal infiltrates, or occlusive vasculitis.

## Discussion

In the present article, we reviewed the most recent available data in the literature regarding Bartonella neuroretinitis that are relevant to ophthalmologist in every day clinical practice. CSD is a worldwide distributed systemic infectious disease caused by a bacterium, *B. henselae*, and transmitted to humans through contact with infected cats. Systemic manifestations are usually mild and self-limited in immunocompetent patients, while immunocompromised individuals are at risk of developing severe, life-threatening complications.[1,25,26]

CSD is the first condition to be considered in the differential diagnosis of neuroretinitis.[1,5–7] Typical fundoscopic findings include unilateral optic disc edema and lipid exudation in the macula arranged in a complete or incomplete star configuration associated with mild vitritis. It is important not to miss a diagnosis of early acute neuroretinitis in the absence of evident macular star that usually develops roughly 1–2 weeks after the onset of optic disc edema. Other clues to the diagnosis of CSD include optic disc telangiectasia, peripapillary exudative retinal detachment, superficial retinal infiltrates, and occlusion of small branch retinal arterioles.[38–41]

Fluorescein angiography confirms that the primary site of inflammation is the optic nerve head, showing progressive optic disc leakage with no evidence of capillary abnormalities in the macular area.[51] Spectral domain optical coherence tomography (SD-OCT) is an essential imaging modality for the detection, evaluation, and monitoring of exudative retinal detachment and retinal thickening associated with optic disc edema.[54] Optical coherence tomography angiography (OCTA) may be a useful tool for non-invasive evaluation of optic disc and retinal vascular changes occurring in patients with CSD neuroretinitis.

The diagnosis of CSD-associated neuroretinitis primarily relies on clinical findings including young age, history of contact with cat, systemic symptoms, and typical ocular involvement.[1] Besides CSD, an array of other infectious and inflammatory conditions may present with neuroretinitis including toxoplasmosis, rickettsiosis, tuberculosis, syphilis, and sarcoidosis.[31,32] Clinicians should also be aware that optic disc edema with macular star associated with unknown malignant hypertension or other non-inflammatory conditions may masquerade as neuroretinitis.[62]

The IFA test is the most used method to detect IgM. However, cross reactivities are possible with other infections.[55] IgM-enzyme-linked immunoassays, IgM-Western blot analysis, and PCR are less commonly used.

In daily practice, a diagnosis of typical Bartonella-associated neuroretinitis is primarily based on clinical findings. Multimodal imaging is useful in characterizing and analyzing optic disc involvement and associated chorioretinal changes in both typical and atypical clinical presentations. Positive serology for *B. henselae* is, however, mandatory to establish the definitive diagnosis. Nevertheless, an empiric antibiotherapy could be started before serological results become available. Alternative diagnoses to Bartonella neuroretinitis should be excluded, especially in atypical clinical presentations. They include other infectious and inflammatory etiologies of neuroretinitis and other causes of optic disc swelling with macular star.

Treatment guidelines for systemic and ocular CSD remain poorly defined, as most patients have a self-limited course, with no randomized controlled trials performed. However, antibiotic treatment is often considered in severe systemic

disease, immunocompromised patients, or sight-threatening ocular involvement, including neuroretinitis.[20] Recent data show that use of oral corticosteroids in combination with antibiotics may further improve the visual outcome in patients with CSD neuroretinitis.[65]

Preventive measures for CSD would require avoidance of close contacts with cats and cat fleas, with increased awareness of the risk of cat scratches.

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