Pediatric Bartonella henselae neuroretinitis masking co-infections

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ABSTRACT

Purpose: Neuroretinitis (NR) is an inflammatory disorder that presents with painless vision loss due to optic disc edema, peripapillary detachment, and macular lipid exudation. We report the first two documented cases of co-infections of pediatric NR due to Bartonella henselae with HSV and Toxocara cati, respectively.

Observations: A 10-year-old female with acute right-sided facial droop, right eye pain, and acute visual loss of the right eye is diagnosed with co-infection of Bartonella and HSV retinitis and is successfully treated with acyclovir, rifampin, and doxycycline. A 13-year-old female with progressive visual loss of the left eye is diagnosed with co-infection of Bartonella and ocular toxocariasis and is successfully treated with doxycycline, rifampin, prednisolone, and albendazole.

Conclusions and Importance: Early recognition and multi-modal treatment is necessary to prevent delayed diagnosis and treat the underlying NR causes for optimal visual recovery.

1. Introduction

Neuroretinitis (NR) is an inflammatory disorder that presents with painless vision loss due to optic disc edema, peripapillary detachment, and macular lipid exudation. Pathophysiology generally involves an agent or trigger that increases permeability of disc vasculature. The causes of NR are broad and are typically categorized into either infectious, inflammatory, or idiopathic etiologies.

While there are a number of infectious etiologies of NR, cat-scratch disease (CSD) by Bartonella henselae is the most common pathogen, causing more than two-thirds of infectious NR cases. Other potential bacterial causes include Rickettsia rickettsii, Mycobacterium tuberculosis, Salmonella, syphilis, Lyme disease, and leptospirosis. Viral causes include Zika, measles, mumps, rubella, varicella, herpes simplex, herpes zoster, Chikungunya, dengue, influenza A, hepatitis B, Epstein-Barr, and coxsackie B. Parasitic causes include Toxocara species, toxoplasmosis and spirochetes.

Despite the broad and various etiologies surrounding NR, there are limited case reports regarding the incidence of NR in the setting of a concurrent infection. We report two cases of Bartonella henselae NR that initially masked a co-infection of the another visual threatening pathogen.

2. Findings

2.1. Case 1

A 10-year-old female with no significant past medical history presented to the emergency room with a seven-day history of fever, right-sided facial droop, right eye pain, and acute visual loss in the right eye. Three days prior to presentation, the patient had been prescribed oral valacyclovir and oral prednisone by a local pediatrician for a cranial nerve VII palsy but had continued worsening of symptoms. Pertinent social history included a vaccinated cat living at her primary occupancy. Review of systems was otherwise negative.

On examination, the patient’s best correct visual acuity was 20/100 OD and 20/20 OS with a right eye afferent pupillary defect (APD). Intraocular pressure was normal bilaterally. Confrontational visual field testing demonstrated a superior visual field defect in the right eye. Motility testing demonstrated a mild restriction in abduction and pain with extraocular movement of the right eye. Ishihara color plates were 9/11 OD and 11/11 OS. Anterior segment exam was remarkable for 1-
A previously healthy 13-year-old female with no past medical or ocular history presented with three weeks of progressive vision loss in her left eye and headaches. The patient was initially examined at an outside hospital emergency room and was diagnosed with probable cat-scratch disease (CSD) given her recent history of cat contact. She was started on rifampin, doxycycline, and promethazine, which was subsequently discontinued by an outside ophthalmologist after several days of treatment without improvement in vision. The patient was then referred to our service for evaluation. Further clinical history revealed that the patient had not only had recent contact with a stray cat but often kissed and licked the cat regularly. The patient also swam in brackish water one month prior and had limited contact with a dog at home. A review of systems was negative, and she had no history of seasonal or sinus allergies.

On initial presenting exam, her visual acuity was 20/20 OD and hand motion vision OS with a left afferent pupillary defect. Color vision was 11/11 OD and 0/11 OS. She had normal intraocular pressure and extraocular motility in both eyes. Confrontational visual fields were unremarkable in the right eye and were unreliable in the left eye. The anterior segment exam was notably quiet and unremarkable in both eyes. The dilated fundus exam was normal in the right eye and showed a clear view of the left eye with grade +4 optic nerve edema (Fig. 2A). The inflamed and elevated left optic nerve had fine angiomatous vessels and was surrounded by disc/flame hemorrhages, subretinal fluid, and exudation (Fig. 2B). Over a period of weeks, the macula began demonstrating an early macular star exudation (Fig. 2C). In the peripheral retina, there was a large creamy granulomatous lesion with clustered dot-blot hemorrhages and a linear track of exudation extending from the optic nerve toward an inferior peripheral granulomatous lesion (Fig. 2D).

MRI of the orbits with contrast was notable for an enhancing lesion in the retina near the fovea with a normal appearing optic nerve and brain. OCT of the macula of the left eye revealed subretinal fluid extended from optic nerve and a blurred and deviated foveal contour.

Laboratory serological studies were positive for Bartonella IgG (1:128) and IgM (1:16) and negative for Toxoplasma IgG and IgM, HSV-1 and HSV-2, syphilis, Lyme antibodies, TPPA, tuberculosis, and HIV. However, the patient had a notable IgE count of 400 UI/mL. Toxocara and Strongyloides were tested given the elevated IgE but were negative. The patient was started on doxycycline, rifampin, and prednisolone for Bartonella. However, given the distinguishing presentation of the optic nerve and retina, the lack of uveitic and systemic signs, and serially elevated IgE levels, an anti-parasitic medication, oral albendazole, was

Fig. 1. (A) Fundus photo of the right eye demonstrates optic disc edema with a superior hypopigmented retinal lesion and a macular star lipid exudation surrounding the fovea. (B) Fundus photo of the left eye with normal optic nerve and foveus. C) OCT of the macula of the right eye demonstrates intra-retinal and sub-retinal fluid extending from the optic nerve. (D–E).
remained negative. An additional month of Bartonella treatment was initiated for one month with repeated serology for Bartonella and presumed Toxocara. Bartonella titers increased to 1:512. Toxocara studies were erroneously diagnosed as reactivated CSD infection from either cat exposure or occult infection by the inpatient service. Thus, IV prednisone was chosen for initial treatment. With no anti-viral coverage, her posterior segment inflammation presumptively worsened in the setting of high-dose steroids, and within a few days develop concurrent primary HSV infection. It is worth noting that this patient had 2 days of valacyclovir prior to transfer of care, while not a therapeutic dosage, it may have delayed the HSV diagnosis. While there are two previously reported cases of patients with unilateral facial droop due to presumed CSD NR, one case was subsequently found to have a secondary granulomatous lesion compressing the facial nerve and neither case was tested for HSV serologies. \(^{10-12}\) Retrospectively, the patient’s right facial palsy was likely secondary to an active HSV infection given the clinical history, serologies, and neuroimaging demonstrating right facial nerve enhancement.

In the second case, cat exposure by actively licking the cat for weeks initiated for one month with repeated serology for Bartonella and presumed Toxocara. Bartonella titers increased to 1:512. Toxocara studies remained negative. An additional month of Bartonella treatment was added given the increased titers. At six months, visual acuity improved to 20/400 and dilated exam showed resolution of left optic nerve edema with residual surrounding peripapillary gliosis as well as resolution of the retinal hemorrhages and peripheral exudations (Fig. 3).

3. Discussion

*Bartonella henselae* is the most common and well-documented infectious cause of NR. \(^{1,2}\) To our knowledge, there has been only one reported case of NR due to herpes simplex virus and five reported cases of ocular larva migrans (OLM) secondary to *Toxocara cati*. Moreover, the literature of NR due to a co-infection is limited. \(^{4-6}\) Prior cases of NR with co-infection include *Bartonella henselae* in conjunction with *Borrelia burgdorferi*, HIV in conjunction with hepatitis B, and *Bartonella henselae* in conjunction with DUSN infection. We report two cases of pediatric NR due to *Bartonella henselae* with HSV and *Toxocara cati*, respectively. In all reported co-infections, early recognition and dual treatment was necessary to prevent delayed diagnosis and treat the underlying NR causes for optimal visual recovery. \(^{7,9}\)

In the first case, our patient’s initial presentation of unilateral facial droop with ipsilateral NR and positive IgG *Bartonella* serology (titres) was erroneously diagnosed as reactivated CSD infection from either prior exposure or occult infection by the inpatient service. Thus, IV prednisone was chosen for initial treatment. With no anti-viral coverage, her posterior segment inflammation presumptively worsened in the setting of high-dose steroids, and within a few days develop concurrent primary HSV infection. It is worth noting that this patient had 2 days of valacyclovir prior to transfer of care, while not a therapeutic dosage, it may have delayed the HSV diagnosis. While there are two previously reported cases of patients with unilateral facial droop due to presumed CSD NR, one case was subsequently found to have a secondary granulomatous lesion compressing the facial nerve and neither case was tested for HSV serologies. \(^{10-12}\) Retrospectively, the patient’s right facial palsy was likely secondary to an active HSV infection given the clinical history, serologies, and neuroimaging demonstrating right facial nerve enhancement.

In the second case, cat exposure by actively licking the cat for weeks and low IgG and IgM *Bartonella henselae* titers alone did not explain the ocular findings and elevated IgE levels in this child. Ocular bartonellosis has a broad spectrum of clinical presentations including optic nerve edema, neuroretinitis, intermediate uveitis, vasculitis, retinochoroiditis and peripheral choroidal granuloma, and systemically can have CNS manifestations of cranial neuropathies and seizures. \(^{13-15}\) However, in cases with an *Bartonella* inflammatory mass lesion of the optic nerve, as in our patient, there are usually associated vitreous infiltrates, anterior chamber inflammation, markedly elevated IgG and IgM titers, and flu-like prodrome prior to presentation. \(^{16}\) These findings were noticeably absent in our patient.

While our patient’s severely inflamed optic nerve and peripheral granulomatous retinal lesion findings can be found in sequelae of ocular bartonellosis, the lack of uveitic inflammation and an elevated IgE with...
no sinus or allergy history was concerning for possible parasitic infection secondary to *Toxocara* ocular larva migrans (OLM) species. OLM is usually a clinical diagnosis and has three unique presentations: posterior pole granuloma, peripheral granuloma, and endophthalmitis. The nematode larvae can enter the eye through choroidal, retinal, or ciliary circulation, and in peripheral retinal tissue, it can be swaddled with eosinophils with resultant eosinophilia. *Toxocara*-excretory secretory (TES) antigen and intraocular assay of aqueous or vitreous humor can be used to detect the antibodies, but it may be difficult to obtain specimen in a pediatric patient with a typically formed vitreous. Enzyme-linked immunosorbent assay (ELISA) has become the standard of serologic diagnosis of *Toxocara*, however, for OLM toxocara the ELISA assay has both poor sensitivity and specificity necessitating a clinical diagnosis. In a histopathology review of 22 cases of tissue confirmed OLM, only 50% had prior serum positive ELISA assays.

Currently, the management of NR is still debated as the condition is typically self-limited, especially in immunocompetent patients. Lack of randomized clinical trials demonstrating the efficacy of antibiotics or steroids makes it even more difficult for experts to reach a consensus. Therefore, we recommend therapy to target the underlying etiology. For NR secondary to CSD, a four-to-six week course of doxycycline and rifampin has been suggested to shorten the duration and systemic symptoms as seen with our patients. Ciprofloxacin or azithromycin may also be beneficial. The treatment of NR secondary to *Toxocara* includes both anti-helminthic agents and corticosteroids. Prior studies demonstrate a decrease in recurrence when combining both agents. High-dose albendazole is preferred as it can penetrate the blood-retina barrier with the addition of steroids to prevent further inflammation from larvae death. Empiric anti-helminthic therapy may also prevent further complications of both tractional and rhegmatogenous retinal detachment.

As treatment courses for NR are dependent on infection sources, a correct diagnosis is crucial for precise pharmacological intervention. Early recognition and diagnosis of NR co-infections are necessary for optimal visual recovery. Consider close monitoring of patients where multiple etiologies are suspected, especially in patients that present with atypical NR, have cranial nerve involvement, or are refractory to initial therapy.

4. Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Research ethics

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

IRB approval was obtained (required for studies and series of 3 or more cases).

Written consent to publish potentially identifying information, such as details or the case and photographs, was obtained from the patient(s) or their legal guardian(s).

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The International Committee of Medical Journal Editors (ICMJE) recommends that authorship be based on the following four criteria:

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Axial and coronal T1-weighted MRI of the brain with contrast demonstrates inversion and enhancement of the right optic nerve head extending to the intraorbital segment of the optic nerve. (F) Coronal T1-weighted MRI shows enhancement of the genu of the right facial nerve.

Declaration of competing interest

Potential conflict of interest exists:

We wish to draw the attention of the Editor to the following facts, which may be considered as potential conflicts of interest, and to significant financial contributions to this work:

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