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Parinaud Oculoglandular Syndrome 2015: Review of the Literature and Update on Diagnosis and Management

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Abstract

Parinaud oculoglandular syndrome (POGS) is an ocular granulomatous inflammatory condition characterized by unilateral follicular bulbar or palpebral conjunctivitis. Although POGS often presents as an atypical manifestation of cat scratch disease (CSD), other infectious and autoimmune etiologies have been described. Due to the rare nature of this ocular syndrome and scarcity of literature on this topic, POGS is often missed on the initial diagnostic work-up. Here, we provide a brief description of disease process, and present a review of the literature on POGS in the past two decades to understand the trends in etiology of disease. Based on the results of this review, we also suggest an algorithm for diagnosis and management of POGS.

Keywords: Parinaud; Cat-scratch disease; Follicular conjunctivitis; Granulomatous inflammation

Background

Parinaud oculoglandular syndrome (POGS) is a suppurative granulomatous inflammatory condition of the eye characterized by unilateral follicular bulbar or palpebral conjunctivitis and intense chemosis that often develops between 3-10 days following inoculation [1]. It is often associated with ipsilateral preauricular or submandibular necrotizing lymphadenitis with or without stellate abscesses, which may occur concomitantly or two weeks following the onset of follicular conjunctivitis. Lymphadenopathy often extends to cervical lymph nodes with possible suppuration and tenderness. Although often benign and self-limited, in a minority of cases, POGS may result in encephalopathy, encephalitis, thrombocytopenic purpura, hepatitis, and splenitis [2].

Corneal involvement, if present, is usually limited to superficial punctate keratitis. Systemic signs and symptoms of malaise and fever may also be present [2]. The disease may extend to the posterior segment, manifesting as neuro-retinitis, unilateral optic disc swelling, and macular star formation. Retinochoroiditis, anterior chamber inflammation and vitritis most often present in POGS when attributed to certain etiologic agents.

POGS often presents as an atypical manifestation of cat scratch disease (CSD), but other infectious and auto-immune etiologies have been described in the literature [1]. Due to similar ocular findings in bacterial or viral conjunctivitis, POGS is often misdiagnosed by the primary care provider [3].

A number of infectious agents have been implicated in the pathogenesis of parinaud oculoglandular syndrome (POGS), but cat scratch disease (CSD) remains the most common underlying etiology to-date [1,3]. CSD is an infectious entity characterized by self-limited regional lymphadenopathy that is most commonly caused by *Bartonella henselae*, and rarely, *Afipia felis*. Cats serve as the natural reservoir for *B. henselae*, with fleas as the horizontal vector of transmission. In contrast, *B. henselae* is transmitted to humans by trauma (scratch), inhaling infected materials, being licked by infected animals, or rubbing one's eye after contact [2]. The acute inflammatory response is initiated by the microorganism's invasion of endothelial cells and activation of a proinflammatory cascade. The exact underlying pathophysiology of disease is not yet elucidated.

The annual incidence of CSD is quoted between 2.4-2.7 per 100,000 persons [1,2], with the highest prevalence in the fall and early winter in a world-wide distribution. Amongst those infected, 90% present with clinical manifestations of disease. Lymphadenopathy, fever, malaise, anorexia and fatigue are the most common associated signs and symptoms, in decreasing order of frequency. After skin, the primary inoculation site is commonly a granuloma in the eye. Ocular manifestations of CSD include POGS, or less commonly neuroretinitis, papillitis, optic neuritis and focal retinochoroiditis. POGS has been reported in up to 5-10% of CSD cases [1,4-6]. Indeed, neuroretinitis with CSD may present as sudden loss of vision, unilateral optic disc swelling and macular star formation. Eye involvement develops primarily in those who have close contact with cats (and most commonly kittens), especially children younger than 10 years of age. Other atypical presentations of CSD also include encephalopathy, severe chronic systemic disease and less commonly, hepatosplenitis, pulmonary or thoracic disease, osteomyelitis and erythema nodosum1.

Along with enlarged tender erythematous lymph nodes, eye redness, irritation and watery conjunctival discharge with a foreign body sensation may occur at around two weeks following the inoculation of skin or conjunctiva.

Several other infectious and less common autoimmune conditions have been attributed to the pathogenesis of POGS. Thus, a differential

should always be considered, and ruled out when empiric therapy is initiated. Tularemia, sporotrichosis, tuberculosis and syphilis comprise the most common causes of POGS after CSD [1,7]. Table 1 summarizes the common causes of POGS with specific features and treatment regimens for each. Less common etiologies are summarized in Table 2.

Causes of POGS	Specific features	Treatment
Cat scratch disease (*B. henselae/A. felis*)	History of contact with cats/kittens (rarely, dogs or rabbits); positive serology, biopsy	Erythromycin/azithromycin, ciprofloxacin, gentamicin, rifampin or TMP-SMX
Oculoglandular tularemia (*F. tularensis*)	History of contact with rabbits, hares, squirrels, rats, mice or foxes; necrotizing conjunctival inflammation and ulceration; vomiting, pneumonia	Streptomycin IM or gentamicin IV; topical gentamicin
Conjunctival sporotrichosis (*Sporothrix schenkii*)	Hard, non-tender nodule on eyelid skin; numerous soft, granulomatous nodules that may ulcerate; biopsy,culture	Itraconazole (systemic)
Conjunctival tuberculosis (*M. tuberculosis*)	History of ocular trauma; small painless conjunctival ulcers; positive tuberculin skin test, interferon gamma release assay, chest x-ray	Isoniazid with ethambutol, rifampin or streptomycin
Conjunctival syphilis (*T. pallidum*)	During primary, secondary or tertiary stages of disease; diffuse, rose red, jelly-like thickening of tarsal conjunctiva; iridocyclitis; corneal pannus and perforation; panophthalmitis	Penicillin
Conjunctival coccidiomycosis (*C. immitis, B. dermatitidis*)	Erythema nodosum, phlyctenular conjunctivitis, episcleritis, scleritis, keratoconjunctivitis or iridocyclitis	Ketoconazole, fluconazole or itraconazole, Amphotericin B in worsening disease

Table 1: Common etiologies of POGS, unifying features and treatment options (adopted with modification from Tu et al. [1]).

S. No	Less common and rare etiologies of POGS
1	HSV-1 [2]
2	*Actinomyces israeli*
3	Epstein-Barr virus (infectious mononucleosis)
4	Mumps
5	*Haemophilus ducreyi*
6	*Pasteurella multocida*
7	*Yersinia pseudotuberculosis*
8	*Yersinia enterocolitica*
9	*Burkholderia mallei*
10	*Listeria monocytogenes*
11	*Rickettsia conorii*

Table 2: List of rare etiologies of POGS, adopted with modification from Tu et al. [1].

Diagnostic Work-up and Management

Traditionally, serologic testing by indirect immunofluorescence test (IFA) and various enzyme-linked immunoassays (ELISA) have been the mainstays of diagnosis for both CSD and POGS [1,2]. Seroconversion is often detected anywhere between three to five days following the inoculation of disease; however, there have been reports of "borderline positive serology" or late-onset seroconversion (up to four weeks) [1,4-5]. In addition, many groups have reported staining or PCR of conjunctival biopsies to aid in accurate diagnosis. As well, the clinical picture with a history of contact with a cat or kitten (and/or presence of a scratch mark) may warrant empiric treatment with appropriate antibiotics.

The prognosis for POGS is excellent, with most cases lasting up to 5-7 days. However, there are a few reports of disease lasting up to 2 years with permanent ocular damage in the absence of treatment [8]. In the case of CSD, topical antibiotics are of questionable benefit and systemic therapy is often warranted. Antipyretics and analgesics may offer some symptom relief. To date, there is no standardized empiric antibiotic treatment regimen for immunocompetent patients with POGS [1,3,9]. The current guidelines for POGS secondary to *B. henselae* recommend a five day course of azithromycin as a first line treatment (in adults and children>45.5 kg: 500 mg on day 1, followed by 250 mg for 4 days or for children<45.5 kg: 10 mg/kg on day 1, followed by 5 mg/kg for 4 days) [1,3]. Alternatively, a 7 to 10 day course of clarithromycin, rifampin or trimetoprim/ sulfomethoxazole (TMP/SMX) is recommended. In individuals older than 17 years old, a 7-10 day course of ciprofloxacin (500 mg BID) may also be used. Since POGS due to CSD may recur, it is recommended that patients are closely monitored and the course of treatment continued if symptoms of CSD/ POGS persist following the initial antibiotic regimen [1,9]. Doxycycline (100 mg bid) may also be used in immunocompromised individuals who are predisposed to more disseminated disease [1]. These recommendations are consistent with successful treatment of CSD-related POGS cases in the past decade, which has included the use of macrolides (azithromycin, clarithromycin, spiramycin), quinolones, TMP/ SMX and in one case, oral amoxicillin/clavulin in conjunction with doxycycline [3-6,10-13] (Table 1).

Treatment for POGS due to tularemia consists of streptomycin (7.5-10 mg/ kg IM BID for 7 days) or gentamicin (1.7 mg/kg IM/IV each 8 hours for 7 to 14 days) in the case of severe disease. In mild to moderate disease (e.g. in the absence of corneal ulceration), ciprofloxacin or doxycycline may be used orally in an outpatient basis. As well, instillation of ocular gentamicin drops is recommended every two hours for 1 week or until the resolution of symptoms [14-15].

In more severe cases of POGS with posterior segment involvement, combination antibiotics may be used. In rare cases of optic neuritis, steroids may be used following the appropriate antibiotic treatment with referral to neuro-ophthalmology [3].

Although aspiration of the swollen painful lymph node for supportive treatment may be offered, surgical incision and drainage is not recommended due to the possibility of a fistulous tract developing. A biopsy is warranted in cases where a patient is unresponsive to treatment or when malignancy is suspected [3].

References	Year	Etiology	Signs and Symptoms	Treatment	Diagnostic work-up
[1]	2003	*Bartonella henselae*	24 patients (37 eyes); 66% history of cat exposure; decreased visual acuity; 50% bilateral disease; fever, lymphadenopathy, organomegaly; retinal infiltrates, angiomatous lesions, neuroretinitis	Doxycycline PO/IV or ciprofloxacin	Serology and clinical history
[2]	2007	Herpes simplex virus 1 (HSV-1)	14 y/o f, conjunctivitis, periorbital edema, tender preauricular and submandibular lymphadenopathy; systemic malaise & fever	Acyclovir PO	PCR (skin and conjunctival scrapings) and late HSV-1 seroconversion (IgG and IgM)
[3]	2005 (1997 to 2003)	*Bartonella henselae*	8 cases of POGS	Macrolides or quinolones	Seroconversion and skin biopsy PCR
[4]	2004	*Bartonella henselae*	65 y/o m, FOB left eye with granulomatous nodule on palpebral conjunctiva, chemosis and swollen preauricular lymph node	Ciprofloxacin PO	Late onset of serologic positive titers
[5]	2003	*Bartonella henselae*	14 y/o f, 12 day history of right eye redness, preauricular lymphadenopathy and low-grade fever for 4 days.	Initially unresponsive to cephalexin (5 d), amoxicillin (4 d) and gentamycin (3 d) by different providers; responded to: spiramycin (3 d), then clarithromycin (15 d) and TMP-SMX (10 d)	Seroconversion (IFA) with history of kitten scratch
[6]	2002	*Bartonella henselae*	2 cases of POGS	2 cases of POGS	Seroconversion (IFA)
[7]	2002	*Bartonella henselae*	65 y/o m; foreign body sensation in left eye, injection, chemosis and preauricular lymph node	Initially steroids (loteprednol) with no improvement; then azithromycin PO	Conjunctival swab PCR and borderline positive serology
[8]	2002	*Paracoccidiodomycosis*	31 y/o m, cervical lymphadenopathy x 5 months, low grade fever, malaise and weight loss, ocular pain and purulent discharge right eye; pre- and retro-auricular lymph nodes	Cotrimoxazole	Cervical lymph node biopsy culture and serology, chest x-ray
[9]	2001	Tularemia (*Francisella tularensis*)	Unilateral granulomatous conjunctivitis, painful preauricular and submandibular lymphadenopathy with general malaise and fever	Streptomycin IM, nafcillin IV	History of encounter with a wild rabbit; conjunctival culture and serology
[10]	1999	*Bartonella henselae*	38 y/o f tender preauricular lymphadenopathy, red left eye; intraretinal lesions and cotton-wool-spots	Amoxicillin, doxycycline, tobramycin PO, and chloramphenicol (topical)	Agar plate colony culture from the eye; PCR; serology
[11]	1995	*Bartonella henselae*	6 y/o f, neuroretinitis and POGS	Erythromycin, rifampin	Seroconversion (IFA)
[12]	1995	*Bartonella henselae*	35 y/o m, enlarged preauricular lymph node, ipsilateral conjunctival granuloma	Surgical removal of granulomatous lesion led to rapid healing	Seroconversion

Table 3: List of all cases of POGS reported between 1995 and 2013. y/o: year-old; m: male; f: female; IFA: Indirect Immuno-Fluorescence; PCR: Polymerase Chain Reaction; FOB: Foreign Object; IV: Intravenous; IM: Intramuscular.

Shift in Etiology, Diagnosis and Management of Parinaud Oculoglandular Syndrome

There has been a significant shift in the etiology and subsequent diagnosis and management of POGS in the past two decades. A review of the literature in the past 20 years revealed 43 reports of POGS, with an overwhelming majority of cases secondary to CSD (*B. henselae* / *A. felis*) (n=40; 93%), followed by one each of tularemia (*F. tularensis*) (n=1), HSV-1 (n=1), and paracocciodiomycosis (n=1). Except for one case of animal POGS caused by tuberculosis [16], there were no reports of POGS caused by previously common agents such as sporotrichosis or syphilis (Table 1). This trend is consistent with the decrease in prevalence of tuberculosis and syphilis in the developed world. Table 3 summarizes all reported cases of POGS in the past 10 years with diagnostic and management strategies. Based on the changes in etiology and the results of this review, we propose a diagnostic algorithm in suspected cases of POGS (Figure 1).

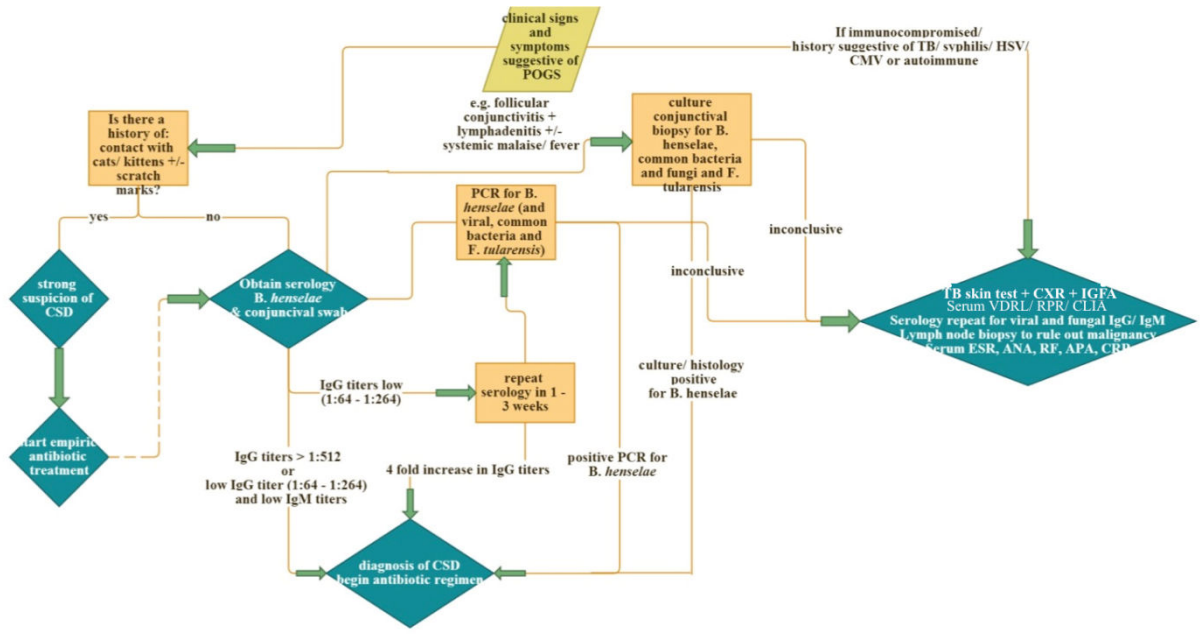

Figure 1: Diagnostic flow-chart for POGS. CXR: Chest X-Ray; IGFA: Immunoglobulin Fluorescence Assay; CLIA: Chemiluminescent Immunoassay; RPR: Rapid Plasma Ragin; VDRL: Venereal Disease Research Laboratory; CMV: Cytomegalovirus; HSV: Herpes Simples Virus; POGS: Parinaud Oculoglanduar Syndrome; TB: Tuberculosis.

POGS is probably a frequently-missed diagnosis and likely remains significantly under-reported. This is due in part to the self-limiting nature of disease and good response to empiric antibiotic treatment. In addition, many etiologic agents of POGS, such as herpes simplex virus, Epstein Barr virus and syphilis manifest with other organ-specific symptoms, and are often treated appropriately prior to the onset of ocular manifestations. However, in cases with signs and symptoms suggestive of this disease process, an accurate diagnosis is a crucial first step on the path to timely management and prevention of complications from POGS.

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